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Farm Animal Models of Organic Dust Exposure and Toxicity: Insights and Implications for Respiratory Health

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Abstract

Purpose of review—Modern food animal production is a major contributor to the global economy, owing to advanced intensive indoor production facilities aimed at increasing market readiness and profit. Consequences of these advances are accumulation of dusts, gases and microbial products that diminish air quality within production facilities. Chronic inhalation exposure contributes to onset and exacerbation of respiratory symptoms and diseases in animals and workers. This article reviews literature regarding constituents of farm animal production facility dusts; animal responses to production building and organic dust exposure, and the effect of chronic inhalation exposure on pulmonary oxidative stress and inflammation.

Recent findings—Porcine models of production facility and organic dust exposures reveal striking similarities to observations of human cells, tissues and clinical data. Oxidative stress plays a key role in mediating respiratory diseases in animals and humans, and enhancement of antioxidant levels through nutritional supplements can improve respiratory health.

Summary—Pigs are well adapted to the exposures common to swine production buildings and thus serve as excellent models for facility workers. Insight for understanding mechanisms governing organic dust associated respiratory diseases may come from parallel comparisons between farmers and the animals they raise.

Keywords

Agriculture; animal husbandry; animal models; respiratory disease; oxidative stress and antioxidant defenses

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Introduction

Livestock and poultry production workers have an increased risk of developing respiratory diseases, such as asthma-like syndrome, rhinosinusitis, hypersensitivity pneumonitis, organic dust toxic syndrome, chronic obstructive pulmonary disease (COPD) and chronic bronchitis, as a result of chronic inhalation exposure to farm animal production buildings [1-4]. When compared to crop workers, livestock workers have a higher risk of developing chronic bronchitis and COPD, and the risk increases in farmers raising two or more types of livestock [4]. Repeated exposure to swine facility organic dust has been linked to diminished inflammation responses by respiratory and immune cells of humans, mice and pigs *in vitro* [5-8**] and *in vivo* [9], a phenomenon referred to as the chronic inflammation adaptive response, which was reviewed recently [1,10]. Findings of these studies are consistent with observations of dampened innate immune responses to continuous concentrated animal feeding operations (CAFO) environment exposures in human subjects [5].

In the past decade, swine models have emerged as excellent tools to study human pulmonary diseases, including cystic fibrosis [11], respiratory distresses in neonates [12], and asthma [13,14]. The availability of the pig genome sequence [15,16] together with metagenomic datasets of organic dust microbiomes [17**,18**] provide insight for investigating and understanding mechanisms of clinical manifestations of farm exposures. This review will highlight relevant farm animal respiratory studies with particular emphasis on swine production environment exposures, the role of oxidative stress and antioxidant defenses in airway inflammation, and implications for respiratory health of livestock and poultry farmers and facility workers.

Diversity and factors affecting agricultural environment exposures

Global consumption of meat, including pork (36%), poultry (33%) and beef (24%) [19], has led to increases in large scale, high-density livestock and poultry production facilities. Increased demand for meat caused 12 and 13% increases in bovine and porcine numbers, respectively, between 1990 and 2010; however, the most significant change occurred in poultry numbers – with an 82% increase [19]. Large scale food animal production programs are typically arranged in a series of growing and finishing steps, which are tightly connected to specialized CAFO-style feeding and housing systems. In the U.S. swine industry, it was estimated that 90% of pigs live their entire life -- approximately 24 weeks for market pigs, and longer for breeding stocks -- indoors [20].

The prevalence and severity of respiratory disease in farmers depend heavily on the type and intensity of animal production environment [21]. Numerous studies have reported constituents and distribution of air pollutants in and around animal production facilities, with particular emphasis on feed particles, gases [22-Pavilonis et al. 2013], microorganisms and their components [23*,24*], particle size, pH altering capacity, volatile compounds and other inorganic compounds and associated health implications [18**,25-27]. Bioaerosol composition varies considerably from region-to-region, farm-to-farm, and even room-to-room [28,29]. Comparison of pollutant levels inside swine hoop barns and conventional

CAFOs revealed lower levels of hydrogen sulfide and odor in hoop barns, higher levels of cultivable bacteria in hoops and similar levels of particulate matter, endotoxin and cultivable fungi [29]. Furthermore, gut microorganisms present in organic dust produce endotoxins that can damage lung tissue and predispose animals and humans to pneumonia [30,31]. There is a direct link between organic dust-related microbial exposures such as: inhalation of gram negative and gram positive bacteria; microbial components -- lipopolysaccharide, peptidoglycans [6], fungal beta glucans [32*]; and lung disease in CAFO workers. Bioaerosol characterization studies demonstrated that microbial agents present in barn dust can deposit in the lungs of farmers and their family members [33,34]. Agricultural bioaerosols also contain fungal 1,3- β -glucan, particles in the respirable range (1 μ m diameter), which can deposit deep within the lungs and cause respiratory illness [32*].

