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SUPPLEMENT: AMERICAN THORACIC SOCIETY: RESPIRATORY HEALTH HAZARDS IN AGRICULTURE

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Respiratory Health Hazards in Agriculture

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1. OVERVIEW

History

Respiratory diseases associated with agriculture were one of the first-recognized occupational hazards. As early as 1555, Olaus Magnus warned about the dangers of inhaling grain dusts, and the risk was again noted in 1700 by Ramazzini in his seminal work *De Morbis Artificum* (1).

Yet, despite this early recognition of respiratory hazards in agriculture, it has only been in the 20th century that this problem has been carefully studied and documented. In general, the investigation of agricultural respiratory hazards has lagged behind the investigation of hazards in mining and other heavy industries. These agricultural hazards, however, are of serious concern.

Because agriculture is so intimately tied to the land, it has generated many myths about the health of farmers (2). The long-standing "agrarian myth" was exemplified in Thomas Jefferson's declaration that "Cultivators of the earth are the most valuable citizens. They are the most vigorous, the most independent, the most virtuous, and they are tied to their country and wedded to its liberty and interests by the most lasting bonds" (3).

Unfortunately, the myth of the robust, reliably healthy farmer was in actuality a myth that does not correspond with the realities of agricultural life. Ample data, described in part in these pages, confirm the magnitude and severity of respiratory and other hazards in agriculture. In this review, we attempt to focus attention on the very real risk of serious respiratory disease posed by exposures in the agricultural environment. The ultimate goal of this effort, as with other reports on occupational respiratory diseases, is to communicate an understanding of respiratory disease in the affected populations and how to prevent it.

Respiratory disease is today an important clinical problem for agricultural workers. Numerous studies, many cited in this document, have demonstrated a significantly increased risk of respiratory morbidity and mortality among farmers and farm workers. This risk obtains despite the lower prevalence of smoking among them, compared with the general population, thus further implicating occupational risk factors for respiratory disease.

Agricultural respiratory disease is also an important public health problem; the affected population is a large one. In the United States, there are more than 5 million individuals involved in agricultural production; in many developing countries, over 70% of the work force may be involved in agriculture.

Respiratory diseases due to agricultural exposures are, at least in theory, preventable. The clinical, social, and monetary

benefits of conquering the array of respiratory disorders caused by farm work may be substantial.

The Agricultural Workforce

An *agricultural worker* was defined by the World Health Organization (WHO) in 1962 as any person engaged either permanently or temporarily, irrespective of legal status, in activities related to agriculture (4). *Agriculture* was in turn defined as embracing all forms of activity connected with growing, harvesting, and primary processing of all types of crops; with breeding, raising, and caring for animals; and with tending gardens and nurseries. Thus, the term comprises a spectrum of pursuits, from growing to processing, and a wide range of commodities. This definition has been used in the present review, but it is recognized that there are some settings that may in part be considered agricultural and in part manufacturing. These have been reviewed on an individual basis, with consideration of whether data exist on respiratory disease and whether exposures may occur in other agricultural settings. For example, animal feed production is included because similar exposures may occur in a variety of agricultural settings. Similarly, studies of cotton dust exposure in manufacturing are included in this review because this industry covers the primary processing of an agricultural product (cotton) and exposures in this setting (e.g., endotoxin) are relevant to other agricultural environments. Some definitions of agriculture also include fishing and forestry, but they will not be addressed in this review.

While the number of farms in the United States has declined by 30% over the past four decades and the number of Americans living on farms has decreased fourfold in the same time period, the decrease in agricultural populations has not been as great (5). Further, the decrease in numbers of traditional farm families has been largely matched by an increase in hired farm workers. Thus, while the traditional U.S. agricultural workforce has declined from 6.8 million to 2.8 million, this decline has been nearly matched by the increase in migrant and seasonal farm workers. Regions with labor-intensive agriculture have a dominance of migrant and seasonal farm workers. In some parts of California, for example, over 80% of the farm work is done by hired labor.

Despite the changing nature of the agricultural workforce, agriculture remains a major industry in the industrialized world. It also remains one of the largest industries in the United States.

The farmer (owner and operator) population in the United States is predominantly older and white. Unlike many other occupations, farmers often continue to work well beyond 65 years of age. Eighteen percent of U.S. farm operators are over age 65 (6). Seasonal farm work generally is performed by migrant—minority and disadvantaged—populations. The seasonal labor force is largely young, male, Hispanic, and not

native to the United States (7). Hispanics account for approximately 70% of the seasonal work force, non-Hispanic whites for 23%, African-Americans for 2.5%, and Asians for 2% (7). Most of these workers have low levels of education and do not speak or read English. Half of seasonal workers' families have incomes below the poverty level, and many lack basic health care services (8). The problems of health care access in rural populations are often accentuated among farm workers.

A similar situation with respect to agricultural labor prevails in Europe. In Germany, for example, there were over 4 million migrant workers in 1986, with one-third from Turkey (9). This proportion represented an increase of 8.6% over the preceding 12 years. As in the United States, the health status of migrant workers in Europe is generally lower than that of the non-migrant population, and occupational injuries and illnesses may be higher in migrant populations (10).

The decline in the number of U.S. farms has coincided with the advent of more intensive and productive agricultural methods. The average farmer's productivity has increased six-fold, but this increase has been associated with the use of agrochemicals, fertilizers, increased mechanization, more intensive animal husbandry, and other far-reaching changes (5). In many cases, these changes have introduced new risks of potential exposures to high concentrations of respiratory toxins.

Unlike most occupational settings, the farm is frequently both residence and worksite. Even family members not directly engaged in the farm work may be incidentally exposed to respiratory hazards (the risk for active workers, of course, is even higher). Thus farming, uniquely among industries, may result in extensive exposure risk to workers' family members, increasing the population at risk by several-fold. That population includes such susceptible groups as children, the elderly, and individuals with chronic respiratory and other diseases. Nonfarming rural residents living near farming operations may also be at significant risk from exposure to grain dusts and pesticides and other chemicals carried by aerial drift. An extended population, by no means restricted to farm operators and workers themselves, is thus at risk.

Globally, agriculture is the overwhelmingly dominant occupation, far eclipsing mining, manufacturing, and service industries. Agriculture continues to play a fundamental role in the economy and daily existence of the populations of developing countries, commonly representing both occupation and lifestyle for entire families, and agricultural output is the primary source of foreign currency for industrial products. The relative size of the agricultural workforce is substantially greater in developing countries than in the industrialized nations (11).

In developed countries such as the United States and Japan, less than 5% of the economically active population is involved in agriculture. This percentage rises to 50 to 70% for many Asian countries and 70 to 90% for many countries in Africa (9). There is an inverse correlation between the size of the agricultural workforce and the level of development. Mexico, for example, with 9% of its gross domestic product represented by agricultural production, counts 31% of its labor force in agriculture; in Nigeria, with 36% of output in agriculture, 66% of the labor force is engaged in agriculture.

While agriculture may be spoken of as a single industry, it is extremely diverse with substantial respiratory hazards occurring from organic and inorganic dusts, chemicals, gases, and infectious agents. This is different from many industries posing the threat of occupational respiratory diseases, which can be characterized by a common method of production and one or two predominant respiratory hazards or categories of hazards—e.g., asbestos, polycyclic aromatic hydrocarbons, silica, or diisocyanates. The nature of agricultural practice also

varies with climate, geography, and other determinants of the commodities grown, and with the degree of industrialization of the country or region. The permutations of potential exposures are virtually infinite.

In the United States, for example, California produces high-value, labor-intensive commodities compared to much of the rest of the country. An acre of farmland in California generates \$1,207 worth of produce, versus only \$209 per acre for the rest of the country—while the farm labor requirements per acre in California are approximately four times as great as in the rest of the country (5). Four-fifths of California agriculture is in vegetables, fruits, nuts, and nursery crops, with just one-fifth as field crops. Nationwide, in contrast, on the average two-thirds of farm production is in field crops. The potential exposures in different regions of the country would be expected to vary with these different crop mixtures and associated farming practices and, indeed, that is the case.

Many features of the agricultural workplace have limited the investigation and control of occupational respiratory hazards. Most traditional industries concentrate workers at a small number of manufacturing facilities. Agriculture is spread over large distances, with only a few persons at each location. Union organization of workers (which, when in place, offers a route for both study and alteration of working conditions), is distinctly rare in the agriculture industry. The migrant lifestyle of many farm workers further limits the ability to perform epidemiologic investigations (12). Many farmers, too, view occupational hazards as "part of the job," although recent research suggests that there is increasing recognition of these perils by farmers (13, 14). Unfortunately, because of the small number of employed workers on many farms coupled with specific regulatory exclusions, the agricultural workplace in the United States has generally been excluded from the regulatory and enforcement activities of federal agencies such as the Occupational Safety and Health Administration (OSHA).

Spectrum of Exposures and Respiratory Effects

Structuring this review presented the formidable challenge of placing in perspective a multiplicity of exposures and exposure circumstances that can result in varying degrees and types of lung responses (5, 15). Modern agriculture subjects the respiratory system to many different exposures. While most exposures—such as those to dusts, bacteria, endotoxins, and spores—are primarily in the workplace itself (both outdoors and within animal confinement and other facilities), such hazards as storage mites, for instance, may be encountered within either the workplace or home, and exposure to various chemicals may occur in the field, yard, garden, or home.

The impact on the respiratory system may also vary considerably. Organic exposures may affect the airways and, depending on the antigenicity of the material and host susceptibility, may result in asthma, asthma-like syndrome, or chronic obstructive airways disease. Inhalation of such material as fungal spores leads primarily to parenchymal dysfunction such as hypersensitivity pneumonitis. Endotoxins found in moldy hay, grain, and similar organic materials may create a complex of constitutional symptoms known as the organic dust toxic syndrome (ODTS), which could represent a same-spectrum counterpart to hypersensitivity pneumonitis.

In discussing and categorizing these disease entities, this review has been limited by the current knowledge and understanding of a too-little-understood area. Some decisions have necessarily been made on the basis of convenience and clarity within those limitations. A distinction has been drawn between *asthma* and *asthma-like syndrome*, basing that distinction on an understanding of asthma as a relatively progressive

condition frequently related to antigenic exposures. Asthma-like syndrome, on the other hand, suggests mild, apparently reversible airway obstruction in the face of transient or mild increases in nonspecific airway responsiveness resulting primarily from nonantigenic exposures.

Further, in dealing with asthma, this review avoids a rigorous definition of occupational asthma. Asthma has been considered in the agricultural setting as encompassing both exacerbation of previous asthma and the development of new asthma apparently triggered by elements in the workplace. In taking this approach, it is recognized that agricultural workers frequently grow up and live in the workplace. An attempt has been made to avoid the strictures of a legal approach to occupational asthma, an approach that, even in the traditional workplace, is more geared to workers' compensation questions than to understanding disease processes.

This review has also summarized existing knowledge in areas less well understood and less publicized. For example, the review addresses the relatively new area of chemical exposures and the lung. While some conditions, such as lung disease due to paraquat exposure, are well known (16, 17), other areas, such as the possible long-term relationships between exposure to inhaled organophosphate pesticides and asthma, are only now being defined (18). Data are also presented on the potential respiratory effects of agricultural silica or silicate exposures, an emerging topic that may be particularly clinically significant in dry and dusty farming areas of the world.

Additional complexities relate to dosage–time relationships. In swine confinement, for example, workers may experience long-term, low-dose exposure to ammonia (NH_3) (19) and, in the same facility, they could be exposed to potentially lethal concentrations of hydrogen sulfide (H_2S) from manure pit gases. The possibility that for some exposures, such as endotoxin, there could be a limitation of the pulmonary inflammatory response at relatively low exposure levels creates additional complexities in describing dose–effect relationships and in suggesting maximum exposure levels.

Recognizing the importance in agricultural respiratory disease prevention of accurately identifying etiologic agents, a section has been included specifically discussing exposures. While the relationships between exposures and known lung dysfunctions and disorders are addressed in each lung disease section, the section devoted to exposures is far more exhaustive, since new knowledge relating the environment and the lung will closely follow delineation of the exposures involved. For that reason, the exposures section also includes other substances, such as solvents and adjuvants, for which the causal linkage to respiratory disease is less well established.

In some cases, increased mechanization in agriculture may not reduce or may actually increase respiratory exposures. Thus, riding a tractor cab could result in higher exposures to anhydrous ammonia for the operator. Similarly, the use of mechanized bedding choppers has demonstrably exposed workers to very high concentrations of endotoxin.

Healthy Worker Effect

The delineation of health effects due to some exposures may be made more complicated by workers' departure from the industry through either self-selection or forced retirement. There is evidence that such departures, a major component of what has been termed the "healthy worker effect," do occur and are related to some agricultural exposures. Young workers with a history of asthma or asthmatic symptoms have been shown to be at risk for the development of symptoms after commencement of exposure to grain dust (20). Therefore, a lower prevalence of asthma among grain workers than among

control subjects (21) may be due to dropout of workers from the workplace (22). Recent research has demonstrated that grain workers who leave their jobs early in their employment suffer greater annual losses in lung function than do workers who stay in the industry for a longer period of time (23).

Thelin and Hoglund (24) found in a retrospective cohort study of Swedish farmers and farm workers that farmers (i.e., farm owner-operators) changed their jobs less often than men in other occupations, but farm workers (i.e., employees) changed jobs more often than control subjects. Allergic disease was one of the common explanations given in this study for farm workers' changing their jobs.

Smoking in Agricultural Populations

In general, farmers smoke less than persons in most other occupations (25), and this tendency is demonstrated by the results of general health surveys, cancer case-control studies, and studies of respiratory disease among farmers and rural populations. The percentage of male farmers who had never smoked, 39.5%, was second only to that among clergy in a report on the smoking habits of over 800,000 U.S. men and women classified by lifetime occupational groups (26). Among females, farmers had the highest proportion of never-smokers, 78.7%, among 44 occupational groups. Among white persons over age 45 interviewed for the U.S. National Health Interview Survey, proportions of persons currently smoking cigarettes were generally lower in nonurbanized areas (27).

In studies of cancer in which occupation and lifestyle factors such as smoking were known, farmers had lower prevalences of smoking than other occupational groups (28, 29). The proportion of farmers using tobacco among over 13,000 cancer cases in a midwestern U.S. case-control study was significantly lower than that of cases with other occupations (odds ratio [OR] = 0.54, 95% confidence interval [CI] = 0.47, 0.62) (28).

The most valid evidence of lower smoking rates among agricultural workers comes from studies on population-based comparison groups from the same area. Such studies minimize the effects of geographic and cultural differences on smoking prevalences. Pig and dairy farmers in France smoked less than the nonfarming comparison group (28% and 27% current smokers, respectively, versus 44% current smokers in the comparison group) (30). In countries such as Japan, where smoking prevalences are generally higher, 67.8% of male agricultural workers in a cancer registry were current or former smokers, but they smoked fewer cigarettes per day on average than men in 19 other occupational groups (31). Fewer female agricultural workers were current or former smokers (3.5% versus an average of 13.5% for all 20 occupational groups), and these agricultural workers smoked fewer cigarettes per day.

Fewer Canadian swine producers and grain farmers were current smokers than the nonfarming comparison group from the same locale (14.5% and 18.3% current smokers, respectively, versus 30.4% current smokers among the comparison group) (32). Swine and dairy farmers in Quebec, Canada, were less likely to be current smokers than were a referent group of their nonfarming neighbors (20.3% versus 34.7% current smokers, respectively) (33). Proportions of nonsmokers were comparable, but more farmers reported having quit smoking than referents (54.7% versus 36.1%).

Some agricultural worker subgroups, it must be added, seem to have *higher* rates of smoking than other farmer populations and the general population. In one study, for example, 33% of grain elevator workers in British Columbia were found to be current smokers, compared with only 9% of civil employee control subjects; however, the number of control subjects was

small ($n = 50$) (34). Smoking prevalences may be higher among some agriculture-related occupational groups, such as abattoir workers (48% were current smokers) (35) and grain elevator workers (38.6% to 50.1% were current smokers throughout a longitudinal study) (36).

Rural Health Care Issues

There is a widening gap between health care services offered in rural and urban areas. Primary health care, emergency medical services, public health measures, and health-related social services are generally less available in rural areas. Barriers to health care for farm workers and many farm families vary widely by region and country but may include higher levels of poverty, fewer primary care facilities, limited transportation services, geographic barriers, and cultural/language differences. Agricultural respiratory diseases must be considered in the context of rural health care delivery, as well as characteristics of the particular population.

Global Issues

While a section on the industrializing countries has been included in this review, most of the available information is from North America and Europe, and this section is representative as opposed to comprehensive. Nevertheless, there are several reasons why it is important to address global issues in agricultural respiratory disease. First, developing countries constitute more than 70% of the world's population, and these countries are undergoing rapid population growth. Second, agricultural activity is inversely related to gross national product; thus, a very large percentage of developing countries' populations are involved in agricultural production. In many developing countries, more than 80% of the economically active population may be involved in agricultural production (11, 37, 38). Third, approaches to prevention may be similar for agricultural workers in the developed and developing countries. How exposures to respiratory toxins among agricultural workers in developing countries compare to exposures in developed countries is not known.

2. EXPOSURES IN AGRICULTURAL POPULATIONS AFFECTING RESPIRATORY HEALTH

Introduction

Farmers and other individuals involved in agriculture have potential inhalatory exposures to a very wide range of agents: inorganic dust from the soil; organic dust containing microorganisms, mycotoxins, or allergens; decomposition gases; pesticides; etc. These exposures occur when dealing with animals, harvesting, processing or storing grains or other plant matter, or when the soil, plants, or stables are treated with chemical agents such as pesticides and disinfectants. This section gives an overview of the scientific information available on exposure levels to these agents and the population exposed, the available (legal and other) health-based exposure standards to evaluate exposure to these agents in the work environment, and possibilities for exposure reduction. For most of the chemical agents, reliable standards exist for the evaluation of exposure to these agents, and exposure levels that occur in agricultural settings are reasonably well documented. For most biologic agents, a more limited insight exists. Analytical techniques for several biologic agents have become only recently available, and serious standardization issues have not been resolved. Generally accepted exposure limits are not available for most biologic agents. Nevertheless, it is clear from this document that farmers are often exposed to high levels of chemical and biologic agents, often above existing recommended limits.

Preventive strategies have been developed for some specific exposures but are not widely available for most specific exposures.

Agriculture involves a very wide variety of activities in diverse geographic and climatic settings. In small, often family-based farms, there may be little task separation, resulting in a wide range of potential occupational exposures for all involved. Swine farmers, for example, are exposed to animal danders, disinfectants, and other chemical substances, organic feed particulates, bacteria originating from feces, and such gases as NH_3 emanating from manure.

Exposure patterns may be cyclic, related to growth cycles of animals or to seasonal variations. Fruit growers' exposure to pesticides, for example, is concentrated in the summer months, the type of pesticide depending on crop type and climate. The exposure of farmers involved in the same or similar activities may also differ between countries, due to differences in climate as well as regional agricultural practices. Fruit farmers in northern countries may use more fungicides, because a humid climate encourages significant fungal growth, while farmers in southern areas may make greater use of insecticides. Dairy farmers experience higher exposures to dust and gases during the winter months, when most activities take place indoors and ventilation rates are reduced to effect energy conservation. In contrast to many occupational settings where exposures are relatively constant, farming involves a number of high-exposure tasks that, while performed infrequently, carry a high disease burden. Examples include grain bin clean out, manure pit cleaning, and silo uncapping. These examples illustrate farmers' exposure to a range of chemical and biologic agents and variable nature of these exposures in terms of time and place.

Exposure assessment and evaluation. The same principles for exposure assessment can be used in agriculture as in general industry (39–42). Sampling and analytical techniques for measurement of gases and dust are widely available and have been well described, although there are complications in calculating exposure to constituents of organic dusts, since measurements of many of these have not yet been standardized.

Exposure assessment generally aims to demonstrate sector-wide exposure levels to particular substances, and these assessments can be costly and time-consuming. A specific difficulty in agricultural exposure assessment is that investigators must often deal with numbers of small facilities spread over large areas. Repeated sampling, often required to accurately evaluate seasonal and other variations in air pollutant levels, may not be possible for economic reasons. Researchers are therefore forced to utilize crude surrogates of exposure instead of more elaborate indices based on laboriously gathered quantitative data. New and promising approaches, including predictive exposure modeling based on farm characteristics and task patterns, have been proposed (43).

Environmental evaluation criteria are used as guidelines to assess the potential health effects of occupational exposures to substances and conditions found in the work environment. These criteria usually arise after years of study of workplace exposures and adverse health effects. They are generally established at levels that can be tolerated by most healthy workers occupationally exposed daily over a working lifetime without adverse effects. Accepted evaluation criteria commonly change over the years as new exposure-response data become available. The primary sources of occupational environmental evaluation criteria include: the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits (RELs); the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs);

the U.S. Department of Labor's OSHA permissible exposure limits (PELs); and occupational exposure limits (OELs) from various European countries. Recently, the Health and Safety Directorate of the Directorate-General of Employment, Industrial Relations, and Social Affairs of the Commission of the European Union has established a Scientific Expert Group on OELs to advise on indicative limits at the European level. Although PELs are legal standards, they do not apply to farms and most agricultural field operations. TLVs, on the other hand, are not promulgated standards but are consensus exposure guidelines. They are revised periodically and are rarely subject to legal challenges.

Exposure standards are set for different averaging times, dependent on the toxicity of the agent: time-weighted average (TWA), over an 8-h workshift; short-term exposure limits (STEL), time-weighted over a 10- or 15-min period; and ceiling levels (C), not to be exceeded for any period of time. In the risk analysis process underlying exposure standards, it is assumed that an exposed worker has an 8-h workday, 5 d a week until the age of retirement. For farmers this is often not the case, and hygienists should correct for deviations from the average work pattern when the exposure time is increased (40). For gases, these exposure criteria and standards are often reported as parts of contaminant per million parts of air (ppm). For heterogeneous particulate aerosols, the exposure criteria are reported in terms of mass per volume of air sampled: milligram per cubic meter of air (mg/m^3) or micrograms per cubic meter of air ($\mu\text{g}/\text{m}^3$).

Standards do not exist for many agents, especially for many of the biologic agents and organic dusts. One could argue that this illustrates the state of the art in occupational hygiene and respiratory health in agriculture. Exposure-response relationships must be established before specific standard setting for an environmental pollutant can be initiated.

Inorganic Dust Exposure

Farmers frequently work in thick clouds of dust as they till the soil and harvest crops. The complex inorganic fraction of this dust comes chiefly from the soil. The association between respirable quartz exposure and respiratory disease is well known (44), but researchers have shown a continued interest in the pathologic potential of other soil silicates (45). The mineral fraction of most soils is dominated by silicates. Soils of very arid climates are exceptions; there the inorganic fraction may be dominated by calcium carbonate and more soluble salts (evaporites). Very highly weathered soils of warm, humid climates, where oxides and hydroxides of iron (goethite and hematite) and aluminum (gibbsite) predominate, are also exceptions.

Silicates are classified on the basis of how extensively the silica is polymerized (46). Generally, the more highly polymerized the structure, the more resistant to chemical weathering. Respirable quartz from soil dust is probably less pathogenic than that from many other occupational exposures (e.g., mining, quarrying, sandblasting). Exposure of quartz to weathering and chemical interactions with organic compounds in soils may attenuate particle-surface free radicals, which have been associated with respiratory disease in occupations where exposure is to freshly fractured quartz (47).

Clays in farm soil dust have the ability to carry potentially hazardous organics. Because these minerals have a large surface area and charge, they may adsorb organic molecules, which could include pesticide residues (48).

Sampling and analysis. Industrial hygiene monitoring and analytical techniques for airborne inorganic aerosols are well established (39). Air from the workplace is drawn through a

filter that collects airborne particles; the filter is then weighed and may be submitted for further tests, such as X-ray diffraction analysis for crystalline quartz. Recently, new international standards definitions for inhalable and respirable dust size fractions have been adopted (40, 49, 50). Analytical techniques are available for particle size characterization, particle speciation, and investigation of particle surface characteristics (40, 51).

Exposure levels. Strikingly few studies of farming include inorganic dust exposure data, and the published studies have serious limitations. Available data reflect exposure for only a small range of activities. The data come exclusively from North America and northern Europe and involve non-randomly selected measurement series. Results are typically reported without any speciation of the inorganic fraction beyond respirable quartz analysis. Published conclusions regarding exposure to inorganic dust must be considered preliminary at this time.

Dust exposure of farm equipment operators has been documented in several studies. Most of these data relate either to soil preparation or to crop harvesting, including both open-cab and closed-cab exposures. Tractors pulling soil preparation implements may generate tremendous dust clouds (52–54). Median open-cab operator exposures for plowing and harrowing are in the range of 2–20 mg/m^3 for total dust, but exposures in an open cab can range up to 80 to more than 100 mg/m^3 (53, 54). Some reports have claimed much higher operator exposure (in the hundreds and even thousands of mg/m^3), but the sampling methods have not been clearly documented (55–57). The fraction of respirable dust compared to total dust for open-cab exposures is in the range of 5% (52, 53) to 40%, the latter on clay soils (54). Personal respirable quartz exposures were reported in one study to average 2 mg/m^3 in an open cab (54).

Operators in closed cabs with effective ventilation systems have much lower average exposure levels, in the range of 0.1–1 mg/m^3 for total dust. Personal respirable quartz exposures were reported in one study to average 0.05 mg/m^3 in a closed cab (54).

Tractor operators involved in haymaking and combine operators harvesting field crops also have high total dust exposures, typically in the range of 1–20 mg/m^3 in an open cab, or less than 0.5–1 mg/m^3 in a closed cab with air filtration. Only about 10% of this dust is inorganic (52–54, 58, 59).

In a study of dust exposure in manual tree fruit and grape harvesting, the vast majority of total dust exposures exceeded general industry standards (20–120 mg/m^3) (60). Quartz content of soil and foliar dusts ranged between 7 and 20% and was nearly at these levels in total aerosols but at lower percentages in respirable aerosols. Nevertheless, respirable mass quartz concentrations frequently exceeded general industry standards.

Although organic dust exposure has been the primary concern in grain handling, there is a significant inorganic component. Dust in this activity has been reported to be 15 to 43% inorganic. As grain is moved from the field through the distribution system, inorganic content tends to drop, presumably due to cleaning procedures (61).

Dust from animal confinement is predominantly organic, and the inorganic fraction is usually not reported (61). There have been several reports of exposure to biogenic silica fibers, however, from sugar cane and rice farming (62–64).

Exposed populations. No estimates exist of the number of farmers significantly exposed to inorganic dust. The type of farming, as well as the specific tasks performed by the individual, are important determinants of inorganic dust exposure.

Approaches exist to estimate a farm worker's inorganic dust exposure with the use of so-called crop task exposure analysis, which is related to farm size (65–69).

Exposure determinants and possibilities for prevention. Despite the availability of some useful data, most of the factors affecting inorganic dust exposure in farming have yet to be understood. It is clear from field observations, for example, that plowing wet soil produces less dust than plowing dry soil. The presence of an enclosed cab substantially reduces particle exposure (70). But an array of other factors also determines exposure, ranging from the tractor's size and speed to implement size, type, and adjustment to soil type and wind speed.

Some general statements about exposure determinants in machine operation may, however, be made. Effective cab enclosure is the most significant determinant (52, 54, 57–59). Whether or not the machine is operated on bare soil is another significant determinant. Soil machine dust exposures are largely inorganic; crop machine exposures are largely organic (52–54, 58, 59, 71).

Legal aspects. Legally enforceable exposure limits in the United States (OSHA PELs) do not apply to agricultural field operations (U.S. Code of Federal Regulations: 29 CFR 1928.21). Individual states may assume responsibility for OSHA activities and may set stricter PELs enforceable within their respective boundaries.

Areas for research. Systematic and statistically valid inorganic dust exposure studies are critically needed, applying both to especially high-exposure tasks and to more routine activities. Better characterization of the components of inorganic dust in farming is needed, including the nature and type of organic molecules carried on the surface of inhaled clay particles from farming operations (40, 72). The capacity of clay particles for sorption of organic molecules is well known, but the significance of this phenomenon to exposure in farming remains unstudied.

Organic Dust and Its Constituents

Airborne and settled particulate material of biologic origin is often referred to collectively, in the field of occupational hygiene, as organic dust. The term is broadly defined as dust with very heterogeneous composition (73). Organic dust exposures may vary qualitatively as well as quantitatively from one occupation to another. As an example, in grain dust the chief constituent is the grain itself, but a variety of other components may be found, including: nongrain plant matter; molds and spores (mainly *Aspergillus* and *Cladosporium* species [spp]); in humid grain, thermophilic *Actinomyces* spp; mycotoxins, such as aflatoxin, zearalenone, vomitoxin, ochratoxin, and T2 toxin; bacteria and their biochemical components and excretions, such as endotoxins, peptidoglycans, and proteolytic enzymes; mites, such as *Lepidoglyphus destructor* and *Tyrophagus putrescentiae*; insects such as the grain weevil; and other animal matter, including parts of insects, rodents, and birds and their excreta. Inorganic matter such as soil and silica, including quartz, is also frequently present. Other organic dusts found in agricultural environments display equally complex composition, although the primary sources differ. In swine confinement buildings, for example, some organic dust particles originate from the animal feed, but the main sources of microorganisms, allergens, and toxins are animal dander, urine, and feces. Other examples of organic dust include cotton dust, paper and pulp dust, flour dust, and tobacco dust (73). Microorganisms are widespread in the environment and are often a major component of organic dusts because of the nutrients the dusts contain. The microflora of organic dust depends on the microflora of the source material, which depends

in turn on a variety of factors, among them substrate composition, acidity, aeration, water availability, and temperature (74).

Sampling and analysis. Gravimetric measurement of organic dusts can be performed using the same equipment as for mineral dusts. Assessment of individual constituents, however, is considered more relevant, and techniques are available for the measurement of mold spores, mycotoxins, bacteria, allergenic proteins, endotoxins, and microorganisms. The American Conference of Governmental and Industrial Hygienists and some individual authors have published general guidelines for the assessment of bioaerosols in the indoor environment (41, 42, 75, 76).

Exposure and populations at risk. Ambient air concentrations and personal exposures are usually described in terms of gravimetric concentrations of dust. Personally monitored concentrations of total or inhalable dust vary, ranging up to several tens of milligrams per cubic meter; the respirable fraction typically accounts for 5 to 10% of total dust. Studies involving large numbers of exposure measurements have been published for grain and cotton dusts, as well as for the dairy and swine confinement industries (77–79, 164). For other agricultural sectors, fewer measurements are available, but levels tend to be in the same general range. Total dust concentrations above 4–10 mg/m³ are commonly reported. Excursions to very high levels, above 100 mg/m³, can be found in most agricultural environments during the performance of specific tasks.

Proposed standards and legal mandates. Legal requirements generally depend on the type of dust. For most organic dusts, no standards exist, and hygienists have treated these substances as nuisance dust. In the United States, hygienists must rely upon OSHA's nonspecific dust standards for particulates not otherwise regulated (PNOR) of 15 mg/m³ for total dust and 5 mg/m³ for respirable dust (29 CFR 1910.1000). In other countries standards for such dust are comparable or slightly more stringent.

For cotton dust exposure, OSHA has promulgated a gravimetric TWA standard of 1.0 mg/m³, based on the vertical elutriator for air monitoring (29 CFR 1910.1043). OSHA has a PEL for grain dust (oats, wheat, barley) of 10 mg/m³ and a wood dust PEL of 5 mg/m³. NIOSH has fixed RELs for grain dust at 4 mg/m³, respirable cotton dust at less than 0.2 mg/m³, and wood dust at 1 mg/m³ but repeated that these limits may not be completely protective when the dusts are contaminated with microorganisms (81). The ACGIH has established its own TLVs for these substances: grain dust, 4 mg/m³; elutriated cotton dust, 0.2 mg/m³; and wood dust, 1 to 5 mg/m³ (40). An ad hoc subcommittee on grain dust of the Canadian Thoracic Society Standards Committee (not a regulatory agency) recently reviewed the evidence regarding the health effects of grain dust and declined to recommend a personal exposure limit but stated that a limit of 5 mg/m³ was deemed advisable to control short-term, transient effects. The National Health Council of The Netherlands has proposed an occupational exposure limit of 1 mg/m³ as an 8-h average (82).

Possibilities for prevention. Measures to control adverse effects of grain, cotton, and other agricultural dusts have depended on reduction of trash content (cotton dust) and the use of modern technologies for dust control. Exposure levels in some of these industries are still unacceptably high, however, and additional measures are required. Since several studies have identified determinants of exposure, prevention is clearly possible. As an example, in pig farming, associations of farm characteristics, such as feed type and flooring type, and tasks in close proximity to pigs, such as repenning and insemination, were strongly correlated with personal dust expo-

sure levels (79, 83, 84). This type of information can be used for implementing low exposure technologies.

Microorganisms

Microorganisms may be conveniently classed as infectious and noninfectious. Within the infectious and noninfectious categories, taxonomic divisions can be marked: the kingdom Monera consists of the eubacteria, which are prokaryotes; within this kingdom are some 580 genera in 35 phenotypic groups (85). The Gram-negative aerobic microaerophilic rods and cocci (group 4), Gram-negative facultatively anaerobic rods (group 5), thermoactinomycetes (group 28), and nocardioform actinomycetes (group 22) are arguably the most significant agricultural bacterial bioaerosols. The kingdom Fungi comprises eukaryotic organisms: molds, yeasts, slime molds, rusts, and smuts. In the agricultural environment, the saprophytic fungi imperfecti (deuteromycetes) are the most commonly represented and include most of the organisms generally referred to as molds.

Infectious bioaerosols have long been the bane of human existence. Although noninfectious bioaerosols are more frequent causes of morbidity in agricultural workers, infectious organisms may present more serious consequences with exposure. Noninfectious bioaerosols in the agricultural environment are responsible for a variety of dust-induced pulmonary conditions, including acute airway inflammation, mucous membrane irritation, chronic bronchitis, organic dust toxic syndrome, occupational asthma, and hypersensitivity pneumonitis. Most of these toxicants are ubiquitous in the agricultural environment. Certain activities, however, give rise to far higher airborne concentrations and concomitant occupational exposure. In particular, the dropping, chopping, and distribution of straw or spoiled hay for animal bedding produces extremely high concentrations of bioaerosols.

Airborne microorganisms and allergens cover a broad range of sizes from the smallest viruses to large pollens and fungi (Table 2.1). Smaller organisms may agglomerate, attaching to dust or droplets, and be suspended as larger aerosols. Large organisms may fractionate and be suspended in air as respirable fragments. Many of these substances, however, exist as free aerosols in the agricultural environment and are readily inhaled.

A number of studies have examined the microorganisms to which farm workers are exposed. In general, bacteria are common soil and plant microbes. A variety of additional organisms may become part of the exposure in animal production. Some microorganisms are found in nearly every air sample collected in barns, generally including examples of such bacterial genera as *Pseudomonas*, *Enterobacter*, *Flavobacterium*, *Bacillus*, and *Corynebacterium*, as well as such mold genera as

Cladosporium, *Penicillium*, *Aspergillus*, *Alternaria*, and *Fusarium*. Dutkiewicz and Lacey (86, 87) have published an extensive listing of microbiologic agents posing occupational health hazards for agricultural workers.

Sampling and analysis. A variety of methods for sampling and analysis of bioaerosols have been developed over the past 50 years. Most bioaerosol techniques rely upon the use of appropriate media (solid, liquid, or agar) for sampling over a period of time, with subsequent microscopic, microbiologic, biochemical, immunochemical or molecular biologic analysis. Both "viable" as well as "nonviable" methods are available. The latter attempts to enumerate organisms without regard to viability. A variety of devices for microbial bioaerosol sampling have been described (41, 42, 88–90), of which the Andersen sampler (91–93) and the all-glass impinger (89, 94) are the viable samplers most commonly used.

With culture-based bioaerosol assessment methods, the culture medium is formulated to test for broad-spectrum bacteria or fungi or to select for specific groups, genera, or species (41, 42, 75). Other techniques such as polymerase chain reaction (PCR) could be used for species identification, but application of PCR to sampling the airborne environment is less well established. Application of fluorescent *in situ* hybridization (FISH) techniques to specific quantitation of bioaerosols in environmental samples has been demonstrated, but further methods development is needed (95). The assessment of microorganisms in the air is difficult, and several serious problems have been identified:

- The concentrations of bioaerosols typically found in agricultural environments are quite high. Thus, TWA must be determined by integrating multiple samples.
- There are very large temporal and spatial variations in bioaerosols, particularly in agricultural environments. This makes representative sampling a difficult task.
- Organisms may influence each other's growth. For viable bioaerosol sampling, this means that the full range of airborne organisms may not be realized, and the true numbers of viable bioaerosols will be underestimated.
- The choice of culture media affects the emergence of colonies. Several studies have investigated the appropriateness of one set of collection or culture conditions over another and considered the use of minimal media versus nutrient media (89, 94).
- Impaction trauma can reduce culturability for viable sampling and impede identification for nonviable methods.
- Vapors in the air of agricultural environments, such as ammonia, hydrogen sulfide, or carbon dioxide, may concentrate in the collection media and differentially affect the viability of organisms.

Nonculturable organisms often represent more than 95% of total bioaerosols, both viable and nonviable. For a number of bioaerosol-induced diseases, dead organisms are as potent causative agents as living ones. This makes it difficult to produce health-relevant estimates of exposure. Various direct counting methods for enumerating microorganisms without culturing using fluorescence microscopy (89) or flow cytometry (95) have been described.

Exposed populations and exposure levels. Levels of exposure to airborne micro-organisms vary widely from minute to minute, and measurements are dependent upon the methodology used to assess the exposure concentration. Bacterial aerosols generally range from 10^4 to 10^7 cfu/m³, while fungi range from 10^3 to 10^6 cfu/m³. Total organisms and spores attain concentrations as high as 10^9 organisms/m³, with occasional short-term excursions to 10^{10} organisms/m³. In some instances iden-

TABLE 2.1
SIZES OF BIOAREOSOL COMPONENTS*

Bioaerosols	Overall Size Range (μ m)	Predominant Size Range (μ m)
Tree pollens	20–150	30–45
Grass pollens	15–170	30–50
Fungi	5–500	20–100
Bacteria	0.3–30	8–20
Fungi conidia	1–50	5–15
Bacterial spores	0.3–10	0.5–3
Viruses	0.003–0.2	0.01–0.05

* Sizes indicated were determined by light or electron microscopy and do not represent aerodynamic size. Fragmentation, agglomeration, or formation of droplet nuclei may alter the bioaerosol size of these components.

tification of the organisms represented in the aerosol may be more important than determining generic microbial concentrations.

Proposed standards and legal mandates. No guidelines exist for microorganisms in agricultural bioaerosols. Standards for viable or total microorganisms by genus, species, or broad-spectrum taxonomic category have not been developed.

Determinants of exposure and potential for prevention. Some of the most clinically significant bioaerosol-induced respiratory disease risks in agriculture are those associated with episodic exposures to very high concentrations of organisms. Examples of high-hazard farm tasks include silo uncapping; chopping, dropping, or pitching moldy hay or compost; handling spoiled grain or feed; tilling poultry barn floors; and manual emptying of enclosed grain bins. A two-strap fiber respirator will not provide adequate protection in these circumstances.

A powered air purifying respirator (PAPR) equipped with a high-efficiency particulate air filter can be an effective device for many agricultural dust exposures but may be inadequate for these extreme exposures. A PAPR with a tight-fitting full face piece has an assigned protection factor (APF) of 50 (96). If concentrations reach 5×10^9 spores/m³, an exposure sustained while wearing the PAPR may be as high as 10^8 spores/m³. For adequate protection, a full face piece, supplied air or self-contained, positive pressure or pressure demand respirator would be needed. Such a device could reduce exposure by 10,000-fold (assuming the APF) to 5×10^5 spores/m³. That is a far safer level, but it could still be hazardous, depending upon the inhaled spores and individual susceptibility. Very few agricultural sites are equipped with this level of respiratory protective device.

