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Respiratory Health Effects of Large Animal Farming Environments

Sara May, MD[1], **Debra J. Romberger, MD**[2,1], and **Jill A. Poole, MD**[1]

[1]Pulmonary, Critical Care, Sleep & Allergy Division; Department of Internal Medicine,; University of Nebraska Medical Center, 985300 The Nebraska Medical Center, Omaha, NE 68198-5300

[2]Veterans Administration Nebraska Western Iowa Healthcare System, Omaha, NE, 4101 Woolworth Ave., 68105

Abstract

With increases in large animal-feeding operations to meet consumer demand, adverse upper and lower respiratory health effects in exposed agriculture workers is a concern. The aim of this study was to review large animal confinement feeding operational exposures associated with respiratory disease with focus on recent advances in the knowledge of causative factors and cellular and immunological mechanisms. A PubMed search was conducted with the following keywords: airway, farm, swine, dairy, horse, cattle inflammation, organic dust, endotoxin, and peptidoglycan that were published between 1980 and current. Articles were selected based on their relevance to environmental exposure and reference to airway diseases. Airway diseases included rhinitis, sinusitis, mucus membrane inflammation syndrome, asthma, chronic bronchitis, chronic obstructive pulmonary disease, hypersensitivity pneumonitis, and organic dust toxic syndrome. There is lower prevalence of IgE-mediated asthma and atopy in farmers and their children, but organic dust worsens existing asthma. Multiple etiologic factors are linked to disease including allergens, organic dusts, endotoxins, peptidoglycans and gases. Large animal confinement feeding operations contain a wide-diversity of microbes with increasing focus on Gram-positive bacteria and archeabacteria as opposed to Gram-negative bacteria in mediating disease. Toll-like receptors (TLR) and nucleotide oligomerization domain (NOD)-like innate immune pathways respond to these exposures. Finally, a chronic inflammatory adaptation, tolerance-like response in chronically exposed workers occurs. Large animal confinement farming exposures produces a wide spectrum of upper and lower respiratory tract diseases due to the complex diversity of organic dust, particulates, microbial cell wall components and gases and resultant activation of various innate immune receptor signaling pathways.

Send Correspondence to: Jill A. Poole, MD, Pulmonary, Critical Care, Sleep & Allergy Division; Department of Internal Medicine, University of Nebraska Medical Center, 985300 The Nebraska Medical Center, Omaha, NE, 68198-5300, japoole@unmc.edu, Fax: 402-559-8210, Phone: 402-559-4087.
(smay@unmc.edu)
(dromberg@unmc.edu)

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INTRODUCTION

Chronic airway diseases that develop from exposure to large animal-feeding operations include a spectrum of upper and lower respiratory tract disorders: rhinitis, mucus membrane inflammation syndrome, sinusitis, asthma, asthma-like syndrome, chronic bronchitis, chronic obstructive pulmonary disease (COPD), hypersensitivity pneumonitis and organic dust toxic syndrome (ODTS) (Eduard et al. 2004, 2009; Girard and Cormier 2010; Kogevinas et al. 1999; Monso et al. 2004; Omland 2002; Reynolds et al. 1996; Von Essen and Donham 1999). These diseases commonly occur following exposure to large animal feeding operation farming environments, particularly swine confinement facilities and commercial cattle feedlots. In North America, changes in farming practices have occurred to meet consumer demand for meat globally. This includes an increase in large animal-feeding operations, which may potentially impact respiratory disease development.

The majority of hogs are currently raised in confinement with confinement facilities housing an average of 4,646 hogs in the United States in 2004, which is an elevation from an average farm size of 945 hogs in 1992 (Key and McBride 2008; http://webarchives.cdlib.org/sw1vh5dg3r/http://ers.usda.gov/AmberWaves/April08/Features/USHogFarms.htm). Similarly, the farm size in Canada also increased, and it was reported for the first time in 2010 that the average number of hogs exceeded 1,600 head (Key and McBride 2008; http://webarchives.cdlib.org/sw1vh5dg3r/http://ers.usda.gov/AmberWaves/April08/Features/USHogFarms.htm). Changes in farming strategies have also occurred in Europe. News sources have reported the formation of factory farms in Poland housing approximately 10,000 swine (http://news.bbc.co.uk/2/hi/science/nature/4035081.stm). Likewise, almost all slaughtered cattle for beef consumption are raised in commercial feedlots. Forty % of all cattle bred for beef are placed on feedlots that hold 32,000 or more head of cattle while gaining weight for slaughtering (United States Department of Agriculture 2009, www.ers.usda.gov/briefing/cattle/background.htm).

These changes from small, family-owned farms that are still prevalent in Europe and parts of United States and Canada, towards large scale framing practices, has potential impact on respiratory diseases. Kirkhorn and Garry (2000) estimated that 50% of swine farmers/workers are at risk of developing respiratory tract symptoms. Cough with or without sputum production, chest tightness and wheeze are symptoms that are more commonly reported by confinement workers than the general population (Von Essen et al. 2010; Zejda et al. 1993). Chronic or repetitive exposure to these organic dust environments is also associated with lung function decline over time (Donham et al. 1995; Reynolds et al. 1996; Von Essen et al. 2010; Zejda et al. 1993). Even though farmers use tobacco significantly less than the general population, this population has a substantial increase in morbidity and mortality from respiratory disease (American Thoracic Society 1998). An overview of the respiratory disease consequences associated with farming practices was last comprehensively reviewed by the American Thoracic Society (1998). The aim of this report was to review the current knowledge of respiratory diseases associated with large animal confinement feeding operational exposures with focus on recent advances in the knowledge of causative factors and cellular and immunological mechanisms underlying disease manifestations.

