Focus

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Danger in the Dust

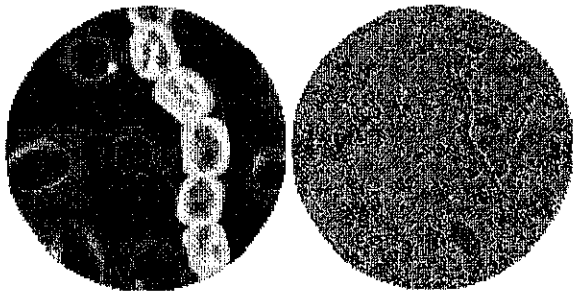
In contrast to widely held images of urban pollution and blight the persistence of an "agrarian myth" that associates life on the farm with healthful, bucolic joys ignores a fundamental reality: agriculture can be a dangerous occupation. In agriculture, a large proportion of acute traumatic injury and death comes from accidents involving farm machinery. Farm equipment also inflicts chronic injuries upon workers including noise-induced hearing loss and vibration-associated diseases of the back. Agrichemicals pose a risk for direct toxicity and possibly cancer. Dermatologic diseases, including cancers, among farmers and farm workers are often linked to ultraviolet light exposure, contact dermatitis, and zoonosis. But the most prevalent agricultural hazard involves the respiratory tract. Says Marc B. Schenker, medical epidemiologist and director of the Center for Occupational and Environmental Health at the University of California, Davis, "Despite this litany of significant occupational health problems, respiratory disease remains one of the most common and important issues for those working in the agricultural field." Indeed, occupational mortality studies from the United States, England, and Scandinavia reveal higher respiratory disease mortality rates among farmers than the general population.

The farming population in the United States includes approximately 3 million Americans fully engaged in agricultural production and as many as 9 million more who are seasonal and migrant workers, part-time farmers, and farm family members, the latter often considerably active in farm work.

Schenker points out that agriculture is different from many occupations that give rise to respiratory disease. "You have a whole range of respiratory hazards. This isn't like asbestos where you're looking for those fibers, or sandblasting when you're just measuring quartz." Schenker's list of potential respiratory hazards includes gases at potentially lethal concentrations (chlorine, hydrogen sulfide, ammonia), diesel exhaust, solvents, welding fumes, infectious agents and viral diseases from animals, and organic and inorganic dusts, "which can exacerbate any of the others," Schenker says.

Written in the Dust

"It is organic dust that accounts for the most common exposure leading to agricultural respiratory disease," says James Merchant, director of Iowa University's Environmental Health Sciences Research Center. "Virtually everybody who works in agriculture gets exposed to some organic dust."



Micro menaces. Bacteria such as *Actinomycetes* (left) and molds such as *Alternaria* and *Botrytis* (right) are among the materials found in hay dust. *(Source: Peter Thorne)*

Indeed, studies indicate that the risk associated with developing respiratory disease appears to be more than threefold greater among those who are heavily exposed to inhalable dust generated in the agricultural environment. According to pulmonologist David A. Schwartz of the University of Iowa College of Medicine, asthma and bronchitis are the main diseases. "Between five and twenty percent of individuals in aggregate will develop some airway disease as a result of agricultural dust exposures," he says.

"The major health effect is airway inflammation, and that extends from the nose to the terminal bronchiole," says Merchant. These dusts and their components are highly respirable, under 10 microns in aerodynamic diameters, so they can penetrate to the terminal bronchiole. "We see an effect in all levels of the airway, but the basic mechanism is airway inflammation, which is manifested clinically as rhinitis, either allergic or irritant; bronchitis, asthma, which can be allergic or irritant; and hypersensitivity pneumonitis."