Prevention of spoilage and automation of dusty processes are therefore the keys to true protection against respiratory hazards in agriculture. Wetting materials prior to handling can reduce airborne dust concentrations substantially, but this approach cannot be used in many agricultural settings. Similarly, oiling systems at feed mills are very effective. Local exhaust systems and dilution ventilation may also be helpful, but require proper design and maintenance. Studies in dairy barns have shown that tunnel ventilation results in lower levels of CO₂ and bioaerosol concentrations than ducted, circulating, or passive ventilation systems (97).

Critical areas of research. The challenge to identify etiologically relevant agents out of the complex mixture that typically characterizes organic dust has been a key topic of discussion at three international workshops held in Skokloster, Sweden (98). A second research challenge is to improve upon the tenuous character of current exposure assessment methodology. The broad range of bioaerosol sampling methods should be standardized in the manner that the Nordic Council of Ministers has followed for mold spore sampling (99). Recent research comparing different bioaerosol sampling and analysis methods has contributed greatly to the understanding of the challenges of accurate exposure assessment (100–104). Development of new methods for bioaerosol assessment, utilizing techniques such as quantitative PCR and fluorescent *in situ* hybridization, and application of new fluorochromes for tagging organisms and oligonucleotide probes, should lead to more accurate, specific, and efficient assays (95).

A third urgent area for research is that of improved approaches to control. The importance of various agricultural practices to the generation of bioaerosols and the effectiveness of various bioaerosol control measures should be studied to guide the introduction of intervention measures. Methods to increase the usage of recognized appropriate control measures also need to be studied.

Mycotoxins: Fungal Toxins

Mycotoxins, produced by fungi, are biomolecules toxic to both animals and humans. They appear to give fungi competitive advantages over other organisms. A given fungal species may produce different mixes of toxins, depending on the substrate. Mycotoxins produced by a fungal species growing on a particular substrate may work synergistically to inhibit the growth of other organisms (105). In the case of *Penicillium*, one such compound is penicillin, which has strong antibiotic properties and has indeed proved a boon to medicine; there is strong evidence, however, linking a number of mycotoxins with animal and human illness in agricultural environments. Thousands of mycotoxins have been classified (106, 107). The health impact of inhalation exposure to these mycotoxins is not known, although trichothecenes (108) and spores of *Stachybotrys atra* (109) have been reported to cause acute illness. *Fusarium* is a genus of mold that infects many grain and dry vegetable crops and is responsible for producing a variety of mycotoxins, including fumonisins, fusarins, zearalenone, nivalenols, T2 toxin and many other trichothecenes (110–113).

One of the most important species is *Fusarium moniliforme*, a ubiquitous soil saprophytic fungi with worldwide distribution (114). *Fusarium moniliforme* grows well on corn, wheat, sorghum, barley, bananas, and rice, but in the field produces fumonisins only when grown on corn. Fumonisin B1, B2, and B3, mycotoxins produced by *Fusarium moniliforme*, are responsible for equine leukoencephalomalacia and porcine pulmonary edema syndrome (115–118). Some evidence suggests a link to human esophageal cancer (119) and cancer in rats (120). On moist corn and corn screenings, very high levels of fumonisin are produced, and concentrations as high as 3,800 mg/g have been measured in feed purchased commercially (121).

Aflatoxin from *Aspergillus* is perhaps the most well-characterized mycotoxin deleterious to human health; it is a known human carcinogen (122). *Aspergillus* has been the subject of epidemiologic studies (123) and has been widely reviewed (124). Ochratoxin A is considered a possible human carcinogen (122). The most relevant route of exposure to aflatoxin and ochratoxin is by ingestion, and respiratory risks associated with their inhalation are not established.

Mycotoxins of *Fusarium*, *Aspergillus*, and *Penicillium* genera contaminate the respirable fraction of airborne corn dust (125) and cotton dust (126); these and other fungal products can be carried into the lower regions of the lung on grain dust (127). Additional research is needed to establish the role of mycotoxins in human disease, and little is known regarding the effects of inhaled mycotoxins in humans (128).

Mycotoxins possess distinct chemical structures and reactive functional groups, including primary and secondary amines, hydroxyl or phenolic groups, lactams, carboxylic acids, and amides. Standard analytical methods for mycotoxin analysis of grains, feeds, and food products have been developed and thoroughly reviewed by professional associations and international agencies, and results from interlaboratory studies have been compared (129–133).

Relatively few data exist regarding airborne concentrations of mycotoxins in agricultural environments, and most of these hover near the lower limit of analytical detection.

Endotoxins

Endotoxins are heat-stable lipopolysaccharide (LPS) protein complexes that are part of the outer membrane of gram-negative bacteria; they are present on the bacterial cell wall and are often liberated as a result of cell lysis.

The LPS molecule is responsible for most of the biologic properties characteristic of bacterial endotoxins. LPS are amphipathic macromolecules containing a biologically active lipid part (lipid-A) and a hydrophilic polysaccharide moiety. These macromolecules have been detected in such taxonomically distant groups of Gram-negative bacteria as *Enterobacteriaceae*, *Pseudomonadaceae*, and *Rhodospirillaceae*; they have not been identified in gram-positive bacteria, mycobacteria, or fungi (134, 135). Even though most of the biologic effects can be reproduced by purified LPS, it cannot be assumed that this term is preferable to the term “endotoxin” in defining biologic responses to this bacterial product, and the terms are therefore often used interchangeably in the scientific literature (135). Endotoxin has been recognized as an important factor in the etiology of occupational lung diseases caused by organic dust exposure (82, 136). Inhalation experiments and intravenous administration of LPS in man have precipitated such acute clinical effects as fever, shivering, arthralgia, influenza-like symptoms (malaise), dry cough, dyspnea, chest tightness, and leukocytosis. Subjects with inhalation exposure display dose-dependent acute lung function impairment (FVC, FEV₁, and flow-volume variables), acute decreased lung diffusion capacity, and acute bronchial obstruction. Acute endotoxin-associated lung function effects found in experimental studies where subjects were exposed to cotton dust or grain dust extract have been confirmed in field studies. A limited number of epidemiologic studies reported dose-related chronic effects such as decreased FEV₁, FVC, flow-volume variables, and respiratory symptoms. In both experimental and field studies “no-effect levels” were calculated based on pulmonary effects (82).

Sampling and analysis. Absolute LPS measures described in the literature have included electrophoresis techniques, gas chromatography-mass spectrometry (GC-MS), and high-performance liquid chromatography (HPLC) (137–140). These methods, however, require elaborate LPS extraction procedures. The most widely used assay since the early 1980s is an *in vitro* biologic assay based on the reaction of *Limulus* amoebocyte lysate (LAL) with LPS. The lysate used in the assay originates from the horseshoe crab (*Limulus polyphemus*) (73, 141–145). The LAL test is a functional assay providing an estimate of biologic activity of LPS rather than the amount of LPS physically present. The variation in sensitivity of the LAL assay for different substrates is suggested to correspond in general with the variation in biologic response in mammals (41, 136, 146). Few comparative studies are performed using different analytical methods. Variable results were found in comparing GC-MS with a functional (LAL) assay (139, 140, 145, 146). The assay was adopted as the standard assay for endotoxin detection by the United States Food and Drug Administration (FDA) in 1980. The detection limit for airborne endotoxin measurements is approximately 0.05 EU/m³ (5 pg/m³) for the more recent kinetic chromogenic LAL assays. Since the method is based on biologic activity, different test batches may give different results. Therefore, an internal standard must be used. The FDA uses a reference standard endotoxin (RSE): *Escherichia coli*-6 (EC-6) as part of its standardization procedures. Large differences in both the hydrophilic and, to a lesser extent, the lipid A moiety between endotoxins of different species or strains make comparison on the basis of weight nearly meaningless (145, 147). The RSE:EC-6 based on purified LPS from *E. coli* is therefore expressed in endotoxin units (EU). Since the RSE is expensive and also exhaustible, a control standard endotoxin (CSE) standardized to the RSE is used and is normally included in commercial LAL tests. Most studies nevertheless publish endotoxin levels in nanograms rather than in endotoxin units, although this should be dis-

couraged. Results may not be valid under different conditions, because other constituents present in the sample may interfere with the LAL assay, causing inhibition or enhancement, and aggregation and adsorption of endotoxin may result in under- or overestimation of endotoxin concentrations (73, 144, 148–150). Techniques such as spiking with known quantities of purified endotoxin and analysis of dilution series of the same sample have been suggested to deal with these interferences (73, 143, 144, 150–152).

Only free cell wall dissociated endotoxin is detectable with the LAL assay (137, 153). Inhalation experiments with animals have shown that cell-bound endotoxin (whole cells) has similar or even increased toxicity compared with free endotoxin (154, 155).

Variations between laboratories are believed to be considerable because of differences in protocols used (82, 139, 142–144). The test will need to be rigorously standardized in the near future to facilitate valid comparisons of results from different laboratories.

Exposure and populations at risk. Endotoxins are common in agricultural environments in which organic dust is produced or handled. Animal feces and bacteria-contaminated plant materials are the major contributors to endotoxin-contaminated organic dusts. Exposure is therefore prevalent in livestock farming, grain elevators, the cotton industry, the potato processing industry, poultry slaughterhouses, the flax industry, and the animal feed industry (Table 2.2).

Endotoxin levels have been quantified in a variety of agricultural and related environments. Large differences in airborne endotoxin levels are found between agricultural commodities but also between different facilities of similar agricultural commodities (156).

Proposed standards and legal mandates. Only one evaluation of occupational endotoxin exposure has been conducted by an international organization. The International Commission on Occupational Health (ICOH), through its Committee on Organic Dusts, reported that ODTs is elicited at an endotoxin concentration of 1,000 to 2,000 ng/m³, while acute bronchoconstriction occurs at levels of 100 to 200 ng/m³ and mucous membrane irritation at levels of 20 to 50 ng/m³ (157). The report states that these levels may be lower for sensitive subjects. A more recent report, however, suggests guidelines for no-effect levels for environmental endotoxin that are substantially lower: toxic pneumonitis (ODTS), 200 ng/m³; airway inflammation, 10 ng/m³; and systemic effects, 100 ng/m³ (157). In the Netherlands, the National Health Council has proposed an occupational exposure limit of 4.5 ng/m³, which is estimated to equal 45 EU/m³ over 8 h (82).

Possibilities for prevention. Multiple determinants of endotoxin exposure are recognized, and the contribution of these determinants to workers' exposure depends on the industrial activity. In general, conditions that permit microbiologic contamination of agricultural products should be avoided. Exposure to fecal particles, important sources of endotoxins in agriculture, should be minimized as well. It must be conceded that in particular situations, these admonitions are unrealistic, since the process itself involves handling microorganisms or uses microbiologic growth as part of the process. In these cases, determinants of the level of exposure should be identified as a basis for developing preventive strategies. Such an approach has already been applied in some sectors of the industry, and these efforts could serve as models for developing preventive strategies in other sectors (42, 43, 79). Wetting feed or bedding just prior to distribution can lower levels of airborne endotoxin. Oil misting systems for swine confinement facilities and grain mills are also effective.

TABLE 2.2
DUST AND ENDOTOXIN EXPOSURES IN VARIOUS OCCUPATIONAL ENVIRONMENTS*

Type of Industry	Dust Fraction	n	Mean Dust Concentration (mg/m ³)	n	Mean Endotoxin Concentration (EU/m ³)
Grain elevator and animal feed industry					
DeLucca and colleagues, 1987 (329)	Respirable [‡]	69	< 0.3	69	0–7.4
Smid and coworkers, 1992 (78) [†]	Inhalable [‡]	530	0.8–9.8	530	12–285
	Inhalable [§]	79	0.8	79	19
Pig farmers					
Clark and colleagues, 1983 (330) [†]	Total [§]	18	1.8–5.2	18	400–2,800
Attwood and colleagues, 1987 (19) [†]	Total [§]	1,701	2.8–4.9	166	1,200–1,280
	D ₅₀ ≤ 8.5 μm [§]	71	0.9–1.5	166	1,050–1,150
Donham and coworkers, 1989 (331)	Total [‡]	57	6.8	57	2,400
	Respirable [‡]	57	0.34	57	2,300
Preller and associates, 1995 (308) [†]	Inhalable [‡]	360	2.4	350	920
Dairy farmers					
Thorne and coworkers, 1997 (97, 164)	Inhalable [‡]	159	1.78	194	647
	Inhalable [§]	252	0.74		
	Respirable [§]	217	0.07		
Chicken farmers					
Clark and colleagues, 1983 (330)	Total [§]	7	1.0–3.7	7	1,200–5,000
Thelin and associates, 1984 (332)	? [‡]	25	5.8–28.1	25	1,300–10,900
Jones and coworkers, 1984 (215)	Total [§]	9	±10–±2	7	240–590
	Respirable [§]	9	±0.5–±0.08	7	38–98
Poultry slaughter houses					
Morris and coworkers, 1991 (333)	Inhalable [§]	17	20.2	17	2,500
	Respirable [§]	19	1.75	19	130
Hagman and colleagues, 1990 (334)	Total [‡]	24	3.1–7.7	24	400–7,800
Cotton industry					
Rylander and Morey, 1982 (335)	Respirable [§]	—	—	36	200–3,700
Kennedy and associates, 1987 (336)	PM < 15 μm [§]	130	0.59–1.17	62	20–5,300
Potato processing industry					
Zock and coworkers, 1995 (337) [†]	Inhalable [‡]	211	0.4–21.1	195	9–102
	Inhalable [§]	81	0.2–19.3	68	1–4,000
Sugar beet processing industry					
Forster and colleagues, 1989 (338)	? [§]	?	1.4–3.5	?	2.5–32

* Exposures are presented as ranges in mean levels per department or job title within one industry, else the exposure is given as the mean of all measurements in the industry.

[†] Data from one group using the same assay.

[‡] Personal sampling.

[§] Area sampling.

^{||} Endotoxin units were calculated from nanograms of endotoxin by multiplication with a factor 10 (156).

Research needs. Longitudinal epidemiologic studies are needed to gain insight into both chronic effects caused by long-term airborne endotoxin exposure and the underlying processes of these effects. Acute effects should be further studied by overshift lung function tests. This research should be conducted in one or more industries known to represent a broad range of individual endotoxin exposures.

Several international “round robin” tests for endotoxin analyses and extraction of dust samples are in progress. These will document the extent of differences in endotoxin measurement among various laboratories. Such studies should lead to recommendations for rigorous standardization of endotoxin measurement, including sampling, extraction, and analysis methods used in occupational hygiene.

Other Microbial Products

Exotoxins are bioactive molecules, usually proteins, secreted during the growth of Gram-negative and -positive bacteria, but also released upon lysis of bacteria. They are broadly categorized as cytotoxins, neurotoxins, or enterotoxins. Though generally associated with infectious diseases such as botulism, cholera, and tetanus, exotoxins may arise in substrates that support bacterial growth and subsequently become airborne. One example is exotoxin A, produced by *Pseudomonas* spp.

Pseudomonads are often plentiful in wet conditions, as in vegetable and fruit washing, and may act as reservoirs for exotoxin A, which could become airborne with the wash fluid aerosols.

A number of bacteria also produce phytotoxins, which have evolved as plant toxins. Phytotoxins may also be toxic to humans and may be components of bioaerosols. Other constituents of bacteria and fungi that appear to have inflammatory or immunomodulatory effects include FMLP peptides, heat shock proteins, and T-cell activating superantigens (157–159). Relatively little is known about these toxins as potential respiratory hazards in the agricultural environment.

Recent evidence suggests that (1→3)β-D-glucans from the cell wall of fungi may be respiratory immunomodulatory agents (157). The (1→3)β-D-glucans are high molecular weight glucose polymers (chains of glucopyranose rings) that act as biologic response modifiers. They appear to stimulate host resistance functions in the immune system in mammalian species. Further studies are needed to define the role of glucans and these other microbial products in agricultural respiratory disease.

Bioallergen Exposure and Type I Allergy

Allergy can be defined as hypersensitivity reactions resulting from immunologic sensitization toward a specific agent or

component, called the allergen. In principle, all macromolecules of nonhuman origin—animal, plant, or microbial—can be immunogenic in humans, and each immunogenic compound may also act as an allergen inducing adverse reactions upon re-exposure. Since microbial exposure in agriculture is extensively discussed above, the remaining part of this section will be restricted to type I allergens. These can be defined as macromolecular agents with a known or presumed capability to induce specific immunoglobulin E (IgE) immune responses and to provoke allergic reactions in sensitized subjects. A summary is given of allergens that may be encountered in the farm environment and which are known or presumed to contribute significantly to the occurrence of respiratory disorders among farmers.

Sampling and analysis. Antibody-based immunoassays are widely used for the measurement of specific major allergens in the air. Antibodies can arise from sensitized humans, animals (e.g., rabbits used to produce polyclonal antibodies), or cell cultures (to produce monoclonal antibodies). Examples have been published using monoclonal antibody-based assays to measure allergens like Der p I, Der f I, and Der p/f II in settled dust (160, 161), as well as in airborne dust samples (162–164). Immune assays have also been developed for bovine urine and epithelial cell antigens (164). However, such assays have not become generally available for the assessment of many other major allergens present in the farming environment.

Exposure levels and exposed populations. Agricultural dust may also contain allergens that are not specific to the farm environment, including well-known common allergens (e.g., house dust mites, grass or tree pollens, or from common pets like cats or dogs). Other compounds might be more specifically associated with agriculture, and thus be considered as potential occupational allergens: proteins derived from domestic animals such as cows, pigs, horses, and poultry, or from plants or plant material such as grain, soy, or corn, etc. The latter may be particularly relevant if present in animal feed. Mold exposure is not an exclusive feature of agriculture. Although mainly known as a cause of type III allergies, many of the IgG-inducing molds can also induce specific IgE sensitization. Modern developments in agriculture (e.g., breeding of new crops or previously undomesticated animals, and the use of specific insects, predator mites, etc., in biologic pest control) are new sources of sometimes very potent but previously unknown allergens of biologic origin (165).

The best-studied source of type I allergens associated with farming are storage mites, which, like house dust mites, flourish in a humid, warm, and usually moldy environment (166). Their presence may be quantitatively expressed as the number of (living or dead) mite bodies per gram of barn dust, and median values of up to 1,000–10,000 mite bodies per gram have been reported (167–169). For comparison, house dust mites in floor or mattress dust have been reported at 100–1,000 mites per gram (160, 170, 171). The actual airborne exposure levels to storage mite allergens may exceed the exposure levels for house dust mites in living or sleeping rooms by 100- to 1,000-fold. However, there is a paucity of actual data regarding airborne exposure levels. No monoclonal assays are available for storage mites, although major allergens have been described for various storage mite species (172). The pathogenic relevance of storage mite exposure has been recognized since Ingram and coworkers (173) reported a high prevalence of sensitization among Scottish farm workers with respiratory “barn allergy” and confirmed the causal relation by specific storage mite allergen bronchial provocation. High prevalences of storage mite sensitization, particularly among farmers with self-

reported or physician-diagnosed respiratory symptoms or disorders, were found in several other population studies in various countries (174–178). A complicating factor in investigations on the pathogenic role of storage mite exposure is the presumed cross-reactivity of its allergens with house dust mite allergens, although results regarding cross-reactivity obtained in different populations are apparently contradictory and evidence for co-sensitization of house dust and storage mites is limited (177–179). Storage mite exposure with resulting sensitization of susceptible individuals might not be highly specific for the agricultural environment (175, 180). The abovementioned studies strongly suggest that atopic sensitization to storage mites is an important risk factor for developing occupational respiratory disease, including occupational asthma. Further confirmation on a population level will require exposure/response studies.

Animal proteins can be very potent allergens, as shown by the high prevalence of type I allergy in the general population to common pets such as cats, dogs, guinea pigs, rabbits, etc. A very high risk of occupational allergy is known for laboratory animal workers exposed to rats or mice, in whom allergen exposure at less than nanogram per m³ levels may cause sensitization and allergic symptoms (181–183). Allergens can be associated with hair, skin scrapings, fecal particles, or any other type of dust components, and may originate from epithelia or from body fluids or secretions such as plasma, saliva, or urine. Workers in livestock farming may also be exposed to significant levels of allergenic proteins, and allergies to cow, horse, pig, or poultry allergens would be expected to be common in these populations. Several case reports of specific allergies have been published, but in only a small number of studies have prevalences of sensitization and/or symptomatic allergy to animals been assessed in agricultural populations (176–179, 184, 185). In Finnish studies, sensitization to cow dander allergen was found in approximately 3–5% of dairy farmers and was associated with work-related respiratory allergy symptoms. Further investigations, including specific allergen challenge studies, have confirmed the role of cow-derived airborne proteins as important occupational aeroallergens in Finnish dairy farmers (176, 184, 186, 187). However, it is not clear whether sensitization to cow allergens is of similar importance in dairy farmers in other countries as well (177, 178, 188).

Major allergens have been characterized and identified as epithelial and urinary proteins. Immunoassays for their measurement in airborne dust samples have been developed, and airborne concentrations of up to 100–1,000 ng/m³ have been reported for cowsheds (97, 189–191). A positive relation was found in a group of 10 dairy farmers between personal exposure concentrations and the titers of anti-bovine urinary antigen serum IgG, but positive relations between exposure and allergen-specific IgE were not found or even inverted (189).

In pig farming, pig-derived proteins in the dust have been mentioned as potential type I allergens. The protein content of organic dust in swine confinement buildings is high—10–20% (192). Proteins from pig epithelium and urine (partially or fully cross-reactive) are present in relatively high concentrations in the airborne dust. Thus, mean concentrations of, respectively, one and several hundred mg/m³ have been found for swine epithelial and urinary antigens in pig stables with relatively high total dust concentrations of more than 10 mg/m³ (193). Like other data regarding airborne allergen exposure levels, these figures should be interpreted with caution, since the results were calculated by relating the activity of test samples to that of an internal standard allergen preparation. There is little evidence that type I allergy to pig epithelial or urinary proteins contributes significantly to the high preva-

lence of respiratory symptoms among pig farmers (194–197). To date, only a single case of occupational asthma due to pig allergy has been reported (198). The prevalence of a positive skin-prick test was considerably higher in several studies, but in some cases remarkably high prevalences were also found in control subjects (199), which raises doubts as to the specificity of the reactions.

Horse dander is a well-known aeroallergen that was intensively studied in the 1970s. However, the occurrence of sensitization has not been studied specifically in relation to the agricultural environment, and reported cases were predominantly among nonfarming populations (200–203). For sheep and goats, as for poultry, no or only incidental cases of specific type I allergies have been reported.

Although farmers, like other inhabitants of rural areas, are probably exposed to enhanced levels of pollens from grasses, weeds, and trees, the prevalence of pollenosis is certainly not higher and possibly is lower than for urban populations, as is found for other types of atopy (178, 188). Pollens from crops such as grain and corn are rarely important allergens. Quantitatively more important is exposure to potentially allergenic proteins in animal feed. Several of its components are well known as IgE-inducing food proteins, and particularly proteins of wheat and soy are also known as aeroallergens, e.g., in bakery workers (204–206) and in inhabitants living around soy mills and the harbor of Barcelona, with its well-described “soy asthma” epidemics during the 1980s (207). Exposure levels might be comparable or even higher for farmers handling animal feed frequently, although quantitative data are not available. In a study among pig farmers, Virtanen and coworkers noted levels of 1–10 mg/m³ of “swine feed antigen,” but in this particular case the material was derived from fish powder (193). Nevertheless, the figures confirm that exposure to immunogenic feed proteins should also be considered as an important component of allergen exposure. The pathogenic relevance has indeed been suggested by a report of cereal flour asthma in three farmers sensitized to wheat and/or barley allergens (208, 209).

Mold spore exposure can be very high in agriculture, as described previously. Prevalence of atopic sensitization to molds is, however, low in farmers, and not enhanced compared to urban populations. Thus, mold exposure does not appear to be an important cause of type I allergic symptoms in agriculture.

Legal mandates. No legal mandates exist for occupational allergen exposure in agriculture.

Areas for research. Prevalences of IgE sensitization and occupational type I allergy among agricultural workers have been assessed in only a small number of population studies. The most important occupational allergens with a proven causal role appear to be storage mites and possibly cow dander or urinary proteins. Thus, although specific sensitization and allergy for some allergens is indeed more prevalent among farmers, the overall prevalences are, in fact, notably low in the context of the very high allergen exposure levels, and in general the role of type I allergy in farmers’ occupational respiratory disorders seems at present to be modest. An explanation might be that for some reason typical “agricultural” allergens such as cow or pig urinary proteins are less “potent” allergens than homologous proteins from rat or mouse urine. Alternatively, farmers may be less responsive to allergen exposure and/or less easily sensitized. Strong arguments in favor of the latter hypothesis are the also relatively low prevalences among farmers of sensitization to common allergens (e.g., cats, dogs, and pollens). These findings agree with several studies that reported lower prevalences of atopy among rural in comparison with urban populations.

Decomposition Gases

Researchers have noted the presence of as many as 150 potentially toxic gases arising from the storage and handling of agricultural animal wastes (210–212). The most important in terms of agricultural workers’ health are NH₃ and hydrogen sulfide (H₂S). Methane (CH₄) and carbon dioxide (CO₂) exposures have also been monitored but have been judged to have less health significance.

The increasing use of modern animal confinement methods in livestock production, with associated long-term manure storage, has prompted several studies reporting worker exposures to potentially toxic gases. In the United States, such exposures have been frequently described in swine, poultry, and cattle settings, with the relative risk of exposure to each gas varying with the particular manure type and storage method. Carbon monoxide (CO), while potentially produced by manure decomposition, is regarded as a significant toxic gas in these situations, mainly due to production by unvented combustion sources and accumulation in confined areas.

Monitoring techniques. Measurement techniques used for decomposition gases include short-term colorimetric detector tubes, long-term detector tubes, impingers, and infrared spectrophotometry. With the exception of impingers, all of these are direct-reading sampling methods. All except short-term detector tubes provide a TWA contaminant concentration.

Exposed population and exposure levels. In the United States, an estimated 700,000 persons, including farmers and their families, employees, and veterinarians, work in livestock and poultry confinement structures. Of all confinement workers, those in swine operations are the most numerous (212).

Measurements have been made of decomposition gases in the swine industry since 1980, both in the United States and abroad. These measurements reflect usual barn concentrations and do not represent rare peak concentrations that can occur during manure-disturbing activities. While these investigators assessed the presence of ammonia, hydrogen sulfide, carbon dioxide, carbon monoxide, and methane, only concentrations of ammonia were judged to be significant from a health standpoint. Ammonia concentrations have generally ranged from 3–35 ppm by short-term detector tube or impinger (TWA).

No reported measurements of other contaminant gases exceeded the evaluation criteria, with the possible exception of one study (213) in which carbon dioxide was determined to range from 825 to 5,013 ppm in 50 swine operations. While carbon dioxide is not considered to be a health hazard in swine production facilities, it has been found to be a good indicator of overall air quality in such structures, since CO₂ concentrations have been found to be proportional to other contaminants, including CO and NH₃ (214).

Of the four studies in which ammonia TWA exposures were measured, two included measurements exceeding the evaluation criteria. In the three studies in which short-term measurements were collected, one measurement was equivalent to the NIOSH and ACGIH short-term exposure level criterion of 35 ppm. Contaminant concentrations were typically higher during the winter months, when less ventilation is provided and temperatures within the structures are higher (195, 214).

Poultry industry contaminant measurements from research reports published since 1980 are considered to reflect typical worker exposures, excluding manure-disturbing activities or equipment malfunction. Ammonia is the only contaminant gas measured above the evaluation criteria (Table 2.3). Two studies monitoring TWA concentrations both found measure-

TABLE 2.3
CURRENT STANDARD AND RECOMMENDED EXPOSURE (ppm) LIMITS

	NIOSH REL		OSHA PEL		OSHA RECOMMENDS		ACGIH TLV	
	TWA	STEL/CEIL(C)	TWA	STEL/CEIL(C)	TWA	STEL/CEIL(C)	TWA	STEL/CEIL(C)
NH ₃	25	35	50		35		25	35
H ₂ S		10 (C)*		20 (C), 50*	10	15	10	15
CO ₂	5,000	30,000	5,000		10,000	30,000	5,000	30,000
CO	35	200 (C)	50		35	200 (C)	25	
NO	25		25				25	
NO ₂		1		5 (C)		1	3	5

Definition of abbreviations: CEIL = ceiling level; PEL = permissible exposure limit; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.

* Acceptable maximum for a single 10-min exposure.

ments in excess of NIOSH, OSHA, and ACGIH evaluation criteria (215, 216). In three studies employing ammonia measurement techniques that could not be precisely ascertained, maximum concentrations of 20, 34, and 58 ppm were recorded; there are significant health implications for workers in these situations (217–219). In general, higher levels were measured in fall and winter than in spring and summer (216).

Many fatal or near-fatal incidents involving cattle, swine, and poultry manure handling activities have been documented (220–230). Few of these reports have included data concerning the measurement of air contaminants. Manure-disturbing activity can result in the creation of oxygen-deficient, toxic, and even explosive atmospheres. Some reports attribute these fatalities to methane asphyxia resulting from oxygen displacement (230). Others have implicated toxic concentrations of hydrogen sulfide as the causative agent (210). Still others have suggested the possibility of combined effects (225).

There have been a number of reports of air contaminant measurements associated with disturbing poultry manure (216, 228). One study found levels of ammonia routinely reaching or exceeding 100 ppm associated with tilling turkey confinement manure (216); another reported that disturbing chicken manure slurry produced one hydrogen sulfide measurement of 200 ppm (228).

Deliberate duplications of conditions associated with fatalities in liquid swine manure agitation in storage facilities have demonstrated hydrogen sulfide concentrations up to 150, 400, 800, and 1,000 ppm (220, 222). Similar duplications of conditions associated with cattle manure storage fatalities have recorded hydrogen sulfide concentrations up to 60, 76, and 500 ppm (224, 226). One study found an airborne methane concentration of 6,360 ppm.

Proposed standards and legal mandates. Table 2.3 lists environmental evaluation criteria for major manure-associated decomposition gases that can be found in the literature (211, 212, 231–234). The exposure criteria are reported as: TWA exposure averaged over the full workshift; short-term exposure limit (STEL) recommendations for a 10- to 15-min exposure period; and ceiling levels (CEIL) not to be exceeded for any amount of time. For gases, the criteria are commonly characterized as parts of contaminant per million parts of air (ppm). NIOSH has recommended that areas with hydrogen sulfide concentrations over 50 ppm be immediately evacuated (225).

Determinants of exposure and possibilities for prevention. To prevent fatal acute exposures to asphyxiating or toxic atmospheres associated with manure-disturbing activities, NIOSH issued a number of recommendations (227). These include:

- Providing educational materials to all workers;

- Fitting all openings to manure pits with substantial metal grill covers to provide natural ventilation and to prevent accidental falls or entries into the pits;
- Initiating powered ventilation before anyone enters the manure pit; and
- Eliminating the need for pit entry by providing access to all serviceable parts from the outside.

To prevent chronic exposure to ammonia concentrations exceeding evaluation criteria, recommendations include:

- Increasing ventilation in confinement buildings;
- Reducing the number of animals per unit area;
- Increasing the frequency of manure removal;
- Using alternative litter materials in poultry confinement in order to reduce the release of ammonia into the atmosphere; and
- Employing sensors to alert workers to elevated ammonia levels.

In the interim, before control is accomplished, a program of respirator fit testing and usage should be implemented. Use of full-face respirators with ammonia cartridges should be considered to afford protection from mucous membrane irritation.

Critical areas of research. Chronic exposure to ammonia is the most common gas hazard to agricultural workers in animal confinement, and little is known about effects of chronic exposure. Research should address economic controls such as recommended rates of ventilation. Measurement research is essential to establish the potential for ammonia adsorption to aerosolized particulates and its significance for worker health. Health communication and research should be aimed at preventing accidental worker exposure to toxic or asphyxiating atmospheres associated with manure-disturbing activities.

Silo Gas Exposure

Silos, a hallmark of many rural landscapes, are feed-crop storage and fermentation structures for livestock production. Harvested field crops such as corn, clover, and alfalfa are typically chopped and blown into the silo. In the silo, fermentation takes place under anaerobic conditions, and the silage pH is reduced through the production of organic acids. These acids reduce bacterial growth and silage degradation, effecting increased storage time without significant spoilage (235–238). A number of gases and vapors are liberated in the fermentation process, including amines, ammonia, carbon dioxide, organic acid vapors (predominantly acetic and butyric acids), and oxides of nitrogen (238–242). Of these, the oxides of nitrogen

and carbon dioxide predominate and have been the focus of exposure assessment.

Exposure to carbon dioxide and nitrogen oxides, as well as the oxygen limited environments created by the evolution of these gases in silos, are recognized causes of respiratory disease and death among agricultural workers. Occupational fatalities related to silo gas exposures were first described in the literature in 1914 (243). It was not until the mid-1950s, however, that the oxides of nitrogen were recognized as etiologic agents in bronchopulmonary disease resulting from silo gas exposure, and the term "silo filler's disease" (SFD) was first used (244). Exposure to nitrogen oxides in silos continues among agricultural workers, as does resultant respiratory disease and death (235, 236, 245–249). Conservative estimates suggest an SFD incidence of five cases per 100,000 farm workers dealing with silage (235).

Monitoring techniques. Several sampling and analytic techniques permit the quantification of CO₂, oxygen, and total oxides of nitrogen as well as such specific moieties as nitrogen dioxide (NO₂) and nitric oxide (NO). For several of these agents portable, direct-reading air monitors using electrical conductivity, potentiometric, colorimetric, infrared, and other analyzers are available, as are passive sampling calorimetric techniques (39, 250).

Exposure levels. Following the filling of a silo, the formation of silo gases begins within hours. Anaerobic fermentation of silage generates large quantities of carbon dioxide and organic acids. The nitrates present in the field crops are converted to nitrites through the fermentation process; they, in turn, react with the organic acids in the silage to form nitrous acid (HNO₃). As the temperature of the silage increases during fermentation, the nitrous acid decomposes to form a mixture of oxides of nitrogen, which can include NO, NO₂, nitrogen trioxide (N₂O₃), nitrogen tetroxide (N₂O₄), and other oxides in lesser amounts (236, 240, 247).

Several studies on the generation of silo gases and silo gas concentrations have been reported. Carbon dioxide, NO, and NO₂ are generally quantifiable, expected constituents (237–239, 241). Carbon dioxide concentrations measured in silos during fermentation can range from near-ambient levels to extremely high levels. Time-weighted average personal exposure measurements for CO₂ were reported in one study to reach a maximum exposure level of 3,800 ppm (238). Nitrogen dioxide concentrations have been reported, from area samples, at concentrations ranging from below detectable levels to a high of 100,000 ppm (241). The highest NO concentration reported in the literature was 630 ppm; it was coincident with an NO₂ concentration of 1,920 ppm (239).

The generation of these fermentation gases in enclosed silos can produce oxygen-limited environments, with oxygen concentrations as low as 1% (238). Silo environments considered immediately dangerous to life and health could result from silo gas concentrations at or exceeding 40,000 ppm for CO₂, 100 ppm for NO, or 20 ppm for NO₂, or from oxygen limitation (251).

The pattern of silo gas evolution suggests that CO₂ concentrations evolve first, followed by the oxides of nitrogen (239). Carbon dioxide concentrations in newly filled silos can exceed exposure standards in as little as 30 min, and lethal concentrations have been measured within approximately 4 h of filling (237–239). In cases of forced ventilation, oxygen levels have been rapidly increased to acceptable levels within the silo, but reductions in CO₂ and oxide of nitrogen concentrations were slower. With the use of a blower, safe levels of oxygen may be accompanied by levels of CO₂ and NO₂ in excess of exposure standards (238).

Proposed standards and legal mandates. Occupational exposure criteria for all relevant silo gases exist (232–234). Comparison of measured silo gas concentrations with the exposure criteria indicate the magnitude of exposures, and the life-threatening environments, found in silos during the fermentation of silage. There is generally no safety margin involved in entering silos during the fermentation process. Some silos are oxygen-limited by design and are therefore not routinely entered. Entry into *any* silo during periods of fermentation should be avoided.

Exposure determinants and prevention possibilities. One of the most important recommendations is that freshly filled silos not be entered by anyone for at least 14 d (233). Restricting access to the base of the silo by fencing or other means can help prevent exposures among children and farm animals. Ventilating the silo, both naturally and mechanically, prior to entry is also an important preventive measure (235, 244, 248).

Critical areas of research. Fatalities from exposures to silo fermentation gases continue despite long-standing recognition of the hazards. Research is needed to identify the most effective intervention strategies and to develop monitoring systems amenable to the agricultural setting that would identify conditions for safe silo entry.

Miscellaneous Chemical Exposures

Exposures to air contaminants from welding, solvent use, and fuel use and storage are considered potential occupational hazards for agricultural workers. The occupational health literature, however, does not generally address these exposures in the agricultural setting. The brief comments that follow offer a limited review of the exposure hazards posed by these activities as recognized in other occupational settings. The absence of exposure characterizations for them in agriculture suggests an obvious research need.

Welding is a process in which metals or other thermoplastic materials are joined together by the use of intense heat. Occupational exposures to dusts, fumes, and gases can occur, and the nature of the air contaminants and the worker's exposure depends on the metal or alloy being welded, the surface coatings, the type of welding operation, and the composition of the flux or shielding gas and the welding rod, as well as the local environment. The occupational exposure hazards posed by various welding processes and materials have been the focus of many occupational health studies and are summarized in the literature (251–254).

Over the years, farming equipment has become larger, stronger, and lighter, thanks to advances in metallurgic sciences. Welding and metallurgic developments have produced improved equipment that is more amenable to repair, with less frequent replacement (255). Farmers commonly repair their own farm equipment, and such repairs may involve welding (256–258). Training in welding is part of the curriculum in agricultural engineering programs (259, 260). The primary welding processes for metal fabrication and repair common to agriculture would include shielded metal arc welding, submerged arc welding, gas metal arc welding, and flux cored arc welding (255).

Although many references indicate that welding is done in agricultural settings, studies of welding exposures among farmers are not described in the literature (255–260). Welding, as practiced in many agricultural settings, would generally be an intermittent, perhaps seasonal, activity. The relative lack of access to occupational safety and health information, services, and control technology, common in many agricultural settings, creates an increased potential for overexposure to welding contaminants among farmers and farm workers. There are

sampling and analytical methods to permit quantification of exposures to welding contaminants (250).

Solvents are among an ever-growing roster of ancillary chemicals used to sustain modern agriculture. Most solvents used in industry are organic (hydrocarbon-based) and commonly used as chemical intermediates (261, 262). Organic solvents commonly used in agricultural settings include degreasers (e.g., toluene), paint thinners, paint and varnish strippers, mineral spirits, and various petroleum solvents (257, 263, 264). Sampling and analytical methods are available for quantification of most of the common organic solvents used in agricultural settings (39, 250). In spite of adequate sampling and analytical methods, studies of solvent exposures or associated respiratory effects among farmers have not been reported in the literature (265).

Fuels and lubricants are increasing in use on the farm, due to the mechanization of agriculture. Farm fuels and lubricants may include various petroleum hydrocarbon fractions such as hydraulic fluids, greases and oils, diesel, kerosene, and gasoline, as well as propane and butane gases. These fuels are used to power both stationary and mobile equipment, as well as to light and heat work areas. Because farms often lack convenient access to commercial fuel sources, on-site storage of gasoline, diesel, or other fuels is common (257). These fuels are hydrocarbons and pose hazards similar to those posed by solvents; routes of exposure are also similar (261, 262). The operation of hydrocarbon-fueled engines within agricultural structures presents the hazard of carbon monoxide generation, and fatalities have been reported from the use of combustion engines inside agricultural buildings (266). As with welding and the use of solvents, agricultural exposures to petroleum hydrocarbon fuels is barely mentioned in the occupational health literature, and detailed exposure assessments have not been reported.

Pesticides

This group of compounds encompasses several subcategories, from herbicides (weed-killers) to insecticides, fungicides, nematocides (anti-roundworm preparations), acaricides (used against mites), molluscicides, rodenticides, and biocides. There are between 500 and 1,000 individual pesticidal compounds registered for use on farm crops, food animals, forests, structures, roadsides, and home gardens, formulated into several thousand products. With the notable exception of sulfur, sodium chlorate, Bordeaux mixture, and a few other inorganics, the majority of the pesticides currently in use are synthetic organics, including organohalogens, such as dicofol, methyl bromide, and 1,3-dichloropropene (1,3-D); organophosphates (e.g., parathion, chlorpyrifos, and malathion); carbamates, such as carbaryl and benomyl; synthetic pyrethroids, such as permethrin; and phenoxy acid and triazine herbicides, such as 2,4-D and atrazine.

