Annals of Agricultural and Environmental Medicine 2013, Vol 20, No 2, 206–221
www.aaem.pl

REVIEW ARTICLE

A review of bio-aerosol exposures and associated health effects in veterinary practice

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Samadi S, Wouters IM, Heederik DJJ. A review of bio-aerosol exposures and associated health effects in veterinary practice. Ann Agric Environ Med. 2013; 20(2): 206–221.

Abstract

Introduction. Occupational exposure to bio-aerosols has been linked to various health effects. This review presents an overview of bio-aerosol exposure levels in veterinary practices, and investigates the possibility of health effects associated with bio-aerosol exposure.

Methods. A systematic literature search was carried out in PubMed. Publications were included if they provided information on bio-aerosol exposure and related health effects through veterinary practice and other professions with similar exposures, occupationally exposed to animals.

Results. Few studies in veterinary settings showed that substantial bio-aerosol exposure levels (e.g. endotoxin and β(1→3)-glucan) were likely occur when handling farm animals and horses. Exposure levels are comparable to those levels observed in farming which have been associated with respiratory health effects. Animal specific allergen exposures have hardly been studied, but showed to be measurable in companion animal clinics and dairy barns. The findings of the few studies available among veterinary populations, particularly those working with farm animals and horses, are indicative of an elevated risk for developing respiratory symptoms. Studies among pig farmers, exposed to similar environments as veterinarians, strongly confirm that veterinary populations are at an increased risk of developing respiratory diseases in relation to bio-aerosol exposure, in particular endotoxin. Exposure to animal allergens during veterinary practice may cause allergic inflammation, characterized by IgE-mediated reactions to animal allergens. Nonetheless, the occurrence of sensitization or allergy against animal allergens is poorly described, apart from laboratory animal allergy, especially known from exposure to rats and mice.

Conclusion. Veterinary populations are likely exposed to elevated levels of bio-aerosols such as endotoxins, β(1→3)-glucans, and some specific animal allergens. Exposures to these agents in animal farmers are associated with allergic and non-allergic respiratory effects, proposing similar health effects in veterinary populations.

Key words

Bio-aerosol, endotoxin, glucan, allergen, health effect, veterinary practice, veterinarians

INTRODUCTION

Practitioners of veterinary medicine typically perform clinical work and deliver healthcare to animals, including farm animals (e.g. cows, sheep, pigs, and goats), companion animals (e.g. cats, dogs, and birds), and horses. Most veterinarians work in private medical practices. They treat animals suffering from infectious and non-infectious diseases and vaccinate against infectious diseases. Some veterinarians are animal-food-product inspectors; their job involves inspection of live animals and their food-products for transmittable diseases. A small proportion of veterinarians work in universities, both as physicians and researchers. Veterinary professions usually involve shift-work, and veterinarians working with farm animals and horses regularly commute between their office/clinic and farms to provide veterinary services at the farms/stables. Veterinary practices often use medical equipment, such as diagnostic and surgical instruments (e.g. radiographic and ultrasound equipment). Collectively, veterinary professions are extremely diverse because of multiple work environments and the performance of various activities. Therefore, veterinarians experience several known occupational hazards that can be categorized into exposures to biological agents (e.g. organic dust, microorganisms), chemical agents (e.g. anesthetic gases, pesticides, insecticides, pharmaceuticals), physical agents (e.g. radiation, noise), and trauma hazards (e.g. needle-stick injuries, bites) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. Exposure to all of these hazardous agents can potentially result in a broad range of adverse health effects, such as respiratory problems [11, 12, 13, 14, 15, 16, 17, 18, 19], dermatitis [20, 21], zoonotic infectious diseases [22], pesticides-associated toxicity [23], certain cancers [24, 25, 26, 27, 28] and physical trauma [8, 29, 30]. It has been known for a long time that occupational exposure to farm animals is linked to a wide variety of respiratory health effects [13, 14, 19, 31, 32, 33, 34], with biological agents as primary causal agents. Working conditions of veterinary professionals are to a large extent comparable to farmers exposed to animals with subsequent similar exposure, although gradual differences may exist. However, the occupational health risks of veterinary professionals associated with bio-aerosol exposure have so far been poorly described.

The main purpose of this review was to systematically summarize the literature on bio-aerosol exposure in veterinary practice and relate to possible health effects. We do acknowledge that, at present, only a few studies have been performed investigating health effects associated with

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Received: 21 February 2012; accepted: 17 January 2013

bio-aerosol exposure during veterinary practice, while the body of evidence on health effects of similar exposure among farmers exposed to animals is considerable. Therefore, the literature on farmers' exposures will be considered where relevant, to fill knowledge gaps.

MATERIALS AND METHOD

Definition of bio-aerosols. '*Organic dust*', dust of biological origin, also referred to as '*bio-aerosol*', is dust originating from microbial, animal or plant materials. Organic dust generally has a heterogeneous composition containing many toxic and immunogenic particles, for instance, pathogenic and/or non-pathogenic microorganisms (e.g. bacteria, viruses, and fungi) and their biological active components (e.g. bacterial endotoxin, mould glucan, and mycotoxin), plant fragments (pollen), and animal-derived materials (e.g. hair, dander, and allergens) [35].

Literature search. Publications investigating bio-aerosol exposure as well as health effects associated with bio-aerosol exposure through veterinary practice were searched in the PubMed database. Because publications on the topic are relatively rare, similar studies related to other animal environment settings were also included. The following search terms were utilized: "respiratory symptoms", "allergy", "sensitization", "infectious diseases", "biological agents", "bio-aerosol", "organic dust", "endotoxin", "glucan", or "allergen", linked with the use of the word "veterinary", "veterinarian", or "animal". Publications were judged to be covered in the review when the following inclusion criteria applied:

- articles should be published in the English language;
- studies reporting bio-aerosol measurements during contact with animals;
- studies concerning respiratory health effects associated with exposure to animals;
- studies concerning allergy and/or sensitization associated with exposure to animals;
- studies concerning zoonotic infectious diseases associated with exposure to animals.

The type of evidence available was explicitly explored, ranging from case series, surveys focusing on health endpoints only, to surveys with (simple) exposure categorizations up to quantitative exposure-response studies. The latter types of evidence are stronger than the first types.

LEVELS OF BIO-AEROSOL EXPOSURE

Initially, bio-aerosol exposure in animal settings was measured as culturable levels of airborne microorganisms [36, 37, 38]. Duchaine *et al.* [38] in pig barns found 4.25×10^5 CFU m^{-3} (1.67×10^5 to 9.30×10^5) of total bacteria and 883 CFU m^{-3} (547 to 2862) of moulds. Donham *et al.* [36] and Chang *et al.* [37] also showed similar results with a mean airborne level around 10^5 CFU m^{-3}. A factor lower total bacterial and fungal exposure levels were found in horse stables [39] and dairy barns (data not published) with a geometric mean of 3.1×10^3 to 1.1×10^4 CFU m^{-3} for total bacteria and 1.9×10^3 to 2.3×10^3 CFU m^{-3} for fungi. Later, culture-independent approaches using *e.g.* direct coloring of bacteria or biological assays, e.g. the *limulus amebocyte lysate* assay to determine endotoxin as general marker of bacterial exposure, as well as molecular biological techniques specifically quantitative real-time PCR for certain microbial products like mycotoxin were deployed [35]. With the fast development of molecular-based techniques during the last decades and the availability of probes, they are now applied to investigate airborne bacterial diversity [40]. Interestingly, a recent study by Nehme *et al.* [41] shifts focus from the aerobic to the anaerobic microbial burden in farm environments by showing that airborne archaea could be detected by PCR. The authors found high levels of archaea up to 10^8 16S rRNA gene copies per m^3 of air, which was on the same order of magnitude as total bacteria reported previously [40].