AIRWAY DISEASE MANIFISTATIONS

Upper Airway Respiratory Diseases

Upper respiratory diseases along the spectrum of airway diseases associated with large animal confinement farming include rhinitis, sinusitis, and mucous membrane inflammation syndrome with allergic and irritant rhinitis symptoms most frequently reported (Kirkhorn and Garry 2000; Poole et al. 2007; Reynolds et al. 1996; Slager et al. 2010; Von Essen and Donham, 1999; Von Essen and Romberger 2003). Within swine veterinarians, 60% reported rhinitis symptoms (Poole et al. 2007a), and amongst farmers in the large United States (US) Agricultural Health Study, 67% of farmers reported rhinitis with 39% having three or more episodes of rhinitis in the past year (Slager et al. 2010). Nasal symptoms including congestion, rhinorrhea, sneezing, and/or pruritus are commonly associated with acute and chronic inflammation of the nasal mucous membrane. Nasal lavage fluid demonstrates increases in levels of neutrophils, interleukin (IL)-8/CXCL8, and IL-6 from farmers following swine barn exposure (Burch et al. 2010; Dosman et al. 2000; Hiel et al. 2009; Palmberg et al. 2002; Von Essen and Romberger 2003). Importantly, proper use of the N-95 respirator results in significant decreases in the pro-inflammatory nasal response in farmers; however, N-95 respirators are not routinely worn at the facility (Dosman et al. 2000).

Mucus membrane inflammation syndrome is a syndrome characterized by nasal, eye and throat complaints found in animal confinement workers and associated with increases in nasal lavage IL-1α, IL-1β and IL-6 levels (Von Essen and Donham 1999; Von Essen and Romberger 2003). It is most commonly reported if workers are exposed to dusts and gases within swine confinement facilities (Kirkhorn and Garry 2000; S. Von Essen and Donham 1999). Nasal symptoms such as congestion, rhinorrhea and pruritus occur in 50% of swine confinement workers and 25% have sinusitis (Kirkhorn and Garry 2000; Von Essen and Romberger, 2003).

Asthma

Asthma, defined as a chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, airway hyper-responsiveness and bronchospasm, is associated with large animal farming environmental exposures. It is now well-recognized that children raised on farms have less allergic, IgE-mediated asthma (Braun-Fahrlander 2003; Eduard et al. 2004; Ege et al. 2011; Ernst and Cormier 2000; Klintberg et al. 2001; Merchant et al. 2005; Rennie, Lawson et al. 2012; Riedler et al. 2000). It was postulated that exposure to endotoxin or other bacterial components abundantly present in various farming environments leads to decreased IgE-mediated disease development (Braun-Fahrlander et al. 1999; Braun-Fahrlander 2003; Chen et al. 2007; Cleave et al. 2010; Ernst and Cormier 2000; Klintberg et al. 2001; Lawson et al. 2011a; 2011b; Pekkanen et al 2001; Portengen et al. 2002; Radon et al. 2004; Riedler et al. 2000), which is also consistent with the so-called hygiene hypothesis. Indeed, data from large European childhood studies including Prevention of Allergy – Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) and multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) demonstrated an increase in exposure to microorganisms in farm children with a corresponding inverse relation with the prevalence of asthma and atopy compared to reference groups (Ege et al. 2011). The PARSIFAL study sampled dust from mattresses of farm children and used single-strand conformation polymorphism (SSCP) to identify bacteria in school children of both rural and suburban Germany. The GABRIEL study was conducted in elementary school children from Austria, southern Germany and Switzerland and sampled bacteria in dust from bedroom floors using culture techniques. Both studies found a lower prevalence of asthma (PARISIFAL study: odds ratio (OR) 0.49, confidence interval (CI) 0.35-0.69; GABRIEL study: OR 0.76, CI 0.65-0.89) and atopy (PARISIFAL study: OR 0.34, CI 0.18-0.34; GABRIEL study: OR 0.51, CI 0.46-0.57) in farm children as well as elevated exposure to the amount and diversity of microorganisms in the dust (Ege et al. 2011).

In Austria, Riedler et al. (2000) conducted a cross-sectional survey of allergic diseases and environmental factors of more than 2000 children aged 8-10 years. Data showed lower prevalence of hay fever (18.8% vs. 10.3%, P=0.0002), asthma (1.1% vs. 3.9%, P=0.017) and positive skin prick test (18.8% vs. 32.7%, P=0.001) in children living on a farm. The risk reduction was only seen when regular exposure to farm animals was evaluated (Riedler et al. 2000). In addition, there was decreased incidence of asthma and atopy in rural Canadian children raised on a farm, especially girls for current wheeze (OR 0.7) and asthma (OR 0.59) (Ernst and Cormier 2000). However, increased rate of respiratory symptoms were reported in children that cleaned large animal pens (Farthing et al. 2009).