Agricultural workers encounter a variety of airborne organic dusts generally containing 30-40% of particles in the respirable range. These include molds, pollens, and dusts generated in silos, barns, and grain elevators. Organic dusts measured in enclosed settings such as dairy, poultry, and swine buildings are particularly biologically active. Along with suspended inorganic matter (primarily silicates), they contain plant material (feed and bedding), animal-derived particles (skin, hair, feathers, droppings, urine), bacteria and fungi, mites and other arthropods, insects and insect fragments, feed additives (including antibiotics), pesticides, and microbial toxins (including glucans from molds, fungal mycotoxins, and endotoxin, the lipopolysaccharide fraction of certain bacterial cell walls).

"One thing that's really important is that farmers in general have a relatively low prevalence of cigarette smoking in comparison to the general population," says Schwartz. "And given that, it's really striking that they have such major problems with airway disease. So even if it turns out not to be endotoxin or grain dust, there's something in the environment that's causing them to have major problems with airway disease in comparison with other groups."

By Any Other Name

In the early 18th century, the Italian physician Bernardo Ramazzini recorded his observations associating respiratory disorders with worker exposure to dusts from vegetable fibers and grain. Only in the 20th century has careful study of these phenomena occurred. Among the factors that may have accounted for this lack of study was the rise of manufacturing. Victorian-era social concerns were focused on factories with their concentrations of workers and related issues of workplace conditions, safety, and child labor. Agriculture was still individual in nature in that people worked for themselves, on their own farms, and in small groups. The art and literature of the day painted a healthy and wholesome picture of agrarian life in contrast to highly publicized industrial disasters such as mine cave-ins, factory explosions, and sweatshop fires. "Occupational health, since its inception, has largely ignored agriculture, even though agriculture was the source of some of the earliest recognized occupational diseases," Schenker observes.

Still, the Industrial Revolution did help draw some attention to adverse health effects of exposure to agricultural dusts. As NIOSH Senior Medical Epidemiologist Robert M. Castellan points out, "The increasingly regular work schedule associated with the Industrial Revolution and its concentrations of workers in manufacturing facilities led to the recognition of a peculiar 'Monday phenomenon' among cotton textile workers. This was characterized by symptoms of chest tightness and other breathing difficulties occurring predominately on the first day back to work after Sunday break." In 1877, the term "byssinosis," derived from the Latin *byssus*, meaning "a fine cotton or linen," first entered the scientific literature.

Since then, adverse health effects arising from exposures to many other agricultural dusts have been described and documented, but myriad syndromes such as silo unloader's syndrome, bark stripper's disease, farmer's lung and grain fever have caused confusion among clinicians and epidemiologists. "People thought they were looking at many diseases, all of which needed to be attacked separately. But essentially they're the same, except one was diagnosed, say, in mushroom growers, the other in British pigeon handlers," says NIOSH physiologist Vincent Castranova. "The most recent understanding of the situation is that there are acute and chronic forms of agricultural dust disease in general, or responses to either isolated or multiple exposures to organic dust." For example, Castranova explains that the flulike mill fever among cotton workers that follows initial, intense exposures to cotton dust is not present after repeated exposures, though chronic exposures can result in byssinosis, with its symptoms of chest tightness, decline in lung function, and bronchitis.

Sifting through the dust. Organic dust in a terminal grain elevator is assessed using an Anderson multistage sampler. *Photo Credit: James A. Merchant/ U. of Iowa EHSC*

Acute responses to isolated exposures have been lumped under the term organic dust toxic syndrome (ODTS). ODTS typically occurs in the presence of large amounts of airborne, organic dust. The syndrome often occurs in small clusters and is characterized by fever occurring 4-12 hours after exposure and flulike symptoms such as general weakness, headache, chills, body aches, and cough. Chest tightness and shortness of breath may also occur.