Table 1 summarizes studies reporting occupational endotoxin and β(1→3)-glucan exposure levels for studies which have been conducted in veterinary settings as well as in agricultural settings in which animals were involved. Not many studies have investigated bio-aerosol exposure in veterinary practice, except for the series of studies performed by us, on bio-aerosol measurements in a broad spectrum of veterinary practices within animal clinics and farms. Overall, exposure levels to dust, endotoxin and β(1→3)-glucan were found to be distinctly high although dependent on animal species involved, sampling sites, and job titles. The highest personal levels of endotoxin exposure were found during veterinary practice with poultry (GM 1498 EU m^{-3}) [42], the second highest in horse stables (GM 608 EU m^{-3}) [39], followed by ruminant clinics (GM 520 EU m^{-3}). In contrast to farm animals and horses, levels of dust and endotoxin during veterinary practice with companion animals were found to be low and close to background [43, 44]. The dust and endotoxin exposure of veterinarians dealing with farm animals are in the same range as has been reported previously for farmers involved in similar farm animal settings, of which a recent selection is presented in Table 1. Concerning β(1→3)-glucan, the highest personal levels were observed in horse stables (GM 9.5 μg m^{-3}) [39], followed by clinics for poultry (GM 3.39 μg m^{-3}) and ruminants (GM 3.10 μg m^{-3}). To our knowledge, no published studies are available on personal exposure of β(1→3)-glucan related to animal settings. Levels of β-(1→3)-glucan within different farm animal clinics, however, were much higher than those previously reported from greenhouses [45] and green waste-composting plants [46, 47]. There are two studies available determining cat and dog specific allergen levels during veterinary practice [43, 44]. The findings of these studies showed the presence of cat (Fel d 1) and dog (Can f 1) allergens in the air of companion animal clinics, although exposure levels differed significantly between job titles. Similarly, two studies reported personal exposure levels of Fel d 1 and Can f 1 in homes, offices and schools [48, 49]; however, comparisons with these studies need to be taken with caution because different sampling and analysis methods were utilized. Allergen exposure levels in farm animal settings have not often been investigated. However, a few recent studies showed that specific allergens of cow [50] and horse [51] within or around animal buildings were measureable and occasionally high.

Table 1. Exposure levels to inhalable dust, endotoxin, and β(1→3)-glucan as determined in various animal facilities.

	Sample type	N	Dust mg m^{-3} GM (range)	Endotoxin EU m^{-3} GM (range)	β(1→3)-glucan µg m^{-3} GM (range)	Reference
Veterinary practice						
Companion animal clinic						
Veterinary students	P	55	<LOD	3.2 (<LOD-75)	NM	
Veterinarians	P	12	<LOD	3.9 (<LOD-24)	NM	
Poultry clinic						
Veterinary students	P	98	1.27 (<LOD-20.9)	1485 (115-49846)	3.0 (<LOD-46)	Samadi et al. [42]
Veterinarians	P	11	1.01 (<LOD-12.4)	1221 (237-16927)	2.2 (<LOD-22)	
Caretakers	P	5	5.72 (1.62-14.7)	2749 (454-10820)	9.7 (2.5-27)	
	S	16	1.25 (0.18-5.37)	938 (140-10655)	1.5 (<LOD-20)	
Ruminant clinic						
Veterinary students	P	64	0.37 (<LOD-1.5)	368 (67-3047)	2.1 (<LOD-106)	Samadi et al. [42]
Caretakers	P	32	1.56 (0.14-20.8)	1042 (60-7492)	8.6 (<LOD-11)	
	S	36	0.15 (<LOD-0.49)	173 (27-1475)	1.4 (0.2-12)	
Horse clinic						
Caretakers	P	42	1.40 (0.20–9.5)	608 (<LOD–9846)	9.5 (<LOD–631)	Samadi et al.[39]
	S	32	0.40 (<LOD-1.1)	167 (<LOD-1385)	2.6 (<LOD-39)	
Animal farming						
Cow						
Dairy farming	P	8	1.30 (0.40–2.3)	560 (62–2230)	NM	Spaan et al.[84]
Dairy farming and cattle breeding	P	4	1.50 (0.70–2.7)	1570 (444–3860)	NM	Spaan et al.[84]
Dairy barns	?	159	1.78 (0.01-53.6)	647 (25.4-34800)	NM	Kullman et al.[83]
Dairy cattle	S	22	NA	16.9 (2.8- 66)	NM	Schierl et al.[216]
Beef cattle (breeding)	S	6	NA	558 (124-1025)	NM	Schierl et al.[216]
Cow sheds	P	23	1.78 (0.25-58.2)	NA	NM	Berger et al. [217]
	S	31	0.22 (0.01-2.43)	36 (4-561)	NM	
Pig						
Pig barns	S	18	NA	669 (43- 7469)	NM	Schierl et al.[216]
Pig barns	P	6	2.60 (1.6–5.4)	1510 (992–6970)	NM	Spaan et al. [84]
Pig feeding	P	?	3.65 (0.16-37.2)	? (95-147885)	? (0.006-5.2)	Szadkowska-Stańczyk et al.[218]
Pig barns	S	236	NA	111.3 (<1-4153)	NM	Ko et al. [219]
Pig barns	P	360	2.40 (0.30-26.6)	92 (5.6-1503)	NM	Preller et al. [220]
Poultry						
Laying hens	S	18	NA	463 (21.8- 21933)	NM	Schierl et al.[216]
Poultry farm (eggs)	P	2	9.50 (6.60–14)	2090 (1716–2550)	NM	Spaan et al.[84]
Poultry farm (meat)	P	2	4.20 (4.00–4.4)	880 (520–1500)	NM	Spaan et al.[84]
Poultry farm (free-range hens)	P	5	3.60 (1.60–11)	2140 (360–8120)	NM	Spaan et al.[84]
Turkeys	S	6	NA	1902 (467- 5292)	NM	Schierl et al.[216]

N, number of samples; <LOD, below the lower limit of detection, P, personal; S, stationary; NA, not available, NM; not measured.

POTENTIAL HEALTH EFFECTS

The most well-known occupational health effects related to bio-aerosol exposure are respiratory symptoms [13, 16, 17, 19, 52, 53, 54, 55, 56, 57, 58, 59], ranging from acute mild and self-limiting to sever chronic, even life-threatening. Respiratory symptoms can be classified on the basis of inflammatory mechanisms into allergic and non-allergic respiratory diseases. Allergic respiratory symptoms are caused by an immune-specific airway inflammation in which antibodies of IgE (type I) or IgG (type III) may play a role in the inflammatory reactions. Allergic asthma and rhinitis are two well-known allergic respiratory diseases that may occur due to exposure of specific allergens present in organic dust (*e.g.* animal specific allergens) [60, 61]. In addition to allergic asthma and rhinitis, organic dust exposed workers might develop extrinsic allergic alveolitis (EAA), referred to as hypersensitivity pneumonitis (HP) or farmer's lung [62]. Asthmatic symptoms may occur in the absence of an immune-specific reaction. A considerable proportion of work-related asthma symptoms are known to be non-atopic asthma. This form of asthma, sometimes referred to as asthma-like syndrome or non-allergic asthma [34], is supposed to be caused by inflammatory components of bio-aerosols such as endotoxin. The underlying mechanism is considered a neutrophil-mediated inflammatory reaction [63]. Workers exposed to organic dust contaminated with a very high endotoxin level may also develop non-allergic systematic inflammatory reactions which are accompanied by flu-like symptoms. This is referred to as "*organic dust toxic syndrome*" (ODTS) [58]. Additionally, exposure to organic dust has also been associated to chronic obstructive pulmonary diseases (COPD) [34].

