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REVIEW

A comprehensive review of levels and determinants of personal exposure to dust and endotoxin in livestock farming

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The respiratory health effects of livestock farming have been on debate for more than three decades. Endotoxin-contaminated organic dusts are considered as the most important respiratory hazards within livestock environments. A comprehensive review of the knowledge from studies assessing the exposure status of livestock farmers is still to be published. The present study reviews research published within the last 30 years on personal exposure of livestock farmers to organic dust and endotoxin, focusing on studies on pig, poultry and cattle farmers. Applied measurement methods and reported levels of personal exposure for the total, inhalable and respirable fractions are summarized and discussed, with emphasis on the intensity of exposure and the size and distribution of the reported exposure variability. In addition, available evidence on potential determinants of personal exposure to dust and endotoxin among these farmers are documented and discussed, taking results from exposure determinant studies using stationary sampling approaches into consideration. Research needs are addressed from an epidemiological and industrial hygiene perspective. Published studies have been heterogeneous in design, and applied methodologies and results were frequently inadequately reported. Despite these limitations and the presence of an enormous variability in personal exposure to dust and endotoxin, no clear downward trends in exposure with time were observed, suggesting that working environments within stables remains largely uncontrolled. Exposure control and prevention strategies for livestock farmers are urgently required. These should focus on the development of novel and improved methods of controlling dust and endotoxin exposure within stables based on the currently available knowledge on determinants of exposure.

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INTRODUCTION

During the last three decades, exposure to organic dust and its health effects among farmers have been investigated in numerous epidemiological and exposure-assessment studies. Currently, organic dust—that is an aggregate of air-suspended particles sourced from plants, animals and microbes[1]—is a well-established major air pollutant within farming workplaces, known mainly through one of its constituents endotoxin. Endotoxin, a building stone of the outer membrane of Gram-negative bacteria, is considered a main cause of respiratory disease among farmers because of its extreme potency in comparison with other pro-inflammatory microbial constituents of organic dust. The recent focus on gene–environment interactions and the suggested important role of organic dust exposures in asthma causality, consistent with the reported high levels of exposure, especially among livestock farmers, have increased the interest in exposure conditions and health effects of farming.

There is little doubt on the importance and casual role of endotoxin—and consequently of the endotoxin-contaminated organic dust—in the development of respiratory disease among farmers. Evidence has been abundant, showing exposure–response relationships with reproducible and mutually supportive observations in both experimental studies involving humans[2–6] and cross-sectional as well as longitudinal observational[7–16] studies. Other bioactive microbial markers like β-glucans, fungal extracellular polysaccharides, peptidoglycans and muramic acid exist,[17] but they have not been as consistently associated with health effects and pro-inflammatory responses as endotoxin in such a wide range of studies with different design and methodology. The health effects of endotoxin and organic dust exposure in livestock farming have been reviewed in several publications.[18–23] Frequently, such reviews included summaries of selected exposure-assessment studies with personal or area-based measurements. Very recently, a critical review on the methods for measuring airborne endotoxin and their need for standardization has been published.[24] However, a comprehensive review of the available knowledge on personal levels and determinants of exposure to organic dust and endotoxin for workers in these environments is still to be published. Such an exercise is of high value given the troublesome assessment of individual bioaerosol exposure in farming populations and the pre-required premium in exposure estimation by studies on gene–environment interactions,[25] and need for re-evaluation of exposure conditions for development of effective exposure control and prevention strategies.[26]

The present study aims to comprehensively review (a) results and methods of studies on personal levels of dust and endotoxin exposure among pig, poultry and cattle farmers, and (b) to

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document available evidence on potential determinants of personal exposure in livestock farming environments.

RESPIRATORY HEALTH EFFECTS

Exposure to organic dust is a health issue for workers inside animal farming environments and a potential health concern for people residing in the surrounding areas.[27,28] Organic dust can stimulate the immune system through inflammatory and allergenic microbial agents (molds, bacteria, virus and allergens) and microbial-associated molecular patterns (e.g., endotoxin, glucans and peptidoglycans), resulting in inflammatory reactions.[29] Exposure to organic dust can take place through inhalation, skin contact, or through the gastrointestinal system; however, for respiratory health in farming, where organic dust is highly endotoxin contaminated, inhalation is by far the most important exposure route.

Endotoxin is the most well-investigated constituent of organic dust and a known strong modulator of the innate immune system acting by binding to the CD14/TLR4/MD2 protein receptor complex located mainly at the surface of macrophages, thereby triggering the production of cytokines and proteins that cause inflammation.[29,30] Studies among healthy volunteers and workers demonstrate symptoms and lung function changes to occur frequently at levels between 100–200 EU/m^3.[9,12,13,31–33] Bronchial hyper-responsiveness, accelerated lung function decline, chronic obstructive pulmonary disease, wheezing, asthma-like symptoms and chronic bronchitis are diseases associated with endotoxin exposure in farming.[7,11–13,34] With very high levels of exposure, acute flu-like systemic effects (organic dust toxic syndrome) can occur.[35,36]

More recently, organic dust exposure in farming has been suggested to have a protective effect against allergic sensitization, allergic asthma and hay fever. Initially, reduced risks to these symptoms have been reported among farm children,[37–39] suggesting early-life exposure to farming to be of importance. Later on, protective effects in relation to both early-life and current exposure to farming were described in studies among adolescent[40] and adult[41–45] farming populations. So far, bacterial endotoxin has been the constituent most well correlated to the protective effects with exposure–response relationships reported for domestic exposure among children[46–48] and for workplace exposure among farmers[10,45] and agricultural workers.[9,12,13] Recently, however, it has also been argued that instead of a single agent such as endotoxin, diversity of the microbial exposure may be of larger importance to the protective effects.[49]

Interestingly, all occupational studies with quantitatively measured exposure demonstrated these protective effects of endotoxin against sensitization and allergic asthma in parallel with significant associations with adverse respiratory symptoms, including non-allergic asthma.[9,10,12,13,45] These findings suggest health responses to inhaled endotoxin to differ, and some individuals appear to be more susceptible than others, for example, for lung function changes demonstrated by Castellan *et al.*[31] and Kline *et al.*,[50] the latter in a series of challenge studies. The mechanisms are not well known, but Smit *et al.*[51] showed that the *ex vivo* inflammatory response to LPS (purified endotoxin) reflects whether individuals were susceptible to endotoxin. It has been argued that interactions between genetic factors and the environment is of importance and more polymorphisms in genes crucial in the innate immune system (i.e., *TLR4*, *CD14* and *MD2*) have been associated with endotoxin responsiveness.[52–54] A recently published study among children, however, did not support common polymorphisms to be important for the observed protective effect of early farming exposure.[55]

Besides sensitization and allergic asthma, a similar protective effect of endotoxin exposure has been proposed for lung cancer.[56] This suggestion is supported by the results of a recent meta-analysis, summarizing results from mortality studies among farmers and textile workers.[57] Exposure–response relationships between cumulative endotoxin exposure and lung cancer have been demonstrated in few studies among cotton textile workers,[58,59] although in a recently published and well-established population-based study this protective effect of endotoxin was not observed.[60]

OCCUPATIONAL EXPOSURE AND THRESHOLD LIMIT VALUES

Different legal exposure limits to organic dust exist, most frequently established on the basis of the available information on exposure levels within certain industries.[61] In Denmark, the occupational exposure limit (OEL) for organic dust is 3 mg/m^3 of "total" dust and in Norway and Sweden it is 5 mg/m^3.[62–64] A permissible exposure limit of 10 mg/m^3 for total grain dust is established since 1989 by the US Occupational Safety and Health Administration.[65] More recently, the National Health Council of the Netherlands has recommended a health-based OEL (HBROEL) of 1.5 mg/m^3 of inhalable grain dust to be adapted by the industry.[66] This recommendation was made in connection with a separate proposal for a HBROEL for endotoxin exposure of 90 EU/m^3.[67] The latter being currently the only available exposure limit for endotoxin worldwide, its establishment was largely based on the lung function results of a series of (a) experimental cross-sectional studies exposing healthy individuals to cotton-derived endotoxins[31] and (b) of an epidemiological cohort study among grain processing and animal-feed industry workers.[68,69] Suggestions for other threshold limit values have also been made.[14,16,70] However, these were outside a formal standard setting process.

METHODS OF DUST AND ENDOTOXIN DETERMINATION

In general, estimation of the concentration of dust on the personal level in agricultural settings follows the basic principles for aerosol sampling.[71] Cascade impactors or direct measurement instruments are used, but, most commonly, filtration sampling with portable pumps followed by gravimetric analysis (post- and pre-measurement filter weighing) is the preferred method. The fraction of interest (i.e., respirable, thoracic or inhalable) determines the sampling head to be used; for organic dust and endotoxin, the inhalable fraction is the most relevant given the wide range of upper and lower respiratory inflammatory and systemic effects. Uncertainty during sampling and dust estimations can arise from different sources, that is, contamination or damage during filter handling and transport due to variations in the measurement flow or in the environmental conditions present during transport, and because of weighing issues.[71]

For determination of environmental endotoxin, the *Limulus* amebocyte lysate (LAL), an assay using isolated amebocyte cells from horseshoe crabs (*Limulus polymphemus*), has been the primary test for more than three decades.[17,72–77] Several variations of the LAL assay exist. The assay is based on an enzymatic cascade process, resulting in clotting of proteins initiated due to the presence of endotoxin exposure in the horseshoe crab—thus reflecting biologically active endotoxins. Initially, endotoxin was determined on the basis of the actual clotting through measurement of gel formation or of the turbidity that precedes it. Through modification of the enzymatic process, the reaction is now mostly monitored by the formation of a coloring product (chromogenic method) either measured quantitatively at one point in time during the reaction (end point) or throughout the reaction by observing the reaction curve for each sample (kinetic).[22,72]

The kinetic are the assays of choice because of the higher accuracy over endpoint assays.[72,78] The application of colorimetric methods for the assessment of occupational endotoxin exposure was partly standardized in the beginning of the previous decade with guidelines published by the European Committee for Standardization (CEN),[79,80] and updates for optimization of these protocols have recently been suggested.[76,77] Currently, the most widely adapted kinetic chromogenic version of the assay[80] following sampling onto glass-fiber filters, extraction in Tween-20 and analysis in pyrogen-free water is recommended.