While feeding, flooring, cleaning and ventilation systems are key determinants in exposure to dust and endotoxins in livestock and poultry facilities [35**,36]; ventilation may be the most manageable and impactful. Good ventilation and robust cleaning practices can improve indoor air quality by reducing exposure to respiratory disease causing agents (e.g., microbes, fecal matter and other particulates $\geq 10 \mu$ m in diameter) [37,38*,39,40**,41,42]. Low ventilation rates were negatively correlated with the concentration of indoor gases -- NH_3 , N_2O , CH_4 , and CO_2 -- in swine barns [43], thus gaseous contaminants decreased as the ventilation rates increased [44]. The level of particulates, ammonia and endotoxin within CAFOs is linked to the severity of lung dysfunction in poultry and livestock workers [45-47]. Dust levels in excess of 2.4 mg/m^3 for humans and 3.7 mg/m^3 for pigs, and 0.23 mg/m^3 respirable dust for both, are reported to have a negative health impact on humans and pigs in swine production facilities [48,49]. Dust concentrations tend to be lower in cage systems for laying hens compared to on-floor poultry houses for broilers. However, larger cage sizes in cage systems resulted in a decline in air quality due to increased bird activity [50]. Bedding material is a major contributing source of significantly increased dust concentrations associated with on-floor broiler buildings [37,50] and animal activity can also exacerbate already diminished air quality [51].

Regardless of the type of animal production system, the common features are a high density stocking of animals, diminished air quality and increased respiratory diseases of farmers and farm workers [52,53]. A comprehensive review of respiratory diseases, cellular and immunological responses associated with CAFO exposures was performed by May et al. 2012 [1]. A major issue related to commercial-scale, confinement-based livestock production is diminished air quality in communities in the vicinity of production facilities. For more than three decades, researchers have focused heavily on understanding the effect of livestock production dust on respiratory health of agricultural workers and local residents [30,54-59]. In rural areas there is a correlation between development of COPD and exposure to poultry/livestock facilities and grain dust [60].

Response of pigs to agricultural environments and organic dust extract exposures

Pigs have adapted to production environments and the preponderate majority of pigs live their entire life in CAFO-style buildings. To evaluate the impact of indoor production

environment on pig health, studies have used exposure chambers to deliver defined pollutants [61-67]. Chronic exposure of pigs to corn dust alone did not elicit clinical respiratory symptoms or affect growth performance; however, exposing pigs to dust combined with pungent gases (*i.e.*, sulfur dioxide and ammonia) resulted in destruction of mucosal structures (*i.e.*, ciliated tracheal epithelia and goblet cells) [61,63]. Pigs exposed to dust consisting of corn/soybean meal and LPS via a continuous flow chamber system displayed a non-specific inflammatory response, mainly involving modulation of neutrophils and eosinophils in their bronchial alveolar lavage fluid, compared to control pigs [66]; however, these findings were confounded by the presence of peptidoglycan contamination in dust samples and air supplied to control pigs. Another study exposed pigs to dust collected from convection tubes within a commercial swine facility for 2-15 weeks with no observable effect on the respiratory system [62]; however, excessively high dust concentrations [300 mg/m³] at well-above typical levels within swine farms [10 mg/m³] resulted in alterations in feed efficiency and growth performance (*i.e.*, average daily gains). Despite challenges with recreating animal barn conditions, it is evident that the complexity of the farm environment and exposures therein mediate respiratory disease and immunological responses in animals.

Recently, computational, *ex vivo* and *in vitro* approaches have been utilized to understand how airway morphology affects deposition of bioaerosols within the airways of animals and man. Airway geometry and tissue morphology -- specifically cartilaginous rings within the tracheobronchial region and associated mucosal lining -- are as important for understanding particle deposition mechanisms and pulmonary responses as the type of inhalation exposure [68-70]. The trachea is a distensible organ with a considerably wide range of sizes and shapes, which are controlled largely by the trachealis muscle [71]. A recent report from our group showed for the first time that pigs reared indoors and outdoors exhibit structural and cellular differences in their tracheae and airway epithelia [72*]. The study showed that pigs reared indoors have larger tracheal diameters and mucosal epithelia that are more densely packed with goblet cells when compared to outdoor reared pigs [72*]. Increased mucus production in the conducting airways is a natural defense response. This high density of goblet cells in the airway mucosa of pigs reared indoors [72*] is likely the result of hyperplasia, mediated by exposure to the indoor swine facility environment, because accumulation of goblet cells is associated with exposure to bioaerosols such as in swine barn air [73] and cigarette smoke [74]. Furthermore, rabbits and guinea pigs that were kept in a swine production building for 12 months showed signs of epithelial cell hyperplasia and metaplasia, submucosal changes and hypersensitivity pneumonitis, compared to controls that were kept in a conventional laboratory animal vivarium [75].