Besides respiratory health effects, other possible adverse health effects have been suggested or proven to be associated with bio-aerosol exposure, such as infectious diseases (*e.g.* Q-fever, anthrax, tuberculosis, swine influenza) [64, 65, 66, 67, 68, 69, 70, 71], certain cancers [24, 26, 72] and dermatitis [73, 74, 75]. Nonetheless, these health effects have not been studied extensively and information about their occurrence is extremely limited. Paradoxically, studies have also suggested a possible protective effect of exposure to microbial agents on the development of allergic diseases [18, 76, 77, 78]. In following paragraphs we will explain more about the mechanisms and the occurrence of the different health endpoints in relation to veterinarians.

RESPIRATORY HEALTH EFFECTS

Table 2 summarizes a selection of studies on adverse health effects associated with bio-aerosol exposure in veterinarians and other related settings. Respiratory health effects associated with bio-aerosol exposure through veterinary practice have not been extensively investigated. Andersen *et al.* [79] investigated the prevalence of self-reported respiratory symptoms and lung function changes in a cross-sectional study among veterinarians during the annual meeting of American association of pig veterinarians. Pig veterinarians in this study reported a high prevalence of work-related respiratory symptoms, including rhinitis (69%), cough and chest tightness (53%), wheeze (31%), and wheeze accompanied with airway obstruction (24%). This study also showed that veterinarians with airway obstruction spent more hours per week in pig barns than those veterinarians with normal lung function [79]. Tielen *et al.* [80] evaluated the prevalence of self-reported respiratory symptoms in a cross-sectional questionnaire-based study among Dutch veterinarians. The authors found that the veterinary practitioners exposed to farm animals had a distinctly higher prevalence of chronic cough (OR 1.8, 95% CI 1.1–2.8), chronic phlegm production (OR 2.1, 95% CI 1.1–3.7), and wheeze (OR 2.8, 95% CI 1.3–6.3), compared to veterinarians with other specialties. Jolie *et al.* [81] investigated the health respiratory problems in veterinary students after visiting of a pig farm for 3 hours. Overall, 72.5% of veterinary students reported respiratory symptoms in relation to pig farm exposure. Symptoms (87.1%) mostly developed the same day of visiting a pig farm, and disappeared 3 days after exposure. A more recent study [82], carried out among veterinary medicine students, similarly showed a higher prevalence of respiratory symptoms in those veterinary students exposed to farm animals compared

Table 2. A selection of epidemiological and experimental studies of adverse health effects associated with bio-aerosol exposure in veterinarians and related other settings.

Study design	Study population	Outcome measures	Reference
Veterinary studies			
Cross-sectional questionnaire-based	Swine veterinarians	An increase of work-related respiratory symptoms and airway obstruction was observed.	Andersen et al. [79]
Cross-sectional questionnaire-based	Pig workers and veterinarians	Exposure to organic dust suggested to play a role for observed respiratory problems.	Donham et al. [33]
Cross-sectional questionnaire-based	Veterinarians	Large animal practitioners reported higher symptoms of chronic cough, chronic phlegm production, chest wheezing, compared to veterinarians with other specialties.	Tielen et al. [80]
Cross-sectional questionnaire-based	Veterinary medicine students	An elevated prevalence of sensitization and self-reported symptoms with increasing years of veterinary study was found, suggesting contact with animals is a risk factor for developing sensitization and symptoms.	Samadi et al. [82]
Cross-sectional questionnaire-based	Veterinarians	About 40% of veterinarians reported animal-related respiratory and/or skin symptoms. The most commonly reported animals inducing symptoms were cats and dogs.	Susitaival et al. [131]
Cross-sectional questionnaire-based	Veterinarians	The majority of subjects were sensitized to rat and mouse. The prevalence of asthmatic and ocular symptoms was more prevalent in sensitized veterinarians versus non-sensitized veterinarians.	Krakowiak A. [134]
Cross-sectional questionnaire-based	Veterinary students	Acute health problems in terms of ODTS appeared in previously unexposed veterinary students following contact in dairy barns	Jolie et al. [81]
Case report	Veterinary surgeon	Occupational urticaria dermatitis	Roger et al. [221]
Laboratory animal workers			
Cross-sectional questionnaire-based	Laboratory animal workers	23.1% of workers had at least one allergic symptom against laboratory animals and two-thirds of them developed allergic symptoms during first 3 years of exposure. Atopy, animal species handled, and time spent in handling associated with developing LAA.	Aoyama et al. [130]
Cross-sectional questionnaire-based	Laboratory animal workers	Prevalence of allergic symptoms caused by rats and mice were 19% and 10%, respectively. Allergic symptoms strongly correlated with sensitization measured by specific serum IgE to RUAs or MUAs.	Hollander et al. [147]
Cross-sectional exposure-response	Laboratory animal workers	Sensitization to rat allergens in sub-group of workers with less than 4 years of exposure was clearly associated with exposure levels: 15, 9.5, and 7.3 times higher in the high, medium, and low exposure groups compared with internal reference group.	Hollander et al. [142]

Table 2 (Continuation). A selection of epidemiological and experimental studies of adverse health effects associated with bio-aerosol exposure in veterinarians and related other settings.