Despite these observations of lower prevalence of atopy and IgE-mediated asthma in children raised on farms, there are also reports of increased incidence of asthma, particularly non-IgE-mediated asthma, in agriculturally exposed children and adults (Lawson et al. 2011a; 2011b). In a large cohort study in rural Iowa, United States, the asthma rate was increased in children of swine farmers with reported prevalence rates of asthma approaching greater than 50% in children living on farms where swine were fed antibiotic-supplement food (Merchant et al. 2005). However, these farm children displayed less evidence for IgE-mediated disease and atopy. Moreover, Merchant et al. (2005) reported that two-thirds of the children had symptoms consistent with severe asthma, yet did not have a physician diagnosis of asthma, suggesting that asthma may be under-diagnosed in this population. It was speculated that while endotoxin levels are higher in agricultural environments (Mayeux et al. 1997) and may be protective of atopy development via modifying the immune response, high endotoxin might also exacerbate already existing asthma (Cleave et al. 2010; Lawson et al. 2011a; 2011b; Reed and Milton 2001). It was also proposed that children with asthma are more sensitive to the proinflammatory effects of endotoxin marked by nonspecific airway hyper-responsiveness (Lawson et al. 2011a).

The European Community Respiratory Health Survey reported that the highest risk of developing occupational asthma was the occupation of farmer (OR 2.6, CI 1.3 to 5.4) followed by agricultural workers (OR 1.8, CI 1.0 to 3.2) (Eduard et al. 2009; Kogevinas et al. 1999). In adult farmers, asthma symptoms are more likely regarded as work exacerbated asthma (WEA) as opposed to occupational asthma (OA) (Eduard et al. 2009). Subjects with moderate or severe asthma and/or subjects not receiving optimal treatment of their asthma may develop WEA when exposed to potential irritants such as dusts, fumes and sprays

(Tarlo and Liss, 2003; Tarlo et al. 2009). OA is new-onset asthma induced by an environmental aspect of the workplace and 90% of the time is IgE-mediated to components, which include animal dander, storage mites, and cockroach (Tarlo and Liss 2003; Tarlo et al. 2009). A small portion of cases is irritant-induced OA, which is asthma induced by high concentrations of inhaled irritants in confinement facilities. Irritant-induced OA needs to be considered if symptoms of asthma occur within 24 hr of the exposure. Finally, gender may play a role in OA because investigators reported 4 new cases of OA with symptoms of wheezing and cough in only females without previous atopy or asthma only a couple of weeks after starting a full-time position in swine production facilities (Von Essen et al. 2010; Dosman et al. 2004). However, two years later, the same authors published three more cases of newly diagnosed OA in swine confinement workers. These three cases were all males, but similar to the females, none had known previous atopy or asthma (Dosman et al. 2006).

There are also reports of an asthma-like syndrome that is described by cough, chest tightness, dyspnea and wheezing. However, unlike asthma, the asthma-like syndrome does not demonstrate signs of airway obstruction on pulmonary function testing (PFT), and lacks signs of persistent airway inflammation and eosinophil influx, but yet methacholine challenge reveals airway hyper-responsiveness in symptomatic workers (Cleave et al. 2010; Von Essen et al. 2010). Asthma-like symptoms are most pronounced upon returning to work after a weekend or vacation holiday, and reported in up to 50% of swine confinement workers and grain elevator operators (Kirkhorn and Garry 2000; Von Essen and Romberger 2003). Future studies are warranted to better define and characterize the spectrum of occupational asthma disorders resulting from large animal farming practices.

Chronic Bronchitis and Chronic obstructive pulmonary disease (COPD)

Farmers and agriculture workers are at an increased risk of respiratory morbidity and mortality from chronic bronchitis and COPD (Eduard et al. 2009). Chronic bronchitis, defined by symptoms of a cough productive of sputum for 3 months of a year for at least 2 consecutive years, affects animal production workers. Eduard and colleagues (2009) reviewed multiple studies from European farmers and found that Danish swine farmers had the highest prevalence of chronic bronchitis at 32%, compared to 28% in farmers that had swine and cattle. Farmers that did not raise any livestock displayed the lowest prevalence at 18.6% (Omland 2002). In addition, livestock farmers and dairy farmers demonstrated significantly increased risk of developing COPD (livestock farmers, OR 1.4, CI: 1.1 to 1.7; dairy farmers, O.R.1.3, CI: 1.0 to 1.7) (Eduard et al. 2009). Moreover, raising more than one type of livestock enhanced the risk of farmers developing chronic bronchitis and COPD as compared to crop farmers (Eduard et al. 2009). The livestock farmers also showed the lowest forced expiratory volume in one second (FEV_1), consistent with the pattern of lung function decline (Eduard et al. 2009).

Organic Dust Toxic Syndrome

Organic dust toxic syndrome (ODTS) is defined as a febrile illness characterized by malaise, myalgias, chest tightness, headache and nausea following exposure to large amounts of organic dust. This clinical syndrome was first described in the United States approximately

40 years ago in silo-unloading (May et al. 1986; Von Essen and Romberger 2003; Von Essen et al. 1990). Whereas farmers were more likely to describe cough or chest tightness while handling grain and grain sorghum (Von Essen et al. 1990), ODTS has since been described following exposure to a variety of organic dust environments (Von Essen and Romberger 2003). Onset of symptoms usually occurs 4-8 hr after exposure and may last for several days. Clinical evaluation demonstrates peripheral blood neutrophilia, but otherwise normal chest radiograph imaging, arterial blood gas measurements, and pulmonary function testing (Von Essen and Romberger 2003). Although this is typically a self-limiting disease, there is an increased risk of developing bronchitis. The reported prevalence of organic dust toxic syndrome may be as high as 34% in swine confinement workers (Donham et al. 1995; Vogelzang, et al. 1999; Von Essen and Romberger 2003).

