Asthma-like diseases in agriculture

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Abstract

Although many studies on asthma have been conducted in farming populations, no longitudinal studies have been published so far. Smoking, work in pig barns, and crop farming together with exposure to endotoxin and quaternary ammonium have been described as environmental risk factors for self-reported asthma and/or wheeze in cross-sectional studies. The prevalence of self-reported asthma has been found to range from 0.7% in female greenhouse workers to 21% in Danish smoking female farming students. Exposure in farming is diverse, but dominated by organic dust containing high amounts of compounds known to trigger the innate immune system. This is confirmed by a wide range of human experimentation where naïve persons have been introduced to swine confinements. Cross-sectional data suggest a protective effect of farming on allergy. However, differences in the diagnostic procedure and the predominantly wheezy asthma type in farming concomitant with a lower rate of allergic asthma makes the comparison difficult. Furthermore, healthy worker selection, misclassification, age differences, difference in time of study and small study populations, resulting in low statistical power, might be factors explaining the findings. Well-designed longitudinal studies of the incidence of carefully defined phenotypes of asthma and risk factors are needed to clarify the risk of asthma, or wheezy phenotypes related to farming.

Introduction

Agricultural work represents a major hazard for respiratory disease. Both asthma and chronic obstructive pulmonary disease (COPD) have been reported related to farming [1, 2]. While farm workers have inhalation exposures to pesticides, diesel particulates and toxic vapors, the major exposure is organic dust composed of mould hyphal fragments and spores, bacteria, endotoxins, glucans, mite allergens, animal-derived material like dander, hair, bristle, urine, and feces together with animal feeds. The vast majority of studies of asthma in agriculture have been performed without agent-specific exposure assessment, and only a few studies have included exposure assessment as part of the design.

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Respiratory symptoms in agriculture

Prevalent work-related lung symptoms in farming are wheeze, cough, and dyspnea, and these are often much more frequent than among control subjects or among random population samples [3–6]. However, these symptoms are nonspecific and might reflect acute lung irritation as well as symptoms associated with respiratory disease. The clinical picture of obstructive lung diseases in agriculture is diverse with major symptoms of asthma, COPD (or both), bronchial hyperresponsiveness and increased yearly loss in FEV_1 associated with few or any respiratory symptoms. The designation of asthma-like syndrome in agriculture has been introduced from studies mainly in the U.S. of highly exposed swine confinement workers [6, 7]. However, farming is probably one of the exposure situations with the most diverse range of asthma phenotypes [8], ranging from clearly IgE-dependent asthma with eosinophilic influx related to allergen exposure (e.g., enzymes or cow dander or horse hair) to non-IgE-dependent asthma dominated by neutrophilic influx and wheezing [9]. The neutrophilic phenotype is characterized by a self-limited inflammatory event that might or might not involve persistent airway hyperresponsiveness [10]. The end stage presents as respiratory symptoms, bronchial hyperresponsiveness, and accelerated lung function decline in the absence of sensitization against swine feed and food allergens [10].

These features have been confounding research into asthma in farming, and only recently has the discussion of asthma phenotypes been addressed by the scientific community [11–13].

Studies of asthma-like symptoms in agriculture

In this chapter we apply the term "asthma-like diseases" as a questionnaire-defined outcome of "asthma" or "asthma-like symptoms" in epidemiological studies in agriculture. No longitudinal studies on incidence of asthma in farming populations have been published and rates of asthma incidence associated with farming are based on data from surveillance systems for occupational diseases including asthma. These systems are mainly made for insurance and compensation purposes for the workforce [14]. In the available data sources there are differences in the definition of occupational asthma (OA) between countries and heterogeneity in classification of occupation. Some surveillance programs are without information as to whether farming is classified as an occupation. Due to weakness in coverage and case ascertainment there might, therefore, be a general tendency in underreporting of asthma in farming. From those surveillance systems in which data from farming occupation are present, the incidence figures from Finland [14] are by far the highest. The mean annual incidence rate was 174 cases/10^6 employed workers and the mean annual incidence rate for male farmers was 1200 and for female farmers 1910. These high

figures in the farming population are probably due to the custom in the Finnish farming to brush their cows daily. Data from Germany [15] arise from the worker compensation system. The annual mean incidence rate was 51 cases/10^6 employed workers, and in farmers the figure was 113 cases/10^6 employed workers. Swedish surveillance data are based on self-reported asthma and here the mean annual incidence rate was 80 cases /10^6 employed workers, while in male farmers and in female farmers it was 170 and 203 cases/10^6 employed workers, respectively [16]. By far the lowest data on incidence of OA has been reported from USA, the state of Michigan [17]. These data arise from physicians' reports, compensation claims and hospitals. The annual mean incidence rate was 30 cases/10^6 employed workers and in agricultural production the figure was 3 cases/10^6 employed workers.