Study design	Study population	Outcome measures	Reference
Cross-sectional exposure-response	Laboratory animal workers	Prevalence of sensitization to rat allergens was 9.7%. About 57% of the sensitized workers had work-related symptoms (asthma or rhinitis). The risk of sensitization elevated with increasing allergen exposure.	Heederik et al. [139]
Retrospective cohort exposure-response	Laboratory animal workers	19.2% of workers reported LAA. The intensity of exposure and atopy were significant predictors for developing LAA.	Kruize et al. [149]
Livestock farmers			
Cross-sectional questionnaire-based	Pig workers	Exposure to pig barns associated with a range of respiratory symptoms, such as chronic cough, chronic phlegm production, wheeze, shortness of breath, as well as lung function decline.	Donham et al. [17]
Cross-sectional questionnaire-based	Pig workers	An increased risk of non-allergic flu-like symptoms (ODTS)	Donham et al. [16] Holness et al. [95]
Cross-sectional exposure-response	Pig workers	A positive association between respiratory symptoms indicative ODTS and endotoxin level was observed. Workers with a high endotoxin exposure had a lower lung function.	Heederik et al. [94]
Cross-sectional exposure-response	Pig workers	A positive association between asthma-like symptoms with endotoxin exposure was seen.	Smit et al. [222]
Cross-sectional exposure-response	Pig workers	An inverse association between endotoxin exposure with lung function was found.	Donham et al. [110] Zejda et al. [13]
Cohort (longitudinal) Exposure-response	Pig workers	Long-term average exposure to endotoxin (105 ng m-3) was clearly associated with lung function decline.	Vogelzang et al. [97]
Cohort (longitudinal) Exposure-response	Pig workers	Lung function decline clearly associated with endotoxin exposure.	Schwartz et al. [111] Kirychuk et al. [12]
Cross-sectional	Pig workers	The prevalence of ODTS was elevated in pig farmers compared to controls.	Vogelzang et al. [31]
Cohort study exposure-response	Pig workers	Exposure to dust and ammonia in pig barns associated with increase in bronchial responsiveness expressed as steps for provocative concentration causing FEV_1 decline.	Vogelzang et al. [223]
Case-report	Pig workers	Authors describe the onset of non-atopic asthma in 7 pig farmers after a short-term exposure to pig barns.	Dosman et al. [92, 93]
Experimental exposure-response	Healthy naïve volunteers	Short-term exposure (3-hr) to pig barns associated with elevated bronchial responsiveness to methacholine, and also increased number of neutrophilic inflammatory cells.	Larsson et al. [63]
Experimental exposure-response	Healthy naive non-farmers and pig farmers	Exposure to dust from pig barn altered lung function and bronchial responsiveness, as well as cell number and cytokines in blood and nasal lavage fluid in non-farmers, while only minor alterations were found in pig farmers.	Palmberg et al. [87]
Cross-sectional questionnaire-based	Dairy workers	Dairy farmers had more significantreactions than teachers to cow epithelium, suggesting the importance of cow epithelium as occupational source of allergen among dairy farmers.	Rautalahti et al. [224]
Cross-sectional	Dairy workers	An increase of respiratory symptoms, such as rhinitis, asthma, bronchitis, hypersensitivities inhumanities, and ODTS.	Radon et al. [14] Choudat et al. [19] Chaude- manche et al. [53] Choma et al. [100] Cormier et al. [32]
Longitudinal	Dairy workers	An increase of respiratory symptoms, such as rhinitis, asthma, bronchitis, hypersensitivities inhumanities, and ODTS.	Gianet et al. [98] Kronqvist et al. [99] Dalphin et al. [102] Manuy et al. [103]
Cross-sectional	Poultry workers	An increase of respiratory problems, such as airway responsiveness, toxic pneumonitis, and chronic bronchitis.	Radon et al. [14] Morris et al. [56] Rylander et al. [104]
Cross-sectional	Poultry workers	Lung functions inversely associated with exposure to bio-aerosol particularly endotoxin.	Olenchock et al. [106] Clark et al. [225]
Dose-response	Poultry workers	Lung functions inversely associated with endotoxin exposure.	Donham et al. [54]
Cross-sectional	Poultry workers	Significantly higher prevalence of work-related respiratory symptoms, eye and skin symptoms was found in poultry workers compared to controls.	Rimac et al. [226]
Cross-sectional questionnaire-based	Horse workers	Exposure to horse environments associated with an elevated prevalence of respiratory symptoms, such as shortness of breath, chronic bronchitis, ODTS, and asthma.	Kimbell-Dunn et al. [11] Mackiewicz et al. [106] Mazan et al. [105] Tautuoglu et al. [107]
Cross-sectional	Children living in northern Swede	Sensitization to horse allergen considered as a risk factor inducing rhinitis and asthma.	Ronmark et al. [164]
Cross-sectional exposure-response	Livestock farmers	Livestock farmers had significantly higher prevalence of chronic bronchitis and COPD than crop farmers. These symptoms was associated with organic dust and endotoxin.	Eduard et al. [34]

to other animal species. This matched very well with the observed trends in endotoxin levels which were high in farm animal related clinics and low in companion animal hospital [39, 44], and also comparable to those endotoxin levels previously reported in farms [39, 44, 83, 84, 85]. Both studies by Tielen *et al.* [80] and Samadi *et al.* [82] showed an association between the onset of respiratory symptoms and duration of animal exposure. This finding is also consistent with the reported association between time exposed to organic dust in pig barns and observed adverse respiratory symptoms [14, 32, 79, 80, 86].

In contrast to veterinary populations, respiratory health effects associated with bio-aerosol exposure among pig farmers is probably one of the best-studied settings considering bio-aerosol related health effects. Studies showed that exposure to organic dust from pig barns are associated with elevated respiratory symptoms, chronic bronchitis, increased bronchial hyper-responsiveness, and accelerated lung function decline. The evidence of these health effects is based on a series of experimental and observational studies among pig farmers. Donham *et al.* [33] first proposed in 1977 that exposure to organic dust, especially in large pig confinement operations, might play a role for the development of respiratory symptoms in pig farmers and veterinarians. This finding has further been confirmed since by several other epidemiological studies among pig farmers [17, 33, 79]. Results of experimental studies on naïve and non-naïve subjects, healthy volunteers, showed that a short-term exposure to organic dust from pig barns induced airway inflammation, characterized by elevated bronchial hyper-responsiveness and increased number of inflammatory cells (mainly neutrophilic granulocytes) in nasal lavage [63, 87, 88, 89, 90, 91]. Dosman *et al.* [92, 93] reported 7 cases of occupational asthma in newly-employed pig workers. All these cases developed symptoms within months after starting employment. A clinical evaluation indicated occupational asthma in all cases in the absence of a clear immunological response to common or work specific allergens. All cases were bronchial hyper-responsive and thus showed lower metacholine or histamine thresholds and the findings were, according to the authors, indicative of non-atopic asthma. In a Norwegian study among farmers, non-atopic asthma accounted for more than 75% of all current asthma and was more frequently observed in livestock farmers, particularly in pig farmers [18].

Several studies give indications for an increased risk of ODTS among pig farmers, characterized by fever, chills, chest tightness, shortness of breath, dry cough, myalgias, and/or fatigue [16, 31, 94, 95], with a prevalence ranging from 26.3%-34% [31, 96]. ODTS cannot be differentiated from HP by clinical symptoms. However, ODTS is a systemic toxic response caused by pro-inflammatory agents such as endotoxins [58], while HP is an immune-mediated response [62]. Studies also give indications for an elevated risk of chronic bronchitis and COPD among pig farmers [34, 97].

Besides exposure to pig barns, which is relatively well-established as an occupational health risk, exposure to dairy barns [14, 19, 32, 53, 98, 99, 100, 101, 102, 103], poultry houses [14, 56, 104], and horse stables [11, 105, 106, 107] are also considered to be risk factors for the development of respiratory problems such as respiratory symptoms, airway responsiveness, chronic bronchitis and ODTS.

Two well-established pro-inflammatory components of organic dust are endotoxins [35, 108] and glucans [109], of which endotoxin has been the most widely studied, also because of its role in sepsis. Endotoxin, often referred to as lipopolysaccharide (LPS), is a non-allergic constituent of the outer cell wall of Gram-negative bacteria and an ubiquitous component of organic dust [84]. The lipid A portion of LPS is known to cause inflammatory reactions [108], with lung function decline as the most serious effect of both short- and long-term exposure. In cross-sectional dose-response studies, an inverse association between endotoxin exposure and lung function changes in pig farmers was first established by Donham *et al.* [110], which was supported further by similar studies [13, 94]. This finding was also corroborated with an experimental study, in naïve healthy volunteers, showing an association between endotoxin exposure and FEV_1 decline [52]. Similarly, a few longitudinal studies among pig farmers found a clear dose-response relationship between endotoxin exposure and lung function decline [12, 97, 111]. Dose-response studies in pig farmers also showed a stronger inverse association between exposure to endotoxin and lung function changes when compared with dust exposure [94, 97].