The LAL assay is very sensitive. Some variation can rise as a result of deviations in potency across different batches of standard and, to a lesser extent, as an extension of the effect of the sources of uncertainty during sampling.[81,82] Across laboratories, the use of dissimilar measurement and analytical protocols is recognized as a main source of uncertainty, with differences in measured concentrations estimated to exceed one order of a magnitude in previous studies comparing in-house assays across 6 (ref. 81) and 13 laboratories.[83,84] Harmonization of the extraction protocols in the latter study reduced the size of outcome variations across laboratories to less than 12 folds, and even smaller differences have been reported when standardization under the original CEN protocols was applied.[85] However, a critical issue is the production of homogeneous and comparable dust samples. As endotoxin is particle bound, high CV values are to be expected between parallel samples at low endotoxin levels and this will certainly have affected some of the interlaboratory studies. Other important factors in cross-lab comparisons include the type of dust investigated and its composition and homogeneity.[86] Batch-to-batch variations are minimized with the more recently developed recombinant Factor C (rFC) assay, which uses a manufactured cloned protein as a reagent.[87] For the assessment of endotoxin exposure in livestock environments, the rFC and the kinetic chromogenic LAL assay have been suggested to be comparable with no differences between the two methods observed in a recent comparison study using agricultural dusts.[88]

As an alternative to the LAL assays, chemical analysis based on gas chromatography–mass spectrometry (GC–MS) can be used. These determine the concentration and chain length of 3-hydroxy fatty acids in the lipid-A, therefore, providing actual information on the composition of the Gram-negative bacteria present in the dust and allowing detection of LPS regardless of its bioactivity.[86,89] Previous research has demonstrated the presence of different chain lengths in different agricultural dusts,[86,90,91] and indications exist that different chain lengths are associated with different toxicities.[92,93] To date, application of GC–MS has been limited among others because of a lower sensitivity, when compared with the LAL assay, and an increased cost and labor need for performance.[89,90] Recently, a more sensitive and less labor-intensive version of the assay has become available.[90]

LITERATURE REVIEW METHODS

Relevant studies on active sampling published in PUBMED indexed periodicals during the last 30 years (1980–2012), which reported levels of personal dust and endotoxin exposure among farmers were included. Systematic literature searches were performed using the following keywords: personal, exposure, dust, endotoxin, particulate matter, swine, pig, hog, poultry, broiler, layer, cattle, cow, dairy, farm, farmers, agricultural or agriculture. Searches were always performed in blocks of a minimum of three words with one of the following terms always included: exposure, dust or endotoxin. Additional references were obtained through the reference list in the identified publications.

Only personal exposure studies among pig, poultry and cattle farmers were reviewed because of the limited number of studies available for other types of livestock farmers (e.g., sheep or mink farmers). Experimental studies or studies involving monitoring of non-farmers, as well as those measuring exposure solely among slaughters, processing workers, or poultry catchers, were excluded, as such studies do not provide adequate information on the actual levels of exposure among farmers and because they describe levels of exposure during post-farming production activities, respectively. In case of several publications reporting exposure estimates from the same measurement series, the one presenting original values with the most adequate and detailed methodology description was used, although supplementary information was extracted from the other publications. When findings were reported in one or more publications using both time-weighted (i.e., values normalized for an 8-h working period) and original measured estimates, the later findings were used. In addition, summary statistics from log-transformed concentrations were preferred. Overall, the literature search resulted in 41 publications reporting dust and endotoxin levels from 42 different measurement series among farmers.[12,16,26,90,92,94–129]

A similar approach was used for literature searches for studies performed in the same period (1980–2012) on determinants of personal exposure to dust and endotoxin using the following terms: personal exposure, exposure determinants, farm characteristics, environmental factors, dust, endotoxin, tasks, pig, poultry, cattle, hog, dust, endotoxin, swine, pig, hog, poultry, broiler, layer, cattle, cow, dairy, farm, farmers, agricultural or agriculture. At least one of the first four of these terms was always included in the searches. Results were supplemented with those from studies reporting effects of determinants identified through the searches for studies on the levels of exposure. In total, results from 21 studies were included, all except one being part of the search results on personal levels of exposure.[26,95,100,102–104,106,109,110,112–114,118–120,123,126–130]

PERSONAL LEVELS OF EXPOSURE

Of the 41 identified studies, 16 were on pig farmers,[16,95–97,101,103,106,109,110,113,114,116,117,123,125,129] 7 on poultry farmers[98,100,104,107,118,120,127] and 9 on cattle farmers,[90,92,94,99,105,119,124,126,128] whereas the remaining 9 studies were comparative studies reporting exposure among several agricultural production sectors.[12,26,102,108,111,112,115,121,122] Exposure levels on the respirable fraction were reported in 17 studies and measurements in coarser fractions were performed in 38 studies (Tables 1 and 2). Of those, 19 publications reported the well-defined “inhalable” dust and endotoxin exposure fraction (defined as the mass fraction of total airborne particles inhaled through the nose and mouth; typically, these particles have a mean aerodynamic diameter of $<100\,\mu$m),[131] whereas the remaining and generally older references reported the less well-defined “total” fraction (all dust particles, irrespectively of their size, defined as dust sampled by sampler inlet velocity of 1.25 m/s) of dust and/or endotoxin exposure.[71]

In general, the organic dust within livestock buildings comprises of mostly particles within the extrathoracic and inhalable fractions[132] with a reported mean mass diameter between 9.4 and 25 μm.[105,109,133–135] Previous comparative studies suggest the 37-mm close-faced cassette—the most commonly used “total” dust sampler—to undersample coarse particles,[136] evidently also in agricultural settings.[137] Therefore, levels of exposure in studies measuring the “total” fraction will most likely tend to underestimate the actual exposure concentrations, but some systematic variation in performance between commonly used inhalable dust samplers has also been described.[138] Variations in the performance of samplers for respirable dust (defined as particles with a mass median aerodynamic diameter of 4.0 μm that can penetrate to the alveolar region of the lungs) can also occur, although to a lesser extent and, in most cases, with a possibility of greater harmonization for sampling under the respirable dust criterion through proper adjustment of the sampling flow.[71,139]

Many of the identified studies do not have adequate descriptions of the applied sampling methodology and strategy. Crucial information such as the type of sampler and the sampling flow, the applied sampling strategy (e.g., full-shift or task-based

Table 1. Inhalable and total dust and endotoxin concentrations alongside sampling characteristics from personal measurements reported in the literature.