For the vast majority of reported cases, the dermal route greatly exceeds inhalation in overall occupational pesticide exposure, but in certain cases, respiratory exposure assumes great importance. For highly volatile pesticides—particularly such fumigants as methyl bromide, ethylene oxide, and 1,3-D—inhalation can be the most important route of exposure. Because fumigants are volatile and evaporate rapidly, occupational exposure is of greatest concern (267), although several accidental deaths are reported annually due to nonoccupational fumigant exposure in confined spaces (268).

Pesticides can become activated after reacting in or on its target soil, foliage, or water to form a product of greater volatility and/or toxicity than the parent (269). A few organophosphates, for example, undergo hydrolysis to form nauseating

mercaptans; methamidophos hydrolyses to methyl mercaptan (270), ethoprop breaks down to n-propyl mercaptan (271), and the defoliants S,S,S-tributyl phosphorotrithioate (DEF) and S,S,S-tributyl phosphorotrithioate (merphos) form butyl mercaptan. Additionally, chloropicrin and metam-sodium photolytically degrade to the potent lachrimants phosgene and methyl isothiocyanate (MITC), respectively. Finally, oxidation on leaf surfaces and in the vapor phase converts organophosphorothioates, such as parathion, to the far more potent oxon form (272).

Even though inhalation can be an important route of pesticide exposure, there are few documented instances of direct respiratory effects. An important exception is the herbicide paraquat, of special interest because its site of toxic action is primarily the lung. Because paraquat's vapor pressure is extremely low, however, exposure is rarely respiratory in nature, except for applicators who might inhale spray aerosols. Exposure is primarily through ingestion (unintentional or suicidal). According to Pasi (273), "lung effects frequently appear only after a latent period of several days when the poisoned patient has already started to recover from the toxic effects of the chemical on other organs. Moreover once signs and symptoms of respiratory insufficiency appeared, in most cases, they progressed rapidly and relentlessly in spite of adequate intensive care until fatality occurred." Death during this second phase of paraquat poisoning is invariably due to progressive respiratory insufficiency characterized by fibrosis.

Monitoring techniques. Direct techniques for respiratory exposure assessment trap gases, vapors, and aerosols present in the air for subsequent analysis. Collection can be accomplished by use of liquid impingers, sorbent air sampling tubes, and solid filter media, including respirator collection pads (274–279).

Pesticide exposure can be quantified indirectly by assaying biologic fluids, commonly urine (280), blood (281), or even in saliva and sweat (282).

Exposed populations. In 1967, Wolfe and coworkers (283) tabulated all exposure studies conducted to that time that included respiratory exposure measurements. Since then, other researchers have studied many pesticide exposure scenarios, a number of which are summarized below. Although in most cases respiratory exposure accounts for less than 1% of total overall exposure, important exceptions are presented.

Farm workers with highest levels of exposure are those involved in mixing and loading. Several studies are available that report inhalatory exposure to a range of pesticides (283–286). In general, the respiratory exposures associated with handling volatile liquids like tetraethyl pyrophosphate (TEPP) and S-ethyl dipropylthiocarbamate (EPTC) are higher than for solids like benomyl.

A second important group are applicators. Numerous studies of these workers have demonstrated that low-volatility compounds, including many herbicides, do not contribute significantly to worker respiratory exposure (278, 279, 284, 285, 287). Not surprisingly, granular insecticides, which have inherently low volatility, contribute very little to respiratory exposure (288–292). Greenhouse application is considered a high exposure risk due to the confined space (293, 294). Boom and span spraying in an open-sided shade-cloth structure were responsible for considerably lower exposures (295).

With a few exceptions, the majority of these exposure studies quantified inhalation rates as less than 100 mg/h. Exposures to moderately volatile pesticides, even when sprayed in enclosed spaces or as fine mists, rarely exceeded 1 mg/h. However, a study by Osterloh and coworkers (296) demonstrated that this is not the case for volatile fumigants.

Flaggers constitute a third at-risk group. These workers stand in fields to direct application sites for pilots during aerial application (283).

Exposure of field workers is usually low in comparison with other agricultural workers and farmers (297–300). Finally, agricultural pesticide use may expose not only workers but also resident populations (283, 301, 302).

The exposure of agricultural populations to pesticides tends to be much higher in developing countries than in the more developed nations, for three main reasons: (1) tropical climates; (2) shortage of personal protective equipment; and (3) lack of safety training.

Proposed standards and legal mandates. Pesticide manufacturers must present data on the risks associated with their products at the time of registration, and labeling must include recommendations for safe handling and other procedures aimed at reducing risks to acceptable levels. Unfortunately, there is no way to guarantee that harm will not occur from handling, disposal, and marketing of these materials as a result of accidents, unforeseen circumstances, and carelessness.

In the United States and some other countries, agricultural populations are exempt from PEL and OEL requirements, which were originally developed for workers in traditional (40-h workweek) occupational settings. Reentry intervals, an important regulatory tool to reduce exposures among field workers, structural fumigators, and greenhouse workers, provide some protection. Reentry limits prohibit individuals from entering an area for a stated time interval following treatment. Such intervals are premised upon the rate of dissipation of the particular chemical in the field or structure of interest. Increasingly, pesticides and other toxic chemicals are subject to additional regulation based upon their potential as air contaminants (303).

Exposure determinants. Inhalation is generally limited except when one or more of the following conditions exists: the chemical in use is quite volatile; application is in an enclosed, poorly ventilated area; or the manner of application leads to an aerosol cloud of finely dispersed droplets or particulates that do not readily settle.

The physicochemical properties of a given pesticide are primary determinants of the form in which it may exist in the air (vapor, liquid, or solid aerosol), the concentrations at which it may occur in air, and its lifetime once present in the air.

Generally speaking, pesticides of concern for inhalation exposure are those of either very high volatility or very high toxicity.

Pesticide formulation and application may dramatically influence entry into, and behavior in, air (304, 305). Manufacturers have improved and calibrated liquid spray nozzles to maximize particle size, thereby ensuring that the majority settle on the intended surface and do not drift downwind. Pesticides applied as granules do not, in general, pose much of a hazard in air, particularly when they are incorporated in soil.

Of particular concern is the backpack or hand-held sprayer still used extensively in developing nations. If a highly toxic chemical is applied without protective gear and without proper training, the potential for dermal and inhalation exposure can be high. In the United States and other developed nations, hand spraying is primarily restricted to home gardeners, who are denied legal access to the more toxic, restricted chemicals used in large-scale agriculture. An exception is greenhouse and indoor spraying, which is still largely done by hand spraying; in these cases, the personnel usually are well trained and safety procedures are well enforced.

Climatic and meteorologic conditions influence the amount of chemical that enters the air, as well as the subsequent trans-

port and fate of the airborne residues. Because temperature also increases the rate of volatilization, agricultural pest control sprayers generally opt for early morning spraying when temperatures (and usually wind speed) are lower. Guidelines for agricultural pesticide use may factor in wind speed, temperature, soil moisture, and the presence of fog (which may trap and concentrate airborne residues) or rain.

Critical areas of research. Biocontrol, integrated pest management, genetic improvement in crop resistance to diseases and insects, and microbial pest control agents are possible tactics, in the long term, to reduce the use of synthetic chemicals. Improvements in air filtration systems used in enclosed tractor or sprayer cabs have contributed greatly to reducing inhalation exposure to pesticides during application. Further work is needed in the design of personal protective equipment, particularly protection that can be used in hot climates.

In the area of improved population monitoring, improved testing of respiratory and absorbent filter pads and air sampling sorbents under conditions that more closely mimic field situations is needed. The significance of multiple exposures should be further explored.

Disinfectants

Most disinfectants used by pig, poultry, and dairy farmers contain chloramine-T or quaternary ammonium compounds used alone or in combination with aldehydes (glutaraldehyde, glyoxal, formaldehyde). There are no studies reporting exposure concentrations to disinfectants in structures housing animals. Some studies have reported exposure levels of disinfectants in hospitals (306, 307), but the different methods of application in the two situations makes it impossible to use these studies to estimate exposure levels in farming.

One recent study did describe exposure to disinfectants and the effects in pig farmers (308). In a study among 200 Dutch pig farmers, strong associations between disinfecting procedures and chronic respiratory health effects were observed. Among farmers with chronic respiratory symptoms, the use of medium or high pressure compared with low pressure was seen more often than among asymptomatic farmers (OR, 7.1; 95% CI, 1.9–27.1). A positive association was also seen with duration of the procedure (OR, 4.2; 95% CI, 1.4–12.7) for more than 10 min per procedure compared with less than 10 min. Farmers disinfecting for more than 10 min also had a lower baseline lung function (308, 309). These associations suggest a harmful effect of disinfectant use. Exposure to disinfectant use was characterized by assessing proxies of exposure; quantitative information about the exposure was not available.

Chloramine-T has been known for years as a potent type I allergen and cause of occupational asthma (310–313). Aldehydes (mainly glutaraldehyde and formaldehyde) are also well known causes of occupational respiratory allergy, although in this case the role of aldehyde-specific IgE antibodies is a matter of controversy (314, 315). Quaternary ammonium compounds (QAC) have been incidentally reported as a cause of occupational asthma (316, 317) and of anomalous reactions in patients with asthma and rhinitis reacting to benzalkonium chloride used as preservative in bronchodilators (318). IgE anti-QAC sensitization, however, has not been described in respiratory allergy but is known as a rare cause of allergy to anesthetics, particularly muscle relaxants (319, 320). It is important to note that the mentioned IgE-mediated or other allergic reactions to disinfectants have been reported mainly for nonagricultural populations, like hospital and laboratory workers. This again raises the question of whether atopic sensitization to occupational allergens may be largely underesti-

mated as a cause of respiratory disease in farmers, or whether for some reason farmers are less likely to develop IgE immune responses to occupational and common allergens, even at high exposure levels.

In the population of pig farmers in the Netherlands, in which many reported the use of chloramine-T for disinfecting the stables (309, 310), no specific IgE was found in an assay with human serum albumin-coupled chloramine-T (321).

The remarkable finding of a so-called “adjuvant” effect for atopic sensitization possibly due to disinfectant exposure (309), particularly for quaternary amines, indicates that technical developments in modern agriculture may not only lead to qualitative and quantitative changes in exposure but also might affect the exposed individuals’ responsiveness to allergen exposure, enhancing the risk of sensitization and symptomatic allergy.

Modern Fertilizers

A fertilizer is any natural or manufactured material, containing one or more essential nutrients, added to the soil or applied to plant foliage for the purpose of supplementing the plant nutrient supply. Its purpose is to enhance crop production. The earliest fertilizer materials were animal manures, plant and animal residues, ground bones, and potash salts derived from wood ashes. Modern fertilizers are manufactured and, based upon their primary nutrient content—nitrogen (N), phosphate (P_2O_5) or potash (K_2O)—are classed as single nutrient or multinutrient products. Fertilizers containing one or more primary nutrients are given a numeric designation consisting of three numbers, representing the proportion by weight of nitrogen, phosphate, and potash, respectively. Examples of fertilizers used in agriculture include:

NITROGEN FERTILIZERS

- Anhydrous ammonia (82-0-0)
- Aqua ammonia (20-0-0)
- Ammonia nitrate (34-0-0)
- Ammonia nitrate-lime (26-0-0)
- Ammonia sulfate (21-0-0-24S)
- Calcium nitrate (15.5-0-0-19Ca)
- Nitrate of soda (16-0-0)
- Urea (46-0-0)

PHOSPHATE FERTILIZERS

- Normal superphosphate (0-20-0)
- Concentrated superphosphate (0-45-0)

NITROGEN PHOSPHATE COMBINATIONS

- Monoammonium phosphate (11-52-0)
- Ammonium phosphate sulfate (16-20-0-15S)

POTASSIUM FERTILIZERS

- Potassium chloride
- Potassium sulfate
- Potassium nitrate

Besides the primary nutrients, fertilizers often contain small amounts of secondary nutrients and micronutrients, such as sulfur, calcium, magnesium, borates, and sulfates of copper, iron, manganese, and zinc. Fertilizers are available in fluid and dry forms.

Fertilizers can be applied by uniformly distributing them over the soil surface with a drop spreader, injecting them into the soil with high-pressure equipment, or adding them to irrigation systems (“fertigation”). Aerial application may also sometimes be used to eliminate crop damage. Fertilizers can be applied before, during, and after the growing season and in combination with seeds or pesticides.

Respiratory health problems have rarely been reported

with fertilizers during farming, except during accidents involving anhydrous ammonia, which can cause severe burns of the respiratory tract and even death (322, 323). In 1985 in Nebraska, one-third of 48 emergency department visits caused by agricultural chemical exposures involved anhydrous ammonia used as fertilizer (324). The focus, therefore, will be on anhydrous ammonia.

The high vapor pressure of anhydrous ammonia at ordinary temperatures requires that it be transported in pressure containers. High-pressure equipment is required for injecting anhydrous ammonia into the soil, and it vaporizes quickly as it is released. It is potentially hazardous, and handling procedures and safety precautions must be observed. Anhydrous ammonia is the third largest volume chemical produced in the United States, with 30% of the volume used as fertilizer (325).

Dry fertilizers can be measured with commonly used techniques for dust monitoring, followed by laboratory analyses for the specific agent of interest (39), and special sampling devices may be used to collect specific size fractions (250). Ammonia concentrations can be measured with several measurement techniques (326).

No data have been published on exposure levels of fertilizers during application, but it is known that exposure to, and inhalation of, ammonia concentrations of 2,500 to 6,500 ppm might result from accidents and could be fatal (327).

A so-called hazard and operability (HAZOP) analysis to examine hazards during the use of anhydrous ammonia by farmers showed that several needs existed regarding training and procedures, hazard awareness, knowledge of procedures, good working practices, use of protective equipment, equipment design, maintenance and inspection, and material compatibilities.

Research is needed on how to provide farmers and other fertilizer users with useful information and training, as well as on exposure levels during application of fertilizers (328).

Feed Additives

Grain and dry vegetable products are mixed with a variety of chemical constituents to make animal feed or feed supplements, which are then supplied to livestock producers. These additives improve the health and growth characteristics of livestock and include vitamins, minerals, antimicrobials, ruminant modifiers, antihelmintics, acaricides, concentrated protein supplements, and amino acids.

Vitamins added to feeds include A, B₁₂, E, D₃, riboflavin, and niacin. Minerals and other supplements include calcium, phosphorus, iodine, magnesium, manganese, selenium, copper, iron, potassium, cobalt, choline chloride, and pyrimidine precursors. Nutritional ingredients in animal feeds have commonly included soybean meal, meat and bone meal, blood meal, fish meal, and wheat middlings. Decreasing costs of amino acids and increasing attention to supplying ideal protein for improved lean gain have led to the addition of amino acids to feeds in complementary ratios based on the amount of supplied lysine. Principal added amino acids are lysine, methionine, tryptophane, and threonine.

Common antibiotics in feeds include tetracyclines (tetracycline, oxytetracycline, chlortetracycline), sulfas (sulfamethazine, sulfathiazole), neomycin, bacitracin, lincomycin, apramycin, tylosin, and lasalocid. Penicillins are rarely used as feed additives because of concern over the development of bacterial resistance. Antihelmintics and antiprotozoal drugs used as feed additives include ivermectin, monensin, and levamisole. Many antibiotics also serve as growth promoters in ruminants by adjusting the gut microbial flora to favor the cellulolytic organisms. Porcine and bovine growth hormones that have U.S.

FDA approval are available in injectable forms only at this time and are not present in feeds.

Mixing and bagging animal feeds are the tasks that appear to lead to the most significant exposures to the feed additives. The gravimetric exposure levels to organic dust associated with these tasks range typically from 1 to 10 mg/m³. However, exposures to these additives, specifically, have not been sufficiently studied and the extent to which such exposure presents a respiratory hazard is unknown.

Areas for Future Research

1. It is important that research be conducted to characterize disease agents in agricultural bioaerosols, develop an understanding of dose-response phenomena, and study mixtures to determine additivity of effects, potentiation effects, synergisms, and antagonisms among various constituents of the aerosols.
2. Efforts should be made to harmonize a wide range of bioaerosol sampling methods in the manner that the Nordic Council of Ministers followed for mold spore sampling (96). This should include methodologies for airborne microorganisms and methods for quantifying bacterial and fungal toxins.
3. Development of new methods for bioaerosol assessment, utilizing techniques such as quantitative PCR and fluorescent *in situ* hybridization; application of new fluorochromes for tagging organisms and oligonucleotide probes should lead to more accurate, specific, and efficient assays. These efforts should be expanded.
4. The importance of various agricultural practices to the generation of bioaerosols and the effectiveness of various bioaerosol control measures should be studied to guide the introduction of intervention measures. Many appropriate control measures are recognized, and these need to be implemented widely.

3. AIRWAY DISORDERS

Introduction

Although hypersensitivity pneumonitis such as farmer's lung is the most frequently recognized lung disease among farmers, airway diseases are more common. The upper airways are often affected, causing considerable discomfort to patients. There are now several new techniques, such as acoustic rhinometry and measurement of nasal resistance and peak flow, that will allow objective assessment of the degree of nasal obstruction. These techniques and nasal lavages will enable enhanced study of pathogenic mechanisms of reactions in the upper airways to contaminant exposures in the agricultural environment.

Many substances in the farming environment clearly aggravate asthma, and some can cause asthma. Diagnosis and treatment of asthma in farmers pose a special problem since farmers often live in the same environment as their workplace. The prevalence of asthma in farmers and the long-term consequences of the disease are unknown.

The term "asthma-like syndrome" is used to describe non-allergic, acute, reversible airway reaction to exposure to inhaled agents such as agricultural dusts. Although the symptoms of chest tightness, cough, and dyspnea are usually mild and self-limiting at the onset, there is evidence to suggest that cross-shift changes associated with these symptoms predict longitudinal decline in lung function in affected individuals.

Severe airway injury from toxic gas inhalation may result in long-term complications, including bronchiectasis, reactive airways dysfunction syndrome, bronchiolitis obliterans, and

chronic airflow limitation. These can occur in farmers exposed to high concentrations of irritant gases encountered in the agricultural environment.

A higher prevalence of chronic bronchitis and chronic airflow obstruction has been documented among certain farming populations, such as grain and animal feed workers, compared with control subjects. With repeated exposures, acute airway disorders in agricultural workers may lead to the development of chronic airflow obstruction.

Despite the progress of research in agricultural health, there are still considerable gaps in our knowledge, particularly in relation to the pathogenesis and natural history of diseases and in the understanding of multiple environmental risk factors, their interactions, and their control.

Upper Airway Responses

In the agricultural environment, exposures may result in inflammation of the upper airways, the nasal passages, nasopharynx, sinuses, and larynx. For the purpose of this review, the nasal passages are emphasized, because the nose plays a critical role in respiratory defenses, and because epidemiologic and clinical data are available on the effects of airborne contaminants on the nose.

The nose serves as an "air conditioner," maintaining humidity and temperature, as a sensor for odors and irritants, as a scrubber of water-soluble gases such as SO₂, and as a filter of particulates (339). Nasal responses to pollutants are of scientific and clinical interest for two reasons: (1) the nose is a target organ for many contaminants, and resultant rhinitis *per se* is a condition accompanied by substantial morbidity; and (2) the nose is a very accessible portion of the respiratory tract and, for investigators of such exposures, may serve as a surrogate tissue for lower respiratory tract responses.

Exposures. A variety of agricultural exposures have been associated with rhinitis. These include grain farming and handling, livestock breeding, feed manufacture and handling, dairy farming, tea farming, and cotton, flax, and hemp processing. Specific agents from these and other agricultural processes that can cause rhinitis include gram-negative bacterial endotoxins, thermophilic bacteria, fungi, arthropod parts, grain dust, silica and silicate dust, pollens, gases (NO_x, NH₃, H₂S), paraquat, and organophosphate pesticides.

Occurrence. Rhinitis is defined as inflammation of the nasal mucosa, whether the result of a direct irritant effect (irritant rhinitis) or as a specific immune reaction (allergic rhinitis). The prevalence and incidence of irritant rhinitis in the agricultural sector is unknown. Allergic rhinitis requires prior sensitization to the offending agent(s). Sensitization to natural products occurs most commonly in the atopic portion of the population, estimated to be between 10 and 20% of the total population. This proportion of the agricultural workforce may therefore be expected to have a higher risk of becoming sensitive to organic dusts when suitably exposed. A recent survey of occupational rhinitis in Finland reported that 20% of all rhinitis cases were occupational, and the most common exposures were from agricultural environments: flour, wood dust, animal dander, and vegetable fibers (e.g., cotton) (340). Swedish surveys of pig and dairy farmers have reported irritation of eyes, nose, and throat in excess of 20% (341).

Precise estimates of rhinitis and mucous membrane irritation of the eyes and throat among agricultural workers do not exist, but these are the most commonly observed symptoms in persons exposed to agricultural dusts, gases, vapors, and fumes (342).

Clinical features. Intermittent or persistent rhinorrhea may be caused by a variety of clinical disorders, including allergic

rhinitis and irritant rhinitis. Rhinitis caused by sensitization to agricultural agents is characterized by rhinorrhea, sneezing, nasal obstruction, lacrimation, and, occasionally, pharyngeal itching. Episodic symptoms are the hallmark of allergic rhinitis. In addition to nasal symptoms, there may be conjunctival congestion and edema. Swelling of the nasal turbinates and mucosa with obstruction of the sinus ostia and eustachian tubes can precipitate secondary sinus and middle ear infections. The latter is more common in perennial (versus seasonal) rhinitis. Washings, swabs, or biopsy of the mucosa will usually reveal eosinophils, but some neutrophils are usually present.

"Irritant rhinitis" describes the situation in which the specific sensitizers have not been identified; it may also be caused by exposure to irritants in the agricultural environment. Nasal washings and biopsies usually reveal a predominant polymorphonuclear (PMN) leukocyte response.

Nasal resistance varies with such factors as nasal congestion, inflammation, and physiologic state. Rhinomanometry may be used to measure nasal resistance and/or airway flow. It is widely used clinically to assess such pathophysiologic responses as allergy. Rhinomanometry has also been applied to assess environmental and occupational factors causing changes in nasal flow or resistance. Resistance is expressed as the pressure difference divided by flow ($R = dP/V$), and both can be measured simultaneously. Manometry has some limitations, notably the need for patient cooperation, collapse of alae, relatively high measurement variability, and unsatisfactory correlation with symptoms.

The development of acoustic rhinometry has reduced measurement variability and improved sensitivity (343–346). This technique utilizes sound reflection to obtain area–distance curve from the nostril through the nasal cavity. It is more accurate and reliable than manometry in measuring patency in terms of anatomical area, but it is based on certain assumptions—lack of turbulence, conservation of acoustic energy, freedom from influence by contralateral cavity, and rigidity of the airway walls. None of these assumptions are necessarily true, and interpretations are therefore limited. But comparison between acoustic rhinometry and the measurement by computed tomography and by nasal model shows excellent correlation. Other techniques that can be used in epidemiologic studies, such as nasal peak flow, can be performed serially throughout the working day in order to detect early reversible nasal airflow limitation (347, 348).

Nasal peak flow measurement is of special interest, because it can be used for repeated examinations, usually by the subject, many times during the workday to detect early reversible signs. Expiratory flow has been measured in many studies, and recently inspiratory flow measurement has been applied with good results.

Nasal lavage has been used to collect secretions and assess the inflammatory response of the upper airway to allergens and irritants (339, 349–353). The technique is simple. The most common method is briefly described below. The seated subject's head is tilted back at an angle of 45 degrees. Using a needleless syringe, 5 ml of warm (37° C) sterile phosphate-buffered saline (without calcium or magnesium) is instilled into the nostril. The saline is retained for 10 s, then allowed to drain passively for 30 s into a sterile specimen cup. The volume of lavage fluid recovered is recorded. Cells are counted on a hemocytometer and differential counts done on slides prepared by cytospin and stained with Wright-Giemsa. Although the method is not yet standardized, recent study indicates that intraindividual variability in PMN counts is less than interindividual variability, supporting the technique's utility

for epidemiologic studies (354). Nasal secretions can also be analyzed for such biochemical components as protein, albumin, histamine, IgE, antioxidants, and complement (355). The intraindividual variability and kinetics of these constituents in nasal fluid is as yet unknown.

Nasal lavage studies in subjects exposed to agricultural dusts are limited. One study reported elevated nasal PMN counts in farmers exposed to sorghum dust (355). Another study, a controlled human-exposure experiment, reported elevated lymphocytes in subjects exposed to dusts from corn and soybean as well as to endotoxin (356).

Inflammatory and immune responses of the upper airways are experimentally studied mainly to understand the pathophysiology of allergic and nonallergic rhinitis. The basic study methodology is to pose a challenge by specific antigen or non-specific agent, such as methacholine, and then collect nasal secretions to analyze the cellular and biochemical components of the secretion.

Biochemical analysis of various mediators in nasal secretions and/or morphologic analysis of cellular components are performed on nasal lavage fluid after centrifugation, if needed. A brush method can be used mainly to harvest cells (357). Other techniques, such as nasal blowing, smears, and imprints, have also been used to collect specimens in some studies. Those methods have been reviewed by Pipkorn and Karlsson (358).

Nasal secretions originate from several sources, including transudated serum components (albumin and other proteins), locally synthesized proteins (enzymes and surface IgA), mucous glycoprotein derived from the glandular elements, and chemical mediators and other products from various cells, including plasma cells, mast cells, basophils, and epithelial cells. Many studies have assessed cellular or biochemical components of nasal lavage fluid before and after challenge test using methacholine or specific allergens (359, 360).

Nasal challenge of sensitive individuals with antigen or cold, dry air increases the levels of histamine, TAME-esterase activity, prostaglandin D₂, and kinins in nasal lavage fluid (361). These mediators originate from the influx of activated cells, such as eosinophils, neutrophils, mast cells, and basophils. Neutrophils represent the greatest number of infiltrating cells in the late phase reaction. The interpretation of the markers is well summarized by Koren and Devlin (339).

Pathogenesis and natural history. The nasal mucosa is covered by a mucosal blanket which carries pollutants posteriorly, toward the pharynx, by ciliary movement. Except for the olfactory cells, nasal epithelium is identical to the epithelium of the lower respiratory tract. The nasal mucosa metabolizes certain chemicals, such as formaldehyde and SO₂. The immune defenses of the nose consist of humoral immunity (IgA, IgE), cellular immunity involving macrophages and PMN, and other immunoreactive materials, such as interferon, lactoferrin, and lysozymes.

Inhalation exposures can produce rhinitis by several mechanisms. Sensitization, with the production of IgE specific for a substance, can lead to symptoms on reexposure via mast cell degranulation and the release of inflammatory mediators. Respiratory irritants can lead to rhinitis through interaction with chemical irritant receptors in the airway, leading to the release of substance P from sensory nerves and neurogenic inflammation (362).

Agricultural dusts, fumes, and gases can exert several kinds of effects on the nasal mucosa, including irritation, increased airflow resistance, impairment of mucociliary clearance, impairment of defenses, inflammation, and direct cell damage (363). Upper airway symptoms will persist at least as long as

exposure to the offending agent(s) continues. The natural history of the upper airway response to agricultural environment exposures is unknown. It is possible that such responses may be early markers of lower airway responses.

Mucus/ciliary abnormalities may result from many environmental exposures, including dry air, acid aerosols, infectious agents, and gases such as NO₂ and SO₂. Mucociliary clearance can be measured by either radioisotope-labeled particles with a gamma camera or by a simple saccharin test. The latter measures the time of mucosal transport by placing a 0.5-mm piece of saccharin on the anterior inferior turbinate, 1 cm from the end. Normally, a sweet taste is detected within 30 min, with an average transit time of 6 mm/min.

Asthma

Agents in the agricultural environment clearly aggravate and may cause asthma. For purposes of this review, asthma is considered in two forms: (1) variable or reversible airflow obstruction caused by specific exposures in the agricultural environment; and (2) asthma exacerbated or accelerated by exposures in the agricultural environment. Asthma is defined as a disease characterized by variable airflow obstruction, airway hyperresponsiveness, and airway inflammation (364). The degree of reversibility of airways is usually greater than 12% (365). Airway hyperresponsiveness is often prolonged and persistent, whereas inflammation of the airways is characterized by infiltration with eosinophils (366). Objective signs of airflow obstruction are often associated with symptoms of chest tightness, wheezing, coughing, and dyspnea. Acute airway injury caused by exposure to high concentrations of vapors (anhydrous ammonia in particular) may result in reactive airway dysfunction syndrome (RADS), which is a form of occupational asthma (367).

Exposures. A large number of agents in the farming environment are capable of causing occupational asthma (368). However, most cases of occupational asthma from these exposures affect workers in the manufacturing sector rather than in the agricultural setting. In general, these agents can be divided into three groups: plant-, animal-, and arthropod-derived materials. Exposure to plant-derived materials, such as grain dust and cotton dust, give rise to asthma-like syndrome rather than asthma (364, 368, 369). However, farmers have been shown to become sensitized to barn and storage mites in grain dust and developed asthma (370–372). Soya bean dust is a potent sensitizer and has caused epidemics of asthma in communities where loading and unloading of soya bean took place rather than among farmers (373).

Animal-derived proteins can also exacerbate and may cause asthma in agricultural workers. Cow epithelium is one of the most important inducers of occupational asthma among farmers in Finland (374). Two main allergens have been identified in cow dander (20 and 22 kilodaltons [kD]) and one in cow urine (20 kD). Specific IgE antibodies have been found to these allergens in farmers with asthma and rhinitis from cow-induced asthma (375). Occupational asthma has also been described in a farmer raising red deer (376). Arthropod-derived materials such as grain and barn mites have been shown to cause asthma in farming populations (364, 368, 369).

Low concentrations of irritants may aggravate underlying asthma but do not usually cause asthma. Thus, 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 preexisting asthma. An extreme form of irritant-induced asthma or RADS may occur following inhalation of high concentrations of fumes or vapors in the agricul-

tural setting, such as noxious vapors from anhydrous ammonia and oxides of nitrogen. Case reports of RADS from ammonia inhalation, however, were limited to jobs outside the agricultural setting (377–378).

Organophosphate insecticides (379) may trigger bronchospasm in agricultural workers. Organophosphates inhibit acetylcholinesterase and result in overstimulation of cholinergic receptors, presumably inducing bronchospasm by increasing the concentration of cyclic glucose monophosphate. Whether organophosphate insecticide exposure causes asthma has yet to be investigated.

Occurrence. A significantly increased mortality from asthma was found among farmers, (smoking-adjusted standardized mortality ratio [SMR] 137; 95% CI, 115–156) and farmer workers (smoking-adjusted SMR, 170; 95% CI, 107–235) in Sweden (380). The annual crude self-reporting rate of occupational asthma in Sweden was 80 per million between 1990–1992; female poultry and dairy farm workers had one of the highest rates at 602 per million (381). In France, elderly farmers were found to have higher prevalence of cumulative and current asthma of 9.3 and 5.9% with OR of 2.3, 95% CI, 1–5.47 and OR of 5.35, 95% CI, 1.33–21.5, respectively, compared with white collar workers, adjusted for smoking, age, and gender (382). In New Zealand, the prevalence for combination of wheeze and nonallergic airway hyperresponsiveness was significantly increased (OR, 4.16; 95% CI, 1.33–13.1) for farmers and farm workers (383). In Denmark, the prevalence of asthma was 5.5% in dairy farmers and 10.9% in pig farmers (384).

The prevalence of asthma specifically caused by exposure to agricultural dusts and fumes is not known. It is likely to depend on exposure and setting. Occupational asthma is estimated to account for between 5 and 15% of patients diagnosed with asthma (385). Among farmers in Orkney, 15% were found to have symptoms consistent with either asthma or allergic rhinitis; about half of them had symptoms of asthma due to allergy to storage mite.

Interestingly, the prevalence of asthma among grain workers is reported to be similar to a comparative population of unexposed workers (386). This apparent disparity may be explained by the factors that select workers into and out of the grain industry. Despite these inconsistencies, a recent review (387) indicates that most studies in grain workers have shown approximately a twofold excess risk of wheezing among grain workers when compared with unexposed workers. Thus, data are sparse and inconclusive regarding the prevalence of asthma in agricultural workers; moreover, *no* data are available concerning the incidence of asthma among agricultural workers and their family members frequently exposed to bioaerosols.

Clinical features. The diagnosis of agricultural asthma is dependent on the demonstration of reversible airflow obstruction occurring in conjunction with inhalation of specific agents known to cause or exacerbate asthma. Therefore, the physician should initially focus on the diagnosis of asthma and secondarily determine if there is an occupational etiology. Typical symptoms of asthma include recurrent episodes of nonproductive cough, chest tightness, wheezing, and dyspnea; they may occur immediately after exposures or may develop several hours later.

The diagnosis of asthma is based on the demonstration of variable airflow obstruction. Standard spirometry showing airflow obstruction reversible with bronchodilators and inducible airflow obstruction with nonspecific airway challenges are considered acceptable physiologic assessments of variable airflow obstruction (388). Demonstration of an FEV₁/FVC ratio

of less than 75% is considered diagnostic of airflow obstruction (389). A decrease in the FEV_1/FVC ratio is usually associated with a low FEV_1 (less than 80% predicted or in the bottom tail of the 90% CI) or a low $FEF_{25-75\%}$ (less than 60% predicted). Variability in airflow obstruction is usually demonstrated by sequential spirometry but may alternatively be documented by improvement in airflow with bronchodilators (at least 12% improvement in FEV_1 is considered significant) (365) or worsening of airflow (20% decline in FEV_1) following inhalation of either histamine or methacholine. In many circumstances, spirometric measures of lung function are normal. The demonstration of nonspecific airway hyperresponsiveness supports the diagnosis of asthma.

Importantly, agricultural asthma requires the demonstration of a clear temporal relationship to specific farmwork exposures known to cause asthma. The history is often helpful in identifying an occupational etiology; for example, the presence of asthma-causing agents in the workplace, the worsening of symptoms during the work week and improvement on weekends and vacations, or the history of exposure to an overwhelming concentration of an irritant gas such as ammonia or oxides of nitrogen prior to onset of symptoms. Unlike other patients with occupational asthma, however, the agricultural worker commonly *lives in the working environment* and often works seven days rather than five. Thus, the temporal relationship between exposures and symptoms may be difficult to establish.

Physiologic testing, whether by spirometry, peak flow measurements, or serial nonspecific bronchoprovocative challenge, can and should be used to critically evaluate the temporal relationship between occupational exposure and the development of airflow obstruction (389). For instance, demonstration of consistent decreases in either FEV_1 or peak flows of at least 15% when exposed to a specific agent in the agricultural setting helps to establish the diagnosis of agricultural asthma. Although serial peak flow monitoring is dependent on patient cooperation, it may be the only feasible approach to investigating work-induced asthma. Portable computerized peak flow meters are now available; their use will enable more effective assessment of the validity of the monitoring (390).

Specific inhalation challenge tests are the most definitive method of making the diagnosis, but these inhalation challenges are not entirely accurate if performed improperly. Very few centers are equipped to perform these exposure-response studies in a way that minimizes risk. On-site spirometric measurement of airflow at intervals throughout the day is the most preferable method to establish a temporal relationship between specific exposure in the agricultural setting and the development of asthma (389).

Several immunologic tests have been proposed to evaluate patients with suspected or proven occupational asthma; however, their ultimate clinical utility is limited (391). Serologic or immunologic testing can assist in determining atopic status with respect to environmental allergens. Very few specific allergens, such as extracts of flour and grain dusts, animal products, and certain chemicals, are available commercially for immunologic testing. Serum IgG or IgE antibodies may be detected by radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) methods. Unfortunately, these tests lack the sensitivity and specificity required for making a definitive diagnosis, but when used in conjunction with other testing methods and a careful patient history, these tests may be helpful in demonstrating a specific etiology. In the most limited context, immunologic tests may be helpful in further documenting exposure and identifying the atopic status of the pa-

tient. Immunologic testing should not be used to definitively diagnose agricultural asthma.

The diagnosis of irritant-induced asthma is based on historic data linking the onset of asthma to an acute inhalational injury. Characteristically, irritant-induced asthma occurs after a single accidental exposure to high levels of irritating gases (367). The worker typically reports a specific event involving exposure to a high concentration of irritant. Symptoms of cough, chest tightness, and difficulty in breathing develop within 12 h of the exposure and can persist for more than 6 mo after the acute episode.

Natural history. Very little is known about the natural history of occupational asthma in agricultural workers. However, among patients with occupational asthma, the majority continue to have asthma despite removal from the exposure (392). Remissions appear to be related to the duration and intensity of the disease, with earlier and less severe forms of asthma more likely to improve after removal from further exposure. Spontaneous recovery has not been reported among workers who remain exposed to the agent causing asthma (393, 394). Thus, among agricultural workers, those with work-related asthma should be strongly encouraged to modify their exposure by either changing jobs or reducing their exposure to inhaled dust and fumes. Because many agricultural workers are unlikely to change their occupation, it is helpful to encourage the use of a two-strap dust mask or, in some cases, an air-stream respirator. One study (395) indicates that symptoms substantially improve when the concentration of allergen is reduced through the use of a respirator. Every effort should be made to reduce exposure because it is difficult for patients to use respirators throughout the day every day.

The treatment of agricultural asthma is similar to that for other forms of asthma (364, 389). Anti-inflammatory medications (preferably inhaled steroids) should be the mainstay of treatment, and bronchodilators should be used as needed. Importantly, the use of inhaled steroids should be continued for at least 6 mo after the patient has been free of all respiratory symptoms.

Pathogenesis. The pathogenesis of asthma induced or exacerbated by exposures in the agricultural setting is highly variable and entirely dependent on the specific nature and intensity of the exposure. Airway narrowing caused by inflammation, edema, or smooth-muscle hyperreactivity results in acute and reversible decreases in airflow. Recurrent episodes of allergic and nonallergic inflammation may result in chronic remodeling of the conducting airways and may lead to development of progressive airflow obstruction (393).

Classic allergic mechanisms of airway inflammation involving mast cells, IgE, histamine, eosinophils, and lymphocytes may be responsible for the development of asthma following exposure to high-molecular-weight allergens such as plant- and animal-derived proteins. These patients usually have an atopic history. When IgE-antigen reaction takes place, mast cell degranulation occurs with the release of histamine and a number of inflammatory mediators (396). Importantly, histamine can stimulate bronchial obstruction by enhancing vascular permeability, increasing smooth muscle contraction and mucous secretion, and upregulating the production of prostaglandins (397).