Chest examination usually reveals normal breathing sounds, although lung crackles and wheezing may be present. Chest X-rays are usually normal. Pulmonary function may be impaired, and an increase in the number of white blood cells (leukocytosis) is common. Circulating blood antibodies to the specific dust are usually not present. ODTS usually disappears within 24 hours to a few days following removal from the exposure. However, repeated ODTS episodes can occur after reexposure to the organic dust. An estimated 30-40% of workers exposed to organic dusts will develop ODTS. Grain fever, pulmonary mycotoxicosis, silo unloader's syndrome, inhalation fever, and mill fever in cotton textile workers are all included under ODTS.

A 1988 case reported by NIOSH researchers exemplifies a typical cluster of ODTS. Eleven male workers, aged 15-60, moved 800 bushels of oats from a poorly ventilated storage bin. The oats were reported to contain pockets of powdery, white dust. Work conditions were described as extremely dusty, and all workers wore disposable masks while inside the bin. The workers shoveled oats for 8 hours in groups of two or three in shifts of 20-30 minutes. Within 4-12 hours, all 9 men who worked inside the bin became ill with fever and chills, chest discomfort, weakness, and fatigue. Eight reported shortness of breath, six had nonproductive coughs, five complained of body aches, and four developed headaches. Upon medical examination, crackle sounds in the lungs were found in two workers, wheezing in one. No symptoms developed in the two workers who remained outside the storage bin. Symptoms in all affected workers disappeared within 2-12 days.

"As to the chronic response," Castranova explains, "symptoms would be similar. But you would have a history of prior exposure, presence of serum antibodies to that dust, and the response in the lung is lymphocytic [an accumulation of specific white blood cells that participate in cell-mediated immune responses]."

Farmer's lung disease (an immunologic lung response involving antibodies to the fungi found in moldy hay), mushroom worker's lung, bark stripper's disease, and allergic alveolitis are examples of chronic responses and are synonymous with hypersensitivity pneumonitis. Symptoms often become progressively worse with increasing exposure and may lead to chronic bronchitis, shortness of breath, loss of appetite, and severe reductions in lung volume and diffusing capacity (the volume of gases that move through lung tissue membranes). Five to eight percent of workers exposed to organic dusts develop hypersensitivity pneumonitis. Although it has been studied for more than 25 years, the precise pathological mechanism of hypersensitivity pneumonitis remains unknown.

The conceptual road from acute to chronic responses to organic dusts may not be so clear. According to Castranova, if dust exposure levels are high enough, an affected worker may have neutrophils and lymphocytes in the lungs typical of both acute inflammatory and immunologic reactions. "It's never quite as simple as we'd like to make it," he says.

From Acute to Chronic

In his five-year longitudinal study of 611 workers employed at six cotton mills, biomedical engineer Henry Glindmeyer of Tulane University Medical Center's environmental medicine section reported a significant association between the acute and chronic effects of cotton dust exposure. Cotton dust exposure levels and acute pulmonary function changes measured across workshifts were predictive of annual declines in lung function. Moreover, an inverse exposure-response relationship was found. Yarn production workers in the initial manufacturing process were exposed to lower dust levels (below OSHA permissible exposure limits of 200 micrograms/ cubic meter of air [$\mu g/m^3$]) than workers exposed to the higher permissible levels (750 $\mu g/m^3$) in their slashing and weaving jobs in the later production process. Yet yarn production workers showed a greater annual decline in lung function, a finding which Glindmeyer and his colleagues interpreted as a dust potency effect, possibly due to endotoxin.

Early processing includes bringing the cotton into the warehouse, opening the bales, then manufacturing the cotton into long yarn. "Slashing and weaving is, number one, generally less dusty, but more importantly, tends to have a less potent dust," Glindmeyer explains. "Whatever might be in the dust is generally scrubbed out in the early process."

He adds, "In yarn manufacturing we were able to pick up a dose-response relationship at the 200 $\mu g/m^3$ level. But we were not able to find one in the slashing and weaving area." The slashing and weaving area of the mill, he points out, does not necessarily have cleaner air. "In fact, it can have more dust, but it's less potent."