Reference	*Farm characteristics*		*Sampling characteristics*					*Endotoxin analysis method*	*Measure*	*Dust (mg/m^3)*			*Endotoxin (EU/m^3)*				*Strategy*
	Type	n	*Fraction*	*Sampler*[a]	*Filter*	*Flow rate (l/min)*	*Sampling Time (h)*[b]			N	*Average*	*Range*	N	*Average*	*Range*	*CTRY*	
Pig farmers																	
Haglind *et al.*[101]	NS	19 Farms	Total	NS	NS	NS	NS	SGC-LAL	AM	8	4.9	2.2–15.2	≤8	NS	200–19,000[c]	SE	FS, OS?
Holness *et al.*[102]	Finishing	36 Farms	Total	NS	PVC	2.0	9	NA	GM	53	2.06[d]	0.27–12.81	NA	NA	NA	CA	FS
Louhelainen *et al.*[108]	All	5 Farms	Total	NS	CE	NS	0.25–1	NA	AM	25	12.6	2.2–40.3	NA	NA	NA	FI	NS
Louhelainen *et al.*[109]	Finishing	7 Farms	Total	NS	NS	NS	0.8 (0.5–1.5)	NA	AM	20	8.6	1.0–29.9	NA	NA	NA	FI	FS, OS[f]
Louhelainen et al.[109]	Sow	4 Farms	Total	NS	NS	NS	0.8 (0.3–1.5)	NA	AM	9	7.9	0.5–25.4	NA	NA	NA	FI	FS, OS[f]
Louhelainen *et al.*[109]	Sow/finishing	2 Farms	Total	NS	NS	NS	NS	NA	AM	7	9.1	NS	NA	NA	NA	FI	FS, OS[f]
Donham et al.[16]	All	29 Farms	Total	CFS	NS	1.7	NS	SGC-LAL	AM	55	6.8	1.8–21.7	NS	2400[c]	200–11,000	SE	NS
Virtanen *et al.*[125]	NS	19 Farms	Total	NS	CE	2–20	NS	NA	AM	31	12.8	NS	NA	NA	NA	FI	NS
Christensen et al.[97]	Breeding	11 Farms	Total	CFS	CE	1.9	5.9	KC-LAL	AM	22	4.13	1.12–6.76	22	640[c]	90–1200	DK	FS, OS
Larsson *et al.*[106]	NS	18 Farms	Total	OFS	CE	2.0	1	SGC-LAL	MDN[e]	NS	7.4–13.8	NS	NS	370–3150[c]	NS	SE	TB, WC
Vinzents and Nielsen[123]	Breeding	11farms	Total	CFS	CE	1.9	NS	KC-LAL	GM	23	4.00	NS	23	702[c]	NS	DK	FS, OS
Vinzents and Nielsen[123]	Breeding	2 Farms	Total	CFS	CE	1.9	~3.3	KC-LAL	GM	16	3.11[d]	NS	16	NS	NS	DK	TB
Choudat *et al.*[96]	NS	28 Buildings	Inhalable	NS	PVC	NS	NS	NA	AM	4	3.63	1.63–7.51	NA	NA	NA	FR	NS
Preller *et al.*[114]	All	198 Farms	Inhalable	PAS-6	TF	2.0	8.3 (5.2–10.4)	KC-LAL	GM	360	2.4[d]	0.3–26.6	350	920[d]	56–15,030	NL	FS
Reynolds *et al.*[117]	NS	108 Farms	Total	CFS	CE	2.0	NS	EC-LAL	GM	201	4.55	NS	201	202.7	NS	US	FS
Reynolds *et al.*[117]	NS	≤108 Farms	Total	CFS	CE	2.0	NS	EC-LAL	GM	151	3.45	NS	151	176.1	NS	US	FS
Simpson et al.[121]	Breeding	11 Sites	Inhalable	IOM	GF	2.0	4.7	KT-LAL	GM	27	5.78	0.76–19.09	27	6600[c]	600–149,923	GB	FS, OS?
Melbostad and Eduard[111]	NS	NS	Total	CFS	PC	1.0	<1	KC-LAL	GM	29–32	3.1	NS	29–32	23,000	NS	NO	TB
Radon *et al.*[115]	All	NS	Inhalable	GSP	GF	3.5	2.3 (1.3–4.3)	KT-LAL	MDN	40	3.95	1.1–13.8	40	580[c]	13–11,017	DK	FS, OS
Radon *et al.*[115]	All	NS	Inhalable	GSP	GF	3.5	0.9 (0.2–2.8)	KT-LAL	MDN	100	5.00	<LOD-76.7	100	763[c]	0.1–20,901	DE	FS, OS
Spaan *et al.*[122]	NS	NS	Inhalable	GSP	GF	3.5	>1.8[g]	KC-LAL	GM	6	2.6	1.6–5.4	6	1510	992–6970	NL	FS
Mc Donnell *et al.*[110]	Weaners	5 Buildings	Inhalable	IOM	GF	NS	6–8	ES-LAL	MDN	12	4.69	0.25–7.6	NS	NS	NS	IE	FS[h]
Mc Donnell et al.[110]	Finishing	5 Buildings	Inhalable	IOM	GF	NS	6–8	ES-LAL	MDN	6	2.31	1.9–5.0	NS	NS	NS	IE	FS[h]
Mc Donnell *et al.*[110]	Farrowing	5 Buildings	Inhalable	IOM	GF	NS	6–8	ES-LAL	MDN	10	1.49	0.29–4.4	NS	NS	NS	IE	FS[h]
Mc Donnell *et al.*[110]	Dry sow	5 Buildings	Inhalable	IOM	GF	NS	6–8	ES-LAL	MDN	11	1.1	0.25–3.5	NS	NS	NS	IE	FS[h]
Mc Donnell *et al.*[110]	General	5 Buildings	Inhalable	IOM	GF	NS	6–8	ES-LAL	MDN	8	2.99	1.1–5.6	NS	NS	NS	IE	FS[h]
Kim *et al.*[103]	Finishing	150 Buildings	Total	CFS	GF	2.0	2–3	NA	AM	NS	3.02	0.64–6.67	NA	NA	NA	KR	TB, WC
Smit *et al.*[12]	NS	NS	Inhalable	GSP	GF	3.5	NS	KC-LAL	GM	NS	NS	NS	6	3400	NS	NL	FS
Bonlokke *et al.*[95]	Finishing	NS	Total	CFS	PVC	2.0	~4 (0.7–7.3)	NA	MDN[e]	41	2.39–3.8	0.61–10.24	NA	NA	NA	CA	FS, OS
Bonlokke *et al.*[95]	Finishing	NS	Total	CFS	GF	2.0	~4 (0.7–7.3)	EC-LAL	MDN[e]	NA	NA	NA	41	6553–25,690	1800–69,096	CA	FS, OS
O'Shaughnessy *et al.*[113]	Gestation/ farrowing	2 Facilities	Inhalable	IOM	PVC	2.0	~7	KC-LAL	GM[e]	34	0.83–3.76[d]	NS	34	400–2500[d]	NS	US	FS
Basinas et *al.*[26]	All	53 Farms	Inhalable	GSP	GF	3.5	6.14 (1.1–9.2)	KC-LAL	GM	354	3.4	<LOD-47.8	354	1490	<LOD-374,000	DK	FS
Cattle farmers																	
Holness *et al.*[102]	Dairy[i]	31 Farms	Total	NS	PVC	2.0	9	NA	GM	43	0.95[d]	0.12–4.0	NA	NA	NA	CA	FS
Louhelainen *et al.*[108]	Dairy	8 Farms	Total	NS	CE	NS	0.7–2	NA	AM	30	5.6	0.5–9.5	NA	NA	NA	FI	NS
Virtanen *et al.*[126]	Dairy	18 Farms	Total	NS	CE	2–20	NS	NA	AM	31	2.4	0.2–7.4	NA	NA	NA	FI	NS
Virtanen *et al.*[124]	Dairy	5 Farms	Total	NS	CE	2–20	NS	NA	AM[e]	NS	0.31–3.16	NS	NA	NA	NA	FI	NS
Kullman *et al.*[105]	Dairy	85 Farms	Inhalable	IOM similar	PVC	2.0	4–6	KC-LAL	GM	159	1.78[d]	0.007–53.6	194[j]	647[d]	25.4–34,800	US	FS, OS
Nieuwenhuijsen *et al.*[112]	Dairy	2 Farms	Inhalable	IOM	PVC	2.0	NS[g]	KC-LAL	GM[e]	17	0.3–0.62	NS	17	10.9–120.4	NS	US	TB

Table 1. (Continued).