Noxious gases and irritants may directly injure the airway epithelia, resulting in edema, inflammation, and cell death. The epithelia may prove to be an important mediator of the inflammatory response by producing and releasing chemotactic factors such as interleukin-8 (IL-8) (398). Sloughing of the airway epithelia and thickening of the subepithelia are common in asthma (366). Thus, the airway epithelia may actually

TABLE 3.1
EXAMPLES OF AGRICULTURAL DUSTS WITH ASTHMA-LIKE SYNDROME

Reference No.	Place	Population (n)	Symptoms (%)	Cross-shift Change in FEV ₁	Dose and Dose Relationship	Other Factors		
						Smoking	Atopy	Age
Cotton dust								
Imbus and colleagues, 1973 (411)	North Carolina, U.S.	10,133	4.6	25% > 10% decrease	+ Dust level (by area of work)	—		
Berry and coworkers, 1974 (413)	Dundee, U.K.	1,857	F 18–33 M 43–45		+ Duration + Dust level	Higher in smokers		
Berry and associates, 1973 (412)	Dundee, U.K.	1,857		Control subjects' mean decrease 4 ml; medium cotton mean decrease 75 ml; coarse cotton mean decrease 148 ml	+ Dust level – Duration	—		—
Merchant and colleagues, 1973 (414)	U.S.	1,257		2.8% > 5% decrease (1.9 mg/m ³)	+ Dust level			
Fox and coworkers, 1973 (415)	Lancashire, U.K.	2,316	16		+ Duration		—	+
Fox and associates, 1973 (416)	Lancashire, U.K.	2,316	0→ 1 mg 6.7 1.1→ 2 12.7 2.1→ 3 17.3 > 3 mg 39.4		+ Dust level	+		
Awad Elarim and Onsa, 1987 (417)	Khartoum, Egypt	186	37	Coarse cotton 48% > 0.2 L decrease		—		
Jones and coworkers, 1979 (418)	U.S.	Cotton, 386 Synthetic, 85	5.7	CS mean decrease 40 ml NS mean decrease 29 ml CS mean decrease 53 ml NS mean decrease 4 ml	+ Dust level	+	+	
Ong and colleagues, 1987 (419)	Hong Kong	2,317	2.3 (1.6–5.6)	Blowing/carding 13% > 10% decrease Spinning 11% > 10% decrease Others 7% > 10% decrease	+ Dust level			
Grain dust								
Gandevia and Ritchie, 1966 (401)	Australia, New South Wales	24 Dock workers	41.6	Wheat dust –291 ml Rock dust –107 ml				
McCarthy and coworkers, 1985 (407)	U.K.	6 Dock workers		Decrease VC 200– 800 ml				
Chan-Yeung and associates, 1980 (403)	Vancouver, Canada	Grain 485 Control 65		Grain 9.7% 5–9% decrease 3.9% > 10% decrease Controls 4.6% 5–9% decrease 0% > 10% decrease	51% Samples > 10 mg/m ³			
Corey and colleagues, 1982 (542)	Toronto, Canada	Grain 47 Control 15			For each 1 mg/m ³ increase in respiratory dust, 50% of subjects decrease 923 ml/s in V _{max} 50% VC			
Revsbech and Andersen, 1989 (543)	Denmark	Grain 132		Mean diurnal variation in PEF –5.9%	4.9→ 6.3 mg/m ³ 6.3 mg/m ³ + Dust level	+		+
DoPico and associates, 1983 (544)	Wisconsin, U.S.	Grain 248		Mean decrease FVC 46 ml Mean decrease FEV ₁ 8 ml	3.3 ± 7 mg/m ³ + Dust level	—	—	—
Swine confinement								
Donham and coworkers, 1984 (408)	Iowa, U.S.	21 Farmers 10 Controls		Mean decrease 5.8% pred.	Correlated with H ₂ S and CO ₂ level	+		
Haglund and Rylander, 1987 (545)	Sweden	29 Farmers	Chest tightness NS –18% CS –38%	Mean decrease 400 ml	Total dust 4.9 mg/m ³ Endotoxin 0.02–1.9 µg/m ³	+		
Bongers and colleagues, 1987 (546)	Netherlands	132 Farmers	Chest and systemic Sx in 28%	ND				
Zuskin and coworkers, 1992 (547)	Yugoslavia	59 Farmers 46 Controls	Cough 71% Dyspnea 57%	M mean decrease 3.8% F mean decrease 4.5%	Dust < 8 µg/m ³	+		
Choudat and associates, 1994 (548)	France	97 Pig farmers 48 Dairy farmers 78 Controls	Cough SOB 24.5 3.1 8.3 2.1 5.1 5.1	FEV ₁ Decrease > 10% 17.9% 35.6% 6.7%	Dust 2.41 µg/m ³			
Zhou and coworkers, 1992 (549)	Saskatoon, Canada	52 Pig farmers		Mean decrease 170 ml	Correlation with total dust, NH ₃ , no. of working hours	*		

(Continued)

TABLE 3.1
CONTINUED

Reference No.	Place	Population (n)	Symptoms (%)	Cross-shift Change in FEV ₁	Dose and Dose Relationship	Other Factors		
						Smoking	Atopy	Age
Poultry Hagman and associates, 1990 (336)	Sweden	Slaughter house 23	50% cough	Mean decrease 4.1%	Dust 6.3/m ³ (0.4–15.3) Endotoxin 0.4 µg/m ³ (0.02–1.5)			
Thelin and colleagues, 1984 (550)	Sweden	Poultry handling 47	40% symptoms	Endotoxin > 1 µg/m ³ decrease 210 ml Endotoxin < 1 µg/m ³ decrease 70 ml	Dust 5.9–23 µg/m ³ Endotoxin 0.1–1.09 µg/m ³	+		
Morris and coworkers, 1991 (333)	Georgia, U.S.	Chicken catcher 59		Mean decrease 120 ml (preshift 3.54 L)				

Definition of abbreviations: CS = current smoker; F = female; M = male; NS = nonsmoker; PEF = peak expiratory flow; VC = vital capacity; $\dot{V}_{max}$ = maximal flow.

contribute to edema and inflammation following inhalation of particularly irritating agents (396).

Asthma-like Syndrome

The term “asthma-like syndrome” is used to describe an acute nonallergic airway response arising from inhalation of various agents in the agricultural environment. The symptoms consist of chest tightness, wheeze, and/or dyspnea and can be associated with cross-shift decline in FEV₁ (usually less than 10%), which is dose-related. The syndrome is associated with airway inflammation, with neutrophils and pro-inflammatory cytokines the most prominent cells. A transient increase in nonspecific airway responsiveness may also be apparent. The asthma-like syndrome is distinguished from asthma in that, unlike asthma, the asthma-like syndrome is a self-limited inflammatory event that does not involve persistent airway hyperreactivity.

Exposures. A number of agents in agriculture environments have been shown to give rise to asthma-like syndromes (Table 3.1). Of these, asthma-like syndrome due to grain and cotton dust exposure have been studied most extensively.

Exposure to grain dust occurs on farms, in transfer at terminals and elevators, and in the vicinity of docks where grain is being loaded (399, 400). Grain dust is complex and contains a mixture of different types of grain, insect parts, fungi, bacteria, bird and rodent droppings, pesticides, and silica. While chronic effects of grain dust exposure have been studied extensively, acute nonallergic airway response has been documented only in a few studies (386, 387). Respiratory symptoms such as cough, chest tightness, and wheeze during a work shift are reported more frequently among grain workers than control subjects. At times, these chest symptoms are accompanied by systemic complaints such as fever, flushing of the face, and headache. Cross-shift declines in FEV₁ were first described by Gandevia and Ritchie (401) among dock workers in 1966. There is a dose relationship between the degree of cross-shift change in lung function and the level of dust exposure in grain elevators (402).

Respiratory problems in swine confinement unit workers have been recognized only in the last two decades. Acute chest symptoms, such as cough, dyspnea, chest tightness, and irritation of the throat, occurring over the course of a work-shift are common (401, 403–407). Cross-shift changes in FEV₁ have been observed in several studies (401, 403–407). Systemic symptoms such as fever, headache, and malaise are also common. In addition to dust, swine farmers are also exposed to gases such as ammonia, hydrogen sulfide, carbon monox-

ide, and carbon dioxide. The dust contains mostly animal feed and aerosolized, manure-rich, gram-negative bacteria. Of these exposures, levels of total dust, endotoxin, and ammonia were found to correlate with chronic respiratory symptoms in swine farmers (408, 409).

Acute respiratory symptoms and cross-shift declines in FEV₁ have been described among poultry workers (chicken catchers), slaughterhouse workers, and poultry farmers (332–334). Airborne contaminants in poultry confinement units include mixtures of organic poultry dust, skin debris, feather, insect parts, aerosolized feed, and poultry excreta, as well as a variety of viable bacteria and gram-negative bacterial endotoxin. High levels of ammonia have been reported (408).

The term “byssinosis” is used to describe a symptom complex that occurs among cotton workers. The prominent feature is chest tightness, often accompanied by cough and shortness of breath, occurring on the first day of the work week after one to two days away from the workplace. McKerrow and colleagues (410) were the first to demonstrate that acute cross-shift bronchial obstruction occurred in some workers with the symptoms of byssinosis. There have been many studies documenting the prevalence and incidence of byssinosis in the work force in Britain, the United States, and other parts of the world (411–419). The prevalence of byssinosis is directly related to the degree of dust exposure. Up to half of the work force may be affected, depending on the condition of the workplace.

Occurrence. Table 3.1 also shows the prevalence of acute respiratory symptoms and cross-shift decline in FEV₁ in different agricultural environments. The prevalence of these acute symptoms may be as high as 50% among exposed populations. The most important determinant of the prevalence of cross-shift decline, as with byssinosis, is the degree of exposure to dust or to endotoxin. While smoking has been shown to be an important modifier, the effect of atopy is not consistent.

Clinical features. At the early stage of the illness, the clinical picture is different from patients with occupational asthma, whose symptoms *worsen* as the week progresses and improve over the weekend and holidays. The acute respiratory symptoms of chest tightness and cough abate or disappear with no demonstrable cross-shift changes in lung function as the week progresses, even though the exposure is the same. They may subside without treatment. Individuals so affected usually do not consult physicians for treatment. However, at a late stage of the illness, symptoms and cross-shift declines in FEV₁ occur every day of the work week (420). Clinical studies of asthma-

like syndromes are limited. Persistent airway hyperresponsiveness to the degree observed in patients with asthma has not been found (421–423). In grain workers, increase in neutrophils rather than eosinophils in the peripheral blood was demonstrated in subjects who developed changes in lung function over a work shift (424).

The clinical features of this syndrome are compatible with a nonallergic reaction. Healthy subjects may also develop symptoms on first exposure (425, 426). Both atopic and non-atopic subjects are involved, although atopic subjects tend to have a greater cross-shift decline in FEV₁ (427, 428). Specific antigens and antibodies have not been identified. Moreover, the degree of airway response is directly related to the level of exposure (Table 3.1).

In the laboratory, inhalation challenge testing with an ex-

tract of corn dust induced symptoms lasting up to 12 h and air-flow obstruction for up to 48 h (424).

Natural history. The relationship between acute airway response to chronic (fixed) airflow obstruction has been reviewed by Becklake recently (429). Acute airflow obstruction has been found to be a predictor of longitudinal decline of lung function in several studies related to cotton, grain dust, and swine confinement exposure (430–436) (Table 3.2). It is difficult to know whether this finding is due to the degree of exposure or to an intrinsic host predisposing factor.

Pathogenesis. The underlying mechanism of these symptoms appears to be associated with airway inflammation. BAL studies of healthy subjects after exposure to swine dust and extracts of grain dust have shown intense airway inflammation (437–439). It is not entirely clear what agent is causing the air-

TABLE 3.2
STUDIES OF FARMERS AND FARMWORKERS (EXCLUDING ANIMAL CONFINEMENT)

Reference	Population	Method Details	Symptom Rates	Pulmonary Function Test Results																																								
Terho and colleagues, 1990 (497)	All farmers Finland	Postal survey 9,669 farmers	Chronic phlegm incidence: 2.0% (farmers), 0.7% nonfarmers Chronic bronchitis: livestock 2× higher than grain farmers																																									
Warren and Manfreda, 1980 (498)	All farmers Manitoba	Mailed question- naire, 833 farmers	Chronic bronchitis, 23% Dyspnea, grade 3–14% No symptom differences according to type of farming																																									
Babbott and coworkers, 1980 (505)	Dairy farmers Vermont	198 farmers 516 controls MRC questionnaire spirometry	Ever smokers/nonsmokers Farm control/farm control chronic Sputum 30%, 21%, 16%, 10% Dyspnea 48%, 35%, 27%, 19%	Ever smokers/nonsmokers Farm control/farm control FEV ₁ /FVC < 0.7, 20%, 18%, 14%, 7%																																								
Heller and colleagues, 1986 (503)	All farmers/workers England, Wales	428 farmworkers 356 controls MRC questionnaire spirometry	Chronic bronchitis: no difference between groups	Dairy farmers and silage workers more likely to have reduced FEV ₁																																								
Milosevic, 1986 (504)	Farm workers Yugoslavia	Workers from one communal farm MRC questionnaire	Chronic bronchitis: smokers/nonsmokers Cattle breeders 47%/28% Plowmen 37%/20% Tractor drivers 29%/11% Craftsmen 29%/ 9%																																									
Dosman and coworkers, 1987 (500)	All farmers Saskatchewan	1,824 farmers 556 nonfarmers ATS questionnaire spirometry	<table><tr><th></th><th>Farmers</th><th>Controls</th><th>p Value</th></tr><tr><td>Chronic bronch.</td><td>11.1%</td><td>7.7%</td><td>< 0.05</td></tr><tr><td>Dyspnea</td><td>33.3%</td><td>18.2%</td><td>< 0.001</td></tr></table>		Farmers	Controls	p Value	Chronic bronch.	11.1%	7.7%	< 0.05	Dyspnea	33.3%	18.2%	< 0.001	<table><tr><th></th><th>Farmers</th><th>Controls</th><th>p Value</th></tr><tr><td>(% pred.)</td><td></td><td></td><td></td></tr><tr><td>FVC</td><td>97.7</td><td>106.1</td><td>< 0.001</td></tr><tr><td>FEV₁</td><td>96.1</td><td>102.8</td><td>< 0.001</td></tr><tr><td>FEV₁/FVC</td><td>97.8</td><td>96.7</td><td>< 0.01</td></tr><tr><td>MMFR</td><td>87.0</td><td>89.8</td><td>< 0.001</td></tr></table>		Farmers	Controls	p Value	(% pred.)				FVC	97.7	106.1	< 0.001	FEV ₁	96.1	102.8	< 0.001	FEV ₁ /FVC	97.8	96.7	< 0.01	MMFR	87.0	89.8	< 0.001				
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Dalphin and colleagues, 1993 (506)	Dairy farmers France	250 farmers 250 controls MRC questionnaire spirometry	<table><tr><th></th><th>Farmers</th><th>Controls</th><th>p Value</th></tr><tr><td>Chronic bronchitis</td><td></td><td></td><td></td></tr><tr><td>Men</td><td>17.7%</td><td>9.2%</td><td>< 0.05</td></tr><tr><td>Women</td><td>5.8%</td><td>2.5%</td><td>NS</td></tr><tr><td>Dyspnea</td><td>24.8%</td><td>30.0%</td><td>NS</td></tr></table>		Farmers	Controls	p Value	Chronic bronchitis				Men	17.7%	9.2%	< 0.05	Women	5.8%	2.5%	NS	Dyspnea	24.8%	30.0%	NS	<table><tr><th></th><th>Farmers</th><th>Controls</th><th>p Value</th></tr><tr><td>(% pred.)</td><td></td><td></td><td></td></tr><tr><td>VC</td><td>95.2</td><td>98.6</td><td>< 0.01</td></tr><tr><td>FEV₁/VC</td><td>94.8</td><td>98.4</td><td>< 0.001</td></tr><tr><td>FEF_{25–75}</td><td>78.8</td><td>90.1</td><td>< 0.001</td></tr></table>		Farmers	Controls	p Value	(% pred.)				VC	95.2	98.6	< 0.01	FEV ₁ /VC	94.8	98.4	< 0.001	FEF _{25–75}	78.8	90.1	< 0.001
	Farmers	Controls	p Value																																									
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Manfreda and coworkers, 1989 (502)	All residents, one rural district, Manitoba	924 males 968 females ATS questionnaire spirometry	No significant association between any symptoms and farming exposures	Slight reductions only in former male farmers																																								
Chen and colleagues, 1991 (501)	All farmers, Saskatchewan	324 grain farmers 1,309 nonfarmers ATS questionnaire	<table><tr><th></th><th>Farmers</th><th>Controls</th><th>p Value</th></tr><tr><td>Chronic bronchitis</td><td></td><td></td><td></td></tr><tr><td>Men</td><td>7%</td><td>4%</td><td>NS</td></tr><tr><td>Women</td><td>13%</td><td>8%</td><td>< 0.05</td></tr></table>		Farmers	Controls	p Value	Chronic bronchitis				Men	7%	4%	NS	Women	13%	8%	< 0.05																									
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Gamsky and associates, 1992 (499)	Hispanic farm workers, grape, citrus, tomato crops, California	747 workers ATS questionnaire spirometry	Rates increased in all smoking categories Ever smokers/Never smokers 300 Men 33 Women/262 Men 139 Women Chronic cough 2% 3% 1% 1% Chronic phlegm 5% 6% 4% 6% Increased symptoms in workers working > 8 mo/yr in agriculture	FVC significantly higher than predicted values from other studies, but FVC significantly lower in grape workers compared to citrus and tomato workers																																								

Definition of abbreviations: ATS = American Thoracic Society; MMFR = maximum midexpiratory flow rate; MRC = Medical Research Council; VC = vital capacity.

way inflammation, but one agent common to many agricultural working environments is endotoxin.

The findings of several studies have suggested that endotoxin is the agent responsible for this syndrome: (1) endotoxin is present in all organic agricultural dusts (Table 2.2); (2) there is a correlation between acute changes in lung function over a work shift or on exposure in the laboratory setting and the endotoxin level. The correlation of changes in lung function with the endotoxin level is at times better than with the total dust concentration (440); (3) inhalation challenge with endotoxin-induced airflow obstruction (440), reduction in diffusing capacity (440), and leucocytosis is similar to inhalation challenge with extract of cotton bract and grain dust (440, 441); (4) airway inflammation has been found after inhalation challenge with endotoxin (441); (5) the concentration of endotoxin in the bioaerosol appears to be the most important occupational exposure associated with the development (440, 441) and progression (435) of airway disease in agricultural workers; and (6) when compared to endotoxin-sensitive mice, mice resistant to endotoxin either by genetic or acquired mechanisms have a reduced inflammatory response to inhaled grain dust (441).

It is not known, however, whether endotoxin is the sole cause of this syndrome for several reasons. There are many studies showing that extracts of cotton dust and grain dust have several biologic properties that can give rise to airway inflammation and cause bronchoconstriction. These include activation of the alternative complement pathway (442, 443), histamine-releasing properties (444–448), and chemotactic activities (449, 450). In addition, extracts of grain dust have been shown to stimulate lymphocytes (451). Both cotton dust and grain dust contain tannins (452, 453), which have been shown to activate phospholipase C and A2, leading to the release of diacylglycerol and mobilization of intracellular free calcium, and stimulate smooth muscle contraction. Gram-positive bacteria, which have no endotoxin, may also elicit potent biologic responses, such as causing the systemic inflammatory response syndrome “sepsis,” and may *in vitro* stimulate human alveolar macrophages and epithelial cells to induce release of inflammatory cytokine.

Toxic Gas Inhalation

The production of noxious gases during the process of ensiling forage was documented in 1879 (454). Pulmonary injury following exposure to oxides of nitrogen, carbon dioxide, and other gases generated by recently ensiled plant material is a phenomenon which has been recognized for at least the past 80 years. More recently, other types of gases evolving from fertilizers, particularly organic material such as manure, have also been demonstrated to be hazardous to agricultural workers (455). Depending upon the solubility of the gases, their concentration, and duration of exposure, a variety of clinical problems may be seen that affect the airway anywhere from the nose to the alveolus. Despite this diversity of presentations, the common thread is that in virtually all these cases there is also some element of airway injury.

Exposures. The phenomena attendant to the fermentation and preservation of forage are similar regardless of the site—pit, silage bag, or upright tower. Any of these sites can provide the relatively anaerobic environment required so that the continued respiration of plant cells will lead to the production of various organic acids. It is the accumulation of these acids that suppresses microbial overgrowth and thus preserves the silage for extended periods of time (456). In addition to the generation of these organic acids, carbon dioxide and several of the oxides of nitrogen may also be produced during the initial few days of ensiling. These latter arise as plant nitrates are con-

verted to nitrites in the presence of heat and organic acids. This process leads to the production of HNO_2 and eventual evolution of a variety of other oxides of nitrogen (457).

The problem of exposure to these toxic gases generated by ensiled feed is one that is largely limited to upright tower silos, which provide an enclosed work space sufficiently airtight to trap these gases in high concentrations. Of the upright tower silos, the oxygen-limited silos are designed to prevent worker entry into the silo headspace, an anaerobic and immediately lethal environment, although this has not entirely precluded occasional asphyxiations in this setting. Thus, it is primarily the non-oxygen limited tower silo that provides an accessible confined work space in which CO_2 and oxides of nitrogen (NO_x) can accumulate.

The design of these silos and the characteristics of NO_2 combine to heighten the risk to workers during the period immediately following filling of the silo. With a specific gravity of 1.58 (458), NO_2 tends to accumulate along the surface of the silage, particularly in depressions (459). Access to the headspace of these silos is via a series of small doors extending vertically up the side of the silo, enclosed by an aluminum chute. When silo gas (CO_2 and NO_2) accumulates at the surface of the silage, it displaces oxygen upward—sometimes out of the breathing zone of a worker—and simultaneously begins to leak through the adjacent door into the chute, where it may accumulate. Thus, the worker attempting to enter the headspace of the silo may receive a significant dose of NO_2 in the chute before actually opening the door into the silo. Upon crawling through the door onto the bed of silage, the worker's head is positioned in the area of the silo most likely to accumulate toxic levels of gas. A person losing consciousness in this setting is likely to roll to a depression in the silage bed where the concentration of the toxic gases is highest and where oxygen concentration is lowest.

One of the challenges of dealing with silo gas is that the levels encountered by farmers are highly variable and in most cases minimal. However, under conditions in which plant levels of nitrate are particularly high, prodigious amounts of NO_2 can be generated. Crops, particularly corn, that have been heavily fertilized and grown under drought conditions tend to produce oxides of nitrogen (460). In experimental silos, levels exceeding several thousand parts per million of NO_2 have been measured (461–463). A level of 50 ppm NO_2 has been designated by NIOSH as “immediately dangerous to life and health” (464).

Equally hazardous is exposure to toxic gases associated with liquid manure storage in pits or large tanks associated with the housing of large numbers of animals in relatively close quarters, such as swine confinement or large dairy farms. Manure stored prior to dispersal as fertilizer can generate substantial amounts of carbon monoxide, CO_2 , ammonia, methane and, most notably, H_2S (455). Both CO_2 and H_2S are heavier than air and tend to accumulate along the surface of the manure slurry. These gases can become hazardous when a worker ill-advisedly enters the slurry for repairs or when agitation of the slurry prior to pumping causes the accumulated gases to well up into the victim's breathing zone (465).

A related phenomenon is the chronic exposure to ammonia inherent in animal confinement work. Often confinement houses are located over or in proximity to manure storage pits or tanks. Gases arising from these, in combination with those arising from animal urine, result in generation of substantial amounts of ammonia gas. Numerous studies have documented occupational exposures to ammonia levels that approach or exceed the 8-h TWA threshold value limit ($\text{TLV} = 25 \text{ ppm}$) (466, 467). Workers in these settings have increased preva-

lence of airway symptoms, such as daily cough, sputum, and wheeze. The signs and symptoms of chronic airway disease in these workers, however, appear to relate primarily to the organic dust and endotoxin exposure (468) and will be addressed elsewhere in this monograph.

Far less common is the occasional exposure to anhydrous ammonia used as a fertilizer. Stored under pressure as a liquid, ammonia boils into a gas at -28°F . Exposure to these highly concentrated fumes can occur when the hoses or couplings on the tanks suddenly fail. On particularly hot and humid, windless days, the resultant cloud of ammonia gas may blanket the farmer for a prolonged period of time (469).

Clinical features. Loss of consciousness and subsequent death of workers during the exposure period is a problem that has been recognized for at least 80 years. Hayhurst and Scott (470) reported "four cases of sudden death in a silo" in 1914. As part of the follow-up investigation of this incident, several small animals were lowered into the silo and observers from above documented their prompt loss of consciousness with death soon thereafter (470). There are numerous other cases of sudden death both within silos and manure systems that have been reported in the medical literature and elsewhere (471).

The etiology of immediate death upon entry to a recently filled silo is likely multifactorial. In the cases reported by Hayhurst, subsequent analysis of gas samples collected in the silo showed an oxygen concentration of 13.5%, with concentrations of CO_2 and NO_2 at 38% and 48.5%, respectively (470). Other measurements of O_2 concentrations in silos have shown levels approaching zero in the breathing zone of a worker entering this space (472). In addition to anoxia, the worker also encounters extremely high levels of CO_2 and NO_2 capable of generating considerable bronchospasm, if not laryngospasm. With high levels of nitrates entering the bloodstream, considerable vasodilatation with associated marked hypotension might be expected (473). The net effect of this is significant cerebral hypoxia, which would likely cause the prompt loss of consciousness and subsequent death described by Hayhurst. Witnesses to such events have described the collapse of a worker within 20–30 s (471).

Similarly abrupt losses of consciousness have been observed in manure storage incidents. These have been even less well studied, although attempts to reproduce these environments following such incidents show that levels of H_2S of 400 ppm or greater were likely present. Although autopsies of victims describe diffuse pulmonary edema (471), the cause of death here is also multifactorial. H_2S at low levels (10–50 ppm) is a local irritant. At levels of 300 ppm it will produce pulmonary edema in animals, and at higher levels it is a potent uncoupler of oxidative metabolism. This latter effect can both immobilize the victim and induce marked respiratory depression. The final insult in this setting is liquid manure aspiration in victims who manage to survive the initial asphyxia (455).

Although less well characterized, it is likely that an analogous set of events occurs with overwhelming exposures to anhydrous ammonia. Because of its very high water solubility, the alkali effects of ammonium hydroxide cause intense upper airway damage, adding considerable edema to the spastic effects occurring at the larynx and large airways (474).

With less dramatic exposures, the effect of toxic gases upon the airway becomes more evident. Such workers experience signs and symptoms of an acute chemical injury to the large and small airways. During the exposure incident, they experience cough, dyspnea, and lightheadedness at the time of the exposure (475).

Subsequently, following an interval of less than an hour to

up to 2 d after inhalation of toxic gases, the farmer may seek medical assistance with complaints of cough, dyspnea and/or chest tightness as well as possible fever, headache, nausea, or chills (476). Individuals with predominant airway injury usually present a number of hours to days after exposure. Physical exam is notable for wheezing or rhonchi present on auscultation of the lung. Although arterial hypoxia has been described, this appears not to be present in the majority. Those with isolated airway injury are evident by their clear chest radiographs.

It appears that those presenting sooner will be at higher risk to manifest evidence of more significant lung injury. Typically these patients will have tachypnea and rales with radiographic evidence of pulmonary edema or, more commonly, soft, diffuse reticulonodular infiltrates. Pulmonary function during the acute phase of the injury shows various combinations of obstructive, restrictive, and diffusion defects (477, 478).

With the resolution of the acute injury, damaged terminal airways rarely can become the sites of formation of excessive granulation tissue, which extends beyond the airway wall into the lumen. Widespread complete or partial obstruction of these airways gives rise to the clinical picture of bronchiolitis obliterans. Within 10 d some affected individuals will note the onset of dyspnea that progresses slowly to significant respiratory distress over the next 10–14 d. More typically, the interval to onset of symptoms is longer (2–4 wk), the onset more abrupt, and the progression more rapid.

These patients are acutely ill with fever, chills, tachypnea, and diffuse inspiratory crackles occasionally combined with expiratory wheeze. They may describe hemoptysis and chest pain. Laboratory studies show hypoxia and may show leukocytosis. Although a wide range of radiographic findings are described for bronchiolitis obliterans (479), the radiographs described in people who have had silo gas exposure are fairly uniform. In most cases there is an initial profusion of 1–5-mm nodules affecting all segments of the lungs, though perhaps more pronounced in the upper lung zones. Nearly all observers note the similarity to miliary tuberculosis. This pattern generally evolves over the succeeding few days, with progressive increase in the size and density of the nodules, which may become confluent in some areas. In reports from the pre-steroid era, this process often did not resolve with supportive therapy and antibiotics but progressed to death from respiratory failure within days. At postmortem examination the lungs were noted to be heavy, congested, and diffusely nodular.

Some workers exposed to an environment with quite high levels of silo gas are likely to note progressive dyspnea within several hours. Subsequently, this may lead to shock and severe adult respiratory distress syndrome (ARDS) due to diffuse capillary injury and the attendant increased permeability. Within 12 h of a serious silo gas exposure, the victim may have either a patchy or diffuse pattern of pulmonary edema apparent on chest radiograph. These individuals will require high fractions of inspired oxygen, often in the setting of mechanical ventilation and positive end-expiratory pressure (PEEP). A further threat to oxygen transport is methemoglobinemia generated by the effects of nitrate upon hemoglobin. Methemoglobin levels as high as 44% have been found in persons dying after a silo gas exposure (471).

Although severe parenchymal injury and ARDS have been described following anhydrous ammonia spills (474, 480), there is no information regarding the frequency of these uncommon occurrences. Patients with severe ammonia exposures are likely to have significant upper airway problems requiring intubation or emergent tracheostomy (474).

Occurrence. There is no good information regarding the incidence of sudden death. These victims are not admitted to the hospital and thus are not accurately recorded in either of the two more recent hospital admission-based studies of silo-related problems (475, 476). As with all agricultural fatalities (481), documentation of acute asphyxia in silos or manure tanks tends to be somewhat haphazard. Of particular concern is the tendency for these events to become multiple with subsequent attempts at rescue by fellow workers and family members (471).

Of the various disease entities that follow inhalation of toxic silo gases, those that manifest evidence of some increased microvascular permeability are relatively common. Recent studies show that mild to severe changes are seen in the majority of individuals presenting for medical care following these incidents. In combining the results of two larger series (475, 476), it appears that almost 80% of hospitalized patients show signs of lung injury with arterial hypoxia and radiographic infiltrates indicative of some element of capillary leak. Only a minority of these (10–20% of all hospitalized cases) developed frank ARDS. It must be recognized, however, that these series describe patients who required hospitalization, sometimes at a referral institution. Thus, they are likely biased toward the more severe (and probably less common) manifestations.

In the only population-based report on silo filler's disease, Zwemer and coworkers (476) studied all hospital discharges in New York state over a 6-yr period. Subsequent chart review confirmed the diagnosis in 20 cases. Based upon the size of the state's farm population, a rate of 5.0 hospitalized cases per 100,000 silo-associated farm workers per year was calculated. This number was stated with the recognition that many, if not most, individuals affected by silo gas exposures are not seen by health professionals. In support of this suspicion are the data reported by Scaletti and coworkers in 1960 (482). They performed sampling in 352 Minnesota silos and found potentially hazardous levels of NO₂ in 42%. In questionnaires from over a thousand farmers, they found that for two consecutive years approximately 10% of farmers reported having seen silo gas in that year and that roughly 30% reported having smelled it.

Clearly these rates are likely to be highest in populations of farmers involved in animal husbandry, where storage of large amounts of forage are common. Although silo gas generation has been reported with a variety of types of feed, this is much more common with corn silage than grasses. Because of this, the occurrence of silo-filling pulmonary injury is considerably higher in September and October, when corn is being harvested and ensiled (475, 476).

Despite a number of case reports describing bronchiolitis obliterans (483, 484), this is probably the least common manifestation of silo gas inhalation. The series of 17 silo gas inhalations from Mayo Clinic (475) and the series of New York state hospital discharge diagnoses each describe one individual suspected of clinically significant bronchiolitis obliterans (476). The majority of the cases are described in the medical literature of several decades ago. The decline in the rate of these reports following the widespread acceptance of corticosteroid therapy for silo gas toxicity suggests that this form of therapy, employed in the acute stages of this injury, may have reduced the incidence of late-stage bronchiolitis obliterans.

Pathogenesis. Injuries following the inhalation of NO₂ relate to its hydration into a highly reactive compound, H₂NO₃. This reaction proceeds relatively slowly, occurring predominantly in the lower and small airways rather than on the mucosa of the upper airway. Thus, the worker experiences some-

what less immediate irritative upper airway symptoms than might be noted with other more soluble chemicals, such as chlorine or ammonia. Because of its limited solubility in upper airway mucosal secretions, relatively greater amounts of NO₂ penetrate to the intrathoracic medium and small airways, where it causes injury to the bronchial epithelium and underlying tissues (485).

With high-level exposures to these gases, victims who escape from the environment are likely to survive long enough to manifest an injury that extends beyond the level of the airways to the alveolar level. A major component of this injury is sustained by the endothelial components of the alveolar wall (485). This results in the leakage of both fluid and osmotically active proteins from the intravascular space into the interstitium and airspace. Animal studies suggest that these types of changes can be seen following only a very brief exposure to NO₂ levels in the 500–2,000 ppm range (486). In exposed humans the extent of this leakage varies with the severity of the exposure, and the clinical manifestations range from advanced ARDS to mild hypoxia with minimal radiographic changes (477).

The situation differs with anhydrous ammonia exposures due to ammonia's remarkable water solubility. In this situation ammonium hydroxide is deposited primarily in the upper airway and reaches the lower airways and parenchyma only with massive exposures. The alkali injury results in a prompt liquefaction necrosis, which permits ever deeper tissue penetration and injury by the alkali. Mucosal surfaces, and particularly the eyes, are susceptible to the most severe injury, although significant dermal burns can also occur in these incidents (469, 474). With ammonia injuries, prominent large-airway damage with edema and mucous plugging, as well as secondary bacterial pneumonias, may be encountered (480, 487).

The bronchiolitis obliterans that is occasionally seen following exposure to NO₂ and other toxic gases appears to result from an exuberant healing phase with formation of granulation tissue that accumulates at the site of the previous bronchiolar injury. In some cases this progresses to a proliferation of this granulation tissue into the airway lumen. This can also be seen in some viral infections, drug reactions, and more recently, in transplant patients (488). Widespread obstruction and/or obliteration of small airways with or without associated peribronchiolar fibrosis occurs as this reaction progresses (488, 489). This occurrence is delayed, often becoming manifest 2–6 wk following the injury incident.

Reports of ammonia injury describe similar loss of small airways. In the one autopsy report of this phenomenon, the nodularity noted following NO₂ exposure was not present at 2 mo. The small airways appeared either normal or virtually obliterated by fibrous tissue (490).

Outcome. Those presenting with evidence of frank pulmonary edema or arterial hypoxia (Po₂ < 60 mm Hg) are those at highest risk for serious complications and death. The vast majority of workers living long enough to see a physician will survive, although hospitalization for several days or more is common. Corticosteroid therapy has been used in nearly all cases of severe silo filler's disease in the literature since 1950. Though never systematically studied, the general impression is that steroids are beneficial, particularly when administered very early (475, 477). The long-term prognosis for treated patients is remarkably good, with few reporting problems of continued dyspnea, cough, or airway hyperreactivity (475, 476). Despite this, some have reported minor long-term abnormalities of pulmonary function (486, 487). In the Mayo Clinic series, seven of 17 exposed workers had airway symptoms with-

out hypoxia or infiltrate, and one additional had hypoxia with a clear radiograph. Over the long term, all of these had normal recovery, although the hypoxic patient experienced several weeks of exertional dyspnea and several months of airway hyperactivity (475). Another report describes airway symptoms without evidence of other injury in 18 of 23 exposed persons. These individuals subsequently had no long-term ill effects from this injury (477). In reports from other settings, this injury apparently seldom leads to any significant permanent effect (490).

Since the general recognition of the efficacy of steroid therapy for bronchiolitis obliterans following silo gas exposure, it is usually employed earlier (477) and significant residual symptoms or pulmonary function abnormalities appear to be uncommon. Of key importance is the awareness of silo filler's disease as a potential cause of delayed-onset respiratory illness with nodular infiltrates in the late summer and fall.

The prognosis is not so promising for victims of massive anhydrous ammonia exposures, presumably because of the intensity of the large and medium airway injury. There are numerous reports of long-term complications following these injuries. These include bronchiectasis, reactive airways dysfunction syndrome (RADS), bronchiolitis obliterans, and chronic airflow obstruction (491).

Chronic Airway Disease and Pulmonary Mortality

There is evidence that agricultural exposures are associated with the development of chronic airway disease, as distinct from asthma and asthma-like reversible airway changes. A distinction should also be made between chronic respiratory symptoms (e.g., chronic bronchitis and/or dyspnea) and evidence of chronic airflow limitation measured by spirometry.

Chronic airflow limitation results from both airway obstruction and loss of elastic recoil in the parenchyma (492). The principal early pathologic component is an inflammatory response in the peripheral airways (493). Agricultural exposures suggested as potential initiators of the inflammatory process in the airways, ultimately leading to chronic airway disease, include dusts from cereal grains, animal feed, and soils; gases and fumes from such sources as manure and disinfectants; and components of micro-organisms, such as endotoxins and fungi. This inflammatory response can lead to fibrotic lesions in the parenchyma and airway walls, to inflammatory thickening of airway walls, or to emphysema. Immunologically mediated inflammation may also lead to chronic airflow obstruction (e.g., chronic asthma), which is discussed elsewhere in this review.

Considerable evidence exists to associate chronic airflow limitation with early mortality from respiratory disease (494–496), and the evidence that agricultural workers may be at increased risk for respiratory mortality will be reviewed here. In this context, it is not always possible to distinguish between various causes for respiratory mortality; there are causes other than asthma and interstitial pulmonary diseases.

Increased prevalence rates for chronic bronchitis have been reported in farmers and agricultural workers in many parts of the industry (Table 3.3). The majority of study designs have been cross-sectional studies or surveys.

Mailed questionnaire surveys among farming populations have reported chronic bronchitis symptom rates varying from 7.5% among Finnish farmers (497) to 23% among grain and cattle farmers from Manitoba, Canada (498). The Finnish study included a repeat survey three years later and reported an incidence rate of 2% per year for new chronic bronchitis symptoms among those free of symptoms at the initial survey. Neither of these surveys included comparison groups.

Relatively low symptom rates were reported among Hispanic farm workers in the citrus, tomato, and grape industries (499). FVC was reported to be significantly higher than predicted values overall, but when compared to citrus and tomato crop workers, grape workers had significantly lower values for FVC.

Rates for reported chronic bronchitis also tend to be low among farmers who are predominantly grain growers but somewhat higher among livestock and dairy producers (compared to rural community control groups) (500, 501). Dosman and colleagues (500) also reported significantly lower FVC, FEV₁, FEV₁/FVC, and maximum midexpiratory flow rate (MMFR) in farmers compared with control subjects, with differences as pronounced in young (< 35 yr old) as in older farmers.

Manfreda and associates (502) did not find significant differences in symptoms or pulmonary function between Manitoba grain farmers and nonfarmers, although significant reductions in spirometry were seen in the small subset engaged in raising dairy animals or pigs rather than grain farming (502). Similarly, Heller and coworkers (503) found no differences in rates for chronic bronchitis comparing farmers and farm workers to control subjects from local industry, although FEV₁ was reduced, especially among dairy farmers and silage workers (503). Higher rates for chronic bronchitis were also reported among Yugoslavian cattle breeders (504) compared with other communal farm workers.

Studies confined to dairy farmers tend to indicate consistently higher symptom prevalence rates. Babbott and colleagues (505) reported chronic bronchitis rates of 30% and 16% among smoking and nonsmoking farmers (*n* = 198), respectively, compared with 21% and 10% among non-mineral industry comparison workers (*n* = 516); rates for dyspnea were even higher. Significant differences in lung function were seen for nonsmokers only. Lower lung function and higher prevalence of chronic bronchitis symptoms were found by Dalphin and colleagues among dairy farmers than among control subjects who were nonsmokers (506). These investigators also found farmers with chronic bronchitis more likely to have obstructive pulmonary function and dyspnea than control subjects, more likely to have a history of previous farmer's lung disease, and a history of cough and dyspnea 4 to 8 h after handling moldy or dusty fodder. Similar findings linking chronic obstructive pulmonary abnormalities and previous history of farmer's lung diseases have also been reported by Lalancette and colleagues (507). These investigators studied 33 farmers (of whom 27 had never smoked) with prior farmer's lung disease and found chronic bronchitis among 24%, obstructive pulmonary abnormalities in 39%, and emphysema in 27% (including seven never-smokers), but restrictive abnormalities in only one subject.

Several studies have focused on animal confinement farmers in particular (Table 3.3), and most indicate increased prevalence rates for chronic bronchitis, but not generally for dyspnea, when compared with other farmers. The findings appear to be consistent in both poultry confinement (508) and swine confinement (509–514). Chronic bronchitis prevalence rates are remarkably consistent at approximately 25–35% across studies. There has been only one exception: one study of hog farmers in the Netherlands, in which chronic phlegm production was reported to range from 2% at farms with fattening barns only (no breeding) to 12% in breeder barns (513).