Hypersensitivity Pneumonitis

Although hypersensitivity pneumonitis shares similar clinical symptoms with ODTS, specific diagnostic guidelines exist. These guidelines include evidence for interstitial lung disease by clinical history and physical examination, restrictive pattern found on pulmonary function testing and chest radiographic imaging findings consistent with interstitial lung disease (Girard and Cormier 2010; Kirkhorn and Garry 2000). Hypersensitivity pneumonitis is induced by a specific antigenic exposure that elicits an antibody response. Hypersensitivity pneumonitis is an important respiratory disease in farmers as the first cases of hypersensitivity pneumonitis were referred to as ‘farmer’s lung’ because the etiologic agent is commonly fungi (and bacteria) associated with moldy grain and hay. Because hypersensitivity pneumonitis is more associated with grain farming and has recently been reviewed in detail by Girard and Cormier (2010), please refer to this review article for more details.

In interim summary, large animal confinement farming is associated with upper and lower airway diseases (Table 1). Rhinitis is a common feature reported by exposed workers with evidence of increased inflammatory markers of neutrophils and cytokines/chemokines by nasal lavage fluid analysis. Overall, studies indicate a decrease in the prevalence of IgE-mediated/allergic asthma, but increased prevalence of non-IgE mediated asthma/asthma symptoms. Chronic bronchitis and COPD are common in the adult workers and leads to increased respiratory morbidity and mortality. Given the large spectrum of potential respiratory diseases affecting exposed agriculture workers, a thorough clinical investigation is warranted to appropriately phenotype the respiratory disease in order to facilitate appropriate therapy.

CAUSATIVE FACTORS IN LARGE ANIMAL FARMING ENVIRONMENTS

Allergens

There are a number of environmental factors that might lead to adverse respiratory health outcomes in workers exposed to large animal feeding operations including allergens, toxic gases, organic dusts and microbial cell wall components. Allergens are antigens defined as macromolecular agents capable of inducing IgE immune responses and provoking allergic reactions in sensitized subjects. In relation to farming, macromolecules that have been shown to be antigenic include animal dander, pollens, insect fragments, storage mites and fungal molds (Kirkhorn and Garry 2000).

Organic Dust

Organic dust is a complex mixture of an abundant variety of substances that includes dust particles of various sizes and microbial cell wall components. Forty % of these dust particles are in the respirable range with a median diameter of 4 μm or less, which may be deposited at the level of the terminal bronchioles and alveoli (Kilburn 1984; Kirkhorn and Garry 2000). In swine confinement buildings, the % of dust within the respirable range may be as high as 60% of the total dust (Kirkhorn and Garry 2000). It was reported that dust levels are highest in finishing buildings, which are buildings that house mature hogs prior to going to market (Kirkhorn and Garry 2000). Dust concentration in confinement buildings was shown to induce adverse pulmonary effects at concentrations above 2.4-2.5 mg/m^3 for swine and 0.16 mg/m^3 for poultry. At these concentrations, workers demonstrate a 5% decrease in post-shift FEV_1 measurements (Donham et al. 1995; Reynolds et al. 1996). Moreover, the size of the respirable fraction may be important in disease development in large animal feeding operations. A recent study examined inflammation produced by different particulate matter (PM) size from dairy farms in California (Vogel et al. 2012). The dust collected from 5 different farms was divided into 4 different size groups and showed that PM with the cutoff of 4.2 μm induced the highest pro-inflammatory cytokine release from macrophages as compared to smaller (cutoff of 2.1 μm) and larger (cutoff of 10.2 μm) PM (Vogel et al. 2012). Also, PM from the farms induced a greater pro-inflammatory mediator response than the same size PM collected from urban sites (Vogel et al. 2012). Similarly, other studies found that coarse PM (2.5-10 μm) induced enhanced inflammatory responses from alveolar macrophages *in vitro* more than fine and ultrafine PM collected from urban areas, and further evaluation found microbial agents in the coarse PM was the major component (Becker et al. 2002; Becker et al. 2003; Ghio et al. 2012). However, Alexis and colleagues (2006) found that coarse particulate, even with neutralizing the microbial components, induced macrophage inflammation more than fine and ultrafine particulate matter, suggesting the size of PM is an important factor. Future studies need to investigate the interplay between microbial components, dust size fractions, and inflammatory potential related to dusts from animal confinement operations.

Endotoxin

Organic dusts are rich in endotoxins from the cell wall of gram-negative bacteria (Mayeux 1997). Several studies associate endotoxin levels in swine confinement structures, livestock farming and animal feed industry with adverse respiratory health outcomes (Donham et al. 1995; Dosman et al. 2006; Reynolds et al. 1996; Schwartz et al. 1995; Vogelzang et al. 1998). In humans, inhalation and intravenous administration of lipopolysaccharide (LPS), a large molecule found in the outer membrane of gram-negative bacteria consisting of a lipid and a polysaccharide commonly referred to as endotoxin, precipitate multiple clinical inflammatory effects including fever, shivering, arthralgia, influenza-like syndrome, dry cough, dyspnea, chest tightness, and leukocytosis (American Thoracic Society 1998; Mayeux 1997). LPS administration also results in an acute, dose-dependent decrease in lung function, diffusion capacity and resultant airway obstruction (American Thoracic Society

1998). Concentrations of endotoxin at 1000-2000 ng/m^3 may produce ODTS and at concentrations of 100-200 ng/m^3 induce bronchoconstriction (American Thoracic Society 1998; Kirkhorn and Garry 2000). However, there is not a universal association with levels of endotoxin within swine confinement facilities and respiratory health consequences because studies reported high exposure without symptoms or low exposure with a possible dose response relationship (Rask-Andersen et al 1989). Moreover, Sundblad and colleagues (2009) found that inhalation endotoxin challenges with endotoxin only did not reproduce similar pro-inflammatory responses as swine barn exposure challenges, even though the pure endotoxin concentration was 200-fold higher than the endotoxin concentration measured within the swine barns.