Macrophages are important innate responders to organic dust exposure and mediators in chronic inflammation. A recent *in vitro* study of pig alveolar macrophages and monocyte-derived macrophages (MDMs) collected from pigs showed repeated exposure to ODE reduced phagocytosis and the ability to kill bacteria [8**]. These findings are consistent with studies using human MDMs, where cells pre-exposed to ODE (ODE-MDMs) had diminished phagocytic and bacterial killing capacity compared to control MDMs that were kept in culture media [6]. What is evident from these studies is that clear similarities exist with regard to human and pig responses to organic dust exposures *in vitro* and such high

degree of similarity may signify *in vivo* overlaps. In an *in vitro* macrophage model, swine barn dust was depleted of endotoxin (lipopolysaccharide, LPS) and peptidoglycan (PGN), singly or in combination, prior to cell stimulation, and PGN seemed to be important in driving an impaired cellular response; however, a combination of LPS and PNG resulted in observations closest to responses to ODE exposure [6]. This finding highlights the complex, multifactorial nature of the inhalation exposures in CAFOs and the impact on responses. Expression of cluster of differentiation 163 (CD163) in mature porcine macrophages has been associated with entry and intracellular replication of the virus that causes porcine reproductive and respiratory syndrome (PRRS). PRRS is a disease of pigs that cripples the immune system by replicating within the macrophages, monocytes and dendritic cells that populate the tonsils and respiratory tract. PRRS is associated with reproductive failure and has 60-80% prevalence in swine herds in the United States [76-79]. Exposure to ODE has been shown to enhance CD163 expression [8**] which may enhance susceptibility to PRRS infection [80]; however, the exact levels of causative organic dust are not currently known. Nevertheless, an important implication for facility workers is exposure to ODE may enhance susceptibility to CD163-associated viral infection; enhanced expression of CD163 by human monocytes/macrophages correlates with susceptibility to viral infection [81,82].

Mechanisms of Organic Dust Mediated Oxidative Stress and Antioxidant Defenses

Reactive oxygen (ROS) and nitrogen (RNS) species have a well-defined role in cell signaling, killing of microorganisms by phagocytes and contraction/relaxation of airway smooth muscles. Beneficial actions of nitric oxide (NO), presumably derived from inducible nitric oxide synthase (iNOS), include enhanced cilia motility [83] and airway smooth muscle relaxation, which have been shown to improve symptoms of hyperreactive asthmatic airways in a guinea pig model [82]. However, elevated levels of ROS/RNS, as seen in obstructive airway diseases [85], have been shown to mediate fibroblast activation, mucus hypersecretion, cell injury and production of pro-inflammatory mediators by epithelial cells, and damage macromolecules DNA, lipids and proteins [84,85,86**,87-91]. Oxidative and nitrative stress is associated with loss of superoxide dismutase activity and downstream events characteristic of asthma, including apoptosis, shedding of the airway epithelium, hyperresponsiveness and diminished antioxidant activity [90,92]. Animal model studies have shown that an increase of oxidant levels correlates with a decrease in macrophage numbers. Pigs infected with *Mycoplasma hyperpneumonea* showed signs of oxidative stress and apoptosis in macrophages [93**,94**] and phagocyte-derived reactive species were higher in swine with viral infections compared to virus-free pigs [93**,94**].

iNOS-derived NO is a marker for airway inflammation in asthmatics in that its production has been correlated with airway eosinophilia, hyperresponsiveness and elevated peroxynitrite levels [92,95]. During times of L-arginine deficiency, iNOS-derived NO reacts with superoxide through a radical-radical reaction to produce peroxynitrite (ONOO⁻) [96, 97], a potent oxidant that promotes inflammation and smooth muscle contraction, thus exacerbating airway hyperresponsiveness [84]. Although exhaled NO measurement is not an established clinical approach for assessing pulmonary disease, it may be a useful

supplementary diagnostic tool. Patients, including farmers, with occupational asthma have significant increases in exhaled NO levels [98]. Whereas both increased [99,100] and decreased [101] NO levels have been reported in COPD patients. These data are potentially confounded by NO detection methods and smoking history [102,103]. Educational intervention – presentations about asthma pathophysiology, medications, and workplace allergen prevention strategies -- has been effective in long-term reduction of exhaled NO levels in swine and dairy farmers with COPD [104].

Potential Therapeutic Benefits of Dietary Phytonutrients and Antioxidants

Currently, there are no therapeutics available that will significantly reduce COPD morbidity symptoms [105] and the standard of care stems from guidance provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [106,107]. Antioxidants, including major endogenous enzymatic antioxidants -- superoxide dismutase (SOD), glutathione peroxidase and catalase -- [90,91] and non-enzymatic antioxidants such as vitamins A, C, and E, and glutathione, present in dietary supplements, are important in maintaining a healthy balance of oxidants.