More than 30 cross-sectional studies of the prevalence of asthma-like symptoms in agriculture have been published, and in 18 the prevalence data have been related to the prevalence in a non-exposed control group (Tab. 1) or associated with the prevalence in the general population or a random sample of the general population (Tab. 2).

The mean prevalence of asthma in a representative sample of 1685 Danish farmers [3] was 7.7%, lowest (3.6%) among farmers aged 30–49 and highest (11.8%) among farmers aged 50–69 years. The prevalence of asthma was highest among pig farmers (10.9%). Age (OR 5.8, 95% CI 2.8–12.2) and pig farming (OR 2.0, 95% CI 2.0–3.5) were risk factors for self-reported asthma. The prevalence of asthma among farmers was the same as in a representative sample of the Danish populations aged 30–49 years, but significantly higher among farmers aged 50–69 years (OR 2.25, $p < 0.001$). The prevalence of current asthma in 1706 farmers from New Zealand [18] was high (11.8%), although lower than the prevalence of asthma measured in the general population (15%). Female farmers had an increased risk for asthma (OR 1.8, 95% CI 1.3–2.5). High prevalence of asthma (18.3%) was also found among 904 randomly selected Swiss farmers [19], but no difference was observed in the prevalence of asthma attack between farmers (2.1%) and a random sample of the Swiss population (3.1%). Current (OR 2.14, 95% CI 1.43–3.19) and former smoking (OR 2.05, 95% CI 1.34–3.14) were risk factors for asthma. The prevalence of asthma was 2.8% (95% CI 2.4–3.2) in a random sample of 7496 European farmers from Denmark, Northern Germany, Switzerland and Spain [20]. In an American rural population, farmers had an asthma prevalence of 9.8% in females and 3.8% in males: the OR for 'ever farmed' *versus* 'never farmed' was 0.77 (95% CI 0.48–1.24) [21]. The prevalence of asthma among the farmers aged 20–44 years (1.3%, 95% CI 0.9–1.7) was significantly lower than in an age-matched sample of the general European population (ECRHS) (3.2%, 95% CI 2.9–3.9; $p = 0.001$). In Norway [22] the asthma prevalence among a random sample of 2106 farmers was 4.0%, significantly lower than among a random sample of 351 rural (5.7%) and 727 urban (7.6%) controls. Recent data from The Netherlands [23] have found a significantly lower

Table 1. Cross-sectional studies of the prevalence of asthma-like symptoms in agriculture and in the general population.

Ref.	Year	Country	No. of subjects	Asthma prevalence among farmers	Prevalence in agriculture vs general population	Environmental risk factors
[3]	1988	Denmark	1685	7.7 11.8 age 50–69 3.6 age 30–49	↑ subjects aged 50–69 OR 2.25 N.D. for aged 30–49	Pig farming OR 2.0
[18]	1999	New Zealand	1706	11.8	N.D.	Female OR 1.8
[19]	2001	Switzerland	904	18.3	N.D.	Smoking OR 2.1
[20]	2001	Denmark, Germany, Sweden, Spain	7496	1.3	Sign lower than controls	
[21]	2002	USA	574+1056	3.8 males 9.5 females	Lower for males N.D. for females	Smoking OR 1.1
[22]	2004	Norway	2106+1078s	4.0	Sign lower than controls, both atopic and non-atopic	
[23]	2007	Netherlands	1205 conv. 593 organic 2679s	5.2 conv. 2.9 organic	Sign. Lower than controls	

s, sample of the general population; conv., conventional farmers; organic, organic farmers; N.D., no difference.

Table 2. Cross-sectional studies of the prevalence of asthma-like symptoms in agriculture and in controls.