Similar observations have also been found in workers exposed to grain [111] and cotton dust [52, 112]. Smit *et al.* [58], in a study among workers involved in the agricultural seed processing industry, proposed exposure to organic dust highly contaminated with endotoxin (GM 1800 EU m^{-3}) as the primarily causative agent for developing ODTS. Smit *et al.* [113] also observed in a dose-response study in agricultural workers, including animal and crop workers, that high endotoxin exposure (GM 319 EU m^{-3}) was a risk factor for bronchial hyper-responsiveness and wheeze, which were characterized by a predominantly non-atopic nature. One study among pig farmers found a clear exposure-response relationship between endotoxin exposure and lung function decline in a longitudinal study over a period of 3 years, indicating that long-term exposure to high endotoxin levels (GM 105 ng m^{-3} ~1050 EU m^{-3}) is a likely risk factor for developing COPD [97].

β(1→3)-glucans are polysaccharides of D-glucose molecules with different molecular weights and degrees of branching [114] which can be found in most fungi, some bacteria, and a number of plants [109]. Occupational exposure data for this component are very limited. When considering animal settings, we found only one study in poultry workers which investigated health effects related to β(1→3)-glucan exposure [104]. This study showed that poultry workers had an elevated prevalence of toxic pneumonitis, chronic bronchitis, and increased airway responsiveness indicative of airway inflammation compared to controls; however, dose-response relationships were not determined and high endotoxin levels were reported as well. Epidemiological studies in other occupational settings suggest that exposure to β(1→3)-glucan is associated with respiratory symptoms, airway responsiveness, toxic pneumonitis, chronic bronchitis, and lung function decline [46, 104, 115, 116, 117, 118, 119], although the evidence is still inconclusive. A few studies also found similar respiratory effects associated with β(1→3)-glucan exposure after adjusting for the levels of endotoxin exposure [116, 117]. Two experimental studies showed that the combination of β(1→3)-glucan and endotoxin synergistically enhances their toxicity causing inflammation [120, 121].

To summarize, both experimental and observational studies strongly support the proposition that exposure to endotoxin is casually related to the development of work-related respiratory effects. Besides endotoxin, exposure to β(1→3)-glucan may also be responsible to a certain extent for work-related respiratory effects. With the knowledge of high endotoxin exposure in veterinary practices handling farm animals and horses, it seems logical to assume that veterinary populations suffer from respiratory diseases related to endotoxin exposure as previously reported for farmers. Similar to endotoxin, occasionally high exposure to β(1→3)-glucan during veterinary practice might also play a role for the development of respiratory effects, as reported in other studies.

SENSITIZATION/ALLERGY TO ANIMAL ALLERGENS

Proteins derived from animals and plants are the most important group of high molecular weight occupational allergens. Exposure to these allergens, especially animal allergens, is more specifically associated with working in animal settings, although not much studied. Exposure to chemical agents (low molecular weight) which form a hapten (*e.g.* disinfectants), also regularly occurs during working in animal settings [2]. Thus, certain jobs dealing with animals are likely to put people at risk of exposure to allergens, *e.g.* veterinarians, animal caretakers and farmers [51, 122, 123, 124, 125, 126]. The most potent animal allergens are associated with mammalians, such as cows, horses, cats, dogs, rats, and mice [127], which may originate from multiple sources such as hair, dander, saliva, urine, and serum. Inhalation of animal allergens is considered the most common route of occupational exposure, although skin and eyes might also be routes of exposurel [128]. Following exposure, individuals might become sensitized (IgE-mediated) [129], subsequently allergic symptoms develop, with allergic rhinitis as the most common symptom, followed by allergic conjunctivitis [130], and ultimately resulting in work-related asthma [131, 132].

Rodents

Rats and mice are the animals most commonly used in scientific experimental studies. Occupational exposure to these animals often occurs when working at animal laboratories. The most important allergen for rat is Rat n 1, and for mouse, Mus n 1; which both belong to a family of proteins termed Lipocalins [133]. A study by Krakowiak *et al.* [134] among veterinarians exposed to laboratory animals showed that the majority of veterinarians were sensitized to rats and mice allergens. The authors gave explanations for this finding, including more frequent contact with these animals, as well as increased susceptibility to become allergic when being sensitized to other allergens as well. Rats and mice seem to be the most important animals inducing sensitization (IgE-mediated) in laboratory animal workers, many of whom are also veterinarians, and probably is one of the best described adverse health effect associated with laboratory animal exposures [130, 132, 133, 135, 136, 137, 138, 139, 140, 141, 142, 143]. The prevalence of allergy against rats in laboratory animal workers ranged from 12–31% in some recent studies [130, 144, 145, 146, 147], and for mice ranged from 10–32% [130, 145]. Several epidemiological studies have shown a strong association between increased intensity of exposure to laboratory animal allergens and elevated prevalence of laboratory animal allergy (LAA) [142, 148, 149]. In a recent study, cumulative exposure to Mus n 1 (median 0.29 ng m^{-3} per years) in a dose-response dependent manner was shown to be a significant risk factor for IgE-mediated mouse sensitization [143]. Hollander *et al.* [142] in a dose-response study found a clear relationship between rat allergen exposure (median 0.68 ng equivalent per m^3) and sensitization only in a group of workers who had worked with rats for less than 4 years. It is important to note that the observed higher prevalence of occupational allergy against rats and mice, compared to other animal allergens, is likely due to the more frequent use of these animals in experimental studies, and not to lesser ability of other animal allergens to trigger allergy.

Farm animals (ruminants)

The most important cow allergen is Bos d 2 (*Bos domesticus 2),* found mainly in cow hair and dander, and belongs to the lipocalin family of proteins [150]. The occurrence of sensitization against cow allergen in the veterinary populations has only been studied specifically in veterinary medicine students, showing sensitization to cow allergens to be present in 3.7% (25 cases) of all participants [82]. Cow allergy has been studied much more extensively among Finnish dairy farmers. Investigations have confirmed the role of cow-derived proteins as important occupational allergens for developing allergy among dairy workers [151, 152], subsequently causing asthma [153, 154]. High prevalence of positive IgE anti-Bos d 2 reactions have also been reported among Dutch dairy farmers [155], which is in agreement with previously reported results from Finland [156, 157, 158], but the occurrence of respiratory symptoms or the development of airway diseases in Dutch dairy farmers was rare [155] contrary to observations among Finnish farmers. Similarly, either positive specific IgE-antibodies (8.8%) or skin prick test (7.4%) against cow allergens have been reported in Polish farmers [159], but allergic symptoms relevant to cow allergen were rare [159].

There is no data available concerning sensitization/allergy to other farm animals, such ase sheep, goats, and poultry. Nonetheless, it cannot be ignored that allergy against these animals might occur.