The commercially available antioxidant, N-acetylcysteine (NAC), a direct precursor to reduced glutathione (GSH) with mucolytic properties [108,109,110], exerts its antioxidant capacity by directly reacting with oxidants [111]. Numerous reports document beneficial effect of dietary supplementation with NAC on improved gastrointestinal health and immune response in pigs that have been exposed to LPS [112*,113-115]. NAC consumption improved antioxidant capacity and reduced LPS-induced serum levels of tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and prostaglandin E2 (PGE₂) in pigs intraperitoneally injected with LPS [112*]. Nutritional supplements improve total antioxidant capacity and reduce systemic oxidative stress in children with asthma [116*]. Preschool aged children with a high intake of vitamins C and E had a reduced association with asthma compared to children with the lowest intake [117**]. Furthermore, taking multivitamins decreased exhaled NO and raised previously low plasma levels of vitamins A and E in asthmatic children [116*,118].

Phytonutrients are bioactive compounds from plants that can boost immunity and antioxidant capacity. The medicinal plant sorrel (*Hibiscus sabdariffa*, rosell), rich in phenolic acids, flavonoids and lignans, possesses antioxidant, anti-inflammatory, antimicrobial and anti-tumorigenic properties [119-121]. In a recent study by our group, *Moringa olifera* Lam leaf extract – a medicinal plant rich in vitamins, including vitamin D [122] -- reduced acute lung inflammation mediated by intranasal exposure to ODE in mice that consumed water supplemented with moringa compared to control mice that drank water [123*]. The study showed mice that drank moringa tea had fewer cells present in bronchoalveolar lavage, despite having higher ODE-driven TNF- α levels, a finding that is consistent with observations of Mahajan et al. [124] in which a moringa seed extract decreased bronchoalveolar lavage fluid (BALF) cell counts, but did not affect TNF- α levels in guinea pigs exposed to aerosolized ovalbumin [124]. Consumption of a vitamin D (1,25 hydroxyvitamin D) rich diet decreased production of neutrophil chemoattractants – chemokine (C-X-C) ligand 1 and CXCL2 – and neutrophil infiltration in mice exposed to

ODE compared to control mice that received standard rodent chow, or a relatively low vitamin D diet, prior to ODE exposure [125**]. Together, these observations imply dietary supplementation with antioxidants, such as vitamin D, may relieve the burden of airway inflammation seen in swine facility workers.

Conclusion

Domesticated pigs have been intensely bred to grow rapidly for market readiness in CAFOs, and their respiratory systems have become adapted to reduced air quality therein. Therefore, swine models of agricultural organic dust exposure provide valuable insight and implications for understanding mechanisms of respiratory symptoms and diseases affecting farmers and facility workers. Pigs are an excellent model for studying respiratory conditions of farmers and ranchers because they live within confinement buildings from birth to market weight (e.g., 5-7 uninterrupted months) and may develop “pre-COPD” lung signatures which will be helpful for understanding COPD in farmers. Formal human studies are needed to assess modification of effects from organic dust environment exposure by endogenous and dietary antioxidants.

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Abbreviations

BALF	bronchoalveolar lavage fluid
CAFO	concentrated animal feeding operations
CD163	cluster of differentiation 163
COPD	chronic obstructive pulmonary disease
CXCL1	chemokine (C-X-C) ligand 1
CXCL2	chemokine (C-X-C) ligand 2
GSH	glutathione
GOLD	global initiative for chronic obstructive pulmonary disease
IL-6	interleukin-6
iNOS	inducible nitric oxide synthase
LPS	lipopolysaccharide
MDM	monocyte-derived macrophages
NAC	N-acetylcysteine
NO	nitric oxide levels
ODE	organic dust extract
PGE₂	prostaglandin E2
PGN	peptidoglycan
PRRS	porcine reproductive and respiratory syndrome
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD	Superoxide dismutase
TNF-α	tumor necrosis factor alpha

Key Points

- Exposure to farm animal production environments is associated with development of chronic respiratory disease of animals, farmers and facility workers; however, the airways of pigs that are maintained within confinement facilities for several uninterrupted months show signs of adaptation.
- Striking similarities exist between the responses of respiratory and immune cells of pigs and humans that have been exposed to swine production environments and organic dust extract; therefore, studies involving production animals may provide insight for understanding disease progression in farmers.
- Oxidative stress is a key feature of respiratory diseases associated with the farm animal production industry and dietary supplementation with antioxidants may reduce symptoms associated with organic dust environment exposures.
- Formal human studies are needed to fully understand the role of antioxidant modulation of health effects caused by organic dust exposure.