Ref.	Year	Country	No. of subjects	Asthma prevalence	Prevalence in agriculture vs controls	Environmental risk factors
[24]	1997	DK	1691 + 407c	Smo 11.3/13.2 Non sm 5.3/5.9	N.D.	Smoking sign ↑
[25]	1999	DK	1901 + 407c	5.4–21.0	N.D.	Smoking OR 1.7
[26]	2001	Croatia	236 + 165c	0.7–7.7	N.D.	
[27]	2001	Croatia	814 + 635c	0.7–7.7	N.D.	
[28]	1999	NL	239 + 311c	5.9	N.D.	Quaternary ammonium OR 9.4
[29]	1998	Fr	265 + 149c	5.3	N.D.	
[30]	1993	Croatia	167 + 81c	0.7–6.3	N.D.	
[31]	1998	South Africa	134 + 122c	4–13	Sign. higher	
[32]	2005	Gr	122 + 100c	6.7	N.D.	
[33]	2005	US	1140 + 10132c	7.73	Sign. higher	Farming OR 1.54
[34]	2007	NZ	4288 + 1328c	14.3–15.6	Sign. lower	

c, controls; Sign., significantly; N.D., no difference.

prevalence of asthma-like symptoms among both conventional farmer (5.2%) and organic farmers (3.9%) compared a random sample of the general population (7.6%).

In a Danish study of 1901 farming students, of whom 210 were females, and in 407 rural controls the prevalence of asthma-like symptoms was between 5.4% and 21%, but no difference was observed between farming students and controls [25]. Asthma in the mother (OR 3.4, 95% CI 2.1–5.7), sex [OR (males) 0.5, 95% CI 0.3–0.8], and smoking (OR 1.7, 95% CI 1.2–2.4) were factors significantly associated with asthma. Data of the prevalence of OA from two studies in farm workers in Croatia [26, 27] showed no differences (0–7.7%) among the 236 livestock and the 814 crop farm workers and food packing controls, for either smokers or non smokers. Vogelzang et al. [35] found in a study of 239 pig farmers and 311 rural controls the same prevalence of asthma in the two groups (5.9%) *versus* (5.5%). In pig farmers the use of disinfectants (quaternary ammonium compounds) (OR 9.4, 95% CI 1.6–57.2) and aspects of disinfecting procedure were associated with the prevalence of asthma. Atopy was significantly less prevalent in pig farmers (4.6%) compared to controls (14.6%) and pig farmers had significantly fewer symptoms of allergy in childhood (9.9%) than controls (17.2%). Atopy in childhood was strongly associated with the prevalence of asthma symptoms (OR 4.1, 95% CI 2.2–7.7). Cross-sectional data from a French study of 265 dairy farmers and 149 non-exposed controls [29] revealed the same cumulative prevalence of self-reported asthma and of current asthma in farmers and in controls; 5.3% and 1.5%, respectively, *versus* 3.4% and 1.3%. Prevalence data of asthma in non-animal farming occupation has been analyzed among 135 female and 32 male greenhouse workers [30]. No significant increase in the prevalence of asthma was observed compared to non-exposed 51 female and 30 male controls, either for males (6.3% vs 0%) or for females (0.7% vs 0%). Among 134 South African poultry workers, the prevalence of asthma was significantly higher (4–11%) than among 122 controls [31], while the prevalence of asthma was elevated but not significantly higher (6.7%) among 120 grape farmers from Crete compared to 100 controls (2.0%) [32]. Among 1140 male New York dairy farmers [33], the prevalence of asthma was 7.73% and significantly higher than among 10 132 male non-farmers (5.03%). New Zealand data involving 4288 farmers and 1328 controls found a significantly lower prevalence of "asthma ever" among dairy farmers (14.8%) and sheep and beef farmers (15.6%) compared to non-farming controls (23.3%) [18].