Reference	Farm characteristics		Sampling characteristics					Endotoxin analysis method	Measure	Dust (mg/m^3)			Endotoxin (EU/m^3)				Strategy
	Type	n	Fraction	Sampler[a]	Filter	Flow rate (l/min)	Sampling Time (h)[b]			N	Average	Range	N	Average	Range	CTRY	
Melbostad and Eduard[111]	NS	NS	Total	CFS	PC	1.0	<1	KC-LAL	GM	33–36	1.2	NS	33–36	2200	NS	NO	TB
Berger *et al.*[94]	NS	23 Farms	Inhalable	NS	GF	3.5	NS	KC-LAL	MDN	23	1.78	0.25–58,22	NA	NA	NA	DE	NS
Firth *et al.*[99]	Dairy	18 Farms	Inhalable	IOM	NS	2.0	4	NA	MDN	18	0.6	NS	NA	NA	NA	NZ	TL
Spaan *et al.*[122]	Dairy	NS	Inhalable	GSP	GF	3.5	>1.8[g]	KC-LAL	GM	8	1.3	0.4–2.3	8	560	62–2230	NL	FS
Spaan et al.[122]	Dairy/breeding	NS	Inhalable	GSP	GF	3.5	>1.8[g]	KC-LAL	GM	4	1.5	0.7–2.7	4	1570	444–3860	NL	FS
Smit *et al.*[12]	Dairy[i]	NS	Inhalable	GSP	GF	3.5	NS	KC-LAL	GM	NS	NS	NS	46	220	NS	NL	FS
Saito *et al.*[90]	Dairy	NS	Inhalable	IOM	PVC	2.0	6–8	rFC	GM	NA	NA	NA	17	752	NS	US	FS
Saito *et al.*[90]	Feedlot	NS	Inhalable	IOM	PVC	2.0	6–8	rFC	GM	NA	NA	NA	48	1097	NS	US	FS
Burch *et al.*[92]	Feedlot	NS	Inhalable	IOM	PVC	2.0	NS	rFC	GM	55	2.4[d]	NS	55	943[d]	NS	US	FS
Burch *et al.*[92]	Dairy	NS	Inhalable	IOM	PVC	2.0	NS	rFC	GM	15	2.4[d]	NS	NS	NS	NS	US	FS
Basinas *et al.*[26]	Dairy	26 Farms	Inhalable	GSP	GF	3.5	4.8 (0.9–12)	KC-LAL	GM	124	1.0	<LOD-9.8	124	358	<LOD-5890	DK	FS
Samadi *et al.*[119]	Dairy	23 Barns	Inhalable	GSP	GF	3.5	NS	KC-LAL	GM	62	0.89	<LOD-6.9	62	392	21–8292	NL	FS
Garcia et al.[128]	Dairy	13 Farms	Inhalable	BS	TF	4.0	NS	rFC	AM	225	0.99	NS.	225	453	NS.	US	FS
Poultry farmers																	
Lenhart *et al.*[107]	Broilers	22 Farms	Inhalable	CFS	PVC	1.5	0.25–1.5	EC-LAL	GM	>26	24.2	12.9–78.2	>26	2100[c]	530–9200	US	TL
Louhelainen *et al.*[108]	NS, floor yard	2 Farms	Total	NS	CE	NS	0.5–1.1	NA	AM	11	7.2	0.5–14.7	NA	NA	NA	FI	NS
Louhelainen *et al.*[108]	Layers, in coops	2 Farms	Total	NS	CE	NS	0.5–1	NA	AM	13	13.0	5.7–37.6	NA	NA	NA	FI	NS
Nieuwenhuijsen *et al.*[112]	NS	1 Farms	Inhalable	IOM	PVC	2.0	NS[g]	KC-LAL	GM[e]	11	1.77–6.67	NS	11	222.3–1,861.2	NS	US	TB
Golbabaei and Islami[100]	Parental stock	4 Barns	Total	NS	TF	1.5	NS	EC-LAL	AM[e]	NS	7.1–21.3	NS	NS	206[c]	NS	IR	NS
Golbabaei and Islami[100]	Layers	3 Barns	Total	NS	TF	1.5	NS	EC-LAL	AM[e]	NS	10.5–15.8	NS	NS	142[c]	NS	IR	NS
Golbabaei and Islami[100]	Broilers	6 Barns	Total	NS	TF	1.5	NS	EC-LAL	AM[e]	NS	3.7–4.2	NS	NS	187[c]	NS	IR	NS
Golbabaei and Islami[100]	Control rooms	NS	Total	NS	TF	1.5	NS	EC-LAL	AM[e]	NS	1.1–3.1	NS	NS	68–138[c]	NS	IR	NS
Melbostad and Eduard[111]	NS	NS	Total	CFS	PC	1.0	<1	KC-LAL	GM	24–32	5.0	NS	24–32	4200	NS	NO	TB
Donham *et al.*[98]	Layers, broilers, turkey and shacklers	NS	Total	CFS	PVC	1.0–2.0	NS	EC-LAL	AM	238	6.5	0.02–81.33	236	1589	0.24–39,267	US	FS
Radon *et al.*[115]	Layers and broilers	NS	Inhalable	GSP	GF	3.5	0.5 (0.2–2.2)	KT-LAL	MDN	40	7.01	0.42–21.75	40	2576[c]	190–16,348	CH	FS, OS
Whyte[127]	Layers, barn houses	NS	Inhalable	IOM	GF	2.0	NS	NA	AM	12	10.8	NS	NA	NA	NA	UK	FS
Whyte[127]	Layers, battery	NS	Inhalable	IOM	GF	2.0	NS	NA	AM	9	4.8	NS	NA	NA	NA	UK	FS
Whyte[127]	Layers, barn houses	NS	Inhalable	IOM	GF	2.0	NS	NA	AM[e]	55	5–71	NS	NA	NA	NA	UK	TB
Kirychuk *et al.*[104]	Broiler and turkey	NS	Total	CFS	GF	2.0	1.6	EC-LAL	AM	80	9.56	NS	80	7484	NS	CA	FS, OS?
Kirychuk *et al.*[104]	Layers, cages	NS	Total	CFS	GF	2.0	2.7	EC-LAL	AM	31	7.57	NS	31	9544	NS	CA	FS, OS?
Spaan *et al.*[122]	Layers	NS	Inhalable	GSP	GF	3.5	>1.8[g]	KC-LAL	GM	2	9.5	6.6–14	2	2090	1716–2550	NL	FS
Spaan *et al.*[122]	Broilers	NS	Inhalable	GSP	GF	3.5	>1.8[g]	KC-LAL	GM	2	4.2	4.0–4.4	2	880	520–1500	NL	FS
Spaan *et al.*[122]	Layers, free-range	NS	Inhalable	GSP	GF	3.5	>1.8[g]	KC-LAL	GM	6	3.6	1.6–11	6	2140	360–8120	NL	FS
Senthilselvan *et al.*[120]	Broilers	16 Operations	Total	CFS	GF	2.0	0.4–3.3	NS	GM	56	2.21–11.2	NS	56	3405–9609	NS	CA	FS, OS
Senthilselvan *et al.*[120]	Layers	17 Oparations	Total	CFS	GF	2.0	0.4–5.3	NS	GM	46	1.09–3.19	NS	46	694.1–1286	NS	CA	FS, OS
Basinas *et al.*[26]	Broilers	1 Farm	Inhalable	GSP	GF	3.5	2.5 (1.6–3.7)	KC-LAL	GM	11	3.1	0.7–18.3	11	596	61–6420	DK	TB
Basinas *et al.*[26]	Layers	2 Farms	Inhalable	GSP	GF	3.5	6.2 (4.2–1.9)	KC-LAL	GM	3	5.5	3.1–8.3	3	2430	1162–7090	DK	FS

Abbreviations: AM, arithmetic mean; BS, button sampler; CE, cellulose esters (organic, i.e., acetate; inorganic, i.e., nitrate or a mixture); CFS, close-faced sampler; CTRY, country ISO abbreviation; EC-LAL, endpoint chromogenic LAL assay; ES-LAL, rapid endosafe assay; FS, full-shift; GF, glass fiber; GM, geometric mean; GSP, Gesamt Staub Probenehmer sampler (including the Conical Inhalable Sampler plastic adaptation); IOM, Institute of Occupational Medicine sampler; KC-LAL, kinetic chromogenic LAL assay; KT-LAL, kinetic turbidimetric LAL assay; LOD, limit of detection; *n*, number; NA, not available; NS, non-specified; OFS, open-faced sampler; OS, only stable work (the whole working period); PAS-6, The Dutch PAS-6 inhalable dust sampler; PC, polycarbonate; PVC, polyvinylchloride; RNG, range; SGC-LAL, semiquantitative Gel-Gnot LAL assay; TB, task-based; TF, teflon; TL, time limited; TWA, time-weighted average; WC, worst case.

[a] Total samplers defined only by the inlet function (open/closed). [b] Given as range or average values (range) based on the information provided. [c] Transformed value using a 1-ng equivalent to10 EU standard. [d] TWA values. [e] Range of averages. [f] Excluding measurements with collected dust weighing <0.5 mg/m^3. [g] Values given for a larger sample of measurements. [h] Excluding breaks. [i] Mainly dairy. [j] Includes area measurements.

Table 2. Respirable dust and endotoxin concentrations alongside sampling characteristics from personal measurements reported in the literature.

Reference	*Farm characteristics*		*Sampling characteristics*				*Endotoxin analysis method*	*Measure*	*Dust (mg/m^3)*			*Endotoxin (EU/m^3)*				*Strategy*
	Type	n	*Sampler*	*Filter*	*Flow rate (l/min)*	*Sampling Time (h)*[a]			N	*Average*	*Range*	N	*Average*	*Range*	*CTRY*	
Pig farmers																
Haglind *et al.*[101]	NS	19 Farms	CL	NS	NS	NS	SGC-LAL	AM	12	NS	0.3–1.4	≤12	NS	100–300[b]	SE	FS, OS?
Holness *et al.*[102]	Finishing	36 Farms	CL	PVC	1.7	9	NA	GM	53	0.17[c]	0.01–4.70	NA	NA	NA	CA	FS
Larsson *et al.*[106]	NS	18 Farms	CL	CE	2.0	1	SGC-LAL	MDN[d]	NS	NS	NS	NS	80–170[b]	NS	SE	TB, WC
Vinzents and Nielsen[123]	Breeding	11Farms	CL	CN	1.9	NS	KC-LAL	GM	23	0.43	NS	23	40.54	NS	DK	FS, OS
Donham *et al.*[16]	All	29 Farms	CL	NS	1.7	NS	SGC-LAL	AM	NS	0.34	0–2.2	NS	2300[b]	200–11,200	SE	NS
Christensen *et al.*[97]	Breeding	11 Farms	CL	CE	1.9	5.9	KC-LAL	AM	24	0.48	0.18–1.04	24	50[b]	10–130	DK	FS, OS
Reynolds *et al.*[117]	NS	108 Farms	CL	CE	1.7	NS	EC-LAL	GM	201	0.23	NS	117	16.95	NS	US	FS
Reynolds *et al.*[117]	NS	≤108 Farms	CL	CE	1.7	NS	EC-LAL	GM	151	0.26	NS	≤151	11.86	NS	US	FS
Radon *et al.*[116]	All	NS	GSP	GF	2.0	1.6	KT-LAL	MDN	99	0.3	0–39.6	96	6.7	0.02–444.4	DE	TB, WC
Chang *et al.*[129]	All	30 Buildings	CL	PC	1.7	6–8	KC-LAL	AM	57	0.14	<LOD-1.45	95	47	0.02–1643	TW	FS
Kim *et al.*[103]	Finishing	150 Buildings	CL	GF	1.7	2–3	NA	AM	NS	1.34	0.43–3.45	NA	NA	NA	KR	TB, WC
Mc Donnell *et al.*[110]	Weaners	5 Buildings	IOM + PUF	GF	NS	6–8	NA	MDN	12	0.19	0.03–0.63	NA	NA	NA	IE	FS[e]
Mc Donnell *et al.*[110]	Finishing	5 Buildings	IOM + PUF	GF	NS	6–8	NA	MDN	6	0.17	0.01–0.3	NA	NA	NA	IE	FS[e]
Mc Donnell *et al.*[110]	Farrowing	5 Buildings	IOM + PUF	GF	NS	6–8	NA	MDN	12	0.09	0.01–3.4	NA	NA	NA	IE	FS[e]
Mc Donnell *et al.*[110]	Dry sow	5 Buildings	IOM + PUF	GF	NS	6–8	NA	MDN	11	0.06	0.01–0.31	NA	NA	NA	IE	FS[e]
Mc Donnell et al.[110]	General	5 Buildings	IOM + PUF	GF	NS	6–8	NA	MDN	7	0.19	0.09–0.63	NA	NA	NA	IE	FS[e]
Cattle farmers																
Holness *et al.*[102]	Dairy[f]	31 Farms	CL	PVC	1.7	9	NA	GM	43	0.08[c]	0.01–4.7	NA	NA	NA	CA	FS
Nieuwenhuijsen *et al.*[112]	Dairy	2 Farms	CL	PVC	2.2	NS[g]	KC-LAL	GM[d]	18	0.08–0.31	NS	18	0.7–4.44	NS	US	TB
Berger *et al.*[94]	NS	23 Farms	NS	GF	2.0	NS	NA	MDN	23	0.12	0–1.0	NA	NA	NA	DE	NS
Poultry farmers																
Lenhart et al.[107]	Broilers	22 Farms	CL	PVC	1.7	0.25–1.5	EC-LAL	GM	26	1.22	0.41–3.77	26	70[b]	20–230	US	TL
Reynolds *et al.*[118]	Turkey	3 Facilities	CL	TF	1.7	NS	EC-LAL	GM[d]	20	0.3–1.4[c]	0–2.1	20	91–568[c]	19–2804	US	FS
Nieuwenhuijsen *et al.*[112]	NS	1 Farms	CL	PVC	2.2	NS[f]	KC-LAL	GM[d]	10	0.14–0.4	NS	10	3.2–29.41	NS	US	TB
Golbabaei and Islami[100]	Parental stock	4 Barns	CL	TF	1.7	NS	EC-LAL	AM[d]	NS	2.3–4.6	NS	NS	236[b]	NS	IR	NS
Golbabaei and Islami[100]	Layers	3 Barns	CL	TF	1.7	NS	EC-LAL	AM[d]	NS	1.7–2.5	NS	NS	145[b]	NS	IR	NS
Golbabaei and Islami[100]	Broilers	6 Barns	CL	TF	1.7	NS	EC-LAL	AM[d]	NS	1.6–2.2	NS	NS	222[b]	NS	IR	NS
Golbabaei and Islami[100]	Control rooms	NS	CL	TF	1.7	NS	EC-LAL	AM[d]	NS	0.5–1.1	NS	NS	54–131[b]	NS	IR	NS
Donham *et al.*[98]	Layers, broilers, turkey and shacklers	NS	CL	PVC	1.9	NS	EC-LAL	AM	210	0.63	0.01–7.73	210	58.9	0.35–639.99	US	FS