In this study, smoking proved also to be a significant determinant of decline in lung function. The Tulane researchers say their findings support lowering cotton dust exposures and excluding smokers from working in yarn manufacturing.

The implications of this and other recent longitudinal studies were summarized by McGill University epidemiologist Margaret Becklake. "There is some uncertainty as to whether the acute responses are always in the causal pathway for chronic responses or are independently related to exposure, or whether both mechanisms operate," she said. However, she points to similar findings for exposure to grain dust among grain elevator workers in Vancouver, British Columbia. These studies, she says, indicate a much broader role for occupational exposures in the development of chronic obstructive pulmonary disease than has been previously assumed.

In Keokuk County, Iowa, Merchant is directing a large-scale longitudinal rural health study. Begun just four years ago, this study comparing farm families, rural nonfarm families, and urban families is still in the first round of data collection. It involves children and adults and focuses particularly on effects on the elderly and women. "We are taking a hard look at not only symptoms, but pulmonary function, airway responsiveness, and immunological factors in terms of lung disease risk, " he says. The study is aimed at assessing and quantitating the risk to a variety of rural, agricultural, and other environmental

exposures ranging from farm equipment to pesticides and agricultural dusts.

Endotoxin: A Critical Component?

Endotoxins are a combination of lipid (lipid A) and polysaccharide side chains and are integral components of the outer membrane of gram negative bacteria. Endotoxins are released into the surrounding environment during active cell growth or breakdown (lysis), or when bacterial cells are engulfed by immune cells called phagocytes.

In the 1930s and early 1940s, widespread outbreaks were reported of an acute, self-limited respiratory illness that appears to have been clinically identical to mill fever, but that also included chest tightness and cough much like symptoms of byssinosis. But rather than textile mill workers, those affected were poor rural families making mattresses for personal use from surplus, low-grade, stained cotton provided by a federally sponsored program.

"With our current knowledge, staining would be indicative of microbial growth on that cotton," says Castellan. "And on subsequent investigation, it was found that this cotton was highly contaminated, much more than it normally is, with an enterobacter species, a gram negative bacteria." The U.S. Public Health Service investigation of this outbreak resulted in the first scientific evidence suggesting that gram negative bacteria or its products are a likely cause of mill fever and possibly also a contributing factor in the etiology of acute and chronic pulmonary effects associated with byssinosis.

Endotoxins have been known to cause profound inflammation of any tissue exposed to them, including lung tissue. "Exposure to endotoxins causes an influx of inflammatory cells into the lungs," says NIOSH immunologist Stephen A. Olenchock. "They bring with them and they release various agents called cytokines, which cause swelling, exudate, or seepage, from blood vessels. These are very potent inflammatory agents."

Initially, the response to endotoxin may seem to be allergic. But unlike allergy, the active component is lipid A, and not an antigenic protein. "This is not an allergy at all," Olenchock explains. "Allergy involves a type of antibody associated with a specific antigen. Here, there is an absence of antibody. Endotoxins activate the complement system, which causes inflammation and then removal of foreign agents."

Occupational inhalation of endotoxins induces fever and constriction of airways. According to Castranova, endotoxins tend to upregulate the activity of lung phagocytes, encouraging pulmonary inflammation. "Many studies seem to show that if you put lung phagocytes in a test tube and add endotoxin, not much happens," he explains. "But if you add endotoxin and then add a second stimulus, the [phagocytic] response to that second stimulus is greater than if the endotoxin weren't there. The second stimulus could be the dust, the particulate matter."

In vitro studies of animal lung phagocytes reveal that endotoxins may initiate this response following a single dose, but decline in ability to do so after multiple doses. Castranova says this may explain the Monday phenomenon in cotton textile workers with byssinosis. "The cells are more responsive to endotoxin given once. After that they downregulate. Their receptors are internalized with the cell wall and are not available to respond again. After a weekend period of no exposure, those receptors are externalized on the cell surface and are ready to respond to endotoxin again."