Exposures in agriculture

Exposures in agriculture are varied and dependent upon whether the operation is producing row crops, livestock or fruits, nuts and vegetables. Common exposures may include diesel exhaust, fuel vapors, pesticides and disinfectants, and welding

fumes. Crop production generally includes exposures to fertilizers such as anhydrous ammonia, while livestock production usually is associated with exposures to hydrogen sulfide, ammonia, and a multitude of odorous sulfur- and nitrogen-containing vapors [36]. Among the most potent odorous compounds are the organic acids, including acetic, butyric, caproic, propionic, and valeric acids; nitrogen-containing compounds such as ammonia, methyl amines, methyl pyrazines, skatoles and indoles; and sulfur-containing compounds such as hydrogen sulfide and dimethyl sulfide [37]. These odors smell like rotten eggs (hydrogen sulfide, dimethyl sulfide) or rancid butter (butyric acid, isobutyric acid) or have a putrid-fecal smell (indole, skatole, valeric and isovaleric acid).

Organic dust is a catchall term for the array of bioaerosols that arise in agriculture and downstream manufacturing that produces value-added food products, animal feed, seeds, ethanol, biomass, and compost. Toxicologically important components of organic dust include pathogenic microorganisms; microbial, plant and animal allergens; and microbial-associated molecular patterns (MAMPs) including endotoxin, β-glucans, and CpG DNA (Fig. 1).

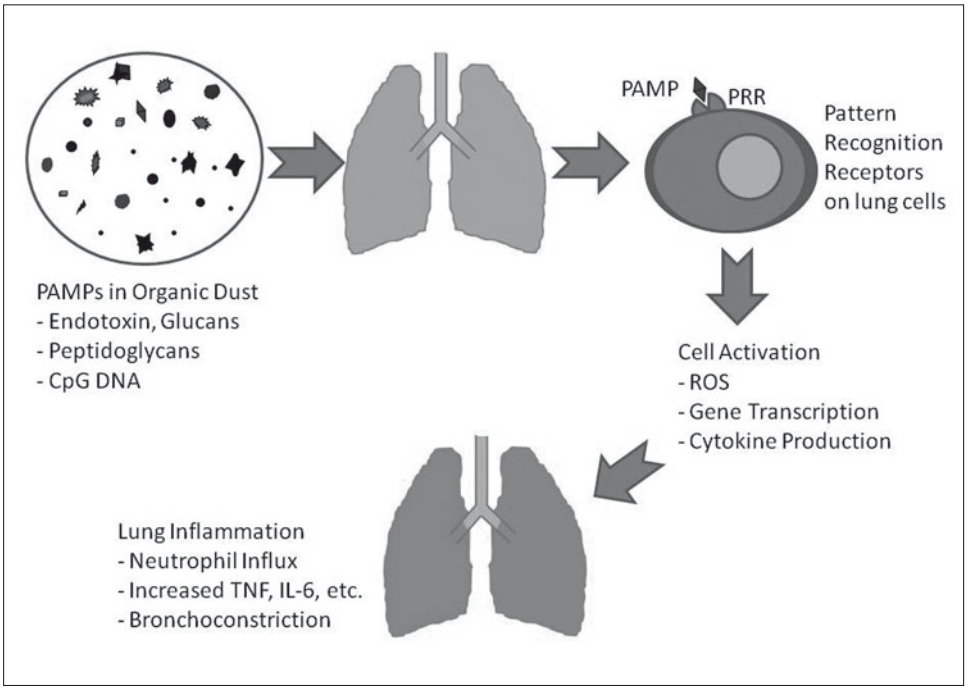

Figure 1.
The role of pathogen-associated molecular patterns (MAMPs) and pattern recognition receptors in organic dust exposure.

Pathogenic bioaerosols from livestock facilities are responsible for cases of infectious disease that extend beyond zoonoses typically seen only among farmers and veterinarians. The use of antimicrobials as growth promotants in livestock production has led to increased antimicrobial resistance of bacteria in swine and calf barn effluents to medically important antibiotics. In the U.S. over 300 scientific, medical, and advocacy organizations have called for legislation to eliminate the non-therapeutic use of antimicrobial agents (Pew Commission on Industrial Farm Animal Production 2008). Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging concern that has been linked to excessive use of antibiotics [38]. Multidrug-resistant culturable bacteria were measured in bioaerosols 150 m downwind of a swine operation with the finding that over 80% of the organisms were resistant to two or more classes of antibiotics [39]. Another infectious disease concern is that conditions inside industrialized livestock facilities will give rise to a pandemic strain of influenza [40]. Past outbreaks in Asia and recent cases in Southern California demonstrate the significance of this threat (CDC 2009). The two cases of infection with swine influenza A (H1N1) virus in the San Diego area occurred in unrelated children living in adjacent counties neither of whom had contact with pigs. The influenza virus they carried was resistant to two antiviral agents used to treat flu and contained gene segments that had not previously been observed in humans or swine. It is presumed that they both contracted influenza *via* human-to-human transmission.