Abbreviations: AM, arithmetic mean; CE, cellulose esters (organic, i.e., acetate; inorganic, i.e., nitrate or a mixture); CL, cyclone; CTRY, country ISO abbreviation; EC-LAL, endpoint chromogenic LAL assay; ES-LAL, rapid endosafe assay; FS, full-shift; GF, glass fiber; GM, geometric mean; GSP, Gesamt Staub Probenehmer sampler (including the Conical Inhalable Sampler plastic adaptation); IOM, Institute of Occupational Medicine sampler; KC-LAL, kinetic chromogenic LAL assay; KT-LAL, kinetic turbidimetric LAL assay; LOD, limit of detection; *n*, number; NA, not available; NS, non-specified; OFS, open-faced sampler; OS, only stable work (the whole working period); PAS-6, The Dutch PAS-6 inhalable dust sampler; PC, polycarbonate; PUF = porous polyurethane foam; PVC, polyvinylchloride; RNG, range; SGC-LAL, semiquantitative Gel-Gnot LAL assay; TB, task-based; TF, teflon; TL, time limited; TWA, time-weighted average; WC, worst case.

[a] Given as range or average values (range) based on the information provided. [b] Transformed value using a 1-ng eq to10 EU standard. [c] TWA values. [d] Range of averages. [e] Excluding breaks. [f] Mainly dairy. [g] Values given for a larger sample of measurements.

monitoring), the monitoring time or even the range of measured concentrations are absent. These limitations complicate performance of direct comparisons between studies. Furthermore, the studies vary considerably in methods of extraction and analysis used for endotoxin determination, that is, all major methods (end point, chromogen kinetic and turbometric kinetic) of the LAL assay are used, and even the newer rFC bioassay for endotoxin determination is applied in a few recent studies.

Nevertheless, reported full-shift average levels of exposure in the included studies are within an order of about one magnitude ranging for inhalable dust between 0.8 and 10.8 mg/m^3, and for inhalable endotoxin between 300 and 6600 EU/m^3 (Table 1). Average full-shift levels between pig (range of means: 0.83–5.78 mg/m^3 and 400–6600 EU/m^3 for dust and endotoxin, respectively) and poultry farmers (range of means: 3.6–10.8 mg/m^3 and 880–2576 EU/m^3 for dust and endotoxin, respectively) appear to be somewhat higher than those reported among cattle farmers (range of means for strictly defined populations: 0.89–2.4 mg/m^3 and 358–1507 EU/m^3 for dust and endotoxin, respectively). This pattern also seems to be consistent when looking at "total" dust and endotoxin exposure estimates. Exposure patterns across different types of production in inhalable endotoxin exposure seem to be more consistent when restricting the results to studies that applied comparable sampling and analytical methodologies based on kinetic versions of the LAL assay.[12,26,115,119,122]

The highest average for endotoxin exposure is reported among pig farmers,[111] but it is derived through task-based measurements and, thereby, apart from the applied analytical method it is also heavily influenced by the short sampling duration and involvement of high exposed activities. The results from studies measuring exposure solely during stable work suggest poultry farmers to be highest exposed both in respect to dust and endotoxin exposure. These findings are in accordance with the results from studies measuring dust and endotoxin exposure with the use of stationary sampling across different livestock production buildings.[140–142] However, stationary sampling in stables tends to somewhat underestimate the level of exposure of the farmer as documented in studies assessing exposure by both stationary and personal monitoring.[16,94,96,105,108,124–126]

Typically, the content of particles in the respirable fraction in dust from livestock stables accounts, on average, between 5 and 20% of the overall amount.[109,133,143,144] Reported cross-shift levels in studies included in the present review average between 0.06 and 0.63 mg/m^3 for respirable dust and between 11.9 and 568 EU/m^3 for endotoxin (Table 2), with differences in levels of exposure between types of farmers similar to the ones observed for the inhalable and "total" dust fractions. The relatively high ratio between respirable endotoxin and endotoxin in coarser fractions in few of the reviewed studies[16,100] contradicts the results from the remaining ones, which generally report respirable endotoxin to account for $<20\%$ of the total airborne amount. The latter observation is further supported by the results of well-established studies using stationary measurements and kinetic versions of the LAL assay.[94,140,142]

The large discrepancies in applied measurement and analytical methodologies between studies and the limitations in the methodology descriptions in some studies hamper the assessment of time trends in personal exposure to dust and endotoxin. A descriptive analysis by sorting all included studies that followed a full-shift measurement strategy by type of farming and year of publication returned inconclusive results. Trends in exposure were absent, with mean levels remaining constantly above the suggested OELs, although with very broad ranges of individually measured concentrations throughout the years and across all types of farmers. This was true even when looking separately for studies on the inhalable and total particle size fractions, or when restricting the sample to studies with adequate methodological descriptions.[12,26,90,92,95,97,98,104,105,113–115,117,119–123,127,128] In addition, as recently discussed by Eduard *et al.*,[61] the absence of standardization and reproducibility in measurement methods between studies affects the comparability of the results of epidemiological studies and, subsequently, also the establishment of legal OELs, especially in relation to endotoxin exposure.

Overall, the results of the reviewed studies suggest livestock farmers to be exposed to levels of dust and endotoxin exposure that are highly variable and, in most cases, exceed by several folds up to orders of magnitude the established OELs. Farmers are clearly exposed at levels at which health effects have been demonstrated. Studies using repeated measurements show that exposure variability is substantially large, both over time and between individuals (Table 3). In most cases, the temporal (day-to-day) within-workers component is much larger than the differences in average concentrations among workers (between-workers component), although that distribution patterns vary depending on the agent, and the type of environment and

Table 3. Literature reported variance component analysis results and estimated fold-range variations in measured inhalable dust and endotoxin exposure concentrations between- and within-workers employed in livestock farming.