In the 1980s, controlled experimental exposures of human volunteers to cotton dusts contaminated with endotoxins provided insight into the roles of endotoxins in eliciting acute respiratory responses. Castellan and his colleagues reported a highly correlated relationship between acute changes in pulmonary function and endotoxin concentrations.

Experimental human exposure studies have been aimed at closely mimicking dust conditions experienced by mill workers. These results show decreases in lung function, such as forced expiratory volume (FEV), to be associated more strongly with endotoxin content than with mass exposures of dust. Moreover, studies involving cotton that was washed to lower its endotoxin content showed such cotton

dust to be a less potent inducer of airway obstruction.

In one experiment, Castellan and colleagues investigated acute respiratory responses (FEV) to a wide range of cotton dust types--cotton raised in different parts of the country and of differing grades. "We note there is a much stronger dose-response relationship using endotoxin as the index of exposure, and in fact, no dose-response relationship [for] gravimetric dust." Gravimetric dust is measured by a device called a vertical elutriator designed to collect lint-free samples of aerodynamic size corresponding to inhaled dust particles deposited at or below an individual's trachea.

Signs and symptoms of respiratory exposures to dusts contaminated with endotoxins have also been reported for grain workers and those involved in animal production, including swine and poultry. Attempting to identify the role of endotoxin in grain dust-induced lung disease, Schwartz and his colleagues conducted a population-based, cross-sectional investigation comparing a cohort of grain handlers and postal workers in eastern Iowa. After controlling for age, gender, and cigarette-smoking status, the researchers found that occupational exposure to grain dust was associated with acute and chronic respiratory symptoms, objective measures of diminished airflow, and enhanced bronchial reactivity (hyperresponsiveness). While it wasn't shown that endotoxin causes airway disease in grain handlers, airway disease appeared to be more pronounced in those exposed to higher concentrations of airborne endotoxin in the work setting.

"Other exposures associated with microbial contamination of grain dust may be involved here," Schwartz says. "Endotoxin may serve as a good surrogate marker for the more pathogenic components. We don't know whether it's the cause, but it seems to be."

Kicking up a storm. Industrial hygiene assessments are necessary to monitor the safety of swine confinement units containing organic dust rich in endotoxin.
Photo Credit: James A. Merchant/ U. of Iowa EHSC

In studying workers in swine confinement buildings, which are minimally ventilated, Schwartz found decreases in lung function that were independently associated with greater cross-shift changes (a measure of a worker's respiratory function over a specific workshift) in FEV and higher concentrations of airborne endotoxins. Moreover, acute declines in lung airflow across the workshift and higher concentrations of endotoxin were linked to accelerated declines in airflow during the period of observation, about two years. According to Schwartz, this indicates that acute airway responses are predictive of chronic changes in airflow.

Animal models have been developed that mimic the fever and acute pulmonary response reactions to organic dust inhalation. These studies have also exhibited a strong correlation between endotoxin levels and lung responses to organic dusts, including grain and cotton dusts. Schwartz used genetic strains of endotoxin-sensitive and endotoxin-resistant mice to perform corn dust inhalation studies. Endotoxin-sensitive mice showed a more profound inflammatory response in the lower respiratory tract to inhaled corn dust than the endotoxin-resistant mice. Endotoxin-sensitive mice that were made tolerant to endotoxins showed a significantly diminished inflammatory response to inhaled corn dust.

In experiments with guinea pigs, in which airway reactivity to organic dust closely mimics that of

humans, Castranova demonstrated that changes in breathing pattern--the "Monday accentuation" response--depended on the endotoxin content of cellulose, which when untreated with endotoxin did not alter respiratory responses in the animals.

"In general, more work needs to be done with animal models," Castranova says. "The importance of various mediators has been brought out, including tumor necrosis factor, a product of lung phagocytes. If one gives the animal antibody to that, so that it's no longer active, the animal's acute pulmonary response to organic dust is mitigated."