Associations between pulmonary function test results and swine confinement work are more variable. Several studies in which average values for spirometry variables have been compared between confinement farmers and other farmers have

TABLE 3.3
STUDIES OF ANIMAL CONFINEMENT FARMING

Reference No.	Population	Method Details	Respiratory Symptom Rates				Pulmonary Function Test Results			
				Conf.	Non-conf.	p Value		Conf.	Non-conf.	p Value
Donham and coworkers, 1984 (509)	Swine confinement, Iowa	24 conf. farmers					(% pred.)			
		24 non-conf. farmers	Chronic cough	33%	8%	0.06				
		ATS questionnaire	Chronic phlegm	58%	21%	0.01	FVC	101.7	97.3	NS
		spirometry	Dyspnea	21%	21%	NS	FEV ₁	109.0	101.0	NS
Holness and colleagues, 1987 (510)	Swine confinement, Ontario, Canada	53 hog farmers		Conf.	Non-conf.	p Value		Conf.	Non-conf.	p Value
		43 non-hog farmers	Chronic bronchitis				(% pred.)			
		ATS questionnaire		26%	7%	< 0.05	FVC	98	95	NS
		spirometry	Dyspnea	23%	12%	NS	FEV ₁	95	94	NS
							FEV ₁ /FVC	97	99	NS
							No significant relationship between PFTs and current or cumulative dust			
Bongers and associates, 1987 (513)	Swine confinement, The Netherlands	160 conf. farmers	Farm: breeder/fattener/combined			p Value	FEV ₁ –90 ml versus expected, p < 0.05			
		ATS questionnaire spirometry	Chronic phlegm	12%/2%/4%		< 0.05	MMFR –700 ml/s versus expected, p < 0.05			
Iversen and Pedersen, 1990 (514)	Swine confinement and dairy farmers, Denmark	1,175 farmers (181 with spirometry)		Conf.	Non-conf.	p Value	No PFT diff. by farm type or h/d in confinement buildings			
			Chronic bronchitis				Conf.	Non-conf.	p Value	
				32%	17.5%	< 0.05	(% pred.)			
							FEV ₁	101	104	NS
Leistikow and colleagues, 1989 (508)	Poultry confinement, U.S.	156 egg farmers	Prevalence rate				FEV ₁ : 12 ml lower FEV ₁ for every year of pig farming (< 0.05)			
		Mailed questionnaire	Cough	48%						
			Phlegm	35%						
			Dyspnea	26%						
Donham and coworkers, 1990 (551)	Swine confinement farmers, Iowa	207 conf. farmers		Conf.	Non-conf.	Nonfarm	p Value			
		158 non-conf. farmers	Chronic cough	20%	14%	7%	< 0.01			
		150 nonfarm controls	Phlegm	25%	11%	10%	< 0.01			
		ATS questionnaire	Work-related cough	84%	73%					
		spirometry	Phlegm	67%	52%					
Morris and associates, 1991 (333)	Chicken catchers, confinement barns, U.S.	59 chicken catchers		Chicken catchers	Predicted	p Value		Chicken catchers	Predicted	p Value
		6 loader operators	Chronic Cough	32.2%	15.3%	0.05	FVC	4.60	4.83	0.04
		MRC questionnaire	Phlegm	39.0%	13.6%	< 0.01	FEV ₁	3.54	3.75	0.05
		spirometry	Dyspnea grade 3	20.3%	6.8%	0.06	FEV ₁ /FVC	76.8%	78.9%	0.06
				Swine	Grain					
			Chronic bronchitis	28%	17%		(% pred.)			
Zejda and colleagues, 1994 (511)	Swine confinement, Saskatchewan, Canada	301 conf. farmers					Swine	Grain		
		Grain farmer controls					FEV ₁	99%	102%	
		ATS questionnaire					FVC reduced with increasing h/d in confinement barns			
		spirometry					No spirometry differences among groups			
Choudat and coworkers, 1994 (512)	Swine confinement and dairy farmers, France	102 conf. farmers		Conf.	Non-conf.	Nonfarm	p Value			
		51 dairy farmers	Cough	13%	10%	4%	< 0.05			
		81 nonfarm controls	Phlegm	10%	17%	8%	NS			
		MRC/IUAT questionnaire	Dyspnea	12%	15%	17%	NS			

Definition of abbreviations: ATS = American Thoracic Society; conf. = confinement; non-conf. = non-confinement; MMFR = maximum midexpiratory flow rate; MRC = Medical Research Council; PFT = pulmonary function test.

not found reduced lung function values despite increased chronic bronchitis rates among confinement workers (509, 510, 512, 514). Similarly, Bongers and colleagues (513) did not find significant functional differences among breeder, fattener, and combined farmers (n = 160 total) but did find overall significant reductions in FEV₁ (–90 ml) and MMFR (–700 ml/s) compared with expected values (p < 0.05).

Exposure–response relationships were demonstrated by Iversen and colleagues (514) among Danish swine confinement farmers (with a 12-ml reduction in FEV₁ associated with each year of hog farming) and by Zejda and colleagues (511) among Canadian swine confinement farmers (with FVC sig-

nificantly reduced in association with increasing hours per day worked in the confinement building). Among poultry confinement workers, Morris and colleagues (333) found significant decrements of approximately 200 ml for FEV₁ and FVC compared with predicted regional values for nonexposed blue-collar workers, with the difference limited to those workers with more than five years of employment.

Animal confinement exposures appear to be associated primarily with acute (cross-shift) pulmonary function changes; cross-sectional studies of farmers in this relatively young industry (less than two decades in most areas) may not yet show whether chronic impairment of pulmonary function will be a

consistent outcome for these farmers. Recently, Schwartz and colleagues (515) found that cross-shift change in lung function and endotoxin level both correlated positively with accelerated longitudinal decline in FEV₁ in swine confinement operators. One published study used a nonfarming comparison population (333) and found lower pulmonary function in the confinement farmers compared with expected. Future results from prospective studies in which both farming and nonfarming control subjects are included may shed further light on this issue.

Two studies of tea production workers have reported high rates for chronic bronchitis. Uragoda (516) found chronic bronchitis rates of 23% in smokers and 33% in nonsmokers among 125 tea-processing workers in Sri Lanka. A comparison population was not included, but the prevalence of chronic bronchitis in the area was reportedly low. Castellan and associates (517) also found high rates of chronic cough and phlegm in U.S. herbal tea production workers, with rates increasing in association with increasing levels of dust exposure (41% and 73% in low and high dust-exposed smokers, respectively, with the rates of 0% and 40% for nonsmokers). Spirometry values did not differ by exposure level in these workers, but tenure was very short.

Chronic respiratory effects of grain dust exposure among grain elevator workers have been recently reviewed in detail (518). Sixteen cross-sectional prevalence studies from 1941–1986 were evaluated and almost all found greater symptom prevalence rates (for cough, phlegm, dyspnea, and wheeze) and lower levels for FEV₁ and FVC in grain workers than in comparison groups, after taking smoking and age into account.

Longitudinal follow-up of Canadian grain elevator workers in Ontario (519) and British Columbia (404, 518, 520, 521), also showed greater rates of decline for FEV₁ among grain elevator workers than among control workers after 2.5 to 3 yr of follow-up, but no differences by 12 yr of follow-up (518). However, those who left between surveys were more likely to be symptomatic, indicating selective loss of these symptomatic workers over the follow-up period.

Exposure–response relationships for grain have been reported by several investigators. Corey and colleagues (522) found a significant relationship between flow rates and dust level in Ontario grain elevator workers. Enarson and colleagues (523) found grain workers with the largest FEV₁ decline over a 6-yr period were significantly more likely to be employed in high-dust jobs.

Huy and colleagues (521) used an industry-specific job exposure matrix to compute cumulative and average grain dust exposure values for 454 Vancouver grain elevator workers and found significant exposure–response relationships between average dust exposure and chronic phlegm, dyspnea, FEV₁, and FVC. Among retirees (520), 36% were found to have an abnormally low FEV₁, compared with 19% of civic workers ($p < 0.05$), with rate of decline in FEV₁ (from 1978–1992) significantly associated with acute cross-shift FEV₁ drop in 1975 (431).

Studies of animal feed workers, also exposed to various grain dusts, show results similar to those seen among grain elevator workers. Studies in Yugoslavia showed increased chronic respiratory symptoms in smokers and nonsmokers and reduced FVC and FEV₁ levels compared with control workers (524, 525). A Dutch study (526) did not find similar increases in respiratory symptoms among 315 animal feed workers, but a strong association was seen between decreased FVC, FEV₁, and MMFR levels and increased dust and endotoxin exposure levels.

In a recent comparison study of Dutch grain elevator and animal feed workers and Canadian grain elevator and loading workers, Peelen and colleagues (527) found exposure–response relationships of similar magnitude for current dust exposure and years employed among these populations when exposure sampling methods and analytic approaches were harmonized.

Population-based mortality studies of farmers have universally relied on usual or last job rather than taking employment history into account, and do not account for the healthy worker effect or for differences in smoking rates. Among 15,000 Norwegians, Zeiner-Henriksen (528) found all-cause mortality to be considerably lower among rural, compared with urban, dwellers. In contrast, white male California farm laborers and foremen aged 20–64 yr were found to have significantly higher rates of respiratory disease mortality than farm operators (529). The farm laborer rates, however, were not different from rates in other nonfarm, nonmine laborers. The deaths were reported to be predominantly from pneumonia. A similarly designed mortality study among white male farm laborers and managers in Iowa did not find rates to be significantly different among these same categories of workers (530).

Mortality studies of California farm workers and owner/managers (531, 532), found significantly elevated proportionate mortality ratios and standardized mortality ratios among male farm workers for all respiratory disease and for pneumonia. Lung cancer mortality was decreased among these farming populations, suggesting that the observed effect was not due to differences in cigarette smoking prevalence.

Similarly, increased mortality from respiratory disease was reported among Finnish male farmers (533) with the increase greatest on small farms ($p < 0.05$) and higher for farmers who did not raise animals. Finnish female farmers on small farms also had greater respiratory mortality disease rates (533) but did not have increased rates overall (534). A proportional mortality study of deaths in Switzerland (535) also found increased mortality among the farming population for all lung diseases, for bronchitis and asthma, for asthma alone, and for pneumoconiosis due to organic dust.

A cooperative study of mortality among agricultural workers in eight member countries of the European community found large between-country differences in respiratory disease mortality (536). Agricultural employers had a higher respiratory disease mortality than men of equivalent social class in England, Wales, and France; a similar pattern was observed for agricultural employees in France. While this study identified apparent areas of increased respiratory disease mortality associated with agricultural work, the large number of comparisons, limitations in exposure classification, and differences between countries limit the significance of these findings.

Hospital admission rates for respiratory disease were not increased among more than 60,000 Swedish farm manager/owners compared with the general economically active population (537), nor was there any increase in spells of sickness due to bronchitis from insurance records among British agricultural workers (538). In the latter study, it is unlikely that the outcome measured was sensitive enough to detect chronic morbidity if it had been present. Workers' compensation claims for respiratory disease in Washington state were, however, increased among farm workers compared with other workers during 1982–1986 (539).

Two population-based studies of retired workers have also indicated increased respiratory morbidity among agricultural workers. From a Dutch study of residents of Zutphen, among 824 men aged 65–84 yr, increased chronic bronchitis was seen in association with agricultural work (540). Among a random

sample of French residents over age 65 ($n = 3,777$), the occupational groups with the highest prevalence rates for dyspnea, grade 3 or greater, were farm workers (37% with dyspnea) and farm managers (32%), compared with 31% among unskilled blue collar workers, 25% among skilled blue collar workers, and 15% among teachers (541).

These studies, together with the study of retired grain workers discussed previously, provide strong evidence that some workers engaged in agriculture or exposed to agricultural products will experience chronic respiratory symptoms and fixed airflow obstruction as a direct result of their employment.

Areas for Future Research

1. Determine the prevalence and incidence of upper airway diseases, asthma and asthma-like syndrome, and chronic airflow limitation in various agricultural environments;
2. Identify exposures, agents and cofactors responsible for various airway diseases in the agricultural environment and standardize methods of environmental assessment and monitoring;
3. Further study the basic mechanisms responsible for various airway diseases and the early markers of these diseases; for example, upper airway disease as a marker of lower airway disease and asthma-like syndrome as a marker of chronic airflow limitation;
4. Study genetic and environmental exposures (including cofactors such as environmental tobacco smoke and viral infection) and their interactions in the pathogenesis and progression of airway diseases;
5. Identify the role of environmental and pharmacologic intervention in the management of airway diseases in the agricultural setting; and
6. Design and evaluate the effectiveness of measures to reduce exposure and other control methods suitable for the agricultural setting to reduce morbidity; identify the most effective educational strategies to enhance the current involvement of practicing physicians in recognizing, treating, and preventing airway diseases in the agricultural setting.

4. INTERSTITIAL LUNG DISEASE

Introduction

This section covers three syndromes or diseases affecting the alveoli or interstitium of the lung: organic dust toxic syndrome (ODTS), hypersensitivity pneumonitis (HP), and interstitial fibrosis from mineral dusts.

While ODTS is not an interstitial lung disease, it is presented in this section because of the overlap in both exposures and symptoms between ODTS and HP. Some of the dusts causing ODTS cause similar symptoms and signs in farmers or agricultural workers with HP, which is characterized by an interstitial lymphocytic pneumonitis. (The transient neutrophilic alveolitis of ODTS is not a true parenchymal disease.) Interstitial fibrosis stemming from exposure to inorganic or mineral dusts represents a true inflammatory and fibrotic reaction of the lung interstitium.

The ODTS designation was proposed at a conference in 1985 (552). The name has been criticized (553), and others have been proposed (554, 555). However, the designation is retained in this document in order to avoid confusion. It is hoped that further knowledge about agents and effects may make it possible to suggest names that are more descriptive of the condition (or possibly conditions) now called ODTS.

HP in agricultural workers is often called "farmer's lung," but this term has also become associated with conditions (no-

tably, ODTS), that are *not* HP. Farmer's lung (in the narrow, specific sense) is one of the most prevalent forms of HP; however, HP is only one of many farm-related lung diseases. Thus, the term "farmer's lung" is necessarily confusing and needs to be reconsidered. A more appropriate term, which will be used here, is "farmer's hypersensitivity pneumonitis" (FHP). Although FHP occurs less often than other farm-related respiratory illnesses (e.g., ODTS, chronic bronchitis, and asthma), the disease is of major importance because of its severity, in terms of both permanent lung damage and psychosocial impact. Half of all FHP patients abandon farming because of their disease, and a third have permanent lung sequelae.

The possibility that silica or other inorganic silicates in farm dusts in certain areas and stemming from certain farm activities might cause interstitial lung disease is a new concept that will be addressed here.

Organic Dust Toxic Syndrome

ODTS is an acute inflammatory condition affecting airways and alveoli. It is caused by the inhalation of one or more agents in organic dusts. With heavy exposure, it includes such nonspecific symptoms as fever and malaise. ODTS occurs in subjects without evidence of hypersensitivity, and with high enough exposure concentrations all exposed individuals may develop the syndrome.

Systemic symptoms occur if the exposure is of sufficient intensity. Symptoms usually have a delayed onset and peak 4–8 h after exposure. ODTS is often seen following inhalation of mold dusts containing large numbers of microorganisms. In immunocompromised subjects, the result may be invasive growth of fungi (556), but that disease is not ODTS. (Fatal invasive growth of *Aspergillus* has been reported in two farmers exposed to mold dusts. Both had a genetic disease affecting the respiratory burst of phagocytic cells, and the name microgranulomatous aspergillosis has been suggested for this rare disease [557, 558].)

An environment causing ODTS in nonsensitized subjects may also cause symptoms in patients with HP, since the latter are often hypersensitive to mold dusts. Febrile episodes in farmers with HP should not be designated ODTS. Establishing whether a farmer with acute symptoms of fever and malaise after inhalation of mold dust has experienced an attack of ODTS or has hypersensitivity to some component of the dust can be difficult.

The degree of hypersensitivity associated with HP is not known but may be limited. In one experiment, previously nonsensitized subjects were exposed, together with farmers suffering from FHP, to the moldy hay dust associated with the disease. The diffusion capacity (DL_{CO}) fell by 26% of predicted in the farmers with FHP and by 15% in the healthy subjects. The FHP farmers had a temperature increase of 1.3°C , the referents 0.7°C . The neutrophil response in peripheral blood was greatest in the referents (559). Thus, it is difficult to use evidence of hypersensitivity obtained from the clinical history as an aid in the differential diagnosis.

Farmers with FHP have interstitial pneumonitis and effort dyspnea. The presence of such changes both before and after the acute febrile attack therefore suggests FHP rather than ODTS. Febrile reactions also occur in environments such as swine confinement work or in grain elevators, where there is relatively little exposure to fungal spores and where the prevalence of FHP is low or nonexistent, rendering a diagnosis of ODTS more certain.

All farmers are exposed to organic dusts, and some may suffer from coexisting febrile symptoms due to unrelated infectious or other diseases. A salient characteristic of ODTS is

its appearance following the inhalation of dusts in quantities that are clearly in excess of normal exposure, a criterion that therefore should be considered in the diagnosis.

Exposures. In countries whose main agricultural activity is dairy farming, most episodes of ODTs are related to exposure to dusts from moldy farm products (560). Such events usually occur after inhalation of very large numbers of spores from fungi and actinomycetes (561, 562). Thus, the estimated dose of inhaled spores associated with ODTs was on average about 2.3×10^{10} spores, more than 100 times higher than the dose measured in reference farms when "worst case" materials were handled. The number of inhaled spores was about 80 times the number of alveoli in human lungs and three to five times the number of alveolar macrophages, representing a considerable challenge to the immune system. The dose associated with ODTs was about 10 times higher than the dose associated with FHP—but a single exposure caused ODTs, while the development of FHP required repeated exposures over several weeks. The composition of spores varied, depending on the materials studied. Both actinomycetes and fungal spores such as *Aspergillus*, *Penicillium*, *Rhizomucor*, and *Wallemia* are common (562–564). It is not currently possible to evaluate the relative potency of different spores—if indeed spores, and not other agents also present in the dusts, are responsible for acute toxic symptoms.

A high cumulative prevalence of ODTs episodes has also been reported in swine farmers (551). The dust in swine confinement buildings usually contains relatively few fungal spores and actinomycetes but does contain large numbers of bacteria, mostly gram-positive organisms (565, 566). They may derive largely from dried fecal material. The endotoxin levels are sometimes high and, in addition, ammonia and other gases may reach high levels. The level of endotoxin, rather than total dust, correlates with over-workshift changes in FEV_1 (331, 567) and with signs of ODTs (568).

Many farmers handle grain, and most grain-related episodes of ODTs are associated with the handling of moldy grain (560). Handling of nonmoldy grain may also cause ODTs, as reported by grain handlers exposed to excessive dust levels in grain silos (569, 570). Inhalation of aqueous grain dust extracts (containing endotoxin) produces airway inflammation (438). Endotoxin-free extracts of grain dust induce chemotactic activity and also activate epithelial cells (571), suggesting that although endotoxin may be the chief cause of inflammation, several components in normal grain dusts may contribute to inflammatory activity.

Although the agents causing ODTs have not been fully identified, it would be useful to identify markers of exposure, which might predict symptoms better than dust levels do. A few such markers have been proposed, including endotoxin and total spore counts. Other potential markers include ergosterol, correlating with the fungal cell wall mass (572), and muramic acid (573), correlating with the mass of mainly gram-positive bacteria. They are determined chemically on dust samples, and a measure of the mass of gram-negative bacteria can be obtained by measuring long-chain 3-OH fatty acids (574). The possible usefulness of such measures requires further evaluation.

Another unresolved issue is whether the more relevant measure of exposure is the quantity of agent in the inhaled fraction or the quantity in the respirable fraction of dust. The respirable fraction of swine farm dust is about 4% of the inhaled quantity (567) but could possibly induce a disproportionate share of the total response.

Occurrence. The incidence of ODTs (as well as that of FHP) varies with climatic conditions and farming activities. Rainy

summers and hay baling are associated with increased incidence of FHP (575, 576). In northern countries, the combination of very short summers (sometimes too short for the maturation and drying of barley in the fields) and inadequate resources to dry harvested material often results in heating and episodes of ODTs (560, 578). In one study, the incidence of hospital-verified cases of FHP was 2–4/10,000 farmers per year; the corresponding figure for definite febrile reactions associated with heavy exposure to farm dusts was about 50 times higher (579). The cumulated prevalence (ever experienced) of fever associated with exposure to farm dusts is on the order of 10–15% of many farming populations (577–579). Some reports stating a high prevalence of farmer's lung based on symptoms questionnaires may actually have included a large proportion of cases of ODTs.

Clinical features. One of the first accounts of ODTs dates from 1949 (580). It illustrates several features of the condition (author's translation):

On the 6th of October, 1949, a whole team of 12 male threshers fell ill during the threshing of moldy oat. The work had commenced at 8 A.M. but had to be stopped at 6 P.M., when 1/2 hour of work remained, since all but one man had fallen ill. . . . All fell ill 6–8 hours after the start of work, with shivering and a strong sensation of illness. They felt a chest oppression, as if the lungs did not meet the demand. Usually there were pronounced pains in arms, legs, and the lumbar region; malaise; and, in some cases, vomiting. Some had slight symptoms from the nose and throat, a little cough but no expectorations. In spite of a strong sensation of disease and fever between 39–40° C, the patients had few clinical signs of distress. Auscultation was negative except in three cases, where slight crepitating rhonchi were heard. Chest radiographs were only positive in 5 of 21 cases and showed thin, streaky spots in the middle field, most pronounced in the right lungs. The symptoms had in most cases disappeared within a few days, but a certain sense of malaise and fatigue may remain for rather a prolonged period.

The contrast with the symptoms of hypersensitivity pneumonitis is illustrated by comparing this account with the 1932 report of FHP by Campbell (581). He describes five patients with severe symptoms who fell ill in the period April–June 1932, when the last of the rain-damaged hay from the previous year was used, causing dense clouds of white dust. In the author's words:

The onset was very similar in each case: a noticeable shortness of breath for some weeks previously whilst carrying out the normal routine, including work with hay, until a climax was reached by some specific act (for example clearing out the remainder of the hay from a barn) and within thirty-six hours the man was extremely dyspnoeic (a step or two being impossible), distressed, and cyanosed, and appeared almost in extremis.

On examination three weeks later:

At this time dyspnoea was still severe, even taking off of a pajama jacket causing distress, and there was still some cyanosis. Cough was never a very troublesome symptom and was almost unproductive. . . . Two men mentioned tightness or oppression across the chest. Temperature was mildly febrile at onset, but soon returned to normal.

Clinical examination revealed dry rales and sibilant rhonchi over most of the lungs, and chest X-ray showed a generalized fine, granular stippling.

Several reports describe clinical findings when "naive" subjects, with no previous experience of farmwork, were exposed to different agricultural dusts (559, 569, 570, 582–586). The dose has often been excessive, representing situations that agricultural workers may encounter only occasionally. Most exposed naive subjects react to these dusts or to isolated compo-

nents of the dusts, but it is possible that atopic subjects are more sensitive than nonatopic subjects (585, 586).

Fifteen healthy volunteers were exposed to dusts in a chamber, while tossing a mixture of moldy hay samples for 1 h (559). Seven developed chills and a slight temperature rise. There was a pronounced granulocytosis in peripheral blood. Vital capacity fell by 5.5% and the diffusion capacity for carbon monoxide by 15 percent (DL_{CO} , percent of predicted value). Farmers with no history of FHP participated in the same exposure and reacted similarly.

In one study, farmers with a history of ODTS in connection with the unloading of silo-covering material had increased alveolar-arterial gradient in oxygen tension but relatively normal oxygen tension and saturation in arterial blood. Total lung capacity was 84% of predicted and FVC was 92% of predicted when examined acutely. The DL_{CO} was normal. Peripheral blood showed leukocytosis due to increased neutrophils (587). Farmers exposed to large amounts of dusts from moldy farm materials and with symptoms of ODTS, but without evidence of HP, exhibit a marked increase in granulocytes in bronchoalveolar (BAL) fluid when examined acutely (588). If the BAL is postponed 7 d, a considerable lymphocytosis is observed in BAL (sixfold increase in total cells, 70% lymphocytes) (589); at follow-up 1 mo later, there was still a mild lymphocytosis (588). The significance of the latter finding is uncertain, since many symptomless farmers have a mild lymphocytosis in the absence of a history of FHP (590–592).

Healthy nonatopic volunteers were exposed to swine confinement building dusts while weighing swine for 3 h. Inhalable dust concentration was in the range of 5–25 mg/m³ and the endotoxin concentration 0.1–1.3 µg/m³ (562, 583). Generalized symptoms included chills and fever in some. Peak expiratory flow (PEF) decreased by 10% during exposure but tended to return to normal within a day. Bronchial responsiveness increased in all subjects. In BAL fluid, 24 h after exposure, there was a fourfold increase in total cells, a 75-fold increase in neutrophils, a doubling of alveolar macrophages, and approximately a threefold increase in lymphocytes; eosinophils were also significantly increased. Lavage fluid albumin and fibronectin increased. The acute phase cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) increased in peripheral blood 3–6 h after the start of exposure (568), and 24 h after exposure there were clear increases in the acute phase proteins orosomucoid and C-reactive protein (583).

Up to 2 h of exposure to grain dusts (84 mg/m³) caused symptoms in all 12 subjects, comprising symptomatic grain workers and referents (570). The symptoms lasted longer than 24 h in some, but all recovered within 36 h. The most common complaints were influenza-like symptoms, including malaise, myalgias, fatigue, feverishness, chills, and facial flushing. FEV decreased by 20% or more in nine. The maximal decrease in FEV₁ was observed immediately after exposure. Maximal expiratory flow at 50% of vital capacity was still decreased at 24 h. Lung resistance increased, and dynamic compliance decreased, immediately after exposure. In 10 subjects, peripheral blood leukocytosis, mainly due to increased neutrophils, was observed. Body temperature rose above 37.8°C in half the subjects.

Similar changes were observed in six naive subjects exposed to grain dust with a total dust concentration of 583 mg/m³, and 31 mg/m³ in the respirable fraction, for 2 h (569). During exposure, there were upper respiratory, skin, and eye irritation along with vague chest discomfort. Four subjects noted malaise, myalgia, irritability, slight nausea, and headache at approximately 6–8 h, with persistence of the chest discomfort and slight pyrexia. There were no changes in serum comple-

ment levels. FEV₁ and FVC were reduced to a numerically similar extent (average, 13%).

Inhalation of an extract of grain dusts caused a neutrophil inflammation in the airways of nonatopic grain handlers. BAL fluid had increased levels of the cytokines TNF-α, IL-1β, IL-6, IL-8, and the IL-1 receptor antagonist (438).

Natural history. ODTS is a self-limiting disease that rarely extends beyond 36 h; in most cases, there is no need for pharmacologic treatment. The prognosis is excellent. Extensive physiologic examinations of subjects who have experienced attacks of ODTS, including measurement of gas exchange during heavy exercise, have revealed no sequelae of rare episodes of ODTS (579).

The incidence of acute febrile reactions in a farming population is much higher than the incidence of hospital-verified FHP (577, 578), and most recover completely within a short time. There is thus a high probability that reaction to a massive farm-dust exposure represents a toxic rather than an adaptive immune reaction. If the patient was in good health prior to the episode, and has completely recovered within a week, it is probably a case of ODTS.

ODTS is associated with extreme exposures, such as removal of moldy material used as cover on silos or removal of material that has by accident “taken heat” and cannot be used as animal feed (560). Such accidents are often due to inadequate techniques of feed conservation. Many patients with a history of ODTS have had several attacks over the years. Repeated acute attacks may therefore reflect poor conservation technique rather than sensitization to mold antigens. On the other hand, poor technique and unawareness of the danger of inhaling mold dust increase the risk of contracting FHP. It is also possible that chronic bronchitis and chronic airflow limitation may result from exposure to high concentrations of moldy farm dusts (593).

If FHP is induced by repeated exposures to high concentrations of mold dusts, an episode of ODTS induced by mold dusts may represent a step toward HP (562, 594). Many cases of ODTS, however, occur in the absence of mold dusts and in environments where FHP is rare or nonexistent. In clinical practice, the two conditions are distinctly different.

Exposure to very high concentrations of fungal spores may cause a condition with a different time course from that typically seen in ODTS. Emanuel and coworkers (595) described the clinical course of ODTS in farmers who had cleaned the moldy materials placed on top of silos. The duration of their illness ranged from a few days to 4 wk. In one farmer, exposure lasted for about an hour. Chills, fever, and dry, irritating cough began in the evening. Symptoms increased the next morning and included extreme malaise and weakness, with the cough increasingly distressing.

Two children were also exposed to a lesser extent and became ill with fever and cough. The farmer was seen 24 h after exposure. Chest examination revealed numerous crepitant rales, but there was no wheezing, cyanosis, or other evidence of bronchospasm. Chest roentgenogram on admission to the hospital revealed reticular and fine nodular densities scattered throughout the lower two-thirds of both lung fields, compatible with interstitial pneumonitis. Findings on previous chest roentgenograms had been normal.

The next day, 48 h after exposure, bronchoscopy and pulmonary biopsy were performed. The tracheobronchial tree was markedly hyperemic. There was a multifocal acute process, which appeared related for the most part to the terminal bronchioles, alveoli, and interstitial areas. Most of the bronchioles were filled with an exudate composed of neutrophils and numerous histiocytes. The exudate extended into the sur-

rounding interstitial tissues as well as into a number of the alveoli, with extensive consolidation in some areas. Aggregates of lymphocytes were also seen.

A large number of stained organisms, generally ovoid in shape, were seen, measuring 1–9 μm in their greatest diameter. They were located in the areas of acute inflammation reaction, as well as in the bronchioles. Culture of the lung biopsy material demonstrated at least five different fungi, including one of the genus *Fusarium* and one of the genus *Penicillium*.

The patient was followed, and fever and cough gradually improved. Chest radiographs showed continued clearing over the next few weeks.

This patient thus had a history of a protracted course of disease with persistence of culturable fungal material. There was no evidence of invasive growth of fungi. Other case reports suggest that some subjects with a history of ODS may have a period of illness that lasts for several days after having inhaled mold dusts (560, 589, 596).

Pathogenesis. Originally, no distinction was made between acute febrile symptoms and FHP. The hypothesis that “acute” farmer’s lung could be an immune-complex mediated disease (597–599) offered a unified explanation for the two conditions. Thus, for a long period of time, acute symptoms following exposure to moldy farm products were believed to be caused by immune complexes formed between inhaled soluble antigens and precipitating antibodies present in sensitized patients with farmer’s lung disease.

Precipitin-negative farmer’s lung was, however, described in 1974 by Edwards and associates (600), who suggested that indirect activation of complement may have caused acute symptoms. This mechanism does not require prior sensitization. The toxic nature of ODS was also appreciated in 1975 by Emanuel and colleagues (595), who described 10 patients who had been very ill from removing excessively moldy materials on top of silos.

Studies in farming populations revealed that the acute symptoms often occurred in conditions of massive exposure, where all exposed were afflicted in proportion to exposure (579, 587, 601). The toxic nature is demonstrated from the classic description of an episode involving college students who attended a fraternity party where there was dense airborne dust from straw that had been placed on the floor (602). Of 67 students present, 82% became ill with symptoms such as myalgia, cough, and low-grade fever. Symptoms appeared within 1.3 to 13 h; duration ranged from 4.5 h to 7 d. Serologic investigation did not reveal a viral cause.

In other studies, previously nonexposed subjects were exposed to moldy hay dust (559) or pig farm dusts (562, 583) and fell ill with typical symptoms. The acute condition was similar to the symptoms of mill fever in cotton cardroom workers (603), to those of rural mattress workers exposed to bacteria-laden, low-quality cotton (584), to humidifier fever (604), and to disease from exposures in grain elevators (569, 570). These dusts also caused symptoms when previously nonexposed subjects were exposed.

The best-documented agent associated with ODS is endotoxin, but the involvement of other agents cannot be excluded. The possibility that different agents in organic dusts cause different forms of ODS needs further study. Mycotoxins (toxins derived from fungi) were suggested as possible agents in 1975 (595) and are still debated (605, 606), but there are little or no data to support the hypothesis that mycotoxins cause ODS.

Many constituents of bacteria and fungi elicit inflammatory responses. They interact with specific receptors on inflammatory and other cells. This provides a mechanism to identify

and react to foreign microorganisms as part of the “natural” or “basal” immune response. Complement is another example of this “natural” immunity (607), which does not require specific antigen recognition. Complement is activated by most microorganisms, but also by plant constituents (608). Apart from endotoxin, a lengthy list of agents might influence the reaction; they include fungal β -1,3 glucan (609), bacterial FMLP peptides, teichoic acids, and peptidoglycans.

Recently, a number of other agents have been added to the list, among them protodine secreted from both gram-positive and gram-negative bacteria (610), other peptides from *Pseudomonas* bacteria (611), bacterial heat-shock proteins (612, 613), and superantigens (614–616). There is even a possibility that the very potent inflammatory cytokine IL-1 may exist in microorganisms and in microbial dusts (617, 618). The alveolar macrophage is probably a principle mediator of the inflammatory reaction to dusts; in recent years, the airway epithelial cells have been shown to take an active part in inflammatory reactions (619, 620).

Fungal spores are cleared by alveolar macrophages. Spores of the fungus *Aspergillus fumigatus* become attached to macrophages but seem to partly resist ingestion (621) and may partly inhibit the respiratory burst (622). In rabbit models, spores were associated with macrophages within 3 h. The macrophages reached the respiratory alveoli, where the mass sometimes obliterated the lumen a few hours after challenge. Some collections of macrophages seemed to undergo central necrosis, liberating their content of spores after 24–48 h and forming lesions resembling granulomas (623). Other studies suggest that spores may reach the lung interstitium, and possibly other organs, after intratracheal injection (624).

Neutrophils arrive in the airways a few hours after challenge with fungal spores, but they seem to be unable to kill spores and may require that the spores begin to grow into fungal hyphae (625, 626). Some observations in man and animal studies, including the study by Emanuel and colleagues (595), demonstrate that spores can be found, and in some instances grown from, materials recovered from lungs several days after the last exposure (588, 628–290). Electron microscopy of lung tissue indicates that where spores are found in the airways of patients with FHP, there is local damage (629). Thus, although direct evidence that fungal and actinomycete spores may cause ODS is lacking, indirect data suggest a possible role.

Inhalation of endotoxin may mimic most of the symptoms of ODS (584, 603, 630). Gram-positive bacteria, lacking endotoxin, may also cause inflammatory changes. The systemic inflammatory response syndrome (sepsis) may be caused by both gram-positive and gram-negative bacteria. It appears from animal models, however, that gram-negative bacteria are some 20 times more potent than gram-positive bacteria in this respect (631).

Gram-positive bacteria might thus contribute to the symptom in environments with a high proportion of such organisms—e.g., swine confinement buildings. Inhalation of 100 μg of LPS causes general symptoms and airway and alveolar inflammation (632, 633). In fact, inhalation of less than 5 μg of endotoxin in dust in the inhalable fraction of dust in air in swine confinement buildings is sufficient to cause ODS symptoms (562, 568, 583). The amount of endotoxin reaching the alveolar region is considerably less (567). Furthermore, the change in bronchial responsiveness associated with endotoxin is small and short-lived (586, 632), in contrast with the change caused by swine dust associated with ODS (529). This suggests that other agents may contribute to toxic symptoms in swine confinement buildings.

Prevention. Since severe cases of ODS are associated with

excessive exposures to dust, prevention is straightforward: (1) adjust farming practices to avoid high risk exposure situations; and (2) use adequate respirators whenever handling materials with excessive moldiness. Efficient respirators should be used whenever a high rate of aerosolization of farm dust and poor ventilation are combined, resulting in high dust levels. Such situations include the weighing of swine (565), the removal of fowl (330, 332, 634), and extensive handling of grain, hay, straw, or wood chips, especially when moldy (560, 562).

There must be awareness in the farming community that such dusts are hazardous to health, and farmers should be familiar with all relevant primary and secondary preventive measures.

This condition should not be ignored, despite the generally good prognosis. On the contrary, an episode of ODTS—or a history of such episodes—should prompt an investigation of farming practices at the site in question. That investigation should be followed by an information effort, educating workers about health threats associated with inhaled dusts and instructing them in proper use of respirators. This situation—evidence of problems, *before* critical or fatal incidents have occurred, provides an excellent opportunity to increase awareness of hazards, reshape attitudes among the farming population, and advise on practical means to prevent tragedy. Such efforts are particularly feasible in countries with active rural health services staffed by knowledgeable technical experts (551, 635, 636).

Hypersensitivity Pneumonitis

FHP is one of the many forms of HP, a pulmonary disease caused by a variety of antigenic substances. The allergens responsible for HP include animal proteins (e.g., pigeon serum), bacteria or fungi, and inorganic molecules such as isocyanates. FHP is caused by moldy organic dust encountered in the farm environment.

Exposure. FHP is caused by *Thermoactinomyces* or fungi found in moldy hay, straw, or grain dust. Although there is evidence of hyperresponsiveness to the inhaled antigens, there is a direct relationship between intensity of contact and the risk for the disease. FHP is more prevalent in cold, wet climates. Within a given region, the number of cases is influenced by the climatic conditions of the preceding summer (637).

A lung disease seen in people who were exposed to grain dust that had been stored in a too-wet state was described in 1705 in *A Treatise of the Disease of Workers* (1, 638). A more modern description, including the association with moldy hay dust, was reported in 1932 (639). Initially, it was felt that the disease was either an infectious process caused by a fungus (bronchomycocytosis) or bacterium, an allergy, or an irritation (640). The allergy hypothesis was considered unlikely, since the subjects had no immediate responses. Since the work by Pepys and colleagues (641, 642), we have assumed that farmer's lung is caused by an allergic process, most often against the bacterium now classified as *Saccharopolyspora rectivirgula*.

This bacterium has been known under different names. When first identified by Pepys as the possible allergen responsible for FHP, it was classified as a mold and named *Micropolyspora polyspora*. Subsequently the names *Micropolyspora faeni*, *Faeni rectivirgula*, and, more recently, *Saccharopolyspora rectivirgula* have been used. It is now generally accepted that the microorganism is a bacterium and not a mold (643). To assure uniformity, it should be designated by its current name: *Saccharopolyspora rectivirgula*.

Although there are many reasons to suspect that *S. rectivirgula* is involved in the disease process, it may not act alone

and is certainly not the only microorganism in moldy hay or straw responsible for FHP. It remains quite possible that the initial sensitization requires a cofactor, a hypothesis supported by the observation that challenges with extracts of total hay dust induce a greater response than simple *S. rectivirgula* extracts (644–646).

Animal models requiring an adjuvant also support the idea of a need for cofactor(s) (647–650). A report in mice demonstrates that a one-time infection with the Sendai virus rendered the animals hyperresponsive to *S. rectivirgula* compared to animals similarly challenged but not pre-infected by the virus (651, 652). Fogelmark and colleagues (653) recently showed that the lung response is enhanced when B-glucan and endotoxins are given simultaneously, as opposed to separate exposures. Animals exposed to both substances develop lesions suggestive of hypersensitivity pneumonitis, while exposure to one of the two alone results in nonspecific inflammation (653).

The above observations suggest that, although *S. rectivirgula* is involved in the pathogenesis of FHP, it probably requires cofactors to induce the disease. A similar need for more than one factor would likely also be true for other microorganisms, found in moldy hay or straw, also responsible for FHP (e.g., *T. vulgaris*, *Aspergillus*).

Occurrence. Over the last two or three decades, many studies in various parts of the world have explored the epidemiologic aspects of FHP. Definite conclusions have been elusive, however, because of two methodologic issues—study design and the definition of FHP (654–656). Most studies have used cross-sectional surveys in order to determine prevalence of FHP or that of such associated conditions as the presence of precipitating antibodies against FHP antigens. Few if any real cohort studies have been published on the incidence of the disease (637, 657, 658). An even more important factor has been the lack of a consistent definition of FHP. Ascertainment of “cases” in large-scale surveys have usually depended only upon questionnaires plus testing for serum precipitating antibodies against FHP antigens. These methods correlate poorly with more comprehensive clinical assessments of FHP.