Type of farmers	*CTRY*	n	k	*BW*	*WW*	$_{BW}R_{0.95}$	$_{WW}R_{0.95}$	*Reference*
Inhalable Dust								
Pig	NL	262	131	0.11[a]	0.30[a]	3.7	8.6	Kromhout and Heederik[145]
Livestock and arable farmers	US	142	73	1.11[a]	1.11[a]	62.4	62.6	Kromhout and Heederik[145]
Pig	DK	354	231	0.25	0.64	6.95	23.00	Basinas *et al.*[26]
Dairy	DK	124	77	0.44	0.57	13.57	19.21	Basinas *et al.*[26]
Dairy	NL	62	NS	0.32	0.37	9.18[a]	10.85[a]	Samadi *et al.*[119]
Inhalable endotoxin								
Pig	NL	250	125	0.13	0.60	4.1	20.9	Preller *et al.*[146]
Livestock and arable farmers	US	142	73	1.78[a]	2.55[a]	187	523	Kromhout and Heederik[145]
Pig	DK	354	231	0.19	1.99	5.49	250.53	Basinas *et al.*[26]
Dairy	DK	124	77	0.47	1.18	14.82	70.14	Basinas *et al.*[26]
Dairy	NL	62	NS	0.71	0.68	27.2[a]	25.34[a]	Samadi *et al.*[119]

Abbreviations: BW, between-worker variance; $_{BW}R_{0.95}$, ratio of the 2.5th and 97.5th percentile of the between-worker variance of the log normally distributed exposure; CTRY, country ISO abbreviation; *k*, number of workers; *n*, number of measurements; WW, within-worker variance; $_{WW}R_{0.95}$ = Ratio of the 2.5th and 97.5th percentile of the within-worker variance of the log normally distributed exposure.

[a] Calculated on the basis of the given information using the following formulas: (1) $_{BW}R_{0.95} = \exp(3.92 * BW^{0.5})$ and (2) $_{WW}R_{0.95} = \exp(3.92 * WW^{0.5})$.

livestock farming involved and whether farmers are classified across farms. For example, in a recent industry-wide study among Danish farmers the variability in daily inhalable dust and endotoxin concentrations among dairy and pig farmers were estimated to exceed those in average personal concentration between a factor of 1.3 and 10.5. However, in the same study the between-workers variability was much larger among cattle than pig farmers. They also observed an up to 30-fold increase in temporal variability among outdoor workers versus stable workers.[26]

The evident large variation in the reported concentrations can partly be attributed to the different sampling and analytical methods between studies; however, a trend toward appliance of comparable methods for dust and endotoxin determination can be observed in recent studies primarily from Northern Europe.[12,26,115,119,122] It follows the establishment of CEN guidelines for the assessment of bioaerosols and endotoxin in workplaces.[79,80] For endotoxin, large differences in measured concentrations as high as 12-folds have been described between laboratories using standardized analytical protocols.[83] However, intralaboratory differences have been described to be much smaller,[81,147] and in a previous analysis of a large database of >2000 endotoxin measurements analyzed with marginally different protocols it was shown that analytical errors explained $<6\%$ of the within-workers variance.[148] The contribution of the analytical errors to the total variability is in general small and inversely related to the magnitude of the environmental variability, that is, the greater the magnitude of the environmental variability the smaller the contribution of the analytical errors.[149,150] Consequently, the considerable variability in measured concentrations can primarily be attributed to alternating tasks of the farmers from day-to-day and several environmental and engineering factors that influence dust and endotoxin exposure within animal buildings.

DETERMINANTS OF ORGANIC DUST AND ENDOTOXIN EXPOSURE IN LIVESTOCK FARMING

All of the 21 identified studies on determinants were observational, with the exception of the study by Choudhry *et al.*,[130] which followed an interventional study design. An assessment of the effect of potential determinants on exposure to organic dust was always included, whereas investigations on potential determinants for endotoxin were included in 15 studies.[26,95,100,104,106,112–114,118–120,123,128–130] Ten of the studies focused on pig farmers,[95,102,103,106,109,110,113,114,123,129] five on poultry farmers,[100,104,118,120,127] four on dairy farmers[119,126,128,130] and two included more than one type of farmers.[26,112] The basic design characteristics, the method of analysis and the main findings of the included studies are summarized in Table 4.

Most of the reviewed studies had simple designs using summary statistics or univariate comparison tests and models, and focused on the assessment of a limited number of determinants, usually including either the type or stage of production.[26,95,100,103,104,110,120,123,129] The results of these studies suggest workers in weaning and finishing stables to be exposed to higher levels of dust and endotoxin exposure compared with workers in sow and farrowing pig stables. Season is consistently shown as an important determinant for stable exposures with higher levels reported during winter than during summer seasons. This effect is mainly attributed to the lower ventilation rates applied in stables during winter,[140,141,151] although the pattern is stronger in pig and poultry stables than in cattle stables. In addition, ventilation and manure collection systems, feeding practices and the age of the chicks and the applied poultry housing system (floor *vs* cages), as well as the working environment (indoor *vs* outdoor), also seem to be of importance. For dairy farmers, very little information on influential farm characteristics is available, with the type of bedding and the milking method highlighted as important in a recently published study among Dutch farmers, which included repeated measurements of exposure in multivariate analysis.[119]

Overall, these results are in accordance with those from studies using stationary sampling.[129,140–144,152–155] However, stationary sampling is well documented to underestimate exposure risks in comparison with personal sampling techniques and, in many cases, results offer limited information for methods of exposure control and reduction, and are probably more relevant for classifying workers into similar exposure groups and optimizing exposure-assessment strategies for epidemiological studies. For example, we have previously reported the day-to-day variability in personal dust and endotoxin concentrations to rapidly increase when moving from an indoor to an outdoor working environment among both pig and dairy farmers.[26] This is in accordance with what is known from the literature.[156] Apart from indicating the need for more measurements per individual to acquire a representative exposure estimate for outdoor activities, this finding also points toward the use of the working environment as a potential classification variable for the establishment of group-based exposure assessment strategies in epidemiological studies among livestock farmers. A similar use can be reserved also for the type and stage of the production involved.

The assessment of the effect of working tasks was the main focus in few of the identified studies. Among pig farmers, O'Shaughnessy *et al.*[113] found increased dust concentrations in tasks related to animal movement during the weaning process. The authors based their results on task-based analysis in linear regression using direct measurement readings and time-weighted estimates derived from full-shift personal sampling to estimate specific concentration levels associated with a particular task. Among poultry farmers, Whyte *et al.*[127] used a task-based measurement approach in workers working in aviary hen houses and reported high levels of personal dust exposure to occur during tasks that resuspended dust or caused bird disturbance. Similarly, Nieuwenhuijsen *et al.*[112] performed task-based measurements in Californian farmers, including a small series of measurements during activities related to cattle and poultry production, and reported the highest levels of exposure in poultry-related tasks to occur during scraping of stables. For cattle farmers, animal handling, milking and feeding were associated with the highest dust levels; for endotoxin, the task with the highest level was feeding.

On the contrary, in a recently published study that evaluated the impact of job task on the personal exposure levels of dust and endotoxin among Californian workers from large dairies (>1000 cows), endotoxin levels while feeding were found to be significantly lower than those while milking.[128] Performance of re-bedding activities was the strongest predictor of exposure, leading to increases in dust and endotoxin concentrations between 90 and 160% in comparison with the levels during milking. However, production in such large dairies probably differs when compared with the much smaller and more enclosed European dairies, where workers tend to more frequently perform intermittent working tasks including outdoor working activities.

This intermittent nature of the work within livestock buildings complicates the assessment of task effects on exposure and it may be the main reason for the small number of studies on tasks determining exposure. In particular, pig farmers are known to perform various short-duration working tasks within several workplaces that usually bear different characteristics. As a result, task-based dust sampling approaches become labor intensive and inefficient because of the involvement of small time intervals per task and department, and the increased chance of failure to collect detectable dust amounts.[114] Recently, task-based methods combining full-shift measurements with readings from direct measurement instruments have been successfully implemented

Table 4. Summary of studies reporting the effect of determinants of the personal levels of dust and endotoxin exposure among livestock farmers.