Horses

The most important horse allergen is Equ c 1 which is a lipocalin protein [160] and can be found in horse dander and hair [161, 162]. Exposure to horse allergen often occurs through direct contact with horses [51] or indirect contact due to transfer of horse allergen on clothes or hair [163]. Occupational exposure to horse allergen mainly occurs among farmers, veterinarians, as well as those individuals who handle horses either for professional or recreational purposes. Only one study [82] investigated sensitization to horse specific allergen among veterinary medicine students, and showed that 1.6% (11 cases) of all participants was sensitized to horse allergen. In this study, the prevalence of sensitization in those students specializing in equine veterinary medicine increased over time (years 3–5: OR 2.4, 95% CI 0.4–15; year 6th: OR 4.7, 95% CI 0.4–49, compared to the year 1–2 students), indicating prolonged years of exposure to horses as a possible determinant of sensitization. Similarly, Tutlouglu *et al.* [107] found in a cross-sectional study that horse grooms had a significantly higher prevalence of sensitization to horse hair (OR 3.75, 95% CI 1.1–12.82) compared to controls. Sensitization to horse hair was associated with an increased risk of allergic conjunctivitis (OR 1.5, 95% CI 0.4–5.1), asthma (OR 4.5, 95% CI 1.5–13.3), and lung function decline [107]. A recent study by Liccardi *et al.* [123] in an urban population in Italy, demonstrated that 35 out of 1,822 adults (3.43%) were sensitized to horse dander. Of these sensitized people, 6 reported direct contact with horse, 10 had indirect contact with horse owners, and 19 reported no direct or indirect contact with horses or horse owners. Twenty sensitized people reported having both nasal and bronchial symptoms and one reported asthma without rhinitis. Ronmark *et al.* [164] in a cross-sectional study found that sensitization to horse specific allergen was a significant risk factor for the development of rhinitis and asthma.

Domestic animals

Fel d 1 has been described as the major cat allergen and Can f 1 as the most important dog allergen [133]. Cat allergen is often attached to particles less than 10 μm (range 1–20 μm) [165, 166, 167, 168], and the particle size distribution for dog allergen appears to be very similar to that of cat allergen [169]. The small size makes it possible that these two allergens are easily transmitted through the air. Spread into the environment by contact with clothing, hair or other surfaces have been described for these allergens [170, 171]. Occupational exposure to cat and dog may cause respiratory symptoms in veterinarians [131] and laboratory animal workers [130]. In a recent study, 4.8% (32 cases) of all veterinary medicine students were sensitized to cat and dog allergens, but the prevalence of sensitization in the specialty of domestic animals did not clearly change over time (years 3–5: OR 0.9, 95% CI 0.3–2.4; year 6th year: OR 1.4, 95% CI 0.4–5.1, compared to the year 1–2 students) [82]. These results, however, are unadjusted for previous exposure to these animals because most subjects had earlier domestic exposures. Further investigation, including measurement of specific cat and dog allergens, has corroborated the presence of cat and dog allergens as important occupational airborne allergens in a companion animal hospital [44]. However, most epidemiological evidence on sensitization/allergy in relation to cat and dog allergen exposure comes from studies conducted in the general population and residential and public spaces [172, 173, 174, 175], indicating the importance of exposure to cat and dog inducing sensitization/allergy against these allergens.

In addition to studies investigating sensitization and related allergic respiratory symptoms, a few studies have also reported a high prevalence of atopic symptoms among veterinarians, such as allergic rhinitis and asthma, but no information is given regarding specific underlying immune reactions against animal allergens [131, 176, 177, 178, 179].

To summarize, exposure to rats and mice are well-established causing sensitization/allergy among laboratory animal workers. Less information is available about sensitization/allergy against other animal allergens; however, a few limited studies among animal workers and veterinary populations still suggest the importance of exposure to animals (*e.g.* cow, horse, cat, and dog) as a risk factor for development of animal specific sensitization/allergy.

PROTECTIVE EFFECTS OF BIO-AEROSOL AGAINST ALLERGY

A reduced risk of sensitization and self-reported allergy was observed among veterinary medicine students who grew up on a farm [82]. In parallel to veterinary populations, numerous publications related to farmers indicate that growing up on a farm may have a protective effect against the development of allergy (Tab. 3). A large number of epidemiological studies consistently show that childhood exposure to farm environments is associated with a reduced risk of developing atopy and atopic asthma [76, 77, 180, 181, 182]. Several epidemiological studies have also found that this protective effect of early childhood exposure may still be present during adulthood [59, 113, 183, 184, 185, 186]. Recent studies among farmers and workers in agricultural industries also strongly show inverse associations between endotoxin exposure with atopic asthma [18], sensitization [78, 187] and hay fever [188]. The underlying mechanisms behind these protective effects are still poorly understood. However,

Table 3. Epidemiological studies regarding association between allergic diseases and farm childhood and/or adulthood exposure.

Study design	Study population	Childhood/ adulthood	Major findings	Reference
Cross-sectional	Farmers' children	Childhood	Farmers' children had lower prevalence of hay fever (OR 0.52, 95% CI 0.28-0.99), asthma (0.65, 0.39-1.09), and wheeze (0.55, 0. 36-0.86) than their peers not living on a farm.	Von Ehrenstein et al. [180]
Cross-sectional	Farmers' children	Childhood	Long-term exposure to stables until age 5 years had a protective effect of asthma, hay fever, atopic sensitization.	Riedler et al. [181]
Cross-sectional	Farmer's children	Childhood	Living on a farm during childhood associated with a lower risk of atopy in Wagga (OR 0.47, 0.32-0.72), but not in Moree (OR 0.97, 0.62-1.53). Authors concluded that children in Wagga were more likely lived on a livestock farm than children from Moree .	Downs et al. [76]
Cross-sectional	Adults	Childhood	Living on a farm during childhood associated with a reduced risk of atopic sensitization (OR 0.76, CI 95% 0.60-0.97).	Leynaert et al. [182]
Cross-sectional	Adults	Childhood	Individuals who lived on a farm during their first 5 years of life had lower prevalence of allergic rhinitis than all other age groups.	Eriksson et al. [77]
Cross-sectional exposure-response	Pig farmers	Adulthood	Strong inverse relationship was found between endotoxin exposure and sensitization to common allergens.	Portengen et al. [78]
Cross-sectional exposure-response	Farmers	Adulthood	Exposure to endotoxin appears to have a protective effect on atopic asthma.	Eduard et al. [18]
Nested case-control	Adults	Adulthood	Current exposure to high levels of house dust endotoxin inversely associated with allergic sensitization to at least one common allergens (OR 0.80, 0.64-1.00).	Gehring et al. [187]

Table 3 (Continuation). Epidemiological studies regarding association between allergic diseases and farm childhood and/or adulthood exposure.