Allergenic components of organic dust include thermophilic bacteria such as *Saccharopolyspora rectivirgula* and *Thermoactinomyces vulgaris* that are responsible for allergic alveolitis (also called hypersensitivity pneumonitis). Grain storage mites, animal danders, plant pollens, enzymes and possibly antibiotics added to animal feed can act as allergens, leading to allergic rhinitis and allergic asthma in some workers.

The constituents of organic dust posing the greatest health burden are arguably the MAMPs of which endotoxin has been studied the most. Endotoxin is an amphiphilic molecule of bacterial cell walls that induces innate immune responses in an amplifying cascade [41], leading to recruitment of neutrophils and macrophages to the lung. Endotoxin exposures in agriculture have been extensively studied and representative exposure data are presented in Table 3.

In recent work, Spaan et al. [42] have carefully evaluated methods for analyzing endotoxin with an eye toward recommending a fully specified standard method. Identical inhalable dust samples were collected to investigate the effects of filter type (glass fiber or Teflon), transport conditions (with/without desiccant), sample storage (–20° or 4°C), extraction solution [pyrogen-free water (PFW) or PFW plus 0.05% Tween 20], extract storage (–20° or 4°C), and assay solution (PFW or PFW plus 0.05% Tween 20) on endotoxin concentration [42]. No differences in endotoxin concentration were attributable to transport conditions or storage temperature of extracts. Extraction in PFW plus 0.05% Tween 20 resulted in 2.1-fold higher estimated endotoxin concentrations. Sampling on glass-fiber filters and storage of sam-

Table 3. Airborne endotoxin exposure values in agricultural operations.

Operation	Air sample	No. of samples	GM endotoxin concentration, EU/m^3	Reference
Livestock operations				
Dairy	Personal – inhalable Area – respirable	194 216	64 17	Kullman et al. 1998 [98]
Swine	Personal – inhalable	350	920	Preller et al. 1995 [99]
Swine	Area – total	81	8290	Thorne et al.1997 [100]
Swine	Area – total	21	3927	Duchaine et al. 2001 [101]
Swine conventional confinements Swine hoop barns	Area – inhalable	40 30	3100 3250	Thorne et al. 2009 [100]
Poultry	Area – total	81	1340	Thorne et al. 1997 [102]
Chicken Dairy Cattle feedlot Horse Swine Turkey	Area – inhalable	200 81 120 118 198 191	5000 35 150 1000 9000 2000	Saito et al. 2009 [44]
Other agriculture				
Animal feed manufacturers	Personal – inhalable Area – inhalable	530 79	12–285 19	Smid et al. 1992 [103]
Grain elevators	Personal – total Personal – respirable	410 410	2860 83.2	Schwartz et al. 1995 [104]
Potato processing	Personal – inhalable Area – inhalable	195 68	9–102 1–000	Zock et al. 1998 [105]
Soybean harvesting (closed tractors)	Personal – total	32	56	Roy & Thorne, 2003 [106]
Agricultural seed processing industry	Personal – inhalable	100	1800	Smit et al. 2006 [107]

GM, geometric mean.

ples in the freezer produced 1.3-fold and 1.1-fold higher endotoxin concentrations, respectively. This study found that there were important gaps in the specification of the CEN protocol and suggested parameters needed to fully specify a standardized protocol. In a second manuscript, Spaan et al. [43] compared four extraction media: PFW, PFW-Tween 20, PFW-Tris, and PFW-triethylamine-phosphate (TAP) to determine which performed best in the LAL assay and extracted the most endotoxin. PFW-Tris produced similar results to the PFW alone. PFW-TAP showed lower yields and a deviant calibration curve. Tween in the extraction medium resulted in significantly higher endotoxin yields from all dust types, independent of the effect of Tween in the assay. Among these four media, only Tween reproducibly enhanced the efficiency of endotoxin extraction from airborne dust samples.