Most questionnaires used in these surveys sought to establish acute chest symptoms and/or fever following clear contact with offending antigens. The sensitivity and specificity of questionnaires to detect past or active cases of FHP is limited, however, since it is now recognized that: (1) FHP may occur insidiously, without acute chest symptoms (659, 660); (2) FHP is only one of several different farm-associated respiratory diseases that include occupational asthma (661), silo filler's disease (662), chronic bronchitis (663, 664), ODTS (587, 588, 665–667), and farmer's fever (668); (3) each of these conditions may be associated with at least some similar symptoms (579, 669, 670); (4) estimation of exposure to organic dust on farms is difficult (671); and (5) reliability of questionnaire data depends on the memory of the subjects (672).

Further, the inclusion of a positive reaction for serum precipitins against FHP antigens is of no diagnostic significance for FHP, since detection of precipitating antibodies is neither sensitive nor specific for FHP (599, 673) and is useful only to identify agents in the environment to which the patient has been exposed (674). Moreover, serum titers fluctuate over time (675) and no additional laboratory parameter is useful to distinguish farmers with antibodies and a relevant clinical history from those farmers with antibodies but no symptom after exposure to moldy hay (667).

Epidemiologic reports based on cases admitted to a hospital where a definite diagnosis can be made using chest radiographs, CT scan, BAL, and/or lung biopsies are likely to identify the most severe cases only and thus underestimate the

true prevalence of the disease (657, 676). In addition, important differences have been observed in the classification of respiratory diseases among farmers by physicians from different European countries (677). In a survey of final diagnostic classifications on hospital discharge, 73% of cases of FHP were erroneously classified (678). These observations demonstrate the unreliability of diagnostic assessment of FHP beyond the framework of clinical studies. To further support this conclusion, fluctuation in the prevalence of FHP has been related in at least one study (676) to a greater diagnostic suspicion attributable to ongoing epidemiologic surveys.

Because of the limitations described above, we have only a rough estimate of the incidence and prevalence of FHP. These parameters vary with the methods of study applied and from one country to another. A summary of reports is presented in Table 4.1. It shows the wide ranges of incidence and prevalence of FHP, differences that can be explained in part by the methods used and definitions of FHP applied.

The difficulties in establishing the incidence and prevalence of FHP are further complicated by geographic variables, including climatic conditions and farming practices. FHP has been extensively reported in many countries, including the United States (679, 680), Canada (662, 681), the British Isles (656, 676), Scandinavia (657, 682, 683), France (672), and other European countries. In fact, no country with some farming activities and a temperate climate is free of FHP. It has been recognized for a long time that new cases tend to cluster following a wet summer, which facilitates the growth of offending microorganisms (655, 657, 684).

Sex differences for both FHP (685) and seropositivity for precipitating antibodies to FHP antigens (686, 687) are likely to represent differences in exposure to offending antigens related to local agricultural traditions. Genetic markers have generally failed to confirm hereditary risk factors for FHP (681, 688–697). The importance of a genetic factor in the immune response to FHP antigens, however, is still debated. If such a factor is confirmed, the population at risk should be educated regarding preventive measures (697). Most epidemiologic studies have reported on patients 20–60 yr of age, reflecting the usual age range of the active farming population most

likely to be exposed to FHP antigens. FHP has been diagnosed in patients of all ages, however, including children (693, 698–702). In adults, the development of either FHP or precipitating antibodies is more influenced by the length of daily antigenic contact than by cumulative exposure (681, 684), so that older farmers are not necessarily more at risk for acute disease.

Smoking is less prevalent in individuals who develop FHP than in control populations (703–705). Most prevalence studies have demonstrated that nonsmokers are overrepresented among patients with FHP (672, 685, 703, 706, 707), as well as among patients with precipitating antibodies against *S. rectivirgula* (681, 684, 685, 707–709). The nature of this apparent protective mechanism of cigarette smoking is unknown but may be related to the profound effect of cigarette smoke on bronchoalveolar cell population and fluids (710–718).

Clinical features. FHP patients may present with an extensive variety of clinical and functional abnormalities. It remains unclear if the disease truly has different forms of presentation or is simply seen at different stages. The classically reported forms of FHP are acute, subacute, and chronic.

The acute form of FHP is the most frequent presenting form and the easiest to characterize. Typically, the subject has acute systemic symptoms, including fever and chills, as well as pulmonary manifestations (chest tightness, dyspnea, cough). Symptoms appear within hours of exposure to moldy hay or straw, generally becoming evident in the late afternoon or evening and persisting for part of the night. By morning, the fever has usually subsided, while dyspnea—although less severe than the evening before—may persist. With recurrences, weight loss can occur, and dyspnea becomes progressively more continuous.

“Subacute” is used to describe a form of FHP that is more insidious. In this form, dyspnea is manifested gradually over several weeks or months. No studies have explored variations in body temperature. It is conceivable that the acute and subacute forms of FHP represent different degrees or stages of the disease, with the subacute form involving no, or markedly lower levels of, fever.

The chronic form of FHP is probably the long-term sequela

TABLE 4.1
SUMMARY OF EPIDEMIOLOGIC STUDIES ON FARMER'S HYPERSENSITIVITY PNEUMONITIS*

Reference No.	Location	Total Farming Population*	Selected Population*	Respondents*	Questionnaire based	Clinical Cases/1,000+ Precipitins	Chart Review
Boyd, 1971 (576)	Scotland	2,000	—	—			5.5
Grant and colleagues, 1972 (655)	Scotland						
	(a) Orkney	?	359	359	86		
	(b) Ayrshire	?	176	148	88		
	(c) Lothian	?	162	148	27		
Smyth and coworkers, 1975 (676)	Devon, U.K.	25,000	—	—			~ 6
Madsen and associates, 1976 (892)	Wyoming, U.S.	471	471	274	29.7		
Gump and colleagues, 1979 (680)	Vermont, U.S.	440 farms	258	258	43		
Shelly and associates, 1979 (893)	Ireland	?	343	343	26	8.75	
Gruchow and coworkers, 1981 (684)	Wisconsin, U.S.	~ 7,000	2,097	1,444		4.2	
Marcer and colleagues, 1983 (894)	Italy	3,225	3,225	2,932	25.6		12.3
Saia and associates, 1984 (895)	Italy	3,225	293	249			14.0
Depierre and colleagues, 1988 (672)	France	2,555	2,555	1,763	153.1	43.7	
Malmberg and coworkers, 1988 (578)	Sweden	10,000	6,267 farms	6,702			~ 2.5
Stanford and associates, 1990 (896)	Ireland	25,000 farms	506	406	108.4		
Terho, 1990 (499)	Finland	14,346	14,346	9,669	14.0		

* Entries are individuals, unless otherwise specified.

of one or both of the other two forms. Chronic cough and sputum production are common in this phase (638). Although transient, mild bronchial hyperactivity and bronchospasm have been reported (716, 717), the disease is usually *not* associated with asthma-like symptoms (716, 718). At least some reports have suggested the possible association of FHP with development of asthma (717, 719, 720).

Persistent bronchial hyperreactivity to inhaled histamine has been found in small numbers of patients weeks after an acute episode of FHP (716), but this abnormality is probably attributable to the bronchiolar involvement seen in HP rather than to an asthmatic-type nonspecific bronchial hyperresponsiveness (721, 722). Discovery of concomitant occupational asthma in a worker with FHP is likely to represent the coincidence, although it is possible that patients who have had an episode of FHP may be at higher risk of subsequently developing asthma (706).

The characteristics ascribed to each of the three reported forms of FHP vary from one report to another. Fuller's "acute" case, for example (640), probably represented what is known today as ODS (588). Sometimes "acute" is used to describe an isolated attack, while "subacute" designates a recurrence of an acute attack (718). In another report, "subacute" was defined as appearing gradually over days or weeks, while the "chronic" form emerged gradually over a period of months (723).

"Chronic" is sometimes used to designate residual lung involvement as a consequence of acute FHP (638). Chemlik and colleagues (724) restrict the designations to two: acute and chronic; here, "chronic" subsumes others' "subacute" through lingering residual disease. In one view, the chronic form "may follow a succession of acute attacks or a single severe attack" (659). It was suggested by Boyd and coworkers (725) that a more useful classification would be in terms of progression: "acute progressive," "acute intermittent nonprogressive," and "recurrent nonacute"; the problem with this classification is that we currently have no way of predicting who will have a less favorable outcome, so the designations could be used only retrospectively.

Diagnostic criteria for FHP have not been firmly established. One difficulty is that, although many symptoms, signs, and clinical parameters are very sensitive, they are nonspecific (726). Numerous criteria recommendations have been published (723, 724). The ones most frequently used are those of Richerson and associates (723) and Terho (727); these criteria were limited to acute disease and need to be updated to include new information and account for the forms in the proposed classification above. Sometimes the only criteria could be the clinical history and residual disease compatible with long-standing FHP. A typical example would be a nonsmoking farmer, seen for the first time with underlying chronic obstructive disease, who reports a long history of recurrent febrile reactions during the winter months; if the patient had now left the farm environment, serum precipitins, BAL, and lung biopsies would be unreliable in supporting the diagnosis.

Diagnostic criteria have been proposed for recently diagnosed and recurrent or progressive disease. A clinical diagnosis of FHP is generally bound on a history of exposure to potential causative agent, symptom, physical findings, and laboratory data.

Required (i.e., diagnosis cannot be maintained in absence of these findings) diagnostic criteria for FHP include: (1) appropriate exposure; (2) dyspnea on exertion; (3) inspiratory crackles; and (4) lymphocytic alveolitis (if BAL is done).

Supportive findings of FHP include: (1) recurrent febrile episodes; (2) infiltrates on chest X-rays; (3) decreased DL_{CO} ;

(4) precipitating antibodies to FHP antigens; (5) granulomas on lung biopsy (usually not required); and (6) improvement with contact avoidance.

With two or more supportive criteria, the confirmation of a bronchoalveolar lymphocytosis may not be required.

As mentioned previously, the diagnosis of residual disease can sometimes be made only by an appropriate history and compatible signs and symptoms.

Clinical evaluation. In a typical acute case of FHP, the diagnosis can almost be made on the basis of information gained by a careful history and physical examination. To support the diagnosis, one must have documented contact with the appropriate farm environment and have inspiratory crackles on physical examination. Besides these auscultatory signs, physical examination is generally unremarkable. Digital clubbing may be seen in chronic forms (728).

Measurement of pulmonary flows and volumes may be optional in the diagnosis but useful in follow-up. Decreased DL_{CO} is probably always present in acute FHP, but since this test has a wide range of normal values (729), in the absence of a predisease measurement, this parameter may be decreased and still interpreted as within normal limits (i.e., $\geq 80\%$ predicted). PaO_2 is needed to decide if supplemental oxygen is required.

Chest radiographs are required to rule out pneumonia, sarcoidosis, and other disorders. The distribution of infiltrates in the acute disease is reported to be diffuse, but infiltrates often spare the bases in the subacute form (730). A variety of distributions and characteristics have been described (679, 731, 732). Infiltrations seen may be micronodular or patchy and confluent (733). Hapke and colleagues (703) proposed a classification of chest X-ray findings as 0 = normal; A = miliary appearance, (1) minimal, (2) definite, (3) marked; C = fibrotic changes, (1) fine diffuse, (2) slightly deforming, (3) grossly deforming. Others have used a scoring system based on the intensity and distribution to give a score from 0 to 24 (734).

The number of subjects studied to support these frequently quoted characteristics is small, and further studies of larger series are needed to confirm or refute these notions. A meta-analysis of available reports suggests that 80% of individuals with acute FHP have abnormal chest X-rays (735). Any modern analysis would require an evaluation by HRCT, especially in cases where standard chest X-ray is normal. The value of current reports on the use of HRCT in FHP is limited by the small number of cases studied (736–739). All but one report show that HRCT is always abnormal in HP. In the single report where some cases of HP had normal HRCT, the diagnosis of HP is questionable (740).

In measuring antibody levels, technique is important. The standard double-diffusion technique (741) may be more relevant clinically than more sensitive but nonspecific methods (742, 743). Regardless of the technique used, false positives and false negatives pose an important challenge. Many asymptomatic farmers have positive results (675, 681, 684, 744), and many cases of FHP have negative precipitins to the commonly tested antigens (*S. rectivirgula*, *Aspergillus*, *T. vulgaris*) (674). These negative results could reflect the incompleteness of antigens tested.

Bronchoalveolar lavage can provide useful supportive elements in the diagnosis of FHP. A normal number of lymphocytes would rule out all but residual disease (745). The presence of alveolar lymphocytosis, however, is not definitive for diagnosis (746, 747). (See further discussion on BAL cells in the section on pathogenesis that follows.)

Although many studies have looked at the possible value of skin tests to farmer's lung antigen (644), such tests are cur-

rently believed to be useless in the diagnosis of FHP (629, 727).

The histopathology of FHP, as obtained on open-lung biopsy, has been well described (659, 718). Granulomatous infiltration is characteristic of the acute form of the disease, while chronic cases present with extensive scarring, fibrosis, and sometimes emphysema. Open lung biopsy is not recommended and is usually not required in establishing the diagnosis of FHP (723). Transbronchial biopsy can yield material adequate to support the diagnosis (728, 729), although the clinical usefulness of this technique remains to be validated (730).

Specific provocations with barn dust, *S. rectivirgula* antigen, or workplace exposure have been used in the past (644, 645). These tests are not standardized and are not commonly used in FHP. The only practical approach in a suspected case of FHP would be to observe reactions to the patient's farm environment exposure.

Pathogenesis. FHP does not fit clearly into any one of the four classic types of allergic reactions defined by Gell and Coombs. The time lapse between exposure and symptoms, as well as possible involvement of antigen-antibody complexes, would suggest a type III reaction, while the late-phase cellular involvement with granuloma formation is more compatible with a type IV response.

Precipitins may not be involved in the pathogenesis of FHP (632, 674). In a farming population, the presence of precipitins was not correlated with chest symptoms (707). Subjects with disease, however, have higher titers of specific antibodies than asymptomatic exposed individuals, and some patients have antigen-antibody complexes in their lungs (748). Serum precipitins are associated with BAL lymphocytosis (746), but this finding may reflect only intensity of exposure. In animals, sensitization or susceptibility to *S. rectivirgula* cannot be effected by transfusing specific antibodies (749). It has been shown that in rabbits, serum antibodies remain high as long as the animal continues to receive the antigen, even when the lung response progressively decreases over time (750).

The role of serum precipitins in FHP becomes even more confusing when their presence is used in epidemiologic studies. Many reports and reviews have challenged the diagnostic value of serum precipitins against FHP antigens for case-finding purposes (599, 667, 673-675). Their lack of diagnostic value, however, does not necessarily preclude an increased risk of developing respiratory disease during continued exposure in the subgroup of farmers with positive reactions (751).

At least three epidemiologic studies have tried to correlate the serologic status of farmers with subsequent clinical and physiologic findings (675, 751, 752). In a program done to evaluate the possible role of precipitins in the later outcome, the subjects were farmers aged 29-59 with a sufficiently long sensitization period. Results obtained from only 117 male farmers suggested that the risk of occupationally disabling respiratory disease (including other than FHP) was three times higher in those who tested positive for precipitins than in precipitin-negative workers. No similar association was found in women.

The report by Guernsey and colleagues (752) found a significant increase in risk associated with a positive antibody status for chronic phlegm, chronic cough, and dyspnea. After stratification by smoking status, a significant relationship remained only for chronic phlegm, suggesting interaction between smoking and seropositivity in the expression of certain nonspecific respiratory symptoms—but in no way diagnostic of FHP. No significant difference in pulmonary function was observed between antibody-positive and antibody-negative subgroups.

Similarly, Cormier and Bélanger (675) demonstrated that antibody status fluctuates over time. In this regard, it is doubtful that detection of precipitating antibodies against FHP antigens in farmers with or without FHP has any prognostic significance for the development or progression of FHP. Reported association of precipitins with respiratory symptoms (752) or respiratory disability (751) cannot be currently related to FHP and needs to be further evaluated.

Although the hallmark of FHP is a bronchoalveolar lymphocytosis, the central event in the pathogenicity of the disease is possibly activation of the alveolar macrophages (753); they are activated in animal models of FHP (754) and in patients with the disease (755). Characteristically, the number of lymphocytes recovered by BAL in FHP is very high, even higher than that commonly seen in sarcoidosis (756, 757). These cells are mostly activated polyclonal or oligoclonal T lymphocytes (758-760), and most studies report an increase of T-suppressor/cytotoxic lymphocytes, with a decreased helper/suppressor ($CD4^+/CD8^+$) ratio (759, 761). A number of these lymphocytes are $CD16^-$ and $CD56^+$; that is, they are activated natural killer (NK)-like cells (760).

Although lymphocyte numbers are always increased in patients with acute FHP (745), the increase is not specific for acute disease. Farmers with a history of FHP, especially those still in contact with the farm (762) and with positive antibodies to FHP antigens (even those who are asymptomatic) can also have lymphocytic alveolitis (746, 747). The difference between asymptomatic and symptomatic subjects is not in the number of lymphocytes but their state of activation. Lymphocytes in BAL of symptomatic subjects have an increased blastogenic activity to PHA and specific antigen (763). BAL levels of hyaluronic acid can also differentiate asymptomatic lymphocytosis from active disease (764).

The number of lymphocytes recovered in BAL of FHP patients is not correlated with disease activity or outcome (745). This lack of predictive value of BAL lymphocytosis is also true for the asymptomatic alveolitis seen in otherwise healthy farmers (765). Studies with animal models have clearly shown that lymphocytes have an essential role in experimental HP (766, 767). In addition, the sensitization can be transferred from one animal to another by primed lymphocytes (750).

Neutrophils are acutely recruited into the alveolar space in response to antigenic challenge in HP (768), and their presence is inversely correlated with the time elapsed since exposure (769). The possible involvement of mast cells in FHP, although extensively studied, remains unclear. In an animal model, the presence of mast cells was required to induce HP-like response to *T. vulgaris* (770). Although some have suggested that mast cells in BAL correlate with disease activity (771-773), others have refuted this finding and show that BAL mastocytosis does not predict outcome (774). The number of eosinophils in BAL of FHP is slightly increased, and this increase parallels that of lymphocytes (774). These cells are unlikely to play an important role in the disease.

A possible involvement of complement in the pathogenicity of FHP is suggested by evidence of type III immune complex and C1q in BAL of HP (769). Surfactant is quantitatively decreased in BAL of HP patients (775) and may also be altered in its composition (776). On the other hand, Schmitz-Schumann and coworkers (777) found no such changes. Although they performed only chemical analysis and did not measure viscoelastic properties of surfactant in their subjects, these authors suggest that altered surfactant is probably not responsible for the alterations in lung function.

Cytokines are involved in all forms of inflammation; FHP is no exception. Although at least some of these substances

(TNF- α , IL-1, IL-6, granulocyte macrophage colony-stimulating factor [GM-CSF], etc.) are increased in FHP (759, 778–780), their precise role remains unclear. Arachidonic acid metabolites (prostaglandins and leukotrienes) are also increased in HP (781–783), but again, their specific role in the disease is unknown. Hyaluronic acid, fibroblast growth factors, fibronectin, vitronectin, and type III procollagen are also increased in BAL of FHP patients (784–786). Their significance is unknown; they are not predictors of outcome (787). Hyaluronic acid levels distinguish FHP from asymptomatic alveolitis (764). The metabolism of collagen is also altered in HP, and studies of these substances may be helpful in predicting outcome of the disease (788, 789).

Prevention. There is some evidence that most agricultural workers who develop FHP may be able to continue their occupation if appropriate measures are taken (686, 790).

The first preventive measure is improving methods of hay-making and storage. The use of hay conditioners and hay dryers greatly decreases the quantity of mold in stored hay. Drying and/or heating of fodder during storage has been shown to be useful in decreasing the thermophilic actinomycete aerocontamination in dairy farms (791).

Farmers know that it is important to prevent mold crusting on the surface of silage. This can be accomplished by either beginning the emptying of the silo as soon as it is filled or by sealing the top with a plastic sheet. Care must be taken that the top of the silo has been well ventilated and that no toxic gases (e.g., NO_x) are present before going into a recently filled silo.

There are also a number of commercial additives that can be applied to hay or silage to improve storage conditions and help prevent the development of mold. These products contain acid-forming bacteria, usually *Lactobacillus* sp and/or *Pediococcus* sp, which will grow in hay or silage, producing lactic acid (which inhibits molding). Some manufacturers warrant that 1 g of stored dry hay seeded with their product will contain at least 500,000 colony-forming units of the bacteria. Another technique is to add lactic, acetic, or propionic acid to the silage or hay (792)—but these acids are very corrosive to farm machinery, and farmers are therefore reluctant to use them. Although these are interesting approaches, there is no proof that this type of treatment will decrease the risk of FHP.

Certain typical work conditions increase exposure to bacteria-laden dust; farmers' awareness of these conditions is important. Most affected farmers are able to adjust their activities to some degree to minimize their contact with moldy hay (793). Dust in the barn will rise to its highest concentration when the animals are fed their hay; workers with FHP should stay out of the barn during this period. Patients should also be advised not to manipulate obviously moldy hay, grain, or straw. The use of straw shredders should be discouraged and, when possible, well-preserved wood chips should be substituted for straw. A worker with FHP—or a history of FHP—should not handle the decapping of a closed silo or participate in cleaning barns, silos, grain bins, haylofts, and similar sites. Animal clipping in a closed building is also a potentially hazardous task; dust accumulates in the animal's hair and is mobilized in large quantities during clipping, with FHP occurring after clipping sessions.

Dust levels in barns and other farm buildings can be decreased by ventilation. Although this fact is well known, farmers are sometimes reluctant to provide adequate air exchange because of resulting heat loss, particularly in the winter months in cold climates. Acute episodes of FHP are often seen during this season. Heat exchange units would provide a valid alternative, but their installation and usage costs are currently prohibitive.

Another preventive measure is the use of respirators. No controlled study has reported on the protective value of dust respirators or masks against FHP, and the ethics of such a trial have been challenged (793). Face masks and airstream filters, which can greatly decrease antigen levels in inspired air, are available, and it has been suggested that they might be effective in protecting subjects from HP (794–797). Several reports have supported their efficacy (793, 796, 798).

Thirty-one FHP patients were surveyed for a 1978 report (658), and Cuthbert and Gordon studied 23 of them 10 yr later, along with six additional patients (720). Although follow-up of the initial patient cohort was incomplete, the authors' conclusions suggested that those who continued to farm had been protected by making silage instead of hay, or by wearing protective respirators in all workplace settings in which farm dust might be encountered. Drawbacks inherent to wearing respirators are numerous and include cost and discomfort (facial sweating and dyspnea). Most farmers who buy these masks tend not to wear them on a regular basis.

One study examining the characteristics of farmers who have obtained personal dust respirators showed that participation in an occupational health study played the most significant role in the acquisition of these protective devices (799). These conclusions indicate that there is a complex relationship among personal, educational, and technical variables in the prevention of FHP.

Ideally, all farmers should be informed of the hazards of exposure to barn dust and encouraged to use adequate preventive measures. For practical purposes, however, major preventive measures (mask wearing, increasing barn ventilation, avoiding the barn when the animals are feeding) can be recommended only for patients with current or prior FHP.

Despite improved technology to control microbial growth in stored materials and to reduce contact with offending dusts, subjects with FHP are more likely than healthy farmers to plan a reduction in their farming work (800), and as many as 50% quit the farm, half of those despite the return of normal lung function (787). Clearly, non-health-related matters are also influential in these decisions; they may include emotional variables (anxiety, depression), the opinions of others (family, friends, physicians), and other psychological, psychosocial, and socioeconomic factors (801).

Medical treatment. Systemic corticosteroids represent the only reliable pharmacologic treatment of FHP. In acute disease, low doses of prednisolone (20 mg per day) was found to be as effective as contact avoidance (802).

In a prospective study of 101 patients followed from initial diagnosis, 70 received corticosteroid treatment at the time of diagnosis; the decision to treat was based on severity of symptoms and physiologic abnormalities (706). Eighty-three were still available at 58-mo follow-up. Recovery of pulmonary function in patients who did not receive corticosteroid treatment at the time of the diagnosis was slower during the initial stages of the disease; still, the maximum values for FVC and DL_{CO} were achieved at the same time as those for the overall study group.

The only randomized, double-blind, placebo-controlled trial that has been reported (803) supported previous general observations (804–806) that corticosteroids hasten the recovery from the acute stage of FHP, but they apparently have no beneficial effect on the long-term prognosis. The treatment for chronic or residual disease is supportive.

Natural history. Numerous investigators have attempted to depict the natural history and prognosis of FHP (686, 706, 792, 803–806). The real picture of the disease, however, has been obscured by inconsistencies among published reports, due to

the different ways in which cases have been collected and followed over time.

Simple principles for the study of clinical course and prognosis of diseases have often not been met in published reports on the outcome of FHP. Failure to start studies of clinical course with patients identified at an early and uniform point has had unknown effects on results (807). The inclusion of newly diagnosed FHP, for instance, along with patients with fibrotic scars on their chest radiographs, will probably lead to spurious conclusions if both groups of patients are classed as acute cases. Again, diagnostic criteria for FHP are crucial if data about prognosis are to be generalized.

Another major concern is completeness of the follow-up. If the follow-up is found to be incomplete, a rule of thumb is to attribute to the dropouts the worst outcome of interest, and then refashion the prognostic judgment. Roughly, a loss of more than 20% of the inception cohort along the course of a study is likely to lead to spurious conclusions. Other relevant concerns are the pattern of referral, the objectivity of clinical outcomes, the blindness of outcome measurements, and the adjustment for extraneous prognostic factors (807).

A report by Hapke and colleagues (703) illustrates some of the preceding methodologic considerations. Thirty-four of 245 patients with FHP were selected to cover the whole range of sequelae that had stemmed from one or more acute episodes. Clearly, no conclusion regarding complication rates could be drawn from such a series. Radiographic findings ranged from normal to severe fibrotic changes. Pulmonary function covered the spectrum of possible findings: interstitial disease, obstructive disease, combinations of airway obstruction and interstitial features, nonspecific findings, and no abnormality.

A first long-term follow-up of a cohort of patients with FHP was published by Barbee and associates (805). Due to the fluctuating and often insidious nature of FHP, it is probable that patients forming the inception cohort were gathered belatedly and unevenly over the course of their disease, a major drawback common to all subsequent reports. Nevertheless, most of the six conclusions reflected by Barbee's report have been supported by subsequent studies. They are: (1) at least a third of FHP patients have progressive or persistent symptoms; (2) most patients, even those who remain asymptomatic, have some physiologic long-term sequelae; (3) residual disease may include interstitial fibrosis and/or emphysema; (4) recurrences of the disease are important determinants of the ultimate clinical outcome; (5) FHP can be fatal; and (6) precipitating antibody reaction to FHP antigens has no prognostic significance.

The conclusion that at least a third of FHP patients have progressive or persistent symptoms was supported by Braun and coworkers (790). Mönkäre and Haahtela (804) found an even higher percentage of symptomatic subjects; 65% of their patients with a history of FHP were symptomatic after 5 yr of follow-up.

Long-term physiologic abnormalities were also reported by Braun and colleagues (790). Twelve percent of their cohort, at follow-up, had a total lung capacity of less than 80% of predicted value; 30% had DL_{CO} of less than 80% of predicted value; a quarter had an obstructive pattern on spirometry, with FEV_1/FVC ratio inferior to 70%; and 42% had a Pa_{O_2} of less than 70 mm Hg. Many investigators have since described the pattern of recovery of physiologic parameters after an acute episode of FHP (686, 706, 803, 804, 806) and the effect of steroids on recovery (803, 804, 806).

Cormier and Bélanger (686) prospectively followed 61 patients who had an acute episode of FHP. Available data were pooled in time intervals and compared to the values at the

acute episode, so that at given intervals subjects were always compared to themselves. The parameter that showed the greatest change between the acute episode and 1 yr after was DL_{CO} ($61.5 \pm 28.5\%$ versus $92.4 \pm 36.9\%$ predicted values, $p < 0.01$). At 6-yr follow-up, DL_{CO} was still higher than at diagnosis. When total lung capacity (TLC) was expressed as percent predicted, results showed similar trends. Pulmonary function, however, decreased over time, so that after the sixth year of follow-up, no statistically significant difference could be found between actual and initial DL_{CO} , FVC, and TLC values. The FEV_1/FVC ratio remained, on average, normal and did not show any significant change over time. No attempt to segregate between patients initially treated with steroids or not was made.

Similar results, except for FEV_1/FVC , were reported by Kokkarinen and colleagues (706). Overall, in a complete follow-up of 86 patients, Mönkäre and Haahtela (804) observed that 40% of farmers sustained at least some minor residual respiratory dysfunction (diffusing capacity less than 80% predicted value). A restrictive pattern on spirogram was also observed in 14% and an obstructive pattern in 7%.

Barbee's observation that residual disease can include interstitial fibrosis and/or emphysema was also subsequently supported by numerous studies. Most early pathologic reports on FHP suggested that widespread fibrotic reaction was the prominent feature in longstanding FHP (659, 703, 718), often with predominant involvement of upper lobes with contraction (659). Emphysema, as well, has been found at necropsy in many cases of chronic FHP (659). It was, however, unclear if those findings were secondary to HP or to a combination of insults (721). Pathologists were at this time reluctant to attribute development of destructive centrilobular or panacinar emphysema, without obvious fibrosis, to the end result of acute FHP, despite additional descriptions of widespread emphysema in various end-stage interstitial lung diseases (808).

Braun and coworkers (790) found changes compatible with chronic interstitial pneumonitis in 36 out of 92 patients (39%). In their first report, Mönkäre and Haahtela (804) suggested that as many as one-third (27/84) of their patients had radiologic fibrosis at 5-yr follow-up. In most of them, however (21/27), the persisting diffuse opacities were already seen at the first evaluation. In their second report of a cohort of 93 patients with FHP followed prospectively over 23 mo, on average, Mönkäre and associates (806) observed that: (1) chronic changes are compatible with interstitial fibrosis; (2) most of the patients who presented with chronic changes on their chest radiographs at the end of the follow-up period had already had these changes at their first evaluation; (3) severe radiologic changes disappear more slowly than less severe ones; and (4) almost one-fifth of the patients presenting with acute changes at first evaluation will evolve to chronic changes.

Despite the fact that both pathologic and radiographic studies have reported mainly on the long-term fibrotic changes (at least in some patients) after one acute episode of FHP, repeated physiologic studies found that increased compliance, reduced recoil (809), and trapped air (810) are important findings in longstanding HP, suggesting that emphysema is also a long-term manifestation in extrinsic allergic alveolitis (809). Some light has recently been shed on this apparent discrepancy between physiologic and radiographic data.

In a radio-physiologic correlation study using HRCT, Lalancette and colleagues (787) reported on 33 patients with FHP evaluated at various stages of the disease 6 yr earlier. Pulmonary function tests revealed normal values in 16 subjects, an obstructive pattern in 13, restrictive changes in one, and an isolated decrease in DL_{CO} in three. HRCT revealed emphysema in nine patients, localized fibrotic changes in three,

and a ground-glass pattern in two; 19 were normal. There was a good correlation between the physiologic findings and HRCT. Chest radiographs were, however, insensitive for the detection of emphysema. This study suggested that: (1) airflow obstruction, with or without emphysema, is a more important long-term sequela of FHP than previously appreciated; (2) pulmonary function tests are more sensitive than plain chest X-rays to detect these changes; and (3) chest radiography is neither sensitive nor specific for the detection of either emphysema or interstitial fibrosis as a long-term sequela of FHP.

To further support earlier findings from Barbee and associates (805), suggesting that repeated attacks of FHP could lead to chronic physiologic abnormalities, Braun and coworkers (790) showed that patients with a history of five or more recurrences more often had decreased vital capacity and DL_{CO} and an interstitial pattern on their roentgenograms. Other studies showed that risks of recurrence are higher in cases of severe, acute FHP (811), and that minimal antigen contact could provoke symptoms in highly sensitized farmers (812). Recurrence rates as high as 8% have been reported (804).

While it has been common practice to recommend that patients with FHP leave their farm (689) to avoid further deterioration of lung function, some studies show no difference in long-term physiologic outcomes between subjects with FHP who stayed on their farms and those who left, leading to a review of this policy (686, 804). Farming is a rapidly evolving activity, with many farm tasks becoming highly automated, and it is difficult to assess the effect of preventive measures in slowing the progression of pulmonary diseases among farmers who stayed on their farms (686). It is possible for some farmers with FHP to continue farming with the usual exposure contacts and careful clinical follow-up.

Early reports on long-term clinical outcomes of patients with FHP were characterized by extremely high death rates attributed to the disease. In the literature, mortality rates as high as 30% have been suggested—but no solid data are available to support such claims (813). Among 141 patients with FHP located for their study, Braun and colleagues (790) reported on 29 deaths, 13 (9.2%) directly or indirectly related to respiratory disease, three of them (2.1%) reported as FHP. At

the time of death, the average duration of FHP was 17 yr. However, causes of death were obtained retrospectively from the patient's physicians or from death certificates, and are very unlikely to tell the real story (676).

The mortality rate for FHP is currently very low. Fewer than 50 deaths annually in the United States have HP mentioned on the death certificate (814). Nevertheless, there is little doubt that, in rare instances, FHP can lead to fatality at any stage of the disease (790, 805, 815, 816). Recognition that emphysema is an important long-term clinical sequela of FHP could add to the case fatality rate.

To summarize: (1) FHP leads to progressive symptoms in at least one-third of affected patients; (2) most symptomless patients suffer at least some physiologic long-term abnormality; (3) steroids are unlikely to positively affect long-term clinical and physiologic prognoses; (4) interstitial fibrosis and/or emphysema may follow longstanding FHP; (5) emphysema probably represents a more important outcome than previously recognized; (6) FHP may lead to fatality if unrecognized; (7) precipitating antibodies against FHP antigens have a controversial but doubtful prognostic significance for the development or progression of FHP; (8) BAL cellularity is of no prognostic value; (9) recurrences of the disease are an important determinant of the ultimate clinical outcome; and (10) new technologies and adjustments of agricultural workers' farming activities are important for the control of the disease.

Interstitial Fibrosis

The focus of this section is on interstitial lung disease associated with mineral dust exposure. Diffuse interstitial lung disease associated with exposure to agricultural chemicals such as paraquat are considered briefly.

Four major types of interstitial lesions associated with mineral dust exposure are recognized: (1) diffuse interstitial fibrosis; (2) macules; (3) nodules; and (4) massive fibrotic lesions, also known as progressive massive fibrosis or complicated pneumoconiosis (Table 4.2).

Diffuse interstitial lung disease is characterized by a proliferation of cells within the interstitium and the progressive deposition of connective tissue elements. Inflammation and edema are variable in severity and extent and may be tran-

TABLE 4.2
PATHOLOGIC REACTIONS TO SILICA AND SILICATE MINERALS

Mineral	Macules	Granulomas	Nodules	Fibrosis	Massive	Diffuse	Fibrosis	Interstitial	Mineral	SAD	Dust	Fibrosis	Pleural
Asbestos	—	—	—	+/-		+			+			+	
Attapulgit	N/A	N/A	N/A	N/A				+					N/A
Feldspars	+	+ [†]	+	+								N/A	
Fuller's earth	+	N/A	+	+		N/A						N/A	
Kaolin	+	+ [†]	+	+		+						+	
Mica [‡]	+	+	+	+				+					+
Mullite	N/A	N/A	N/A	N/A		+						N/A	
Olivine													
Mixed dust	+		+		+			+			+		
Sepiolite	N/A	N/A	N/A	N/A		+						N/A	
Shale	+	N/A	+	+		N/A						+	
Silica	—	—	+	+		+			+				
Talc	+	+	+	+		+						+ [§]	
Wollastonite	N/A	N/A	N/A	N/A		+						N/A	
Zeolite	N/A	N/A	N/A	N/A		N/A						+	

Definition of abbreviations: SAD = small airways disease; N/A = not known or not reported.

* By radiographic/pulmonary function data only.

[†] These granulomas appear as collections of dust-containing macrophages, but giant cells are apparently not formed.

[‡] Largely muscovite mica.

[§] Pleural fibrosis in those with talc exposure may be caused by contaminating asbestos.

Adapted from Reference 827.

sient. Initially, the fibrosis—which includes collagen, elastic fibers, and smooth-muscle cells—extends in linear fashion within the alveolar walls. In later stages, the lung architecture is remodeled, with formation of thick-walled cystic spaces often termed “honeycomb lung.” In the early stages, the fibrosis may take one of two forms—one like that of typical interstitial pneumonia, the other associated with macules and nodules, forming bridges of fibrosis between the lesions; the first type is indicative of exposure to fibrous minerals (e.g., asbestos), the latter characteristic of exposure to silica and silicates.

Macules are defined as focal collections of dust-laden macrophages within the walls of respiratory bronchioles, associated with mild reticular fibrosis. They are characteristic of exposure to dusts of low fibrogenic potential—for example, coal, graphite, and silicates. They range in size from 0.1 to 0.6 mm in diameter, are soft to palpation, and are more numerous in the upper lung zones.

Nodules are the most common lesions following exposure to silicate minerals and to mixtures of dust containing less than 20% free silica (817). These lesions vary in diameter from a few millimeters to a centimeter or more, are rounded and firm to palpation, and like macules, have a predilection for the upper lung zones. They may be located throughout the interstitium, including the subpleural area and adjacent to bronchovascular structures. Microscopically, nodules consist of hyalinized collagen and dust. A concentric orientation of the collagen fibers and smooth borders are features highly indicative of silica exposure (silicosis); silicates and mixed dusts produce nodules with irregularly arranged collagen and serpiginous borders. Sheet silicates such as talc and mica are associated with a giant-cell, granulomatous response.

Progressive massive fibrosis (PMF), also referred to as complicated pneumoconiosis, usually occurs against a background of simple pneumoconiosis (macules and nodules). PMF is associated with disability and premature death and tends to progress in the absence of further exposure. The lesions, defined arbitrarily on the basis of a size greater than 1 cm, are most common in the upper and posterior portions of the lung and are usually bilateral. They have been described in association with exposure to silica, nonfibrous silicates, and coal mine dust. On cut surface, the lesions are usually pigmented, firm to rubbery in consistency, and may contain cavities filled with pigmented fluid. Superimposed infection with tuberculosis or atypical mycobacteria is uncommon today but must still be considered in the clinical setting.

The radiologic appearances of the pneumoconioses are in themselves nonspecific and may be seen in other types of lung disease. Further, any given pneumoconiosis may manifest more than one pattern of abnormality. Despite these limitations, the chest film, in conjunction with a history of exposure, is probably the single most useful clinical tool for diagnosing pneumoconiosis (818–820).

A standardized classification system for the pneumoconioses has been developed by the International Labor Office (ILO) (821). Originally designed for evaluating nodular lesions such as those of silicosis, the current version permits the classification of asbestos-associated diseases as well as other pneumoconioses. The major intended application of the ILO scheme is ensuring comparability in epidemiologic research and medical surveillance. In this system, the trained reader compares the patient's film with a set of standard anteroposterior chest films. The X-ray is assessed for technical quality, parenchymal abnormality shape and profusion, and pleural and other changes.

The term “interstitial lung disease” is generally considered by consensus to refer to diseases of the alveolar interstitium. It

is apparent, however, that the interstitium exists as a continuum from hilum to pleura. Because of the marked interdependence of the alveolar interstitium and the interstitium of the small airways (i.e., airways < 2 mm in diameter), small airways diseases must be considered here. Clinical features of small airways disease and interstitial lung disease may be similar. Three major forms of small airways disease have been described: bronchiolitis obliterans, respiratory bronchiolitis associated with cigarette smoking, and mineral dust-associated small airways disease.

Bronchiolitis obliterans is a clinicopathologic syndrome involving progressive small-airway injury, with a variable onset from acute to chronic and insidious. The chest X-ray may be normal but more usually shows bilateral hyperinflation with subtle (bibasilar) micronodular infiltrates. Physical examination reveals dry crackles over the lower lobes, particularly on inspiration, with a mid-expiratory squeak. Pulmonary function tests in the early stages show obstructive changes and a mottled distribution of defects on the ventilation/perfusion scan. Lung biopsy at this point shows inflammation and ulcerative changes in the terminal and respiratory bronchioles, with variable luminal occlusion due to the formation of polyps of granulation tissue.