Peptidoglycans

Because human studies have not shown a universal association with endotoxin and respiratory disease outcomes, and lab studies demonstrated that organic dusts from large animal feeding operations scrubbed of endotoxin retain significant inflammatory ability (Poole et al. 2008; Romberger et al. 2002), recent studies searched for potentially important, non-endotoxin agents. Culture-dependent and culture-independent techniques demonstrated a high burden of gram-positive bacteria (10^8 16S rRNA gene copies per cubic meter of air), rather than Gram-negative bacteria, in organic dust samples from swine confinement buildings (Nehme et al. 2009). Applied molecular approaches found that the majority (93.8% of sequences related to gram-positive anaerobic bacteria) of the bacteria in organic dust from swine facilities were anaerobic gram-positive bacteria with the most likely source from manure (Nehme et al. 2009). Larsson and colleagues (1999) found that Gram-positive bacteria elicit inflammation in alveolar and epithelial cells (Larsson et al. 1999). Moreover, a higher concentration of total bacteria was found through these techniques as compared with standard culture-dependent identification techniques (Nehme et al. 2008). Actinomycetes and molds were also reported (Letourneau et al. 2010; Letourneau et al. 2010). Peptidoglycan is derived predominately from gram-positive bacteria as it is 85% of the cell wall, but it is also found in gram-negative bacteria making up approximately 5% of the cell wall. Muramic acid, the basic backbone of peptidoglycan, is detected by mass spectrometry techniques (Szponar and Larsson 2001). Levels of muramic acid have been associated with airway inflammation in European swine farmers. High concentrations of muramic acid were reported in swine confinement facilities (15 ng/mg) and dairy barns (5 ng/mg) in the United States (Poole et al. 2010). These concentrations were statistically higher than comparative environments, such as grain elevators or domestic houses, but their association with airway disease manifestations in U.S. agriculture workers is not known. Poole and colleagues (2011b) demonstrated that exposure to peptidoglycan alone elicits pro-inflammatory cellular mediator release and airway inflammatory consequences in rodents similar to that observed with swine facility organic dust extracts.

Animal Confinement Gases

Large animal feeding operations release high levels of gases due to byproducts of animal waste, primarily manure. Hydrogen sulfide (H_2S) is found in both swine and dairy confinement building and although uncommon, may lead to death from asphyxiation and/or pulmonary edema while cleaning manure pits in buildings with under-building manure pits

(CDC 1993). H_2S at lower levels has an odor of “rotten egg smell” but at levels that produce pulmonary edema or unconsciousness, the gas is odorless due to olfactory paralysis (Kirkhorn and Garry 2000). Studies linked ammonia exposure of greater than 2 hr a day for 6 years to sinusitis and chronic obstructive pulmonary conditions (Von Essen and Donham 1999). The threshold limit value for ammonia is 25 ppm and this level is rarely exceeded in swine confinement buildings, but studies documented decrease in FEV_1 at levels above 7.5 ppm in swine confinement workers (Von Essen and Romberger 2003).

In interim summary, recent advances into understanding the causative factors eliciting respiratory disease within large animal confinement exposures has identified multiple important components as opposed to a single agent. These components included allergens, toxic gases, particulates, organic dust and microbial cell wall products. These environments are now recognized for the wide-diversity of microbes, particularly focused on the influence of gram-negative endotoxins and gram-positive peptidoglycans. Future research to investigate the association of particle size with microbial components human respiratory disease consequences from large animal farming exposure environments is warranted.

INNATE IMMUNITY

To help determine biologic relevance of these microbial components known as pathogen associated molecular patterns (PAMP) such as endotoxin and peptidoglycan, studies targeted specific pattern recognition receptors (PRR) to determine functional significance. Of the many PRR, Toll-like receptor (TLR) 2 recognizes Gram-positive bacteria through peptidoglycans, lipoteichioic acid and lipoproteins (Akira et al. 2006) and the TLR4 complex recognizes Gram-negative bacteria endotoxins (Akira et al. 2006). In general, activation of TLR results in signaling through common intracellular signaling molecules (i.e. MyD88) and transcription factors (i.e. NF-κB, MAP kinases) to elicit production of pro-inflammatory mediators including IL-1, IL-6, IL-8 and TNF-α (Senthilselvan et al. 2008, 2009).