Beyond the Tip of the Iceberg

The interaction between environmental and physiological factors may play a significant role in exposure to organic dusts, but the specifics remain to be clarified. As Schenker observes, "The determinants of the hypersensitivity pneumonitis response remain poorly understood. Initiation [of this response] in farmers who may have had similar exposures for years without pulmonary problems is unexplained."

Cigarette smoking is associated with diminished lung function responses to cotton and grain dusts, but the prevalence of hypersensitivity pneumonitis is higher in nonsmokers than in smokers. Some investigators point to cigarette-mediated immune alterations such as reduced cytokine production by lung macrophages. Others suggest that smokers are generally less susceptible to irritants, which may be a factor in why they smoke.

Clarification of environment and host interactions is often complicated by another element: "the healthy worker effect." Rates of long-term ill effects may be reduced because of early departure of sensitized workers from an industry. In grain workers, for example, smoking, mite allergy, and nonspecific bronchial hyperreactivity may increase departure rates.

Studies in the cotton industry have shown that mill workers may still have accelerated declines in lung function related to cotton dust in the absence of symptoms characteristic of the Monday syndrome. "To many of us, that's not surprising," says Castellan. "The more we study the phenomena of occupational respiratory disease, the more we realize that the gross symptoms and gross findings are the tip of the iceberg. There's much more going on in terms of very subtle effects."

Minimizing Health Risks

Prevention, ventilation, and avoidance of exposures appear to be key recommendations for workers facing occupational health risks from agricultural dusts. According to some authorities, primary prevention through dust control, though more readily applicable in some agricultural industries such as cotton, is difficult elsewhere. "Dust presents a challenge because of its ubiquity," says Schenker.

In many situations there are steps that can effectively prevent dust generation," he said. Some of the steps he outlines for specific work practices include reducing levels of microorganisms in cut grasses to be used for feed or bedding via adequate drying in the field before baling, adding fat to the diet of animals in confinement facilities and using covered feed troughs filled through enclosed spouts to reduce ambient dust levels, capping silage materials to reduce spoilage, and pouring a quart of water on the cut surface of a hay bale prior to use in a bedding chopper, which can reduce dust levels by 85%.

What the hay? Workers are exposed to a number of potentially dangerous microorganisms in moldy hay at a Wisconsin dairy.
Photo Credit: James A. Merchant/ U. of Iowa EHSC

In terms of ventilation, NIOSH recommends local exhaust ventilation for barns and confinement houses. *NIOSH Alert*, an agency publication, advises agricultural workers and employers on a number of practices aimed at minimizing risk of exposure to dusts, including wearing respirators with the

highest assigned protection factor. In accordance with the OSHA respiratory protection standard, employers must train and monitor personnel in the use of respiratory protection equipment, as well as how to maintain, inspect, store, and clean it.

Cotton dust is the only specific agricultural dust that currently has an OSHA standard, although the main regulatory requirements apply only to regulated cotton industries and processes. Growing, harvesting, ginning, classing, warehousing, and knitting of cotton are not currently regulated. Handling and processing of woven or knitted cotton fabrics are also not regulated. Several different exposure limits ranging from 200 $\mu g/m^3$ to 750 $\mu g/m^3$ apply in textile mill operations. The cotton dust standard also requires medical examinations for new employees as well as periodic monitoring for all workers exposed to cotton dust. OSHA also has a standard for nonspecific dusts: 15 $\mu g/m^3$ for total dust and 5 $\mu g/m^3$ for respirable dust.

Future Needs

The extent of risks associated with dust exposures needs to be refined. Specific agents within agricultural dusts that are responsible for toxic and immunologic responses remain in question, as do methods for quantifying these components. Research is also needed to elucidate susceptibilities to these exposures. And more work is needed in the area of education and intervention to develop sound strategies aimed at preventing acute and chronic respiratory symptoms for a widespread and varied population of agricultural workers.

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