The early stage is followed by a cicatricial stage in which the small airways are distorted by stellate bands of dense collagen extending into the alveolar septa. The variable geometry of the airways, loss of airway smooth muscle, and altered laminar airflow, combined with peribronchiolar and interstitial fibrosis, produce a complex clinical picture with both obstructive and restrictive components.

Many exposures in farming are associated with bronchiolitis obliterans. They include oxidant and irritant gases (e.g., NO₂, NH₃, Cl), as well as organic dusts associated with hypersensitivity. These substances have been discussed earlier.

Respiratory bronchiolitis is often associated with cigarette smoking or respiratory bronchiolitis–interstitial lung disease (RB-ILD). It is covered here because it is a common finding in farm workers and needs to be distinguished from airways disease associated with mineral dust. The clinical features are cough, dyspnea, and rales on physical examination. The chest X-ray may be normal, but bronchial wall thickening, prominence of the perivascular interstitium, small regular and irregular opacities, and small peripheral ring shadows have been described (822).

As with bronchiolitis obliterans, pulmonary function tests reveal a mixed obstructive and restrictive pattern, often with an increased residual volume. Diffusion (DL_{CO}) may be normal or mildly reduced. Histopathologic changes are characteristic. There is chronic inflammation of the terminal bronchioles, respiratory bronchioles, and alveolar ducts, associated with mild fibrosis of their walls and adjacent alveoli (823). There is also variable smooth muscle hyperplasia and accumulation of tan pigmented macrophages in the respiratory bronchioles and adjacent air spaces.

Mineral-dust-associated small airways disease is also a distinct pathologic entity (824), caused by exposure to both fibrous and nonfibrous mineral particles (825). The disease is characterized by deposition of mineral dust in the walls of small airways and alveolar ducts, particularly at their bifurcations. Although cigarette smoke and mineral dust affect the same anatomic locations, they can be distinguished on qualitative and quantitative criteria. Studies by Wright and coworkers (826) have shown that mineral dusts produce small airways fibrosis above and beyond that caused by cigarette smoke. Further, the fibrosis caused by mineral dusts extends farther into the alveolar ducts and is more severe than that associated

with cigarette smoking, and it is characterized by striking deposition of mineral dust particles, many of which can be readily observed by polarized light microscopy.

There is considerable overlap between mineral dust-induced small airways disease and the dust macule; in fact, there is reason to believe they result from the same pathogenetic mechanism. They are both centered on the respiratory bronchiole and have similar physiologic correlates (826). Perhaps the most useful approach is to view them as two ends of a continuous spectrum of changes. The term "macule" is best applied to large deposits of weakly fibrogenic dusts (coal or carbon, for example) in the walls of respiratory bronchioles, with mild and predominantly reticular fibrosis and a tendency to be associated with centriacinar dilatation or focal emphysema.

At the other end of the spectrum, the strongly fibrogenic mineral dusts such as asbestos and silica are associated with small quantities of visible dust, a predominance of mature collagenous fibrosis, and variable degrees of airway narrowing. Moderately fibrogenic dusts, such as the nonfibrous silicates, produce lesions with intermediate characteristics (827). Whether these anatomical differences are associated with meaningful physiologic distinctions has not been determined.

Exposures. Farming is a dusty occupation. Atiemo and Yoshida (828) have shown that concentrations of respirable particulates within farm tractor cabs in prairie areas may exceed the threshold limit value of 3 mg/m^3 . Although soil consists of a mixture of organic and inorganic materials, potential health effects from the ever-present mineral dusts have been largely overlooked. In theory, soil should contain representative portions of all major mineral classes in the earth's crust; in reality, most agricultural soils contain a large proportion of crystalline silica (quartz) and silicate minerals (e.g., feldspars, mica, clay minerals) with varying amounts of other mineral classes, depending on the local geologic history.

Fibrous mineral species are generally uncommon in soil but may be important locally—for example, richterite and anthophyllite asbestos in Finland (829, 830), tremolite in Cyprus (831), and erionite in Turkey (832) and Nevada (833). In addition to naturally occurring minerals, soil contains mineral dusts derived from agricultural chemicals and feed additives for livestock. Minerals such as talc, zeolite, kaolin, attapulgite clay, and vermiculite have been used in the agricultural industry as fillers and carriers for pesticides, as additives to livestock feeds, and in the treatment of animal wastes (834). Industrial grades of at least some of these minerals may be contaminated with fibrous particles, notably tremolite asbestos (835, 836).

In dry and windy regions, dusts entrained by farming activities may be a source of regional air pollution (837, 838). Windom and colleagues (838) concluded that the majority of airborne talc particles are derived from farming activities. A study of two farming regions in rural Alberta showed peaks in total suspended particulates in the spring and fall, corresponding with periods of intense farming activity (839). Loss of ground cover, exposed rocky outcrops, and unpaved roads will also increase the likelihood of mineral particles becoming airborne.

The composition of the airborne dust will depend primarily upon the geochemistry of the soil, but it will also be influenced by factors such as the predominant farming pattern (crops, forage, pasture) and use of irrigation. A study of farm dusts in rural Alberta found that dusts from irrigated farms contained a greater water-soluble component and a smaller and more uniform particle size distribution (837). Periodic flooding of topsoils during irrigation is likely to lead to differential sedimentation of soil suspensions according to particle size, with

the finer particles deposited on the surface. After drying, these particles and associated salts would be readily suspended in the air by wind or farming activities.

Most studies indicate that airborne farm dusts have a large respirable fraction. The respirable mass fraction ($< 5 \mu\text{m}$ in diameter) of dusts taken from tractor air filters at the end of harvesting operations at 12 farms in Alberta was 50% or greater for all samples. The mass median diameter ranged from 0.9 to $5.0 \mu\text{m}$, with geometric standard deviations ranging from 2.0 to 7.0 . A recent study of rice farming in California found respirable dust concentrations outside the harvester of 0.52 – 2.16 mg/m^3 , and outside the tractor during field preparation from 1.77 to 5.24 mg/m^3 (840). An earlier study of manual harvest operations in California found the median diameter of dust particles to be $3.9 \mu\text{m}$ (geometric SD = 2.6). The median concentrations of respirable aerosols in grape, citrus, and peach harvesting were 0.95 , 0.90 , and 0.50 mg/m^3 , respectively (841).

There have been few studies of the quartz and fibrous mineral content of farm dusts. The silica content of the dust samples taken from 12 Alberta farms (determined by infrared absorption spectrophotometry after ashing) ranged from 0.8% to 17.5% . X-ray diffraction analysis revealed that the most common minerals were feldspar, quartz, illite, kaolinite, chlorite/montmorillonite, anhydrite, and calcite. In addition, variable amounts of dolomite, pyrite, goethite, halite, marcosite, smectite, hornblende, and gypsum were identified (837). Particle morphology by scanning transmission electron microscopy revealed that the majority of respirable particles had smooth, rounded borders. Very few fibrous minerals were encountered. X-ray analysis and selected area electron diffraction of 50 particles with aspect ratios greater than $5:1$ showed that they were predominantly composed of silicon, titanium (rutile), aluminum silicate (mullite/kaolin), magnesium silicate (fibrous talc), and muscovite. The fibers ranged in dimension from $1.4 \mu\text{m}$ to $7.5 \mu\text{m}$ in length and from $0.08 \mu\text{m}$ to $1.5 \mu\text{m}$ in width. Asbestos fibers were rarely identified; in fact, their frequency was not significantly higher than their frequency in blank controls.

The few case reports and case series describing pneumoconiosis in farmers provide evidence that the primary hazard is from silica (quartz) and silicate minerals (842–845) and that exposures are to a mixture of minerals. To this extent, the disease can be classified as a mixed-dust pneumoconiosis. In general, the silicate minerals are weakly fibrogenic, and prolonged and intense exposures are usually required for clinical disease. There is also evidence that quartz is less fibrogenic when it has been "weathered" and when it is mixed with other minerals.

Exposures to mineral dust in agriculture will almost certainly be to mixtures of minerals containing varying amounts of quartz. It is likely that the toxicity of inhaled dust will vary markedly from region to region and from farm to farm and will be influenced by factors other than mineral composition—e.g., weathering, particle distribution, and particle size and shape.

Occurrence. There is evidence that human exposure to mineral dusts outside of agriculture can cause interstitial lung disease. Pulmonary fibrosis has been observed among workers with exposure to Fuller's earth (attapulgite, bentonite, montmorillonite, sepiolite), kaolin, mica, slate (muscovite and quartz), talc, vermiculite, and wollastonite. For many of these mineral dusts the free silica content was 2% or less. The evidence that mineral dust exposure poses a significant hazard to agricultural workers for interstitial lung disease is based on a handful of case reports, on inferences from exposures to mineral dusts in other industries, and on studies of wild and farm

animals exposed to environmental mineral dust. Unfortunately, there are no reported epidemiologic studies that have directly assessed environmental exposure to mineral dusts and interstitial lung disease in farmers or farm workers. A few studies, however, have suggested that pneumoconiosis and restrictive lung disease are increased in some agricultural populations, and an ongoing study of autopsied agricultural workers in the California Central Valley is an attempt to obtain data on dust composition and disease prevalence (849).

An early report by Heatley and coworkers (847) described a case of silicosis in a 55-yr-old man who unloaded wheat from railroad cars. The subject worked for 8 yr in an atmosphere thick with dust from wheat. Silica content of the wheat dust in two samples was reported as 9.96 and 19.96%.

Another early report was of 11 cases of pneumoconiosis in dock workers who handled grains and seeds (848). Most of the cases were dyspneic, and all had chest X-ray abnormalities. The authors described shoveling of the grains as associated with thick clouds of dust, especially when done in the ship holds. Various chemicals were also present in the dusts, including bauxite, iron ore, sulphur, and manganese. Analysis of dust samples revealed 1.1 to 9.1% total silica (free and silicates). Between 23 and 60% of the ash from the wheat, oats, or barley was silica in some form.

A Pakistani farmer was described with nodular opacities on chest X-ray and restrictive pulmonary function (845). Analysis of dust particles from the farm revealed muscovite, quartz, kaolin, and rutile. Bulk chemical analysis of the dust deposits were 58.4% silica, 20.5% aluminum oxide, 9.3% iron, and 11.8% various oxides.

A Russian study reported on silicosis among tractor drivers working on sandy soils in forestries (844). The average concentration of dust in the crawler tractor cabs was over 100 mg/m³, and the free silica content in the dust from air samples was 82–85%. Silicosis was diagnosed by X-ray in 11 of 82 tractor drivers examined.

Sherwin and coworkers (842) reported silicate pneumoconiosis in seven patients (five vineyard workers, one produce farmer, and one rural resident) living in the central valley of California. Six of the seven were nonsmokers at the time of death. All five vineyard workers died of respiratory failure. Interstitial fibrosis, chronic inflammation, and foreign body granulomata of varying degrees were the primary pathologic abnormalities. The lesions were associated with deposition of birefringent particles. Scanning electron microscopy combined with X-ray microanalysis of respirable-size (< 5.0 μ m) particles from the lungs of four of the cases and corresponding soil samples showed that silicates of the mica group predominated. No evidence for copper salts (potentially derived from vineyard sprays) was found.

A mild silicate pneumoconiosis has been reported in a 53-yr-old farmer in Norway undergoing lung resection for a carcinoid tumor (843). The lung adjacent to the tumor showed patchy pleural fibrosis with peribronchial and interstitial fibrosis. These lesions were associated with mineral dust particles, observed by polarizing microscopy, which showed fibrous, needle-shaped, and platy morphology. Nonasbestos ferruginous bodies were also observed. Analysis of ashed lung samples by X-ray elemental and X-ray diffraction analysis showed that muscovite, mica, talc, silica, and feldspar were the most abundant minerals. Fibrous mullite and anthophyllite asbestos were present in concentrations of 4.5×10^6 and 2.7×10^6 fibers per gram of dried lung tissue, respectively. Analysis of soil from the farmer's potato storehouse revealed mica along with quartz and plagioclase feldspar, but no talc. Rutile fibers were also detected in the dust. The authors concluded

that the mica, silica, and feldspar-like particles came from soil derived from schists, which are the most abundant rocks in the region.

Other reports have appeared implicating exposures during farming in interstitial lung disease. These include a 62-yr-old male who had worked for 20 yr as a farmer and presented with progressive exertional dyspnea and irregularly distributed infiltrative shadows in both lung fields (849). Lung biopsy revealed interstitial fibrosis with alveolar proteinosis. The authors speculated that (unnamed) agricultural chemicals caused the disease but presented no evidence to support their conclusions.

Another study from Japan of human lungs obtained at lobectomy or autopsy for lung cancer showed that farmers had increased levels of silicon and aluminum in their lungs compared with other occupational groups, indicating accumulation of silicates as a result of environmental exposures. The study was designed to assess the possible contribution of environmental dusts to lung cancer. No data on interstitial lung disease were included.

A mineralogic study of lung tissues from 25 patients diagnosed as having IPF showed that the IPF group had significantly higher silica/silicate (Si/S) ratios than 25 samples from normal lungs (850). Moreover, 12 of the patients had Si/S ratios in the range associated with pneumoconiosis, and six of the 12, on subsequent investigation, had histories consistent with exposure to silica or silicates. Although the report did not specify that any farmers were included in the study, there is an implication that cryptogenic exposures to silica and/or silicates may be an important cause of IPF.

A study of 122 Malaysian rice millers and 42 control agricultural workers without exposure to rice husk dust found an increased prevalence of mucous membrane and pulmonary irritant symptoms among the rice workers (851). Nodular opacities were present on chest X-rays of 14.8% of the rice millers but none of the control subjects, and 3.3% of the millers had a "generalized haze" on chest X-ray. Pulmonary function studies showed a mixed picture, more suggestive of obstructive deficits. Dust levels were reported as 2.3 to 5.4 mg/m³ total dust and 0.5 to 1.2 mg/m³ respirable dust in the low season; these levels increased by as much as tenfold in the peak season.

A cross-sectional survey of pulmonary function among 759 California farm workers found significantly reduced FVC among grape workers compared with citrus or tomato workers (852). The study was undertaken because of measurements of high concentrations of respirable quartz in grape harvesting (853). While the pulmonary function abnormalities suggested restrictive lung disease, there was no radiologic confirmation or direct measurement of dust exposure.

A prevalence survey of 8,340 Norwegian farmers in three counties (78% response) revealed an overall prevalence of small interstitial opacities (ILO score of 1/0 or 1/1) of 2.7% on 10 $\times$ 10-cm miniature X-rays (854). The prevalence of positive X-rays increased among cigarette smokers and those who had spent 10 yr in agriculture but was not associated with work-related respiratory symptoms.

A recent survey of California rice farmers reported a prevalence of 10.1% of 178 chest radiographs as having ILO profusion scores of more than 1/0 for small irregular opacities, consistent with dust or fiber exposure (855). There was no association with specific farming practices, however, and selection factors in the study sample cannot be excluded.

Studies of animals exposed on farms, in zoos, or in the wild provide evidence that airborne mineral dusts cause interstitial lung disease. Schwartz and coworkers (856) reported findings from the Monterey-Carmel peninsula of California, where

nine horses presented with exercise intolerance and varying degrees of respiratory distress. Morphologic examination of pulmonary tissue obtained at biopsy or autopsy showed a granulomatous interstitial pneumonitis associated with birefringent particles on polarizing microscopy. No infectious agents were identified in the tissues.

Electron microscopy combined with X-ray microanalysis of lung tissue from five horses, as well as a sample of soil from one stable, showed large numbers of submicron-size particles in the granulomas. Some 32 to 59% of the particles were aluminum silicates, and 29 to 42% of the particles had almost pure silicon peaks, indicative of silica. Silicates containing iron, phosphorus, potassium, and magnesium made up the rest. X-ray diffraction analysis of ashed lung and the soil sample removed from the stable revealed cristobalite, quartz, feldspar, and mica. These mineral findings combined with the pathologic findings are indicative of a mixed dust pneumoconiosis.

The identification of cristobalite is of considerable interest. Cristobalite is more fibrogenic than quartz and, unlike the other species of silica, is not widely distributed in nature. The Monterey formation contains deposits of diatomaceous shale, which may undergo diagenesis to cristobalite. The authors concluded that the cristobalite was more likely to be of biogenic than volcanic origin.

A simple silicate pneumoconiosis has been reported in animals dying in the San Diego Zoo (857). One hundred autopsies from 11 mammalian and eight avian species were studied by light and electron microscopy and X-ray microanalysis. Interstitial fibrosis associated with mineral dust deposits were found in 20% of lungs. Ninety percent of the particles were silicates, which on X-ray diffraction were predominantly muscovite, mica, and its hydrothermal degradation product, illite clay. A similar mineralogic profile was found on analysis of atmospheric air samples taken at the zoo.

Silicate pneumoconiosis has also been described in 94 of 134 autopsied camels from the Somali Desert. In addition to diffuse interstitial fibrosis, classic hyalinized nodules of silicosis were seen in six cases. X-ray microanalysis showed a mixed dust exposure containing silica and silicates of aluminum, potassium, and iron.

Four cases of silicate pneumoconiosis were described in pigs raised near chalk quarries and cement works in Italy by Roberto and associates (858). Interstitial and peribronchial fibrosis associated with deposition of dust was the characteristic lesion. X-ray microanalysis of the dust revealed particles composed mainly of silicon, calcium, potassium, sulphur, aluminum, and iron. Air samples from the region showed similar particles.

Paraquat (1,1-dimethyl-4,4'-bipyridylium dichloride) is a defoliant and contact herbicide used extensively in many agricultural and forestry applications. Its ability to cause interstitial fibrosis and death from respiratory failure was recognized in 1965 following deaths due to accidental and intentional (suicide) ingestion (839).

An early epidemiologic study in Malaysia compared 27 paraquat spraymen to 24 plantation workers without a history of spraying and 23 factory workers (859). No difference in pulmonary, renal, or kidney function or in blood counts was observed between the spraymen and the control subjects. The spraymen used conventional spray equipment with dilute paraquat (0.15%) and were reported not to use any protective equipment. Measurement of paraquat in urine demonstrated very low but detectable concentrations (840). While these reports suggested that normal use of low concentrations of paraquat was not associated with pulmonary function impair-

ment, accidental occupational exposure to paraquat was associated with respiratory failure and death (841). Five deaths from respiratory failure appeared to result from exposure to concentrated paraquat from sucking on blocked sprayer jets or leaking sprayers.

Paraquat continues to be a cause of acute irritant effects on the skin, eyes, and mucous membranes and of nonspecific systemic symptoms (860). It is also a major cause of intentional deaths (suicide) in developing countries (861–863). The question of whether nonaccidental exposure to paraquat with usual agricultural practices results in subclinical changes in pulmonary function remains unresolved.

Clinical features. The clinical features of interstitial lung disease due to silica or silicate of agricultural origin are similar to those of restrictive lung disease due to similar exposures from other sources, and will not be reviewed in detail here. As is characteristic of these disorders, radiographic changes may be present before the onset of symptoms or pulmonary function abnormalities (864). Respiratory symptoms are often subtle in the early stages, the most notable being dyspnea upon exercise. With progression, at-rest dyspnea and a dry cough predominate; in the late stages, congestive cardiac failure as a result of cor pulmonale may supervene. Reduced lung volume, impaired gas diffusion, and preserved flow rates (FEV_1 /FVC) are characteristic, but the spectrum of abnormalities will vary according to the underlying disease. Differences in fibrogenic potential among various silicates may result in variability in the relationship between roentgenographic changes and respiratory symptoms or pulmonary function.

Following paraquat ingestion, there is severe irritation of the oropharynx and esophagus, followed by kidney and hepatic dysfunction with progressive respiratory failure. Most significant is fulminant pulmonary inflammation with diffuse alveolar damage, followed by interstitial inflammation and fibrosis (865). Early case reports of paraquat overdoses documented that ingestion leads to progressive pulmonary fibrosis, with death occurring after 2 to 3 wk (866). Later reports of paraquat poisonings revealed a more variable clinical course, with the majority of ingestion cases surviving without residual effects. Of 931 cases of paraquat poisoning in the United Kingdom between 1980 and 1985, there were 190 fatalities (867, 868). Analysis of fatal cases suggested that there were more deaths within 7 d of ingestion than those occurring later (868). Clinical observations suggested that pulmonary edema was more significant in the early deaths, while pulmonary fibrosis was the cause in the late deaths. The dose of paraquat appeared to be significant, with low concentration formulations (2.5% granular) less lethal than the 20% liquid concentrate.

Pathophysiology. A detailed discussion of pathogenic mechanisms of mineral dust-induced lung disease is beyond our scope here. A large number of factors affect the toxicity of mineral dusts, including chemical and crystalline form, particle morphology (fibrous versus nonfibrous), particle size, shape, surface area, and particle charge. On an equivalent weight or surface area basis, silica is much more toxic than other nonfibrous dusts likely to be encountered in the farm setting. Why one mineral is highly toxic, while another similar one (crystalline silica, for example, versus noncrystalline, amorphous silica) is not, is the subject of intense research. The generation of free radicals at particle/cell membrane interfaces is one area of research that looks promising (869).

Free radicals may be intrinsic to the particle—for example, Si radicals on the surface of quartz—or may be generated by inflammatory cells after interaction with the particle—e.g., oxygen-free radicals released by macrophages and polymorpho-

nuclear neutrophils. Free radicals are highly reactive and readily degrade proteins, nucleic acids, and unsaturated lipids.

Weathering, chemical modification, and coating of quartz particles may considerably reduce their toxicity (870–872). In contrast, etching of the surface (873) or fresh fracturing of the particle (874) increases its toxicity. Farm dusts are likely to contain quartz particles that have been weathered and in which cations of K, Al, Na, etc., have been substituted on the surface. The surface of the particle will thus be “seen” by the body as a relatively nontoxic silicate mineral instead of the highly toxic quartz. These subtle surface changes in particle chemistry will not be recognized by standard techniques for measuring quartz—for example, infrared spectroscopy and X-ray diffraction analysis; they require more sophisticated techniques for identification.

Particle length, diameter, and durability in biologic tissues are the critical determinants of toxicity for fibrous minerals. In general, durable fibers with a minimum length of 8 μm and maximum diameter of 0.25 μm have the greatest fibrogenic and carcinogenic potential (874).

Complement-dependent chemotactic and inflammatory factors may be an important mechanism of mineral dust toxicity. Mineral dust particles, like organic dusts, are able to directly activate complement via the alternate pathway, as has been shown for a number of mineral types and mixtures of minerals, including silica (875, 876), iron oxide (876), chrysotile asbestos (875), glass fibers (877), wollastonite fibers (878), and soil (879).

Soil samples from a Mexican city (Mexicali) were shown to be potent activators of complement proteins from both serum and BAL fluid (879). The soil from this region consists predominantly of potassium aluminum silicates (illite) (75%) and silica (approximately 20%) and is geographically related to soils in southern California that have been linked to pneumoconiosis in the farm population (842). In addition to activating complement, the Mexicali dust was shown to be highly cytotoxic *in vitro* as well as capable of inducing interstitial fibrosis in exposed rats.

Activation of complement by mineral dusts may also play a role in immune-mediated tissue damage at sites remote from the lung. Olenchok and colleagues (880) have shown that loggers exposed to volcanic ash dust had significantly lower levels of serum complement factors C3 and C4 during periods of intense exposure to dust, indicating dust-induced concentration of complement. They also demonstrated dust-related effects on serum IgG and IgA. A study of subject subjects exposed to silica dust and matched controls revealed a remarkable association between dust exposure and the presence of circulating immune complexes (881).

Immune complex deposition is an important cause of glomerulonephritis. Increased mortality from renal disease has been reported in several cohorts exposed to mineral dusts and mineral fibers (882). California occupational mortality studies have shown excess mortality from renal diseases for farmers and farm laborers (883). Chronic renal disease is also higher in the Bedouins exposed to dust storms in the Negev Desert than in Jews (882).

Biogenic silica fibers are common to many important agricultural plants. These include sugar cane, flax, and grasses. Exposure to biogenic silica fibers have been linked to excess deaths from lung cancer (884), mesothelioma (885), and esophageal cancer (886, 887). The fibers have structural similarities to asbestos (888) and are able to promote mesothelial tumors in rats (889). Their potential role in fibrogenesis has not been studied; however, it is likely based on their physical characteristics, that they would be capable of causing pulmonary fibrosis.

Prevention. The major strength of the studies of humans and of environmentally exposed animals is the demonstration of a good correspondence between interstitial fibrosis and mineral dust deposits, as well as correlation of dusts found in subjects with samples taken from the environment. In addition, these studies are consistent with much better data obtained from other occupational groups.

Their limitations are many. Reported cases are few, and exposure histories have often been poor or nonexistent. None has provided quantitative lung dust analysis, and most have lacked analysis for fibrous minerals—a potentially major confounding factor. Because exposure to fibrous and nonfibrous silicate minerals is universal, it is important to know that the amount of dust in the lung is greater than in the general population. Stettler and coworkers (890) have shown that the median value for the number of nonfibrous mineral particles in the general population is 0.5×10^{-9} particles per gram of dry lung. For asbestos fibers, the upper limit in the general population is 1×10^{-6} fibers per gram of dry lung (891). Finally, the classification of the interstitial lesions has been incomplete, and diagnostic criteria have been lacking. In particular, none of the studies has specifically mentioned airway disease induced by mineral dust; yet, this is the lesion most likely to be encountered in the agricultural population. Careful studies of agriculturally related inorganic dust diseases are necessary for the recognition and ultimately the prevention of this disease in exposed populations by reducing mineral dust exposure.

Areas for Future Research

1. What are the specific etiologic agents, exposure patterns, and critical exposure levels for ODS and HP?
2. What are the personal factors, environmental conditions, and specific tasks associated with increased risk of HP and ODS?
3. What are the effects of repeated exposures to different etiologic agents and episodes of ODS on lung function and chronic airway obstruction?
4. What environmental assessment methods need to be developed to identify high-risk environments for ODS and HP?
5. What methods need to be developed to reduce bioaerosol generation in the agricultural environment?
6. What specific mineral dusts in the agricultural environment cause interstitial lung disease?
7. What is the magnitude of mineral dust-induced interstitial lung disease among agricultural workers?
8. What are the specific tasks, commodities, geographic areas, and environmental conditions associated with mineral-dust-induced lung disease in agriculture?

5. AGRICULTURAL RESPIRATORY INFECTIONS

Introduction

The agricultural work environment holds the potential for exposure to many agents that may cause respiratory disease (897, 898). However, relatively few epidemiologic data are available addressing pulmonary infections in the context of the agricultural work environment. Agricultural workers may fall victim to the normal range of respiratory infections experienced by persons from the general population, yet there are many infectious conditions for which agricultural work represents a clear risk factor because of unique exposures.

Infection may result when agricultural workers are exposed to infectious secretions, aerosols, and fomites in the course of their work. The infectious agent may be human pathogens from other workers or zoonotic agents transmissible to hu-

TABLE 5.1
SELECTED AGRICULTURALLY RELATED PULMONARY INFECTIONS

Disease and Causative Organisms	Exposure Setting	Clinical Characteristics	Preventive Measures
<i>Bacterial</i>			
Anthrax* (<i>Bacillus anthracis</i>)	Exposure to anthrax spores, which may persist for years in soil and animal parts. Exposure may involve inhalation, skin inoculation, or ingestion. Two cases reported in U.S. since 1988 (936).	URI-like prodrome, followed by pneumonia, pulmonary edema, and death in several days.	Minimize contact with untreated hide, hoofs, bone, meal. Spores can be killed by processing and/or properly disposing of animal materials. Gloves and respirators are recommended. Vaccinate animals. A human anthrax vaccine is available from the Michigan Department of Public Health. Obligatory reporting in most states and countries.
Brucellosis* (<i>Brucella abortus</i> , <i>B. melitensis</i> , <i>B. suis</i> , <i>B. canis</i>)	Exposure to infectious secretions of livestock, especially during parturition. Rarely through consumption of unpasteurized dairy products. Livestock producers and meat packers at greatest risk. 112 cases in U.S. in 1996 (937).	Influenza-like syndrome with potential chronic undulating fevers.	Surveillance of herds for infection, immunization of animals, pasteurization of dairy products, adequate skin and eye protection. Obligatory reporting in most states and countries.
Leptospirosis (<i>Leptospira interrogans</i>)	Exposure to contaminated urine from farm or domestic animals. Persons working in bodies of water are at special risk. 38 cases in U.S. in 1994 (938).	Systemic febrile disease that may include pneumonitis and hemoptysis.	Boots and gloves to prevent dermal contact with contaminated water. Immunization of animals and humans. Reportable in many states and countries; reportable in the U.S. until 1995.
Melioidosis (<i>Pseudomonas pseudomallei</i>)	Typically seen in rice farmers in undeveloped countries. Exposure occurs when damaged skin comes into contact with contaminated soil and water. Persons with underlying disease, such as diabetes, are at increased risk (939).	Absence of disease to asymptomatic pulmonary consolidation, necrotizing pneumonia, and septicemia.	Persons with underlying diseases such as diabetes mellitus should avoid contact with soil and water, such as rice paddies.
Nocardiosis (<i>Nocardia asteroides</i> , <i>N. brasiliensis</i> , <i>N. otitidiscaviarum</i>)	Inhalation of contaminated dust.	Pneumonitis that may disseminate.	No specific control measures. Not generally reportable.
Pasteurellosis (<i>Pasteurella multocida</i>)	Usually associated with bite or scratch exposures to animal saliva, particularly from cats.	The disease is usually local dermatitis, but dissemination and pulmonary disease can ensue.	Avoid exposure to animal saliva.
Plague* (<i>Yersinia pestis</i>)	Transmission by flea bite from infected rodent. Ground squirrels, rabbits, and domestic cats are affected. Endemic among rodents in western U.S. and many other countries. 5 cases in U.S. in 1996 (937).	Septic dissemination from local lesions may produce pneumonic plague. Respiratory secretions of affected persons are infectious.	Rodent control measures. Avoid contact with wild animals. Human vaccines are available. Reporting is universally required.
Psittacosis* (<i>Chlamydia psittaci</i>)	Inhalational exposure to desiccated droppings or secretions of infected birds. Turkey, duck, and geese farms, as well as household birds, are potential sources. 42 cases in U.S. in 1996 (937).	May cause upper and lower respiratory disease. Symptoms frequently less than suggested by radiographic appearance.	Disease surveillance in commercial operations, with treatment or destruction of infected birds. Reportable in most states and countries.
Q fever (<i>Coxiella burnetii</i>)	Exposure to aerosolized bacteria, frequently from parturient farm animals and cats. Slaughtering and dressing carcasses.	Pneumonitis.	Spray cattle to reduce ticks. Pasteurization of dairy products. Skin and respiratory protection when working in contaminated environments. Human and animal vaccines are available. Reportable in some locales.
Streptococcal upper respiratory tract infection (<i>Streptococcus zooepidemicus</i>)	Dairy farms, consumption of unpasteurized milk.	Upper respiratory tract infection; postinfection nephritis has been described (940).	Handwashing and general hygiene; avoidance of ill persons and unpasteurized milk.
Tularemia (<i>Francisella tularensis</i>)	Contact with the bacterial agent during handling of wild game, e.g., rabbits, squirrels, foxes, deer, etc. Exposure may also be inhalational, by ingestion, or by bites from hard-bodied ticks or deer flies. 96 cases in U.S. in 1994 (938).	Cutaneous infections tend to cause prominent ulceration and lymphadenopathy with fever. Respiratory exposure may lead to upper and lower respiratory infection. Pneumonia may be accompanied by hilar adenopathy, hemoptysis, and patchy infiltrates.	Minimize exposure to wild animals. Gloves and personal protective equipment, including respiratory protection, when skinning or dressing wild game. A human vaccine is available, but does not protect well against cutaneous disease. Not reportable in the U.S. since 1995.
<i>Mycobacterial</i>			
Tuberculosis* (<i>Mycobacterium tuberculosis hominis</i>)	Exposure to aerosols of respiratory secretions from infectious persons. Total of 22,813 reported cases in the U.S. in 1995 (8.7 cases per 10 ⁵ -yr) (903). Recent statistics show 21,337 cases for 1996 (904). Farm workers have up to sixfold increased risk (901, 902).	Tuberculosis	Identification and treatment of active cases. Surveillance and prophylaxis of high-risk groups (901).

(Continued)

TABLE 5.1
CONTINUED

Disease and Causative Organisms	Exposure Setting	Clinical Characteristics	Preventive Measures
Tuberculosis (<i>M. bovis</i>)	Ingestion of unpasteurized milk or exposure to aerosols of respiratory fluids from infected cattle. Abattoir workers and persons working with infected animals are at increased risk.	Tuberculosis. Extrapulmonary infection is most common where exposure is by ingestion of infectious dairy products.	Pasteurization of dairy products, slaughter of infected cattle. Surveillance of animal herds, imported cattle, and exposed human populations. Vaccination of animal herds. Measures to reduce aerosols and respiratory protection for exposed workers. The efficacy of prophylaxis with INH has not been studied (920).
Atypical mycobacteria (<i>M. avium-intracellulare</i> complex)	As for <i>M. tuberculosis</i> .		As for <i>M. tuberculosis hominis</i> .
Fungi			
Adiaspiromycosis (<i>Chrysosporium parvum</i>)	Contact with infected rodents and small mammals.	Adiaspiromycosis: self-limiting granulomatous lung disease with potential for fatal dissemination (941).	Rodent control measures.
Aspergillosis (<i>Aspergillus fumigatus</i> , <i>A. niger</i> , <i>A. flavus</i>)	Found in compost piles undergoing decay, damp hay, stored cereal grains.	Allergic bronchopulmonary aspergillosis in asthmatic and allergic patients, aspergilloma, pneumonia with potential dissemination. Rare in healthy persons; immune suppression is a risk factor.	Ordinary cleanliness. Stored food with high levels of aflatoxin should be condemned. Not ordinarily reportable.
North American blastomycosis (<i>Blastomyces dermatitidis</i>)	Inhalation of spore-laden dust.	Acute pulmonary syndrome, generally self-limited. A chronic granulomatous form also occurs and may disseminate.	No specific preventive measures. Not ordinarily reportable.
Coccidioidomycosis* (<i>Coccidioides immitis</i>)	The fungus grows in soil and is aerosolized with dust. Epidemics due to wind-borne arthrospores have been described (924, 925).	Generally presents as a self-limited pneumonitis (San Joaquin Valley fever). It may progress to a chronic pneumonia and dissemination. Animals may also be affected.	Plant ground cover and other dust-control measures. Reportable in some locales. Human vaccines are not available.
Cryptococcosis (<i>Cryptococcus neoformans</i>)	Saprophytic growth of fungus in soil and in pigeon droppings, leading to inhalational exposure.	Pneumonitis, frequently associated with dissemination to the meninges and other organs.	Removal of collections of pigeon droppings, with wetting and dust control measures.
Histoplasmosis (<i>Histoplasma capsulatum</i>)	Inhalational exposure to mold growing in soil, especially around chicken houses and bird or bat roosts.	Usually acute and self-limited respiratory illness. Chronic illness and dissemination may occur.	Dust control measures, personal respiratory protection. Reportable in some locales.
Sporotrichosis (<i>Sporothrix schenckii</i>)	Skin infection starts locally with inoculation of fungus from thorn pricks or laceration.	Local skin infection may disseminate and produce pneumonitis. Pulmonary disease may also follow inhalation of conidia.	Treatment of lumber with fungicides. Not generally reportable.
Viruses			
Equine morbillivirus	Exposure to ill horses. An outbreak in Queensland, Australia in September 1994 killed 13 of 21 naturally infected horses and one of two infected human beings. The natural reservoir remains unknown.	Febrile influenza-like syndrome with hemorrhagic pulmonary edema.	Avoid exposure to ill horses.
Hantavirus pulmonary syndrome* (<i>Hantavirus</i>)	Exposure to deer-mice (<i>Peromyscus maniculatus</i>) droppings. As of May 1, 1997, 160 confirmed cases have been identified in 26 states (case fatality rate: 47.5%); 22 of these cases occurred in 1996 (937).	Influenza-like syndrome followed by respiratory failure.	Hygienic measures to keep environment free of rodents. Avoid contact with mouse droppings, including aerosols.
Swine influenza (<i>Swine influenza virus</i>)	Exposure to swine. Transmission from ill pigs to humans has been described at an agricultural fair, with probable subsequent person-to-person transmission (935).	Influenza syndrome.	Immunization of workers with vaccine incorporating the relevant strain; oral amantadine; isolation of ill animals; closure of pig barns to public when illness suspected; animal vaccination available for turkeys but not for pigs (958).
Parasites			
Ascariasis (<i>Ascaris lumbricoides</i>)	Ingestion of contaminated soil or inadequately cooked food.	Pulmonary ascariasis with eosinophilic pneumonia.	Sanitary toilet facilities. Proper hand washing and food handling. Not usually reportable.
Dirofilariasis (<i>Dirofilaria immitis</i>)	Dog heart worm, transmitted to humans by mosquito bite.	The worm may lodge in a pulmonary artery and subsequently form an embolism, leading to an area of necrosis and fibrosis ("coin lesion").	Mosquito control measures. Not generally reportable.
Echinococcosis (<i>Echinococcus granulosus</i> , <i>E. multilocularis</i> , <i>E. vogeli</i>)	Larval stage of the canine tapeworm; cattle and other farm animals may be intermediate hosts. Transmission is oral-fecal involving contaminated feces.	Larvae migrate through the blood vessels and form cysts in lungs and other organs.	Prevent access for dogs to uncooked animal viscera. Environmental measures to reduce dog feces. Not reportable in most states or countries.
Paragonimiasis (<i>Paragonimus kellicotti</i> , <i>P. mexicanus</i> , <i>P. westermani</i> , and others)	Ingestion of inadequately cooked crab or crayfish.	Cough, hemoptysis, pleuritic chest pain. Infiltrates and pleural effusions may be seen on chest radiograph.	Adequate cooking of crustacea. Not generally reportable.

Definition of abbreviations: INH = isonicotinic acid hydrazide; URI = upper respiratory infection.

* Nationally reportable in the United States.

mans. Exposure may lead to asymptomatic infection, as seroepidemiologic studies in farmers show for *Brucella*, *Hantavirus*, *Chlamydia psittaci*, *Coxiella burnetii*, and other agents (896). Exposure and infection may also lead to frank disease, with significant health and economic costs to individuals and society.

The purpose of this section is to review the current state of knowledge regarding infectious respiratory conditions as they relate to the agricultural work environment. It is beyond the scope of this article to include all agriculturally related infectious diseases that may have a pulmonary component. Consideration was therefore limited to conditions for which respiratory effects are an important part of the clinical syndrome (Table 5.1). In addition, several of the most important or topical conditions for which epidemiologic data addressing agricultural work as a risk factor exist are discussed below. Readers wishing further detail about specific conditions should consult the relevant literature, including the American Public Health Association's excellent text, *The Control of Communicable Diseases in Man* (899).

Selected Respiratory Infections

Tuberculosis. In 1995, there were 22,813 cases of tuberculosis reported nationally, yielding an incidence of 8.7 cases per 10⁵ among the general population (900). Based on a Centers for Disease Control (CDC) survey addressing occupational and residential characteristics of tuberculosis cases from 1985–89, it was estimated that farm workers accounted for 5% of all employed cases, leading to an estimate that the risk of tuberculosis in farm workers was sixfold that of the general population of employed adults (901). A study of tuberculosis cases in 29 U.S. states from 1984–85 showed an SMR of 3.7 (95% CI: 3.4–4.1) for agricultural workers (902). These studies may underestimate the true increased risk for farm workers if foreign-born farm workers disproportionately tend to return to their home country when ill, thus escaping detection in the United States.