Study design	Study population	Childhood/ adulthood	Major findings	Reference
Cross-sectional exposure-response	Workers from diverse agricultural sectors	Childhood/ adulthood	A significant inverse exposure-response relationship between endotoxin exposure and atopic sensitization was observed during both childhood and adulthood farm exposures.	Smit et al. [113]
Cross-sectional	Adults	Childhood/ adulthood	The risk of sensitization to pollens was inversely associated with farming exposures during adulthood (OR=0.93, 95% CI 0.44-0.2.0), childhood (OR=0.55, 95% CI 0.26-0.1.2), and both childhood and adulthood (OR=0.18, 95% CI 0.08-0.42).	Koskela et al. [183]
Cross-sectional	Farmers	Childhood /adulthood	Exposure to farms during either childhood or adulthood associated with a lower risk for atopy (identified by positive SPT or IgE to common allergens) and allergic respiratory symptoms.	Portengen et al. [184]
Cross-sectional	Adults	Childhood /adulthood	The risk of sensitization to common allergens was inversely associated with farming exposure during childhood (OR 0.7, 0.5-0.9) , and in both childhood and adulthood (OR 0.4, 0.3-0.6).	Radon et al. [185]
Cross-sectional exposure-response	Farmers	Childhood /adulthood	Combination of adulthood and childhood exposure to farm environment was more inversely associated with asthma symptoms than adulthood or childhood exposure alone.	Douwes et al. [186]
Cross-sectional	Conventional and organic farmers	Childhood /adulthood	Living on a farm during childhood, combined with current livestock farming, is associated with a lower prevalence of hay fever in both conventional and organic farmers.	Smit et al. [59]
Cross-sectional exposure-response	Farmers and agricultural industry workers	Childhood /adulthood	Endotoxin exposure inversely associated with hay fever and self-reported allergy: hay fever [childhood OR 0.64 (0.43-0.95), adulthood 0.59 (0.44-0.80)], self-reported allergy [childhood OR 0.89 (0.70-1.12), adulthood OR 0.75 (0.60-0.93)]	Smit et al. [188]

it has been hypothesized that bio-aerosol components, particularly endotoxin, may protect from the development of allergic diseases by modifying the immune responses against allergens. The initial explanation was that bio-aerosol components particularly LPS shift towards a TH_1 (innate)-type response that further suppresses the development of TH_2 response against allergens [189, 190]. More recently, an alternative concept has been suggested to explain TH_1/TH_2 paradigm: T-regulatory (Treg) cells balance both TH_1 and TH_2 responses [189].

INFECTIOUS DISEASES

Biological agents may contain a large variety of pathogenic microorganisms, such as bacteria, viruses, fungi, and parasites that can pose a threat to human and animals. More than 1,400 microorganism species are known to be pathogens for human [191]. Of these, 175 can be categorized into "*emerging or re-emerging pathogens*" [191]. Emerging and re-emerging pathogens are those that either have been seen in humans for the first time or have occurred previously; either the incidence is increasing or they expand in locations where they have not previously been observed. About 75% of the emerging and re-emerging pathogens are capable of causing infectious diseases in animals (termed as zoonotic pathogens), proposing that they can be transmitted from animals to humans. Zoonotic infections (*e.g.* Q-fever, avian and swine influenza, and anthrax) in humans are predominantly attributed to exposure in specific occupational settings, such as livestock farms, animal stores, and veterinary practices, but accurate information for most is absent. Veterinarians are probably at high risk of developing infectious diseases because of their high likelihood of contact with infected animals [192]. A study among all 565 US members of the American Association of Zoo Veterinarians has shown that 30.2% of veterinarians reported to have had a zoonotic infection [193]. A recent review [194] summarized published literature about infectious diseases among veterinarians, in which the authors concluded that veterinary populations are at an increased risk of several zoonotic pathogens, e.g. *Coxiella burnetii*, swine and avian influenza A virus, *Brucella* spp, methicillin-resistant *Staphylococcus aureus (*MRSA*)*, avian and feline *C psittaci* and swine hepatitis E virus. However, exact numbers on the prevalence of most zoonotic infections is lacking. It has also been suggested that veterinary populations may act as biological sentinels for emerging pathogens and could potentially spread zoonotic pathogens to their families and community members [194]. Exposure assessment studies which involve infectious agents have scarcely been published. Some examples of recently encountered infectious diseases will be discussed in more detail.

Q fever

Q fever is generally an occupational disease caused by the bacterium *Coxiella burnetii*. Occupational exposure to *Coxiella burnetii* often occurs through contact with infected farm animals (*e.g.* cattle, sheep, and goats), as well as their birth-products [65]. In sero-epidemiological studies among veterinarians, elevated specific IgG antibodies against *Coxiella burnetii* were found in 13.5% in Japan [65], 12.9% in Sweden [67], 7.5% in Turkey [68], 9.5% in Australia [66], 22% in the USA [195] and 36% in Slovakia [196], which were higher than those reported for the general population. Among others, working with ruminants was identified as a risk factor.

Influenza A viruses

Infections with influenza A viruses have been reported in several animal species (*e.g.* birds, swine, and horse). Avian (bird) and swine influenza are two of the well-known infectious diseases caused by influenza A viruses. All birds are thought to be susceptible to avian influenza disease (*e.g.* chickens, ducks, and turkeys). The transmission risk of influenza viruses to human is low, but some cases of human infection have been reported since 1976 [197]. During an outbreak of highly pathogenic H7N7 avian influenza virus in Dutch poultry farms in 2003, the highest self-reported influenza-like symptoms were found among veterinarians of all those exposed to poultries [71]. In sero-epidemiological studies among American veterinarians exposed to poultry, positive specific IgG antibodies against avian influenza viruses were observed in 12.2% (type H5), 23.8% (type H6), and 14.6% (type H7) [198]. In another study among American veterinarians exposed to swine, 10.9% and 19.1% had positive serological evidence to swine influenza viruses of N1H1 and N1H2 [199]. A 57-year-old Dutch veterinarian died because of infection by H7N7 avian influenza virus following visiting an infected poultry farm [70].

Methicillin-resistant Staphylococcus aureus (MRSA)
Staphylococcus aureus is a Gram-positive bacterium that can be found in humans and numerous animal species [200]. After the introduction of antibiotics, *Staphylococcus aureus* has become resistant to certain antibiotics, such as methicillin, oxacillin, penicillin, and amoxicillin; which is called methicillin/(oxacillin)-resistant *Staphylococcus aureus* (MRSA). Animals can act as a reservoir for MRSA, thus humans can be infected through close contact with MRSA colonized animals. In recent years, two outbreaks of MRSA infections were reported in veterinary clinics in Canada and the United States [201, 202]. In the American study, the outbreak most likely had a human source and animals became carrier through the owner or in the clinic, but the source was not identified [202]. Of particular interest is a Canadian study. After recognition of a cluster of MRSA infection in horses and humans at the Ontario Veterinary College Veterinary Teaching Hospital, environmental contamination with MRSA was evaluated [201]. Relatively widespread contamination of the hospital environment was observed, which suggests that the environment may be an important source of MRSA infection. In Ireland, the occurrence of MRSA during veterinary practice was studied [203]. The pulsed field gel electrophoresis patterns of the isolates showed that transmission of two strains of MRSA occurred in veterinary practices in Ireland, and that one strain may have arisen from human hospitals. The source of the second strain remains to be determined [203]. Since 2004, MRSA has been found to be emerging in livestock animals, especially in pigs and veal calves [204]. From 2007, a specific MRSA strain (ST398) emerged in animal husbandry not seen before in hospitals, termed as livestock associated-MRSA [205]. MRSA strain ST398 can cause invasive infections and outbreaks, although so far only incidentally reported [205]. Exposure to livestock animals, in particular pigs, among Dutch veterinarians [206] and pig farmers [207] is considered a risk factor for MRSA (4.6 and 26%, respectively), compared to the general population (0.03%) [208]. However, occupational epidemiological studies which involve MRSA associated with exposure have not yet been investigated.