Reference	*Type of farming*	*Exposure agents*	n	*Design characteristics*	*Determinants studied*	*Method of statistical analysis*	*Main findings*
Holness *et al.*[102]	Pig	Dust	53	Full-shift measurements in 53 farmers from 53 finishing farms	Feeding method (floor, place automated), grinding area (indoor *vs* outdoor), type of feed (high moisture, low moisture, barley)	Comparisons between means, Students *t*-tests	Exp. levels higher in farmers that used floor feeding methods, feed with high moisture or indoor grinding.
Louhelainen *et al.*[109]	Pig	Dust	36	Full-shift measurements in x workers from 4 sow, 8 finishing and 3 intergraded production farms	Production stage (sow *vs* finishing)	Comparisons between means, (measurements with a dust load $<0.5\,\text{mg/m}^3$ were excluded)	Dust exp. higher in finishing than sow units.
Virtanen *et al.*[126]	Dairy	Dust	31	Measurements during 2 daily working shifts of 31 farmers from 18 farms	Performance of cow brushing during monitoring, number of animals	Mann–Whitney *U*-tests, correlations	No increase in exp. by cow brushing. Low correlations between exp. and number of animals.
Larsson *et al.*[106]	Pig	Dust and endotoxin	NS	1 h Task-based measurements in 20 workers from 18 farms	Feeding activities *vs* animal-tending activities	Comparisons between means, Mann–Whitney *U*-tests	Higher dust and endotoxin levels during feeding tasks.
Vinzents and Nielsen[123]	Pig	Dust and endotoxin	~32 (Survey A) and 23 (Survey B)	Task-based (Survey A) and full-shift (Survey B) measurements	Tasks performed close and far from animals (Survey A), fat content in feed (Survey B)	ANOVA (Survey A), correlations (Survey B)	No exp. effect of tasks. Increased fat content in feed associated with decreased dust exp.
Reynolds *et al.*[118]	Poultry (turkeys)	Dust and endotoxin (respirable)	20	Full-shift measurements in 5 repeated seasonal visits in 3 workers from 3 farms	Season (summer *vs* winter), barn type (brooder, tom and hen stables), ventilation rate, bird age, tilling frequency	ANOVA, correlations	Highest exp. in the hen barn/lowest in the brooder and during the winter season. Increased bird age assoc. with increase in dust exp. Increasing tilling frequency assoc. with decreased endotoxin.
Preller *et al.*[114]	Pig	Dust and endotoxin	354	Full-shift repeated measurements in 198 workers from 198 farms	Season (summer *vs* winter), outdoor temperature, working tasks (11 distinct), farm characteristics (feeding methods, flooring type, ventilation characteristics, hygienic conditions)	Paired *t*-tests (season), multiple linear regression (tasks, temperature and farm characteristics)	Higher exp. during winter. Feeding, controlling, cleaning and tasks involving active animals (e.g., castration and teeth cutting) increased exp. Use of wet feed, full concrete floor and ventilation via other departments largely decreased dust exp. Largest decrease in endotoxin when a convex floor, air exhaust via pit or manual dry feeding was applied. Increased outdoor temperature decreased exp.
Nieuwenhuijsen *et al.*[112]	Poultry, diary and crop	Dust and endotoxin	140	Task-based measurements in x workers from 10 farms, including 2 dairy, 1 poultry and 7 crop and vegetable farms	Working tasks stratified by production type including feeding, milking, animal moving (cows), animal handling, scraping of stables, disinfection (poultry), field work (harvesting, ground preparation, etc), power washing and equipment repair	Comparisons between means, ANOVA	Highest exp. for cattle tasks during feeding and animal handling, lowest during animal moving and stable scraping. For poultry, highest exp. during stable scraping and feeding and lowest during stable disinfection
Golbabaei and Islami[100]	Poultry	Dust and endotoxin	NS	Seasonal (summer and winter) measurements in x workers from 6 broiler, 4 parental stock and 3 poultry layer farms	Season (summer *vs* winter), barn type (parent stock, broilers, layers, control alleys), production system (enclosed, open), litter in control alleys, chicks age (for broiler)	Comparisons between means (stratified by barn type, season, production system and chick age), correlations, ANOVA	Highest exp. in workers from enclosed parental stock buildings. Winter season, increased chick age, presence of litter in control alleys and enclosed production system assoc. with higher exp.
Chang *et al.*[129]	Pig	Dust and endotoxin (respirable)	95	Full-shift measurements in x workers from 6 farms with 30 open-style designed houses	Production stage (breeding, farrowing, nursery, growing, finishing), surface area, animal density, cleaning frequency and method, temperature, humidity, wind velocity.	Comparisons between means, ANOVA (only for exp. levels)	Highest exp. for workers in finishing stables. Lowest dust exp. in breeding and endotoxin in farrowing workers. Animal density and cleaning intervals largest in growing and finishing houses
Whyte[127]	Poultry	Dust	NS	Parallel full-shift and task-based measurements in 21 farmers performed in a single winter visiting day	Production type (floor *vs* cage), working tasks	Comparisons between means	Higher exp. in floor systems. Tasks related to nest cleaning, brushing down surfaces and sweeping, removal of wire partition and litter spreading assoc. with highest exp. Lowest exp. during post collection egg-handling activities
Kirychuk *et al.*[104]	Poultry (including turkeys)	Dust and endotoxin	111	Full-shift measurements in 80 workers from floor-housing farms and 31 workers from cage-housing farms	Housing system (floor *vs* cage)	Comparisons between means, Students *t*-tests	Higher dust levels in floor than cage systems with an opposite, but non-significant trend, for endotoxin exp.
Kim *et al.*[103]	Pig	Dust	NS	2–3 h measurements during stable cleaning in x workers from 5 different types of finishing stables categorized on the basis of type of ventilation and manure collection system	Manure collection system (scrapper, slatted floor with pit, deep litter), type of ventilation (natural, mechanical)	ANOVA	Highest total dust exp. in workers from mechanically ventilated buildings with scrapper manure collection. Highest respirable dust exp. in buildings with natural ventilation and deep litter. For both fractions exp. was lowest in natural ventilated buildings with slatted floors
Mc Donnell *et al.*[110]	Pig	Dust	47	Full-shift measurements in 41 workers from 5 farms	Housing system/production stage (weaners, finishers, farrowing, dry sows, general)	Comparisons between means, ANOVA and *t*-tests (non-parametric)	Highest exp. among workers in weaning stables, lowest in dry sows
Bonlokke *et al.*[95]	Pig	Dust and endotoxin	41	Full-shift seasonal repeated measurements in 24 stable workers	Season (summer *vs.* winter), temperature, area per animal, relative humidity	Mann–Whitney *U*-tests or Student's *t*-tests	Higher endotoxin levels in winter, significantly lower temperatures during summer
O' Shaughnessy *et al.*[113]	Pig	Dust and endotoxin	34	Full-shift repeated measurements in 12 workers from 2 farms	Season (summer, winter, spring), site, working tasks (performance and duration of tasks belonging to 9 general categories: recording, breeding, feeding, heat checking, setting-up/breaking down, sow/gilt handling, treating pigs, walking aisles, weaning)	Comparisons between means, general linear regression model	Levels of exp. decreased from winter to summer (significant for dust). Tasks performed close to moving animals and especially to piglet weaning increased exp. to dust. Duration of performance altered the exposure importance of tasks
Senthilselvan *et al.*[120]	Poultry	Dust and endotoxin	102	Full-shift repeated measurements in 33 workers from 16 broiler and 17 cage-layer farms	Production type (broiler *vs* layer), season (summer *vs* winter), flock age	Comparisons between means, random intercept linear models	Higher exp. levels among broiler farmers that increased with the flock age (significant only for

Table 4. (Continued).

Reference	*Type of farming*	*Exposure agents*	n	*Design characteristics*	*Determinants studied*	*Method of statistical analysis*	*Main findings*
							winter). For layer farmers flocks age assoc. with a decrease in dust levels. Seasonal patterns were unclear
Basinas *et al.*[26]	Pig, dairy, poultry	Dust and endotoxin	507	Full-shift repeated measurements in 77 dairy and 231 pig farmers from 80 farms. Full-shift measurements in 3 farmers from 2 layer farms. Task-based repeated measurements in 5 farmers from 1 broiler farm	Season (summer *vs* winter) for pig and dairy farmers, flock age and type of production for poultry farmers	Comparisons between means, paired *t*-tests (season)	Higher exp. during winter (significant only for pig farmers). For broiler farmers, increased flock age assoc. with increased exp. Increased involvement in outdoor activities assoc. with increase in day-to-day variability among pig and cattle farmers
Samadi *et al.*[119]	Dairy	Dust and endotoxin	62	Full-shift repeated measurements within at least 3 consecutive days in workers from 23 barns with different bedding materials	Main (compost, sawdust, rubber and rubber-filled mats) and extra bedding material. Milking method (parlor *vs* robot), surface area by cow	Comparisons between means, linear mixed effect models	Compost bedding assoc. with higher dust and endotoxin exp. compared with other types of bedding. Levels of exp. decreased with increased surface area per cow, but dust exp. increased by robot milking
Garcia *et al.*[128]	Dairy	Dust and endotoxin	225	Full-shift in 225 workers from 13 large (>1000 cows) dairy farms.	Tasks (break, feeding, maintenance. Medical work, moving of animals, re-bedding, waste handling)	Comparisons between means, linear mixed effect models with levels during milking as a reference	Highest dust exp. during re-bedding and feeding, lowest in milking. Highest endotoxin exp. while moving animals, lowest while feeding. Re-bedding, animal moving and waste handling were the strongest exp. predictors in multiple analyses
Choudhry *et al.*[130]	Dairy	Dust and endotoxin	20	Interventional design. Full-shift measurements during parlor milking: $n=10$ with and $n=10$ without intervention	Intervention: increase of frequency of cleaning the parlor with an automated system from 4–8 times during a working shift	Comparisons between means, Mann–Whitney *U*-tests	Lower dust and endotoxin exp. after intervention (significant only for respirable dust)

Abbreviations: assoc., associated; exp., exposure; *n*, number of measurements; NS, not specified.
Only results for the types of production and agents of interest are reported.

among workers in very large pig farms,[113] although for workers in smaller farms empirical modeling based on full-shift measurements and simultaneously collected information on both tasks and workplace characteristics is the preferred approach.

An example of a study using empirical modeling approaches to gain in-depth knowledge on the determinants of personal dust and endotoxin exposure among livestock farmers can be found in the study of Preller *et al.*[114] Exposure levels to inhalable dust and endotoxin were obtained by seasonal (summer/winter) personal monitoring of 198 Dutch farmers. Information on 95 *a priori* identified distinct farm characteristics were collected through walk-through surveys, and all farmers filled in their working tasks on detailed activity diaries. Using classical stepwise regression techniques, the authors fitted multiple models accounting for >30% of the variability in exposure being explained by 10 tasks and 10 farm characteristics for dust and 12 tasks and 8 farm characteristics for endotoxin. The predictors for dust exposure included low outside temperature and tasks with intense animal handling such as castrating, ear tagging and teeth cutting, as well as activities related to feeding, floor sweeping and removal of dry manure. Important farm characteristics were the presence of dry manure, a dusty overall environment or a dusty feeding path, the use of pig starter and wet feeding practices. For endotoxin, exposure decreased by the presence of a convex floor, the use of automated dry feeding and the air sucking through the pit. Exposure to endotoxin increased as a consequence of a full slatted floor, use of floor heating and a working environment deteriorated by dust. Among others, the most highly associated tasks with endotoxin exposure included ear tagging, teeth cutting, floor sweeping and iron injections.