A proportionate mortality study of 2,206 pulmonary tuberculosis deaths occurring between 1979–90 from the National Occupational Mortality Surveillance database showed that farm workers (Standard Occupational Classification [SOC] 479) were at approximately twofold increased risk (903). Among male farm workers, greater risk was seen among blacks (proportionate morbidity/mortality ratio [PMR], 239; 95% CI: 162–342) than among whites (PMR, 2.06; 95% CI: 110–352). A similar race-specific pattern was seen among male farm operators (SOC 473–474), but the magnitude of risk was lower (for black males: PMR, 159, 95% CI: 122–205; for white males: PMR, 117, 95% CI: 97–140). Insufficient data were available for white females. Among black females, PMR was 259 (95% CI: 124–477) for farm operators, and PMR was 160 (95% CI: 44–411) for farm workers.

Several prevalence studies of tuberculin skin-test reactivity and active tuberculosis have been conducted recently among U.S. migrant farm workers (Table 5.2) (904–912). Taken together, these studies document a high prevalence of tuberculosis exposure among migrant farm worker populations. Risk factors for skin-test reactivity include age, male gender, and ethnicity. Non-Hispanic whites had the lowest prevalence rates (4%), followed by Hispanics (20–36%) and African-Americans (29–46%). Haitian and Caribbean farm workers had the highest prevalence rates, ranging from 55–83%.

Persons infected with human immunodeficiency virus (HIV) are at increased risk for tuberculosis and atypical mycobacterial diseases. Villarino and coworkers (910) measured the prevalence of skin-test reactivity to tuberculin and control

antigens (tetanus, candida, and mumps) and HIV serology among a group of 271 Florida farm workers. Of 253 persons with data sufficient for analysis, the prevalence of HIV seropositivity was 5%, and 43% had reactive tuberculin skin tests. The 5% HIV seropositivity rate is greater than the 2.6% prevalence observed in migrant farm workers in North Carolina (916).

Studies of tuberculosis prevalence and risk factors among agricultural workers are limited by several factors. Selection bias may influence whether farm workers are included in surveillance programs or other studies. Ill farm workers born outside the United States may return to their native countries rather than seek care in the United States. This is especially likely for undocumented persons, who may be at increased risk compared to legal immigrants due to socioeconomic and other confounders. The venue of study may also affect results. For example, persons contacted at a migrant labor camp may differ in important ways from subjects recruited at a specific workplace. Persons with a standard domicile may not be comparable to the homeless or persons living in nonstandard housing circumstances, such as in cars or in the open countryside. Response bias is also a potential source of error. For example, many of the existing studies of tuberculin reactivity (Table 5.2) have participation rates below 60%. Participants may differ from nonparticipants in important and unpredictable ways.

The CDC Advisory Committee on the Elimination of Tuberculosis has recommended that the highest priority be given to detection and diagnosis of persons with symptoms of active tuberculosis, treatment (directly observed therapy if possible) and contact investigation for persons found to have tuberculosis, and screening and preventive therapy for persons who may be immunocompromised, e.g., due to HIV (901). Screening and preventive therapy should also be available for children of migrant and seasonal farm workers and for agricultural workers and their families in general. Tuberculosis control activities should utilize outreach workers with the same cultural and linguistic background as the patient population.

Tuberculosis is most commonly caused by *Mycobacterium tuberculosis hominis*. Prior to the widespread introduction of milk pasteurization, between 6 and 30% of human tuberculosis cases in developed countries were caused by *Mycobacterium bovis* (914). Although pasteurization has largely eliminated *M. bovis* as a public health problem in developed countries, it remains important in the developing world, where poverty, malnutrition, HIV infection, and inadequate public health infrastructure increase the human toll (915–918).

M. bovis is endemic in wild and farm animals throughout the world; nonhuman hosts include cattle, deer, elk, nonhuman primates, pigs, cats, dogs, badgers, rhinoceros, and others (916). Consumption of infected animal products is more likely to involve extrapulmonary sites, whereas occupational exposures, which usually involve aerosols, more commonly lead to respiratory infection (916). Humans constitute a “spillover host”; infection in human populations is usually not self-sustaining in the absence of continuing exposures to animal sources (916). Persons occupationally exposed include abattoir workers, farm workers, zookeepers, and others with occupational exposure to potentially infected animals (916, 919).

The potential for this organism to cause human infection in agricultural workers is illustrated by a recent outbreak related to *M. bovis* infection in a domesticated elk herd in Alberta, Canada (920). Unrecognized *M. bovis* tuberculosis developed in an animal in a registered herd. Sixty-nine of Alberta's 110 registered elk herds required quarantine because they had purchased animals from the index herd. Ultimately, 446 hu-

TABLE 5.2
STUDIES OF TUBERCULIN SKIN-TEST REACTIVITY IN U.S. AGRICULTURAL POPULATIONS

Reference No.	Location and Population	Prevalence of Tuberculin Skin-test Reactivity among Risk Groups
Centers for Disease Control, 1986 (904)	Virginia. Clinic-based cross-sectional survey of 496 migrant farm workers in 1984 and 633 farm workers in 1985. Participation: Estimated 5–21% of local farm worker population.	0–15 yr: 2% 15–34 yr: 49% ≥ 35 yr: 59% Non-Hispanic white: 4% Hispanic: 25% Non-Hispanic, non-Haitian Black: 43% Haitian: 66%
Jacobson and coworkers, 1987 (905)	Delmarva Peninsula (Maryland, Delaware, Virginia). Cross-sectional study of population-based sample from 709 farm labor camp residents (≥ 5 yr of age) in 1982. Participation: Estimated refusal rate 5–10%.	Men: 41% Women: 25% U.S.-born Hispanics: 20% U.S.-born Blacks: 29% Mexican migrants: 36% Haitian immigrants: 55% Prevalence increased with age.
Simmons and colleagues, 1989 (906)	Surry County, NC. Cross-sectional study of 435 migrant farm workers in 1988. Participation: Numerator data only; unable to determine participation rate.	Hispanic migrants: 31%
Hibbs and associates, 1989 (907)	Franklin County, PA. Cross-sectional study of convenience sample of 71 persons from two farm labor camps in 1988. Participation: Of 138 camp residents, 78 (57%) were interviewed.	0–14 yr: 0% 15–34 yr: 47% ≥ 35 yr: 68% Similar rates for males and females. Mexican: 27% African-American: 46% Caribbean: 83%
Ciesielski and colleagues, 1991 (908)	North Carolina. Cross-sectional study of 543 migrant farm workers living in migrant camps in five North Carolina counties. Participation: Nonresponse varied from 5% or less (in African-Americans and Haitians) to 20% among Hispanics.	Hispanics: 30% African-Americans: 44% Haitians: 76% Active tuberculosis found in 3.6% of African-Americans and 0.47% of Hispanics.
Ciesielski and coworkers, 1994 (909)	North Carolina. Follow-up study in 1991 of 94 persons from initial 1988 cross-sectional study involving 543 migrant farm workers. Participation: Of 543 migrant workers from the 1988 study, 94 (17%) were located and participated.	14/46 (30%) conversion to tuberculin reactivity over 3 yr; 2 subjects developed active tuberculosis.
Villarino and associates, 1994 (910)	Florida. Cross-sectional survey of 253 migrant farm workers > 15 yr of age. Participation: Of 518 persons > 15 yr of age, 310 (60%) agreed to participate. Sufficient data for analysis were available for 253 (50%).	44% with reactive tuberculin skin test. 5% positive for HIV.
Garcia and colleagues, 1996 (911)	Indiana. Cross-sectional survey of 354 adult and 107 adolescent migrant farm workers ≥ 11 yr of age living in migrant labor camps. Participation: Of approximately 595 eligible persons, 464 (78%) participated. Tuberculin skin testing was performed for 318 persons (53% of eligibles, 69% of participants).	28.3% with reactive tuberculin skin test among adults; prevalence comparable in men and women. Among adolescents (age 11–18), tuberculin reactivity was seen in 7.5%, with comparable prevalences in males and females. Of 48 persons eligible for INH, 22 were available for assessment of compliance. Six months of treatment were completed by 9.1% of this group.
McCurdy and associates, 1997 (912)	Northern California. Cross-sectional survey of 469 persons living in migrant housing centers serving families. Participation: 70% of residents completed interviews. Of those, 296 (63%) completed tuberculin skin testing.	16.6% showed tuberculin reactivity. Increased prevalence of reactivity was noted in the 15–39 yr age group (OR, 2.59; 95% CI, 0.79–8.47); former smokers (OR, 3.11; 95% CI, 1.20–8.09); and foreign-born (OR, 2.09; 95% CI, 0.66–6.61). No active tuberculosis found. INH recommended for 23 persons; 9 completed therapy.

Definition of abbreviation: INH = isonicotinic acid hydrazide.

man contacts were identified, and 81 of 394 (21%) persons were found to have reactive tuberculin skin tests. The veterinarian treating the index animal developed active *M. bovis* tuberculosis. The prevalence of reactive tuberculin skin tests was 27% (8/30) among veterinary surgeons treating affected herds and 5% (1/20) among veterinarians treating unaffected herds. The highest prevalence was seen in tanning plant workers, 64% (23/36). However, these results represent the initial tuberculin skin tests placed to begin evaluation. Of 106 per-

sons who underwent a follow-up skin test, conversion was documented in six (6%). Three of these individuals were exposed at the rendering plant (two who unloaded or skinned carcasses and a meat inspector stationed at the plant), one field inspector, and two laboratory technicians carrying out necropsies.

Preventive measures include vaccination of animals, control of aerosols, use of high-efficiency particle respirators when appropriate, and surveillance of animal herds, imported cattle, and exposed human populations (915, 916, 919, 921).

Medical surveillance of migrant and seasonal farm worker populations may also be appropriate.

Coccidioidomycosis. Coccidioidomycosis is a fungal respiratory disease occurring in semiarid areas, including the southwestern United States and areas in Mexico, Central America, and South America (922, 923). It is endemic in the California San Joaquin Valley; hence the terms "valley fever" or "San Joaquin Valley fever." Exposure occurs when aerosolized arthrospores are inspired. Although most cases are mild and self-limited, persistent pneumonia or dissemination and death may occur. Case reports and series over the past six decades have shown a predominance of agricultural and outdoor occupations among persons contracting the disease (922, 923).

Weather conditions may affect the epidemiology of coccidioidomycosis. In particular, dry windy conditions may aerosolize arthrospores and cause epidemics. In California in late December 1977, a windstorm in the southern part of the state aerosolized arthrospores and resulted in several hundred cases in nonendemic parts of the state several hundred miles north of the San Joaquin Valley (924, 925). Soil disruption caused by the Northridge earthquake of January 17, 1994 may also be responsible for an increase in the number of diagnosed cases in Ventura County, California (926). Within 2 mo after the earthquake, the county recorded 170 cases, compared with 52 during all of 1993.

Most recently, California has experienced an outbreak beginning with a period of heavy rains following a several-year drought. In the 1980s, California reported approximately 400 cases per year. Since 1992, annual reported cases have exceeded 4,000, focused in Kern County and surrounding agricultural areas. Other factors include disruption of soil (e.g., farming activities) and immigration of susceptible persons to economically and demographically growing areas (926, 927).

The major preventive measures for coccidioidomycosis involve dust control (928). However, exposure to contaminated dust cannot be completely prevented. Although work continues on developing a human vaccine, efforts to date have yielded limited success (929).

Equine morbillivirus. In September 1994 horses in Queensland, Australia contracted a febrile respiratory illness that proved fatal in 13 of 21 naturally infected animals. A trainer and stablehand also became ill with a severe influenza-like syndrome; the trainer died within approximately 1 wk of severe interstitial pneumonia. Laboratory detective work subsequently classified the infectious agent as a morbillivirus (930). The agent exhibits a number of unique features. No new human morbilliviruses have been described since measles in the 10th century, and known morbilliviruses, prior to identification of this agent, have been specific to a single mammalian order (930). Whereas other morbilliviruses have a single type of surface glycoprotein projections yielding a "single-fringed" appearance by electron microscopy, this virus demonstrated 10- and 18-nanometer surface projections, giving a "double-fringed" appearance (934). The virus appears to cause a giant-cell interstitial pneumonia with clumping of endothelial cells, leading to fatal hemorrhagic pulmonary edema (931). Subsequent seroepidemiologic investigation in the outbreak's locale revealed no evidence of infection among 1,600 horses and 90 humans. The virus' natural reservoir remains unknown.

A second death apparently due to equine morbillivirus occurred in a 35-yr-old farmer over 1 yr after the patient's initial infection (932). In August 1994, approximately 1 mo before the Queensland outbreak described above, two horses sickened and died on the patient's property. The patient assisted his wife, a veterinary surgeon, with an autopsy on the two animals. The animal deaths were attributed to avocado poisoning

and brown snake bite. In August and September 1994, the patient developed a mild meningoencephalitis syndrome but appeared to recover. However, he was admitted to the hospital in September 1995 with signs of encephalitis. The patient's neurologic condition worsened and he succumbed on October 21, 1995. The patient's serum from his initial illness contained antibody to equine morbillivirus. Cerebral spinal fluid collected before his death showed high serum-neutralizing antibody to equine morbillivirus and a positive polymerase chain reaction. Testing done on one of the horses confirmed it was infected with equine morbillivirus. In contrast to previously described cases, there were no respiratory symptoms until development of aspiration pneumonia prior to his death. The chain of transmission to the horses has not been established. No link was shown with the original Queensland outbreak, and serologic tests of horses and domestic animals on the property were negative.

Swine influenza. The ability of influenza viruses to transcend species barriers holds the potential for human pandemics of awesome proportions (933). The 1918–19 influenza pandemic resulted when swine influenza, a type A influenza virus, infected human hosts, claiming over 20 million victims worldwide (934). Although influenza has not achieved the scale of the 1918 pandemic in the intervening 80 years, outbreaks have occurred. Agricultural workers working with swine may be at high risk because of their close contact with infected animals.

A case of fatal infection with swine influenza traced to a Wisconsin agricultural fair illustrates the potential for human disease. A 32-yr-old woman visited a pig barn at the fair and subsequently developed fatal swine influenza pneumonia (935). Investigation revealed that the pigs had been ill with an influenza-like illness. Seroepidemiologic studies showed high antibody titers to the contemporary strain of swine influenza virus (A/Wisconsin/3523/88) in the patient and among exposed swine exhibitors and among health care workers caring for the patient early in the course of her illness.

It is fortunate that the biologic behavior of swine influenza virus strains since 1918 has not been such to cause another worldwide pandemic. Because swine workers have close contact with pigs, it is possible that this group would be among the first victims. Preventive measures include immunization of workers, effective if the relevant strain is incorporated in the vaccine. Amantadine may also be effective. Vaccination of animals may also prevent disease and epidemics. Currently, a swine influenza vaccine is available for turkeys but not for pigs (935). Isolation of ill animals and closure of pig barns to the public when swine influenza is suspected is also appropriate (935).

Preventive Strategies

The underlying approach for prevention is reducing exposure. As in nonagricultural industry, the ideal way to achieve this is to remove the harmful agent from the environment or make engineering or process changes to prevent human exposure.

1. For animal-borne diseases capable of causing human infection, herd surveillance and proper animal vaccination, if available, will minimize exposures and should reduce human disease.
2. Maintenance of a clean and safe farm work environment is also important for reducing human exposures, e.g., proper handling of animal excreta and parts.
3. Personal protective devices, e.g., protective clothing and respiratory protection, will also reduce or prevent exposure with infectious materials. From a practical standpoint, however, it may be difficult to use personal protective equip-

ment if it interferes with safely completing tasks or if environmental conditions (e.g., heat) make their use very uncomfortable.

4. Human vaccination where available is warranted for high-risk workers.
5. For tuberculosis, recommendations for migrant and seasonal agricultural workers and their families have been formulated by the Advisory Council for the Elimination of Tuberculosis (904). These are shown below in order of decreasing priority:
 - a. Detection and diagnosis of those with current symptoms of active tuberculosis;
 - b. Treatment and monitoring of those with current disease;
 - c. Contact investigation and appropriate preventive therapy for those exposed to infectious persons;
 - d. Screening and appropriate preventive therapy for asymptomatic infected workers who may be immunosuppressed, such as those with HIV infection;
 - e. Screening and appropriate preventive therapy for children of migrant and seasonal farm workers; and
 - f. Widespread tuberculin test screening for workers and families, with preventive therapy as appropriate.

Areas for Future Research

The most appropriate areas for future work are in developing surveillance programs to monitor the health burden of specific conditions. Identification of risk factors and their interactions is also valuable. With respect to interventions, much has already been done that is not likely to be the subject of efficacy or effectiveness studies. For example, hygienic measures to minimize exposures to animal parts are logical and appropriate. It would not be feasible or ethical to conduct a controlled study to test their efficacy in preventing anthrax, for example. However, as new exposure reduction techniques become available, it is appropriate to evaluate their efficacy against existing standards by monitoring outcomes more sensitive and less devastating than human disease. Surveillance of human health should be retained, however, to detect unsuspected problems or breakdowns in hygienic measures. Finally, valuable research continues in developing animal and human vaccines for agriculturally related infectious agents.

There is much literature describing the current state of knowledge for each of the agents and conditions described in Table 5.1. It is beyond the scope of this paper to summarize this for each of these conditions. With respect to the epidemiologic and prevention aspects as they relate to the agricultural work environment, however, several relevant points emerge.

Epidemiologic surveillance data are limited or incomplete for many agricultural respiratory infections. In particular, reporting requirements vary with locale, and compliance is imperfect. In addition, analytic epidemiologic studies addressing risk factors (especially those relating to the human host and the environment) and potential interactions (e.g., with smoking, HIV infection) have not been performed for many conditions. Finally, there are few epidemiologic studies documenting efficacy of preventive strategies.

Research is ongoing addressing the biology of the agents included in Table 5.1. These efforts may yield information or advances, such as vaccines, that will have important implications for prevention. However, research efforts to characterize the epidemiology and efficacy of preventive measures are also needed.

1. Improved surveillance for infectious respiratory conditions in the agricultural setting. Tuberculosis among agricultural

workers is of primary importance because of its public health implications.

2. Descriptive and analytic epidemiology identifying high-risk groups and situations. In particular, studies are needed addressing the confluence of tuberculosis and HIV among agricultural workers.
3. Studies documenting the efficacy of preventive measures, to include cost-benefit analysis.

6. RESPIRATORY DISEASE IN INDUSTRIALIZING COUNTRIES

Although the types of respiratory diseases caused by agricultural exposures may be similar in industrialized and industrializing countries, the nature of agricultural production is considerably different, posing differences in the likelihood of exposure to harmful substances, resulting in dramatically different disease burdens and distribution. There are considerable differences in availability and accessibility of preventive services and protective equipment and in the implementation of regulations. Moreover, the agricultural workforce in industrializing countries often consists of a considerably younger population, including children.

Definition and Overview

For purposes of discussion, industrializing countries are defined as those countries with an economic level in the mid to low range (943). Over the past four decades, there has been unprecedented population growth in the industrializing countries of the world. Presently, these countries constitute more than 70% of the world's population (944), and this population is likely to double in the next 50 years, even under the most optimistic projections. Although industrial activity has also expanded greatly in these countries, agriculture still accounts for a substantial, often the major, proportion of economic activity.

Climatic conditions impact the agricultural environment in industrializing countries in a manner quite different from that in industrialized countries. A high proportion of these countries are clustered in the tropical and subtropical regions of the globe. They are heterogeneous but share common characteristics of relevance to this discussion: rapid population growth, lack of access to safe water, and low literacy rates; high mortality rates for infants and children under the age of five are common. Most of the world's largest cities are in industrializing countries, and in recent years have experienced dramatic increases in population, with many attendant health problems (945).

Agriculture in industrializing countries is defined by production of animal or plant products from identifiable portions of land, usually situated away from urban areas. Agricultural products may be used primarily for personal and family consumption or may be the source of cash or barter for trade. Rapid urbanization notwithstanding, agriculture continues to be the chief economic sector contributing to employment in these countries, with 50 to 90% of the population of most industrializing countries dependent on agriculture for their livelihood (946). Systems of production, land ownership, and land use are very diverse across the globe. Within this diversity, it is useful to distinguish between the formal sector (commercial and cash crop, plantations, including multinational agribusiness), the informal sector (market gardening and petty trade), and the agricultural food procurement (domestic subsistence) sector.

Subsistence and informal sector production typically occurs on small areas of land and is carried on by individual owners, tenants, or communal landowners. Production is primarily directed to providing the subsistence needs of farmer and fam-

ily, with marketing of any surplus. Women and children make major contributions to agricultural work. Such farmers are frequently in their countries' cultural minority groups and may be politically and economically marginalized for a variety of historical reasons. Their land may also be the least suited to agriculture. Traditional technologies and practices continue to be used, often reinforced by strongly rooted beliefs and customs and a reliance on oral rather than written forms of communication.

Due to inroads by the agrichemical industry, increasing use is likely to be made of agrichemicals within the informal and domestic sectors. This type of production is relatively invisible from the point of view of indicators like gross domestic product (GDP) and tends to be overlooked in importance. These sectors, however, account for a significant part of the livelihood of the majority of the populations of most industrializing countries, particularly in the production of food. Remoteness, lack of economic and political influence, and other factors frequently mean that the populations in small-scale agricultural areas lack access to schools and essential health care services, including occupational health services (947–950).

In contrast, formal sector production typically occurs on relatively large land areas, usually owned by individuals, companies (agribusiness), or the state. Large-scale plantation production favors monoculture and usually occupies the best agricultural lands. It also includes family plots farmed for cash crops linked to cooperative production and marketing arrangements. Successful formal agricultural production typically uses agrichemicals and is mechanized. This sector is fully visible and makes the major contribution to GDP. Agricultural products such as coffee, tea, rubber, and cotton are the most important exports of many countries. Such products are also the basis on which secondary industries such as textiles are developed.

With its orientation toward production of cash crops and exports, large-scale production has been traditionally favored by the governments of many countries, as well as by development agencies (951, 952), although there has been a recent trend to stimulation of the informal sector. The influence of this favored status has nevertheless been slow to trickle down and affect working and living conditions of agricultural workers in the formal sector (948, 951, 953).

The most serious respiratory diseases associated with agricultural exposures are those affecting the lung, and the most common ones are asthma and other forms of airflow obstruction, HP (extrinsic allergic alveolitis), pulmonary fibrosis, and infection. ODS, while not a localized disease, is a result of inhalation and is considered here. Other adverse health effects of respiratory exposure to harmful substances in the agricultural environment include cancer of the upper airways and mucous membrane irritation.

Exposures

Organic dusts are probably the most ubiquitous respiratory insults in the agricultural setting. Plants such as tea, coffee, tobacco, cotton, cereal grains, sisal, and jute are major products of the formal sector in many industrializing countries. During production of these crops, agricultural workers risk exposure to substantial quantities of dust. For example, estimates of the levels of organic dust exposure in a grain-milling operation in South Africa were substantially higher than those documented in industrialized countries (954). Similar higher levels of grain dust were reported in small-scale rice granaries in China (400, 402). Similarly, higher levels of exposure to cotton

dust (as compared with industrialized countries) have been documented in Sudan (231, 955) and China (956, 957).

Tropical climates with high levels of heat and humidity create a perfect environment for the development of fungi and gram-negative bacteria endotoxins, particularly when plant products are stored for prolonged periods of time before being processed or consumed. Sugar cane is the best-known example, but tea, coffee, tobacco, and cereal grains all have the potential for growth of both fungi and bacteria.

The risk of exposure to dust from animals varies with the nature of the production methods. Although livestock confinement facilities are less common in industrializing countries, they are used in certain areas. Traditional methods of managing livestock vary widely: in some areas, livestock management is predominantly an outdoor activity with very low risk of exposure to substantial levels of dust. In others, livestock are guarded from predators and thieves at night, and from some seasonal weather extremes, by keeping the animals within the same small dwellings inhabited by their owners; in these conditions, the risk of high-level animal dust exposure is great.

Inorganic dust exposures represent less of a hazard, since farming practices in industrializing countries encourage relatively low exposure to these substances; only with mechanization of cultivation techniques are substantial levels of exposure to inorganic dusts common.

Products of combustion, however, may pose a heightened hazard. Prolonged and sometimes very intense outdoor exposures to such products are common in Africa and stem from several sources: traditional "slash and burn" techniques, accidental fires, and burning as an integral part of crop cultivation, as is the case with sugar cane. Indoor exposure to combustion products, mainly from the use of biomass fuel for cooking, is common, but actual exposure levels are poorly documented.

The risk of exposure to a large variety of toxic agrichemicals is very high in industrializing countries and is widely recognized as the most apparent and serious occupational health hazard related to agriculture in Africa (947, 958–962). Agrichemical exposures, particularly to pesticides such as the organophosphates and carbamates, are toxic and potentially lethal, with death by paralysis and respiratory failure. Herbicides may also be toxic to the respiratory system and potentially lethal, even in small quantities (e.g., paraquat). Chronic effects may ensue from long-term, low-dose exposure; again, paraquat is an example, although such effects have not been documented in published studies (963). Many agrichemicals banned in industrialized countries are marketed and freely available in industrializing countries, and their use is increasing, in both large- and small-scale farming.

In Africa, exposure to toxic chemicals is often related to spraying or cattle dipping (961). Field studies of spraymen, using such biomarkers as serum cholinesterase levels, have usually yielded positive results, indicating substantial exposures (959, 960). Few attempts have been made to estimate the extent of agrichemical use in Africa. A recent survey in South Africa's Western Cape Province estimated that, of 120,000 workers employed in deciduous fruit production, 8.5% may be directly exposed (and 14% indirectly exposed) to agrichemicals (958).

In Central America, banana production relies heavily on the use of herbicides and pesticides. Some observers believe that consumption of these toxic chemicals is so high there as to represent a substantial risk to the entire population.

Under some circumstances, potential hazards may combine to present respiratory threats. Fibrous silicates, for example,

may contaminate smoke from fires in cane fields, and a link to mesothelioma has been postulated (964).

Infections posing risks to agricultural workers in industrializing countries are markedly different from those that threaten U.S. farmers; the differences relate to both climate and farming practices (951). Agents carried by insects or transmitted in water are particular farm-associated hazards, especially in wetland areas such as those focusing on rice culture. Among major infectious threats are malaria, diseases caused by arboviruses, and schistosomiasis and other parasitic sicknesses.

As with all large-scale employment, agribusiness depends on migrant labor and must of necessity supply or arrange for worker housing; often, the facilities are characterized by overcrowding and poor ventilation. In these circumstances, the risk of airborne infection is very high; tuberculosis is a particular concern. The disruption of social structures in such migrant communities also poses a risk for sexually transmitted diseases, most catastrophically HIV. Such transmission also endangers the home communities to which these workers eventually return.

Climate may be an important factor for both good and ill. On the one hand, the tropical climate common to most industrializing countries encourages more outdoor activities, thus avoiding indoor ventilation problems. But hot and often humid conditions also promote the growth of bacteria and fungi and typically increase the likelihood of exposure to microorganisms.

A final factor is that even in the formal sector, safety and health conditions are frequently ill-regulated. Such matters as indoor ventilation, frequent inspection of premises and equipment, and the mandating of protective devices are unfortunately frequently substandard in many of the industrializing countries.

Pathogenesis

The pathogenesis of respiratory diseases caused by environmental exposure in industrializing countries is similar in many respects to that in industrialized countries, usually involving one or more of these familiar processes: inflammation, sensitization, direct toxicity, infection, and carcinogenesis. The difference is in the modifying roles played by host factors and by combinations of environmental agents to which individuals are exposed.

A number of studies have shown that the past medical history of individuals is also relevant to their later risk of disease. A history of childhood pneumonia or atopy, for instance, is associated with subsequent respiratory illness. It is well known that respiratory infections in childhood are much more common in industrializing than in industrialized countries. It is probable that atopy is more common in industrialized countries as compared with industrializing countries. Whether this influences susceptibility of individuals to adverse respiratory health effects of occupational exposures and thus leads to a difference in the occurrence of disease in the two situations is unknown. Nor have such host factors as racial or genetic characteristics been systematically investigated.

Certain exposures act in a synergistic manner to produce disease; this is particularly true of exposures leading to carcinogenesis (the combination of radon and cigarette smoking is a familiar example). Moreover, certain host factors such as nutritional status play clearly demonstrated roles in modifying exposure responses, especially to carcinogens. The relatively lower prevalence of tobacco smoking in many low-income countries might influence the rates of lung cancer in exposed populations; the prevalence of tobacco smoking is even lower

among farmers than among the general population, further leading to difficulties in detecting carcinogenic risks.

The time course of a disease may also influence the ability to detect it—a particularly pertinent consideration in studies of such conditions as HP. The acute illness in the usual acute cases of farmer's lung (FHP) is brief and nonspecific, making the usual cross-sectional epidemiologic research methods of low sensitivity and specificity (see Section 4). The failure to find the disease using this type of approach cannot be taken as evidence that it does not occur.

Somewhat different problems are encountered in dealing with cross-sectional studies of occupational asthma. Excessive susceptibility to exposure to dust and fumes in the environment leads many patients with asthma to stop working in such environments or to avoid exposure to the more heavily contaminated areas—leading to an underestimation of risk due to the “healthy worker effect.”

Extent of the Problem

Many studies have been reported from countries throughout the world, and it is clear that occupational respiratory disease in agriculture is widespread.

- A comparative health study of agricultural and industrial workers in Nigeria showed many more health problems among the former (963). Most of the problems identified were related to nutrition and communicable diseases. Chronic bronchitis, nevertheless, was less common in the agricultural workers as compared with those exposed to cement dust (0.7% versus 13.2%).
- Epidemiologic studies of rice farmers in China began in the early 1980s and have shown clear evidence of both upper and lower respiratory disease among millers (400, 402). Studies of rural workers exposed to a variety of organic dusts, such as tea, straw, hay, mushroom compost, and wood dust, have been reported (430).
- Chronic respiratory disorders have been demonstrated in Egyptian flax farmers (965) and in West African jute workers (664).
- Studies of long-term exposure to tea dust have been reported (665), and further studies are now under way in China.
- Chronic airway obstruction has been shown to be related to particulate exposure within homes, caused by the use of wood or other biomass fuels in Saudi Arabia (669).
- A hospital-based study in Zambia has identified agricultural products as second only to chemicals in causing occupational asthma (532).
- ODS has been reported among workers exposed to grain dust in China (400, 402). Long-term studies have explored the problems of extrinsic allergic alveolitis and ODS in China (430); these studies have included measurement of dust levels as well as evaluation of precipitating antibodies and have identified cases of occupationally related extrinsic allergic alveolitis.
- Pulmonary fibrosis due to inorganic dust exposure has been reported among rural women in South Africa. This condition, termed “hut lung,” is of varied etiology and has been attributed to coal dust as well as mixed dusts (966). Occasionally, true silicotic nodules have been identified. A high proportion of cases have evidence of previous tuberculosis. The etiology of this condition is thought to be related to exposure to particulates from biomass fuels, such as cow dung used in the home. In addition, exposure to quartz occurs, due to traditional grinding of cereals using stone implements. The condition appears to be most common in areas

with relatively cold winters, where enclosed household environments are more common.

- Case series from urban-based referral hospitals in southern Africa have shown that most cases of acute toxicity involving agrichemicals have resulted from suicide attempts or accidental ingestion (e.g., contaminated fruit and vegetables, discarded containers, or aerial spraying) (967–969).
- A recent South African report of a study among Western Cape farm workers exposed to the herbicide paraquat revealed a significant association between chronic paraquat exposure and arterial oxygen desaturation on exercise (970).

Clinical Features

The management process of any clinical problem entails the familiar steps of recognition, diagnosis, treatment, and prevention of recurrence. While the clinical features of a disease may not differ between industrialized and industrializing countries, the management process is dramatically different. Probably the most striking difference is the recognition of occupational exposures as a potential cause of a respiratory illness. In many low-income countries, where diagnostic facilities are severely limited, these factors may not be taken into account in differential diagnosis.

An example of the impact of these differing approaches is the management of the patient with chronic respiratory symptoms. In most low-income countries, any patient presenting with an illness accompanied by cough of more than 3 wk and less than 1 yr duration is defined as a “tuberculosis suspect.” If the examination of sputum by microscopy fails to identify the bacterium, the patient is given a trial of antibiotic treatment followed by further sputum examination. If the organism again fails to appear and the patient remains symptomatic, treatment for tuberculosis might nevertheless be given. A file of “chronic tuberculosis cases” thus accumulates. If and when these patients are investigated more systematically, it is often found that the majority never had tuberculosis at all but rather another chronic respiratory illness. That illness is usually a common condition such as bronchiectasis, but individuals with chronic respiratory illnesses due to occupational exposures would likely be found in the group as well.

The availability and accessibility of medical facilities also reflects on the application of preventive measures. The majority of agricultural workers live in remote areas where diagnostic and treatment facilities are severely limited. The implementation of prevention procedures is highly dependent in this situation on awareness of the risk, concern that something should be done, willingness to assume responsibility, and the means to carry it out. For the majority of agricultural workers in industrializing countries, this confluence of circumstances does not exist.

Natural History

A chronic disease, such as a respiratory disease due to occupational exposure, often proceeds through the following stages: initiation, latency, exacerbation and remission, chronicity, and fatality. The last three stages may be influenced by the health services available in the community. As noted previously, there is a great difference between industrializing and industrialized countries in this regard, with relatively greater risks in industrializing countries of exacerbation, chronicity, and fatality. These circumstances tend to increase the prevalence of disabling illnesses in the community and make them easier to detect by epidemiologic methods.

The long latent period associated with the majority of these conditions, on the other hand, would tend to reduce the num-

ber of cases in a given workforce or even in a community, due to the fact that the life expectancy of individuals in many industrializing countries is substantially shorter than that in industrialized countries. Further, in either setting, many of the chronic effects of occupational exposures are seen only as functional impairment in old age. Moreover, most wage laborers are young—especially so in many industrializing countries, with rapid personnel turnover and little accumulation of seniority. It is thus difficult to detect chronic effects of exposure.

Areas for Future Research

There is a great need for epidemiologic studies of agricultural respiratory disease in industrializing countries. Moreover, methodologies need to be developed for setting an occupational and environmental health education agenda to make research results available to those most affected. With resources limited, there is a pressing need to closely integrate general economic development projects with environmental and occupational health considerations. Hence, environmental health impact studies should be an essential part of any development project.

The strengthening of research capability implies the development of appropriate research methods, the identification of relevant problems, and allocation of available resources. Emphasis on field epidemiology and industrial hygiene would therefore seem to be high priorities for rural projects addressing respiratory health. For example, applications or simple techniques for exposure assessment using questionnaires (971) have been shown to be effective. Establishing and validating simple and reliable biomarkers of effect are also needed for population studies.

Evaluation of health planning and establishment of occupational health systems (along with general preventive medicine) are necessary to generate appropriate information for action anywhere. Such health systems research, combined with information and (appropriate) technology transfer from the industrialized nations, could help build the necessary preventive and primary care medicine infrastructure to serve the needs of the rural workforce. Such a network would be valuable in that it would be integrated with other preventive activities—e.g., immunizations. Services could include education regarding safe handling and procedures and simple technological industrial hygiene practices (328). Importantly, the informal sector of respiratory health can be addressed by the regional and local infrastructure (972).

7. AGRICULTURAL RESPIRATORY DISEASE: SYNTHESIS

Participants in the Agricultural Respiratory Disease Workshop, held in Berkeley, California, April 1–4, 1995, discussed and debated disease/syndrome definitions and terminology regarding an inclusive taxonomy for agricultural respiratory diseases. When possible, the workshop adopted generic terminology for respiratory diseases that have been documented, but are not unique, in the agricultural setting (Table 7.1).

Two conditions sparked considerable debate—asthma-like syndrome and ODS.

It was concluded that asthma-like syndrome is distinct from asthma as a clinical entity. Workers with asthma-like syndrome typically present with chest tightness without wheezing, have a linear and progressive but modest decline in expiratory flow rates over a working shift, show a pattern of increased chest tightness and greater declines in expiratory flow rates after two or more days away from exposure, and develop progressive airway obstruction with exposure over many years. Asthma-like syndrome is recognized as byssinosis among

TABLE 7.1
AGRICULTURAL RESPIRATORY DISEASE COMMON EXPOSURES AND EFFECTS

Respiratory Region	Principal Exposures	Diseases/Syndromes
Nose and nasopharynx	Vegetable dusts Aeroallergens Mites Endotoxins Ammonia	Allergic and nonallergic rhinitis Organic dust toxic syndrome (ODTS)
Conducting airways	Vegetable dusts Endotoxins Mites Insect antigens Aeroallergens Ammonia Oxides of nitrogen Hydrogen sulfides	Bronchitis Asthma Asthma-like syndrome ODTS
Terminal bronchioles and alveoli	Vegetable dusts Endotoxins Mycotoxins Bacteria and fungi Hydrogen sulfide Oxides of nitrogen Paraquat Inorganic dusts (silica, silicates)	ODTS Pulmonary edema/adult respiratory distress syndrome Bronchiolitis obliterans Hypersensitivity pneumonitis Interstitial fibrosis

workers exposed to cotton, flax, and soft hemp and is also described among grain handlers and animal confinement workers. All of these exposures may also result in typical asthma via both immunologic and nonimmunologic mechanisms. Epidemiologic studies of agricultural workers with asthma-like syndrome demonstrate a transient increase in nonspecific airway responsiveness to methacholine and histamine.

While there was general agreement among workshop participants regarding asthma-like syndrome, there was disagreement regarding ODTS. This term was adopted at an international workshop held in Skokloster, Sweden in 1988 (578). "ODTS" provided a generic terminology to replace a large number of syndromes attributed to exposure to organic dusts—mill fever, grain fever, inhalation fever, mycotoxicosis, atypical farmer's lung, silo unloader's lung, and others. In agriculture, ODTS typically arises from very high exposures to organic dust aerosols containing extraordinarily high concentrations of fungi and their mycotoxins, bacteria, and endotoxins. All exposed workers with massive exposures become ill, typically 6–8 h after exposure began. The respiratory response is a dramatic airway inflammation affecting airways from the nasal mucosa to terminal bronchioles. In the rare severe case, pneumonitis in the form of airway-filling opacities may be observed on the chest radiograph.

An alternative term, "toxic pneumonitis," was proposed. It was argued that toxic pneumonitis was consistent with the other anatomically based respiratory terminology, that it accurately described the inflammatory process as a toxic pulmonary response, and that it avoided linking the definition to organic dust, which does not adequately convey all etiologic agents or the type of response. It was pointed out that toxic pneumonitis could accommodate other causes, including humidifier fever and even chemical causes of pneumonitis. It was further suggested that the term could be modified to convey both the result and the exposure—e.g., toxic pneumonitis from exposure to moldy cotton.

While there was not unanimous agreement, the workshop participants decided against adopting the term toxic pneumonitis largely for two reasons: (1) ODTS is primarily an airway response with a terminal bronchiole/alveolar component, and only rarely does the syndrome result in clinically detect-

able pneumonitis; and (2) there was also concern expressed that toxic pneumonitis, because of similarity in terminology, might be confused with HP, which occurs in terminal bronchioles, alveoli, and interstitium via a mechanism of delayed hypersensitivity.

While the participants in this workshop decided against adopting the term toxic pneumonitis to replace ODTS, it was concluded that this terminology deserves further review and discussion in order to reach an international consensus.

The workshop participants attempted to reach a consensus on matrices describing common agricultural environments or processes and agents, and common agricultural agents and respiratory diseases/syndromes. It quickly became apparent that both the large variation in types and extent of exposures made construction of a useful matrix for agricultural exposure by process or agent impossible. More success was achieved in constructing a matrix of principal agricultural agents by respiratory diseases/syndromes. Attempts were made to define common and rare health outcomes for each cell of the matrix. Again, this proved to be difficult. Results of this exercise resulted in the distribution of respiratory conditions and agents in three respiratory regions (Table 7.1).

Summary

Specific research needs for the different areas covered in this document are presented at the end of each chapter. A few research needs were identified that apply to the entire area of agricultural respiratory disease. These focus primarily on the identification and prevention of respiratory disease in the agricultural workplace. They include:

1. High quality educational materials need to be developed and widely disseminated to health care professionals regarding definition, diagnosis, and prevention of agricultural respiratory disease.
2. Surveillance systems need to be developed for assessment of trends in agricultural respiratory diseases and common agricultural exposures.
3. Priority needs to be given to the development of primary prevention strategies to control exposures to agents causing agricultural respiratory diseases.

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