A recent study evaluated endotoxin exposure assessment in six types of livestock operations using four types of air samplers in two regions of the U.S. [44]. This study demonstrated excellent agreement in 906 samples between analysis of endotoxin using the kinetic chromogenic LAL assay and the recombinant factor C assay with a correlation coefficient of $r = 0.91$ ($p < 0.01$) and the relationship overlaying the line of identity.

The other MAMP for which there has been exposure assessment in agriculture, albeit limited, is fungal β-glucans. These polysaccharide components of fungal cell walls can be measured using the Factor G pathway of the LAL assay [45] or by single-antibody ELISA [46, 47] or sandwich ELISA [48, 49]. Most studies that have measured glucans were focused on mold exposures in the indoor environment.

Human experiments

The first systematic studies of farming responses in humans were performed at the University of Iowa using extracts of corn dust (CDE) and LPS [50–53]. This research initiated the human experimental approach to the basic mechanism of the innate immune system on acute respiratory inflammation. The results showed that neutrophils increased in nasal lavage from 17×10^3 to 40×10^3 cells/ml in grain workers exposed to 2372 EU LPS/m^3 compared to postal workers exposed to 4 EU/m^3. However, no association was found to the LPS concentration among grain workers [52]. A study with an inhalation of aerosolized CDE confirmed the inflammation related to CDE. This initiated a series of experiments on the kinetics of the human and the mouse reaction to CDE. The response in humans was shown to start immediately after inhalation and last 2 days for bronchoconstriction, 4 days for neutrophilic influx, and 7 days for the increase in proinflammatory cytokines IL-1β IL-6 and IL-8. These changes were mirrored in the mouse model, although within a shorter period, leading to the conclusion that the mouse model would be an appropriate model to study grain dust-induced inflammation [53]. No increase in the reaction was found in atopic subjects compared to non-atopic subjects. In a

study of grain workers with bronchial hyperresponsiveness (BHR), it was shown that those workers with BHR had a greater decline in FEV_1 compared to "normal" workers. Surprisingly, this was not reflected in any differences in the bronchoalveolar lavage (BAL) fluid sampled 4 h after the exposure to 0.16 μg/kg nebulized endotoxin in CDE [52].

Swine

In farming, the first studies to suggest that LPS is the causative agent were from the Sweden and the Netherlands, and showed that endotoxin exposure was related to symptoms and FEV_1 in pig farmers [54, 55]. These initial studies have been followed by a range of quasi experiments in which the farming environment has been used to study the effect of the innate immune system. A group from Stockholm has been especially active in this field. Their work has elucidated the time course of the inflammatory events occurring after an acute exposure to organic dust [56–61]. In one study, this group showed that the acute changes they had observed in non-farmers were attenuated or totally abolished in healthy farmers adapted to the environment, and speculated on which mechanisms might be responsible for such an adaptive mechanism [62].

In a study of farmers experiencing asthma-like symptoms during work in swine confinement buildings and controls, it was shown that inflammatory responses in a work-like environment with low concentrations of LPS (0.5 μg/m3) and dust (4 mg/m^3) are similar to responses found after exposure to higher concentrations often used in experimental situations. Acute neutrophilic inflammatory responses and increases in BAL IL-6 and IL-8 were found; however, this response was attenuated among farmers who had already experienced asthma-like symptoms during exposure in swine confinement buildings [63]. In the same experiment, differences in complement response were found that may compensate for variation in the inflammatory response [64].

Laboratory animal-exposure studies

Inhalation experiments using guinea pigs, rats and mice have been extremely informative for identifying inflammatory agents in organic dust, establishing their potency and elucidating their mechanistic underpinnings. Studies in the 1980s in guinea pigs investigated the pulmonary effects of cotton dust and demonstrated that the effects on breathing patterns and production of fever were due to the endotoxin content. In more recent work, mice have been the animal model of choice due to the availability of inbred strains and knockout mice with specific characteristics or gene deletions [65]. Murine studies in the 1990s demonstrated that endotoxin was the principal

inflammatory agent in extracts of organic dust recovered from the air handling system of grain elevators handling corn (CDE). Inhalation-exposed mice developed a dose-dependent influx of monocytes and neutrophils to the lung and increases in TNF-α and IL-6 [36, 53, 66]. C3H/Hej mice bearing a mutation in the TLR4 gene exhibited a blunted response to a semi-purified endotoxin preparation [67] with a 1000-fold lower neutrophilic response than C3HeBFej normoresponsive mice [68].