These findings are further supported by the results of a preliminary analysis,[157] exploring determinants of personal exposure to dust and endotoxin within the subpopulation of pig farmers in the large Danish study of Basinas *et al.*[26] Separate multivariate models for tasks and farm characteristics were established. Important exposure determinants included feeding, ventilation and flooring (slatted coverage and dampness) parameters, as well as tasks related to intense animal handling (castration, teeth cutting, etc) and movement, and to preparation and distribution of feed. High-pressure washing was a strong exposure predictor, but only for personal endotoxin exposure.

The latter observation is further supported by the results of a recent study among the US pig farmers that assessed exposure to endotoxin during high-pressure washing activities using task-based measurements and reported an average level of personal exposure as high as 40,000 EU/m^3 (range: 5401–180,864 EU/m^3).[158] However, in a recent interventional study among dairy parlor workers, it was shown that increased cleaning frequencies can potentially decrease the levels of personal exposures.[130] The authors increased the frequency of automated parlor washing from four to eight times per work shift and determined the level of personal exposure to inhalable and respirable dust in 10 workers under each condition. They observed reduced levels of personal exposures with increased washing frequency, although differences were statistically significant only for respirable dust.

Aside from the studies reviewed, determinants of dust and, to a lesser extent, endotoxin exposure, primarily in relation to pig farming, have been assessed in several previous studies using area-sampling methods.[95,103,129,140–144,151–155,159–169] Only few of them captured the complexity of the working environment within stables,[151,154,159,160,169] and most were simplistic in design and statistical analysis, and relatively small regarding farm characteristics and engineering parameters tested. Their findings are supportive to the ones by reviewed studies on personal exposure. Stationary sampling underestimates the personal levels of exposure, which largely depend on the task performed, and studies with stationary measurements by design ignore the influence of the presence of the human factor.[170] However, given the pervasive nature of the main sources of dust and endotoxin inside livestock buildings (i.e., feeding and bedding materials, animals and their feces), these studies provide useful information on the development of exposure control interventions.

To sum up, studies on potential determinants of personal exposures to dust and endotoxin among livestock farmers have been limited in numbers, especially with concern to cattle farmers. In most cases, the description of the working environment was oversimplified with only few potential influential farm characteristics tested. With the exception of the study of Preller *et al*.,[114] studies reviewing determinants of exposure evaluated the effects of working tasks and stable characteristics on personal exposures separately, thereby ignoring the fact that processes occur under certain working and environmental conditions. However, there is a strong agreement in findings between area and personal exposure studies concerning farm characteristics as ventilation and flooring parameters, as well as feeding and building hygiene practices, supporting the establishment of effective control strategies.

GENERAL DISCUSSION AND CONCLUDING REMARKS

The present paper reviews current and past research on personal exposure to dust and endotoxin among livestock farmers in order to formulate issues and research needs in both an epidemiological and industrial hygiene perspective. It summarizes the accumulated knowledge within the last three decades on the intensity as well as the distribution and sources of variability in personal exposure to these agents among pig, poultry and cattle farmers.

A prime conclusion that can be drawn from the reviewed studies is that no clear downward trend in exposure of livestock farmers is observed. As a result, farmers remain exposed to levels of dust and endotoxin that are potentially harmful for their respiratory health. This has occurred in spite of the 30 years long-running discussion on health effects from farming.[18–20] These results indicate that novel improved methods of exposure control and prevention strategies for these workers are of utmost importance and are urgently required.

Small decreasing trends in exposure cannot be totally excluded, especially when considering the enlargement in production and number of animals in Western countries over the years. However, these passed unnoticed because of other countereffective effects, such as the larger density and ratio of tended animals per worker and potential changes in applied farming practices and technologies used. In fact, although farm enlargement is present on both sides of the Atlantic, actual farm size in terms of acreage or number of animals is generally higher in the US than in European countries. This might explain differences in exposure (Table 1) but it will create further issues in the future, as it, in principle, alters the traditional structure of the industry by decreasing the number of farm owners while increasing the number of farms with employees. Employees will have less intermittent but more permanent exposures. They will also frequently tend to comprise immigrant workers who are generally less informed without a background in agriculture, with barriers in communication and a will to take more risks.[171,172] These further increase the need for effective exposure control and prevention strategies in farm workplaces.

In principle, control of airborne exposures in livestock stables can be achieved through both engineering and administrative methods (e.g., regular cleaning and maintenance of stables, and educational training). However, as well demonstrated by the relatively consistent exposure results in reviewed studies, the implementation of effective engineering or administrative exposure control measures for organic dust exposure in livestock farmers has historically been a challenge. Several methods for reduction of aerosol exposures in pig stables have previously been proposed, including application of ionization, air filtration and sprinkling with oil. In most cases, these methods were evaluated to be non-cost-effective or non-efficient, and thereby remained largely unapplied,[173] although oil sprinkling has been experimentally demonstrated to be both cost-effective and efficient.[173] In the few farms that used the method in our SUS cohort study,[26] the system was not operational due to frequent plugging, resulting in increased needs and costs of maintenance (personal communication with the farmers). Plugging is identified as probably the most important technical issue in relation to the method and further research toward solutions has been suggested.[174] It should also be noted that interventions such as oil-sprinkling and ionization may not be without adverse health consequences of their own. These still have to be adequately evaluated.

In addition, stable construction characteristics and related engineering parameters are governed by requirements for maximum animal productivity that complicate the application of environmental control measures. For example, pig and broiler production requires animals to remain within their zone of thermal neutrality and, thereby, ventilation systems are designed or used primarily to maintain these conditions rather than to remove aerosols or gases. Consequently, increase of ventilation to dilute aerosols even when concentrations are high, as in winter seasons, becomes very expensive and, hence, insufficient.[113]

On top of the previously mentioned, more problems have arisen from the trend in Western countries toward constant intensification of livestock production. This has resulted in rapid changes both in farm structures and used technologies, as well as in processes applied, that have further been complicated by the implementation of new legislations toward improved animal welfare (e.g., Sweden has banned the use of pig gestation crates, which are to be phased out from all European countries by 2013). Given the above complexities and the intermittent working tasks and intense handling of animals and organic materials performed by the farmers, sole interventions on limited engineering parameters might not be sufficient to control exposure for these workers. Any new initiatives toward effective exposure control strategies will require better perceptiveness of factors affecting the personal exposure levels of livestock farmers.

Recently, the use of personal protection equipment (PPE) during selective tasks was highlighted as an alternative toward health protection among workers in pig and beef stables.[175] This recommendation was made in recognition of the consistently reported very low use of PPEs among livestock farmers,[75,92,128] and owing to the demonstrated effectiveness of these devices in reducing exposures and inflammatory responses among healthy wearing individuals.[176–178] The protection level offered by PPEs depends on the suitability of the selected equipment, its proper use, as well as the personal characteristics of the wearer,[179] and farmers are suggested to face difficulties and discomfort when using PPEs.[180] Results from intervention programs suggest education to increase PPE use among farmers, leading to reduced episodes of acute symptoms.[181] However, so far, very little has been done to facilitate such a prevention approach by identifying tasks that increase the levels of dust and endotoxin exposure in livestock farmers (Table 4). In addition, intermittent use of PPEs has been suggested to cause cross-shift inflammatory and respiratory reactions at return to unprotected work.[182]

Besides the high levels of dust and endotoxin exposure, results from the reviewed studies demonstrated high variability of both temporal and personal nature in personal exposure concentrations to dust and endotoxin among livestock farmers. A detailed description of this issue is not within the scope of the present paper. Details and thorough discussions on variability in exposure and its implications, including for studies in farming populations, can be found in previous review papers[145,183,184] In general, the presence of a substantial variability in personal exposure complicates both the acquisition of valid exposure estimates to be used in epidemiological studies and the establishment of effective control and prevention strategies. For the assessment of risks for chronic health outcomes especially, the direct use of the measured concentrations as long-term average exposures will bear the potential for considerable misclassification that will usually tend to attenuate the estimated exposure–response relationships toward the null. To increase accuracy, for example, among pig farmers, a substantial larger number of measurements per worker will be required, but such an approach is hampered by increased logistics and costs. Alternatively, empirical modeling or group-based exposure-assessment strategies could be applied.[185] Then again, a thorough knowledge on the determinants of variability in personal exposure for these workers is required in order to develop the most efficient exposure assignment to be followed within a study. This implies an investigation on the variability distribution using different grouping strategies in order to maximize contrast across groups and acquisition of information on tasks performed by farmers for several days, as done by Preller *et al*.[146]

In conclusion, studies on the personal exposure of livestock farmers to dust and endotoxin performed within the last 30 years have been heterogeneous in design. Their results suggest the working environments within stables to remain largely uncontrolled and direct toward a need for innovation of new methods of controlling dust and endotoxin exposure within stables. The wealth of knowledge on exposure determinants can facilitate such an approach. The effectiveness of new methods of exposure control can be tested in studies with an interventional design where potential production and animal-health side effects could also be evaluated. A wider adaptation of proven methods of exposure reduction (e.g., ionization, spraying with oil, etc) should also be encouraged and educational training of farmers should be provided. Finally, better reporting and standardization of measurement methods for dust and endotoxin exposure is required both for comparisons between epidemiological study results and the establishment of valid health-based exposure limits, as well as for the use of the measurement results in future retrospective epidemiological studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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