Review

**Occupational Endotoxin-Exposure and Possible Health Effects on Humans**

Verena Liebers, PhD,* Thomas Brüning, MD, and Monika Raulf-Heimsoth, PhD

**Background:** Endotoxins are commonly found at workplaces where large amounts of bioaerosols are generated. In Germany, especially since the Ordinance on Safety and Health Protection related to work involving biological agents (Biostoff-Verordnung) became effective (1999), threshold limit values are widely discussed. Up to the present, endotoxin values are measured with non-uniform methods and therefore values are of limited benefit for classification of exposure groups. In Germany there is no threshold limit value for endotoxin.

**Methods:** Relevant literature of the last 20 years was selected from Medline and discussed.

**Results:** In this review we focused on the impact of endotoxin exposure on human health with special respect to the measurements on workplace and methodological aspects of endotoxin determination. Methods for sampling and endotoxin determination have to be validated, optimized, and standardized first.

**Conclusion:** The adverse health effects of endotoxins are known, standardization of measurements is a necessary goal and protection measures should be established immediately. Am. J. Ind. Med. 49:474–491, 2006. © 2006 Wiley-Liss, Inc.

**KEY WORDS:** bioaerosols; endotoxin; health effects; LAL-test; occupational exposure

**INTRODUCTION**

Airborne and settled particulate material of biological origin is often referred as organic dust. Organic dust exposures may vary qualitatively from one occupational setting to another [Heederik et al., 2000]. Apart from the general inconvenience caused by dust, it can have adverse effects on human health induced by inhalation, skin and/or eye contact, or ingestion. Harmful effects will be dependent of the dust composition and the degree and duration of exposure. The Health and Safety Executive in Germany distinguishes between two size dust fractions when setting limits for total inhalable and respirable dusts. Total inhalable dust approximates to the fraction of airborne material, which enters the nose and mouth during breathing and is therefore available for deposition in the respiratory tract. Respirable dust approximates to that fraction which penetrates to the gas exchange region of the lung. The respirable dust fraction comprises normally between 5% and 10% of total dust. Endotoxins are associated with dust particles in many environments. Studies which differentiated inhalable and respirable dust fractions, described that endotoxin was found in both fractions but with predominance in the inhalable fraction [Mandryk et al., 1999; Nieuwenhuijsen et al., 1999; Donham et al., 2000].

Endotoxins are integral components of the outer membrane of Gram-negative bacteria and are composed of...
proteins, lipids, and lipopolysaccharides (LPS). LPS of Gram-negative bacteria is an amphiphilic, heat-stable, and water-soluble macromolecule responsible for most of the biologic properties of bacterial endotoxins. Toxicity is associated with the lipid component (lipid A, a phosphoglycolipid) and immunogenicity is associated with the polysaccharide component of the LPS-molecule. The hydrophilic polysaccharide moiety is composed of O-specific side chains and core sugars. The composition of O-specific chains varies considerably between bacterial species [Heederik et al., 2000]. Endotoxins have been detected in such taxonomically remote groups of Gram-negative bacteria as Enterobacteriaceae, Pseudomonadaceae, and Rhodospirillaceae but have not been found in cell walls of Gram-positive bacteria, mycobacteria, or fungi. Even though most of the biological effects can be reproduced by purified LPS, it is not correct to assume that this term is always preferable to the term “endotoxin” in defining biological responses to this bacterial product. However, the term “endotoxin” is often used as a synonym for “lipopolysaccharides” and vice versa [Heederik et al., 2000; Martin, 2000].

Endotoxin exposure at workplaces has been linked to fever, cough, shortness of breath, wheezing, headache, nose and throat irritation, chest tightness, acute airway flow restriction, and inflammation [Burrell and Ye, 1990; Heederik et al., 1991; Douwes and Heederik, 1997]. Response to endotoxin varies with dose, location, route, and time of release in the blood. Endotoxin can increase disease severity by acting as a natural adjuvant to augment asthma and atopic inflammation or may act on its own, causing adverse effects on lung function and inflammatory responses. Epidemiological studies showed protective effects of environmental endotoxin exposure with regard to atopic asthma and allergy development in early childhood [von Mutius et al., 2000; Remes et al., 2003]. This is consistent with one aspect of the “hygiene hypothesis,” describing microbial exposures or infections associated with a lower incidence of atopic disease. The hygiene hypothesis has been proposed as possible explanation for the increasing prevalence of allergic diseases in the western world over the last decades. Reduced microbial stimulation of Toll-like receptors in early life may lead to a stronger Th2 response to allergens. The individual immunological response is determined by the interplay between the dose and timing of exposure to endotoxins, other environmental factors and genetic pre-disposition [Vandenbulcke et al., 2005]. Another positive effect of endotoxin is assumed in the context of cancer: reduced cancer rates in agricultural workers may be a benefit of endotoxin exposure, stimulating the immune system [Lange, 2000]. Furthermore, endotoxin and microbial components are necessary for the development of an intact immune system (microbial pressure). Therefore the nature of endotoxins is somehow paradoxical [Liu, 2002; Radon, 2006].