Toll-like receptor 4

The TLR4 complex includes TLR4, CD14 and LPS binding protein (LBP). Polymorphisms of the TLR4 gene (299 and 399) were shown to alter the signaling pathway such that changes in pulmonary function are reduced, but IL-6 and IL-8 levels are not down-regulated, following exposure to LPS in human studies (Senthilselvan et al. 2009). Moreover, humans with the variant in TLR4 (299/399) demonstrated a decrease in cross-shift FEV_1 following a high endotoxin swine barn exposure challenge as compared to wild-type humans (−8.48% +/−1.52% vs. −11.46% +/− 1.79%, P=0.0001), but no difference after a low endotoxin swine barn exposure challenge (Senthilselvan et al. 2009). In addition, CD14 is a high-affinity receptor for endotoxin and transfers endotoxin to TLR4. Polymorphisms of CD14 (CD14-159TT) were associated with elevated levels of soluble CD14 (LeVan 2005), and moreover, LeVan et al. (2005) found that these polymorphisms in non-smoking farmers (CD14/-1619GG and CD14/159TT) were associated with decreased FEV_1 and decreased self-reporting of wheeze. Finally, in animal studies, mice deficient in TLR4 signaling demonstrated a reduction in neutrophil influx, but not cytokine production, following a one-day exposure to swine barn air (Charavaryamath et al. 2008). However, these TLR4-

deficient animals were not protected from developing acute airway hyper-responsiveness following swine barn air exposure.

Toll-like receptor 2

Investigations directed at determining the functional importance of gram-positive bacteria in organic dust environments focused on the TLR2 signaling pathway in cell culture and animal studies. TLR2 gene and protein expression is increased on airway epithelial cells following incubation with swine facility organic dust extract in a concentration-dependent manner (Bailey et al. 2008), and organic dust-induced airway epithelial cell cytokine release is dampened with anti-TLR2 antibody blockade (von Scheele et al. 2010). Further, TLR2-deficient mice displayed an altered airway response following organic dust exposure marked by a reduction in dust-induced airway inflammatory cell influx (approximate 55% reduction) and cytokine/chemokine production (Poole et al. 2011b). However, similar to observations in TLR4-deficient animals, TLR2 mice are not protected from the enhanced organic dust-induced airway hyperresponsiveness. In human studies, there appears to be a role for TLR2 polymorphisms. Eder and colleagues (2004) found that children of farmers with polymorphism in TLR2 gene (TLR2/-16934) have less atopy (14% vs. 27%, P=0.023), IgE-mediated disease (3% vs. 14%, P=0.01) and asthma (3% vs. 13%, P=0.012) as compared to farm children without the polymorphism. However, this same polymorphism was not protective against atopy in children that did not live on a farm.

Other PRRs

Nucleotide oligomerization domains (NOD)-like molecules are intracellular molecules that can sense and respond to bacterial components. Less has been described about the role of NOD in exposed large animal farmers. However, NOD2, which recognizes muramyl dipepetide, is upregulated in antigen presenting cells following organic dust exposure, and mice deficient in NOD2 display an increased, as opposed to decreased, airway inflammatory response following swine confinement facility organic dust exposures (Poole et al. 2011a). Additionally, gene polymorphisms in NOD1, which recognizes γ-D-Glu-mDAP from Gram-negative bacteria and also known as Caspase Recruitment Domain (CARD) 4, have been associated with respiratory disease in farm children. Namely, children of farmers with the T allele in CARD4/-21596 have decreased atopy (5.8% vs. 19.4%, P<0.01) and IgE-mediated diseases (hay fever 1.7% vs. 13%, P<0.01; asthma 1.7% vs. 7.6%, P<0.05) compared to reference group (Eder et al. 2006).

Intracellular Signaling Pathways

Although investigations focused on upstream innate immune receptor events found roles for TLRs NODs, there have been several studies determining relevant and potentially important intracellular signaling molecules. Protein kinase C (PKC) is an important catalytic enzyme that mediates proinflammatory cytokine release from human bronchial epithelial cells following swine confinement feeding operation and cattle feed lot organic dust exposure (Romberger et al. 2002; Wyatt et al. 2007). Moreover, activation of specific PKC isoforms in a sequential manner was described (Wyatt et al. 2010). In human bronchial epithelial cells, PKCα is rapidly activated by 1 hr with dust exposure, which subsequently leads to activation of PKCε. Inhibition of PKCα results in decreased dust-induced IL-6 and IL-8 release, whereas, inhibition of PKCε results in decreased dust-induced IL-8 release. Adhesion of lymphocytes to epithelial cells, epithelial cell migration and wound healing in the setting of dust exposure is dependent on PKC (Mathisen et al. 2004; Slager et al. 2007). NF-κB is a known signaling pathway that is activated by TLR4 receptor recognition and hence, induces inflammation with exposure to Gram-negative bacteria. It was shown that NF-κB has enhanced binding and reporter activity when macrophages are treated with organic particulate matter from dairy farms (Vogel et al. 2012).

In interim summary, several innate immune receptors/sensors including TLR2, TLR4, NOD1, and NOD2 are implicated in recognizing and mediating large animal confinement organic dust exposure induced inflammatory consequences (Table 2). These studies also underscore the complexity of the environmental exposure because targeting one receptor alone does not explain the entirety of disease inflammatory manifestations. Therefore, further studies to understand the host response to this diverse exposure environment is needed with focus suggested on common signaling pathways or multiple receptor targeted approaches.