Endotoxin exposure studies in mice of different strains have demonstrated a wide range of inflammatory responsiveness [69]. Among inbred strains without recognized genetic defects in endotoxin response genes, there was a 3-fold range of neutrophilic response between the least responsive to the strongest responder. Among mutant strains there was a 50-fold range. These studies used the Sigma *E. coli* 0111:B4 preparation of endotoxin which is believed to contain other MAMPs.

Recent murine studies [41], informed by previous *in vitro* studies [70–72], have shown that responsiveness to highly purified endotoxin requires functional CD14, MD-2 and TLR4 [41]. MD-2 knockout mice do not mount an inflammatory response when exposed to purified endotoxin, but the response can be reconstituted if the same amount of endotoxin is delivered to the lung as a monomeric complex of endotoxin and recombinant MD-2 [41]. Lung exposure to mutant penta-acylated endotoxin produces a blunted inflammatory response as compared with treatment with wild-type, hexa-acylated endotoxin. Treatment of CD14 knockout mice with endotoxin is also blunted but can be restored by treating with endotoxin:MD-2 complex.

Simultaneous exposures to endotoxin and allergens in lab animals have produced conflicting results. Studies using ovalbumin as the allergen found that concomitant endotoxin exposure suppressed the development of allergy [73, 74], while studies that used environmental allergens such as *Aspergillus flavus*, cat dander or cockroach allergen observed amplification of antibody production and pulmonary hypersensitivity [75–77]. In a neonatal exposure model, mice inhaling endotoxin (300 EU/day) and cockroach allergen (10 ng/day) on days 2–21 of life demonstrated increased pulmonary inflammation, increased total and specific IgE production, and lung remodeling compared to mice that inhaled endotoxin alone or allergen alone [77]. The inflammatory response measured in lung lavage fluid was marked by an influx of neutrophils and cytokines (TNF-α, IL-6, MIP-1α, KC, RANTES, G-CSF, and IL-12p40) that were 4–18-fold higher than observed in the mice treated with endotoxin only. These data illustrate that the complex mixtures we encounter in complex settings such as agricultural environments can be synergistic, and therefore need to be studied as mixtures rather than one compound at a time.

The modification of disease by farming exposure

It has been known for some time that being brought up at a farm decreases the allergic manifestations among the children concomitantly with an increased risk

of wheezing among the children associated to high concentrations of endotoxin [78–80], with an effect still detectable during young adulthood [81]. Recently, it has been shown that this effect is still observable even later in adulthood. Studies in a rural community in Norway [82] have shown that farmers have a lower prevalence of atopic diseases including asthma. However, they have a higher prevalence of inflammatory wheeze associated with endotoxin exposure.

Studies of agricultural workers from New Zealand [83] and The Netherlands [23, 84] have demonstrated that being brought up on a farm has a bearing on the subsequent reaction to agricultural exposures. This was most clearly demonstrated in a recent study of Dutch agricultural workers, where Smit et al. [84] showed that the place of upbringing was an effect modifier for the association between wheeze and endotoxin exposure (Fig. 2).