OCCUPATIONAL THRESHOLD LIMIT VALUES

Occupational exposure limits (OELs) or threshold limit values (TLVs) of hazardous agents provide reference levels for which it is assumed that workers can be exposed continually for a working lifetime without adverse health effects. Although several health risks associated with bio-aerosol exposure have been described, exposure-response relationships have been shown for some components of bio-aerosol only, particularly for endotoxin in relation to non-infectious health effects and attempts have been undertaken to derive occupational exposure limits. In the literature, mainly based on experimental studies,, “no observed effect levels (NOELs)” for various health endpoints associated with endotoxin exposure have been reported ranging from 50 to several hundred EU m^{-3} [52, 209, 210]. Rylander *et al.* [209] evaluated the effects of endotoxin containing cotton dust with concentrations ranging from 700–56200 EU m^{-3} in an experimental study in cotton mill workers. Endotoxin exposure was significantly associated with changes in FEV_1, with an estimated NOEL of 330 EU m^{-3}, at which no changes occurred in FEV_1. Haglind and Rylander [210] found a relationship between endotoxin exposure and decline in $FEV_{1,}$ also in an experimental study. The NOEL was calculated for absence of change in FEV_1 at an endotoxin level of 80 EU M^{-3} for smoking mill workers. In a pooled study by Castellan [52] among healthy volunteers exposed to cotton dust containing endotoxin, a significant correlation between endotoxin levels and the changes in FEV_1 was observed. The authors calculated a NOEL for changes in FEV_1 at 90 EU M^{-3}. Estimates of NOELs for acute and chronic respiratory effects on the basis of evidence from epidemiological studies are relatively comparable [12, 54, 57, 94, 97, 211]. Following the recognition of adverse health effects associated with endotoxin exposure, an occupational health-based exposure limit of 50 EU m^{-3} was proposed in 1998 by the Dutch Expert Committee on Occupational Standards (DECOS) [212]. This standard was mainly on the basis of the mentioned study by Castellan *et al.* [52] and the corresponding NOEL of 90 EU m^{-3}. By incorporating a safety factor to take into account uncertainties and to protect also more vulnerable workers, the proposed exposure limit was set at 50 EU m^{-3}. This exposure limit was adopted in 2001 by the Ministry of Social Affairs and Employment allowing higher exposure levels during the initial introduction period of 200 EU m^{-3}, which was used as a reference for a few years. The DECOS [213] has recently re-evaluated the health-based recommended occupational exposure limit (HBROEL) for endotoxin and advised a value of 90 EU m^{-3} (eight hours time-weighted-average), based on acute respiratory effects resulting from airway inflammation. The committee adopted a higher value than earlier because they concluded that more studies are available in the low exposure range, contributing to less uncertainty about the exact level at which early effects of endotoxin can be observed. This exposure limit was based on the same study by Castellan, in which healthy volunteers without respiratory symptoms were exposed to endotoxin in cotton dust [52], a cross-sectional study of the chronic lung function changes of animal feed mill workers [211], and a five years follow-up study of such workers [214]. Exposure levels in veterinary practices, (Tab. 1), indicate that exceeding the standard regularly occurs in clinics related to farm animals [44] and horses [39], suggesting that veterinary populations during working in these animal settings probably experience health effects related to endotoxin exposure. It is obvious that endotoxin levels during veterinary practice in the companion animal hospital [44] is lower than the recommended health-based exposure limit of 90 EU m^{-3}, presumably leading to no adverse health effects on the basis of low endotoxin exposure. To date, no OELs have yet been established for $\beta(1\rightarrow3)$-glucan exposure due to inconclusive evidence of heath effects. In addition, there are no OELs for allergen exposure levels, although few exposure-response studies showed an association between exposure to some animal specific allergens and health effects [142, 143]. Nonetheless, a framework for deriving OELs for allergens has been proposed [215]; however, methods for exposure assessment of animal specific allergens have not yet been standardized, which compromises development of standards and are not commercially available.

CONCLUSIONS

There are only a few studies available that investigated bio-aerosol exposure in veterinary settings. These studies showed veterinary populations, especially those working with farm animals, such as cows and poultry as well as horses, are exposed to substantial levels of inhalable dust, endotoxin, and β(1→3)-glucan. Exposure levels of animal specific allergens have hardly been investigated, but animal specific allergens proved to be measurable in companion animal clinics (cat and dog allergens), dairy barns (cow allergen), and horse stables (horse allergen). The limited available information on health effects related to veterinary practice give some indications for an increased risk of respiratory effects, especially for those veterinarians handling farm animals and horses. Nonetheless, accurate estimates of the occurrence and prevalence figures of respiratory diseases are lacking. Dose-response studies between exposure to bio-aerosols and health effects during veterinary practices have not yet been performed. Since exposure levels through veterinary practices, especially for endotoxin, are similar to those previously found in farming, one can speculate that similar to results of experimental and observational studies among farming populations, veterinary populations are at an elevated risk of developing respiratory diseases in relation to bio-aerosol exposure, in particular endotoxin. Workers in animal settings are not frequently exposed to just one biologically-active agent of organic dust, but to a mixture with different exposure levels. Animal workers in some situations may also come into contact with chemical agents such as ammonia [18]. In such cases, it seems logical to assume that at least a part of respiratory effects among veterinary populations are likely attributable to exposure to other agents rather than endotoxin.

The occurrence of work-related sensitization and allergic symptoms among veterinary populations and animal workers has not yet been extensively studied, except for laboratory animal workers exposed to rats and mice. Nonetheless, the few studies available give indications for sensitization and allergic respiratory symptoms in veterinary populations being exposed to animals, such as rats, mice, cats, dogs, cows, and horses, but the role of exposure pattern and level to these animal allergens is still poorly described. So far, dose-response relationships between allergen exposure and health effects through veterinary practices have not yet been conducted. In general, it seems logical to assume that reactions to animal allergens in veterinary populations would be an important issue because they are likely often exposed to a number of animal allergens for prolonged periods of their working time.

Besides adverse health effects, some protective effects of bio-aerosol exposure on developing sensitization/allergy have been proposed among veterinary populations. However, respiratory health effects seem to occur at the same levels as the protective effect of allergy, thus the protective effect is counterbalanced and symptoms in higher exposed individuals are more likely to be due to non-allergic mechanisms.

SUGGESTION FOR FURTHER STUDIES

A large variety of respiratory symptoms associated with animal environmental settings containing bio-aerosols during veterinary practice have been reported. However, it is not obvious which bio-aerosols are primarily responsible, mainly due to the absence of exposure data. As a result, cross-sectional and longitudinal exposure-response studies need to be conducted in order to investigate allergic and non-allergic respiratory diseases associated with exposure to bio-aerosol components. Measurement of inflammatory markers could assist in proving the occurrence of airway inflammations and subsequent respiratory diseases. Moreover, there has been no evidence on the incidence of sensitization against animal allergens among veterinary populations. For this reason, new studies are required to investigate the incidence and the prevalence of sensitization/allergy during veterinary practices.

Bio-aerosol exposure is inherent through veterinary practice with animals. Thus it is necessary to apply measures to reduce bio-aerosol exposure, in particular endotoxin, with a priority of removal of exposure sources, as well as exposure reduction through substitution of bedding material or other exposure reducing approaches, such as ventilation.

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