ACUTE AND CHRONIC INFLAMMATORY-ADAPTATION RESPONSE

Acute inflammatory response

The acute inflammatory response following swine confinement facility organic dust exposure has been well-characterized. Collectively, swine confinement organic dust exposure in humans and rodents shows an acute inflammatory response marked by neutrophil influx and TNF-α, IL-6 and IL-8/CXCL8 release in both the upper and lower respiratory tract (Larsson et al. 1994, 1997, 2002; Palmberg et al. 2002; Poole et al. 2009; Sundblad et al 2009; Von Essen and Romberger 2003). Specifically, healthy volunteer subjects with no prior agriculture exposure demonstrated a 100-fold increase in neutrophils and a 3-4 fold rise in lymphocytes and macrophages in bronchoalveolar lavage fluid (BALF) following a swine barn exposure challenge (Sundblad et al. 2009). Exhaled nitric oxide was slightly elevated in controls compared to farmers when exposed to dust (11.7 ppb +/− 0.6 SEM vs. 10.2 +/− 1.6; $p = 0.023$) and exhaled nitric oxide measures almost doubled from baseline readings in healthy controls following a swine barn exposure ($p=0.002$) (Sundblad et al. 2009). Finally, bronchial hyper-responsiveness to methacholine challenge occurs in healthy volunteer subjects following swine barn exposure challenges (Ek et al. 2005; Larsson et al. 2002; Sundblad et al. 2002).

Chronic Inflammatory Adaptation Response

Less is known about the chronic inflammatory response to large animal farming environmental exposures observed in agriculture workers. Schwartz et al. (1995) showed that there is basement membrane thickening with increase in fibronectin and hyaluronic acid in swine farmers. It is now appreciated that following repetitive or chronic exposure to these organic dust environments, the airway inflammatory response is less pronounced as compared to naïve subjects, but yet exposed agriculture workers experience lung function decline and chronic airways disease. This phenomenon has been termed the chronic inflammation adaptation response (Palmberg et al. 2002; Pedersen et al. 1996; Sundblad et al. 2009; Von Essen and Romberger 2003).

In support of the chronic inflammatory adaptation response, studies demonstrated that bronchial responsiveness to methacholine challenge was significantly higher in naïve, healthy controls as compared to swine farmers following an organic dust exposure challenge. Farmers displayed less exposure-induced symptoms of chills, runny nose, cough, and chest tightness (Palmberg et al. 2002; Sundblad et al. 2009; Von Essen and Romberger 2003). Moreover, baseline BALF sampling from swine confinement workers showed increased numbers of neutrophils, macrophages and levels of TNF-α, IL-6 and IL-8 as compared to healthy controls, but the magnitude of the inflammatory response following an environmental challenge was less pronounced in these farmers as compared to naïve individuals (Sundblad et al. 2009). The mechanisms to explain the chronic inflammation adaptation response are not entirely clear. L-selectin may play an important role because shedding of this molecule into its soluble form is associated with a decrease in inflammation, and swine farmers have elevated serum L-selectin, which suggests its role in the adaptation or tolerant response (Israel-Assayag and Cormier 2002).

Cell culture modeling revealed that repetitive exposure to swine confinement organic dust extracts impairs the development of human macrophages marked by down-regulation of 1) innate immune cell surface markers such as MHC class II and co-stimulatory molecule, CD80 and CD86 expression, 2) impaired phagocytic and bactericidal ability and 3) diminished cytokine/chemokine responsiveness, which was also found to be independent of endotoxin (Poole et al. 2007b; 2008). Animal models have been developed that resemble the human chronic inflammatory adaptation response. Namely, rodents demonstrate an increase in airway hyper-responsiveness to a one-time exposure of swine barn air and/or dust extracts, which was not observed following repetitive exposures. Further, acute exposure-induced cytokine/chemokine significantly diminishes with repetitive exposures; yet, repetitive dust exposures induce histopathologic changes in the lung parenchyma evident by an influx of neutrophils, T cells, B cells, and macrophages dependent on length of exposure (Charavaryamath et al. 2008; Poole et al. 2009). Th17 skewing is proposed because acute organic dust exposure increases soluble Il-17 and IL-17A-expressing lymphocytes in BALF of healthy volunteers (Ivanov et al. 2005) and repetitive organic dust exposure promotes a Th1/Th17 lung microenvironment in rodent lungs (Poole, et al 2012).

Overall, the acute inflammatory response following large animal confinement organic dust exposure is well-characterized and marked by influx of neutrophils and lymphocytes and pro-inflammatory cytokine/chemokine release. With repetitive or chronic exposures, there is a dampening of the acute inflammatory response, consistent with an adaptation-like phenomenon. This chronic response appears to be, in part, mediated by T cell responses, particularly a polarized Th1/Th17 state. Future investigations to further understand the chronic inflammatory-adaptation response and to investigate therapies to reduce disease burden in chronically exposed workers are warranted.

CONCLUSION

Since the late 1990s, there has been knowledge of multiple respiratory diseases associated with working in animal confinement environments including rhinitis, chronic bronchitis, COPD, asthma, asthma-like, ODTS, and hypersensitivity pneumonia. Although the development of IgE-mediated respiratory disease is decreased in farming children, reports show that non-IgE mediated respiratory diseases are prevalent in children and adults exposed to modern large animal feeding operations, and that large animal farming is a strong risk factor toward the development of occupational asthma diseases. Recent studies highlight that confinement workers have an increased prevalence of rhinitis (Poole et al. 2007; Slager et al. 2010) and non-IgE mediated occupational asthma (Dosman et al. 2004; 2006). Importantly, Merchant and colleagues (2005) demonstrated that children exposed to swine confinement environments in the United States had an increased prevalence of non-IgE mediated asthma symptoms, approaching 50% of the study population. The agents responsible for respiratory diseases are not completely understood, but it is increasingly appreciated that these environments are complex and include endotoxins, peptidoglycans, and respirable dust particles. Advances into understanding specific causative factors determined that PM size is important, with coarse PM inducing enhanced inflammation (Vogel et al. 2012). Endotoxin, signaling through TLR4 (Charavaryamath et al. 2008), remains an important causative agent, but recent studies show important roles for gram-positive bacteria (Nehme et al. 2009; Poole et al. 2008; 2010) and for targeting the TLR2 pathway. Finally, advances in understanding the chronic inflammatory adaptation response in humans and animal modeling should provide the tools to implement strategies to ultimately prevent and/or reduce respiratory disease burden in exposed workers.