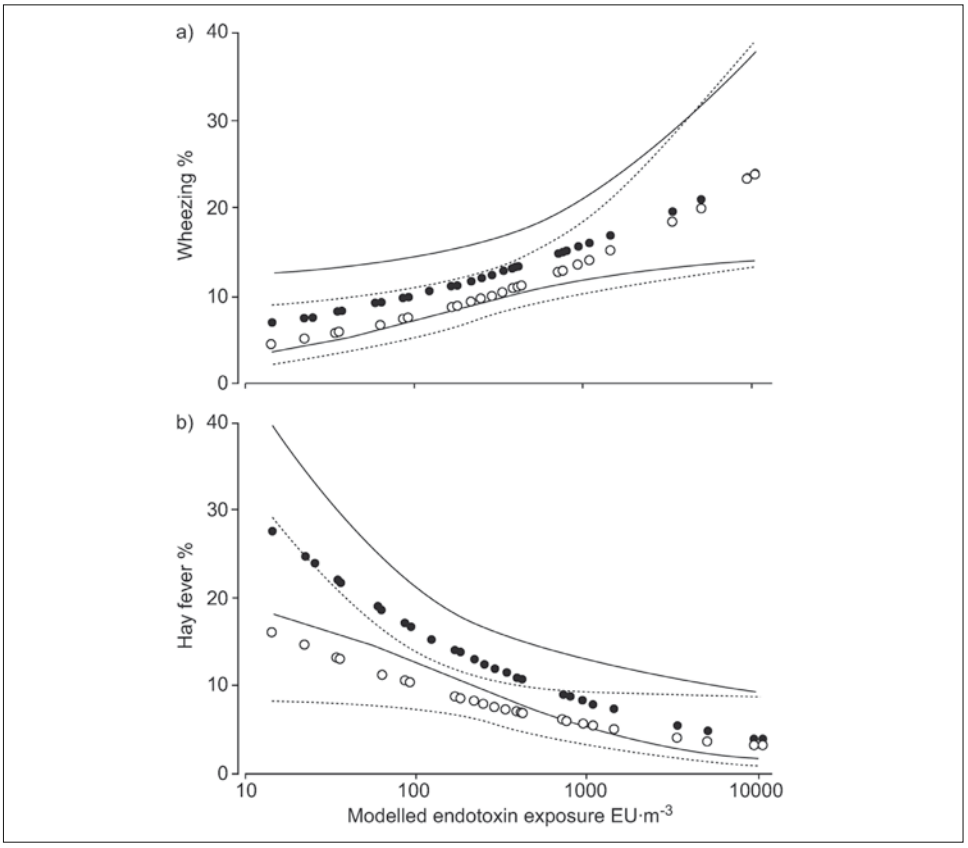

Figure 2.
The association between hay fever, wheezing prevalence and endotoxin exposure stratified for place of upbringing. From [84].

Susceptibility factors

There is a great variability in the individual response to organic dusts. Almost 50% of Caucasians respond to LPS exposure [85], and people with α-1-antitrypsin deficiency are hyperresponsive to organic dust exposure [86, 87].

Atopy has been proposed as one of the factors associated with increased susceptibility to organic dusts. The evidence is scarce; however, people with mild asthma or with BHR do have an increased reactivity towards LPS exposure [88, 89] and garbage workers with OA of the neutrophil type are not able to recruit PMNs in the nose as readily as workers without OA after nasal installation of LPS [90]. Furthermore, atopic subjects seem to react differently to LPS in the whole blood assay [91].

A few studies have shown α-1-antitrypsin to be a risk factor for respiratory symptoms among workers exposed to organic dusts such as cotton dust and grain dust [86, 92]. CD14 polymorphisms have been studied as a risk factor for OA; however, the data are conflicting regarding the possible effect of such polymorphisms, which might relate to differences in the techniques used for LPS analysis or to different study designs. The first polymorphism related to LPS susceptibility was demonstrated in a study by Arbour et al. [93] who found that a few co-segregating mutations in the TLR4 gene were responsible for LPS hyporesponsiveness in humans. The allele frequency was around 8% in the Iowa population, and, hence, it cannot explain the high number of non-responders reported by Castellan et al. [85] in the cotton-exposure study. TLR4 polymorphisms have not been associated with asthma in studies of populations [94], and it has not been possible to demonstrate any association with the protective effect on atopy that is seen among farmers' children [95]. TLR4 is one factor in a complex and long response pathway, which may accumulate mutations in other components of the pathway [96].

In Germany, a study of atopy among children from farms and non-farms has demonstrated that the protective effect of being raised on a farm was abolished if the children had a mutation in the TLR2 gene. Although TLR2 was previously thought to play a role in LPS recognition, other receptors like β-glucans and peptidoglycans are now considered as candidates for agents responsible for the protection against atopy, such as that observed among the farmers' children [95].

Very recently, a polymorphism in TLR10 has been shown to be a risk factor for asthma, consistent within different samples of the American population. Whether this will have any implications for persons exposed to organic dust is presently unknown, since the ligand for TLR10 is not known [97].

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