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Table 1

Respiratory Diseases Associated with Large Animal Farming

Disease	Symptoms	Diagnosis	Subjects Studied	Pathophysiology	Source
Rhinitis	Congestion, rhinorrhea, sneezing, pruritus	Defined by the presence of one or more symptoms	Swine veterinarians Agricultural workers -Livestock breeding -Livestock Handling -Dairy production	Neutrophil influx IL-8/CXCL8, IL-6 levels	(Slager et al., 2010) (Poole et al., 2007) (Dosman et al., 2000)
Mucous Membrane Syndrome	Combination of nasal, eye and throat complaints with congestion, rhinorrhea and pruritus	No defined criteria, based on reported symptoms in confinement workers	Swine confinement workers	Increased levels of IL-1α, IL-1β, IL-6	(Romberger et al., 2001) (Kirkhorn et al., 2000) (Von Essen et al., 1999)
Asthma	Variable and reoccurring: wheeze, cough, chest tightness, shortness of breath	History of intermittent symptoms with either 1) reversible airflow obstruction by spirometry or peak flow monitoring, or 2) positive bronchoprovocation test	Children of farmers Farmers Agricultural Workers	IgE-Mediated Eosinophilic influx Occupational Workplace Exacerbated	(Lawson et al., 2011) (Riedler et al., 2000) (Merchant et al., 2005) (Eduard et al., 2009) (Kogevinas et al., 1999) (Dosman et al., 2004) (Tarlo 2003)
Asthma-like Syndrome	Cough, chest tightness, dyspnea, wheezing	Symptoms similar to asthma Positive bronchoprovocation if symptomatic No obstruction noted on PFT No eosinophil influx	Swine confinement workers Grain elevator operators	Normal pulmonary function testing Airway hyper-responsiveness to methacholine challenge Increased Neutrophils Absence of eosinophilic infiltrates	(Kirkhorn et al., 2000) (Romberger et al., 2001) (Von Essen et al., 2010)
Chronic Bronchitis COPD	Productive cough for at least 3 months/year for at least 2 consecutive years	Symptoms of chronic cough, sputum production, dyspnea or wheezing Known risk factor exposure $FEV_1 < 80$ % predicted, $FEV_1/FVC < 70\%$ predicted, decreased DLCO	Farmers -Swine -Multiple livestock -Dairy	Organic dust: multiple agents -Muramic acid -Endotoxins -Storage mites -Ammonia -Hydrogen sulfide	(Eduard et al., 2009) (Omland et al., 2002) (Zhiping et al., 1996)
Organic Dust Toxic Syndrome	Fever, malaise, myalgia, chest tightness, headache, nausea	Flu-like illness Occurs 4-8 hrs after exposure No sensitization Resolution of symptoms within days	Farmers -Grain -Swine Confinement Workers	Symptoms start 4-8 hours after exposure Neutrophilia, Neutrophils on BALF Normal imaging, Normal blood gases Normal lung function	(Romberger et al., 2001) (Donham et al., 1990) (Vogelzang et al., 1999) (Von Essen et al., 1990) (May 1986)

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Disease	Symptoms	Diagnosis	Subjects Studied	Pathophysiology	Source
Hyper-sensitivity Pneumonitis	Fever, malaise, nausea, chest tightness, headache	*Acute exposure* -Flu-like illness -Occurs 4-8 hrs after exposure -CXR with infiltrates -Hypoxia Sensitization occurs *Chronic exposure* -Exposure history -Interstitial disease	Farmers: -Moldy grain -Moldy vegetables -Cattle feed	Specific antigenic exposure with antibody response Lymphocytes influx Granuloma formation Production of TNF, IFN-γ, IL-12, IL-18	(Girard et al., 2010) (Kirkhorn et al., 2000) (Zhiping et al., 1996)

Table 2

Immune Signaling Pathways Implicated in Mediating Large-Animal Confinement Exposure-Induced Respiratory Diseases

Implicated Pathways	Associated Response and/or Disease
IgE-Mediated/Allergen-induced	Rhinitis Asthma
Toll-Like Receptor Pathways -TLR4 -CD14 -TLR2	Innate immune response to microbial cell wall products from gram-negative (TLR4) and gram positive (TLR2) bacteria Lung function decline Lower respiratory tract symptoms Absence of TLR2 or TLR4 associated with decreased inflammation following organic dust challenges in mice. *Human Genetic Variants:* Cross-shift changes in FEV_1 (TLR4 299/399 variant) Decreased FEV_1 (CD14/-1619GG and CD14/159TT) Decreased asthma (TLR2/-16934)
Intracellular nucleotide oligomerization domain (NOD) sensors -NOD1 -NOD2	Absence of NOD2 associated with increased inflammation following organic dust challenges in mice. *Human Genetic Variants:* Decreased asthma (NOD1, T allele in CARD4/-21596)
Activation of PKCα, PKCε	Mediates IL-6 and IL-8 release in airway epithelial cells. Important in wound healing, epithelial cell migration, and adhesion in dust exposed epithelial cells.
Activation of NF- κB	Enhanced binding and activity following dust exposures Important transcription factor in TLR signaling