CELLULAR MECHANISMS FOLLOWING ENDOXOIN CONTACT

During inhalation airways are permanently in contact with bacteria and their “pathogen-associated molecular patterns” (PAMPs). Organic dust often is burdened with high amounts of these factors like endotoxins and their components [Beutler and Rietschel, 2003]. After deposition in the airways, endotoxins may interact with macrophages. This process is accelerated by the binding of LPS to lipopolysaccharid-binding protein (LBP), which is present in the fluid on the airway surface and is part of the unspecific immune defense. Together with other proteins, LBP has the task to transport foreign substances to the site of metabolism and destruction, for example, monocytes and macrophages. Macrophages (in the lung) and monocytes (in the blood) carry the cell surface protein CD14 to which the LBP–LPS complex attaches (Fig. 1). In addition, supported by factors like CD14 and the accessory protein MD2, the signal of LBP-LPS attachment may be delivered to the Toll-like receptor TRL4 [O’Neill, 2004; Alexis et al., 2005]. Furthermore soluble CD14 (sCD14) allows epithelial or dendritic cells to bind endotoxin in spite of the fact that they do not express CD14. After internalization of endotoxin, a complex signal transduction cascade is activated coupling to NF-κB and results in the expression and production of a variety of inflammatory mediators, particularly IL-1β, TNF-α, and IL-6 [Douwes et al., 2002; Liu, 2002; Rylander, 2002]. LBP can be displaced by the bactericidal-permeability-increasing protein (BPI), released from activated neutrophils. Therefore, several bioactive molecules involved in the LPS activation cascade may be a valuable marker for the internal (bio)monitoring of endotoxin effects (LBP, BPI, cytokines, CD14). In addition, the interaction of LPS with monocytes and the induction of cytokine release (especially IL-1β and IL-16) may be useful tools to measure endotoxin activity ex vivo.

THRESHOLD LIMIT VALUES

The European Union has consistently endeavored to ensure a high level of safety and health protection against risks related to chemical agents at work. Several directives have been adopted by the Scientific Committee on Occupational Exposure Limits (SCOEL) to achieve this objective. Exposure limits for dangerous substances in a working environment play a major part in the control of occupational diseases.

In Germany, the Technical Rules for Hazardous Substances (TRGS) [Technische Regeln für Gefahrstoffe, 2001] describes substances with respect to the current status of knowledge about health hazards, typical industrial application, safety, and hygiene requirements. Although TRGS refer
to German control equipment, they are in agreement with most EU-guidelines. They are based on the Hazardous Substances Ordinance (GefStoffV), which is derived from the Chemicals Act (ChemG). All exposure limit values are consistent national values based on common national legislation. The Federal Ministry of Labour and Social Affairs publishes new or revised limit values every 6 months. Limit values for airborne dust at the workplace are published in TRGS 900.

Dust exposure at the workplace has to be controlled for protection of the employees. The current dust limit value is 6 mg/m³ for respirable dust and 10 mg/m³ for inhalable dust (TRGS). For wood dust the airborne exposure limit is set for the EU member states at 0.5 mg/m³ although some authors maintain that this value is not reasonable due to the lack of validated study designs supporting it [Schulze et al., 2003]. The National Health Council of the Netherlands (DECOS) has proposed a health-based recommended threshold value for endotoxin of 50 EU/m³ (endotoxin units, EU), which equals 5 ng/m³, using the reference standard endotoxin E.coli-5 (EC-5). This decision was mainly based on the study of Castellan et al. [1984, 1987] who showed a no-effect-level (NEL) of 90 EU/m³ for healthy subjects in a 6-hr work exposure. Calculating a safety factor for risks of certain workers they agreed to 50 EU/m³. In a next step the Social and Economic council (SER) in the Netherlands introduced a threshold limit value of 200 EU/m³ (which equals 20 ng/m³). It was planned to establish the occupational exposure limit of 50 EU/m³ step by step. However, various studies showed that even this higher value of 200 EU/m³ still exceeds at several workplaces [Wouters, 2003]. In many occupational settings, different potential biological agents exist in the dust at workplace atmosphere, which may lead to similar health effects or to effects that can either strengthen or weaken each other (synergistic). Only in a few cases interaction of components and their impact have been described. For example in pig farming, low levels of endotoxin can lead to inflammatory response of the airways, because of chronic exposure to ammonia and detergents and the risk of extremely high exposures to H₂S. Further problems arise as information is collected only from a limited number of industries with exposure to complex mixtures. Data of health effects cannot be extrapolated from one industry to another. Therefore, further studies are necessary if useful threshold
DETERMINATION METHODS OF ENDOTOXIN are unknown. Therefore reliable values, which cause defined symptoms, is based on different methods, which yield different results. et al., 2002]. A main problem is that endotoxin measurement limit values for endotoxin should be established [Heederik b 1 pg/ml–10 ng/ml). The action of Limulus polyphemus clotting enzyme present in the lysate of haemolymph of the Limulus amoebocyte may cause pyrogenic side effects [Trivedi et al., 2003]. The LAL-assay is adapted as the standard assay for endotoxin detection by the American Food and Drug Administration in 1980. Three methodic types of the LAL-test for a quantitative endotoxin measurement exist: turbidimetric (measuring turbidity), chromogen-kinetic (measuring color change over time due to enzymatic turnover of substrate), and the endpoint assay (measuring gel clotting). Especially the chromogen-kinetic versions of the LAL-assay are very sensitive and have a broad measurement range (approximately 0.01–100 EU/ml ≈ 1 pg/ml–10 ng/ml). The action of β-glucan and endotoxin is similar. Therefore LAL-test is used for endotoxin as well as β-glucan determination. In the latter case factor C is blocked. Since LAL-test gives no information, whether the measured endotoxin has any impact on humans, further methods are of interest. To measure endotoxin exposure of humans several parameters may be evaluated: concentrations of proteins involved in human endotoxin metabolism like LBP, CD14, or other receptors; inflammatory cytokines, which were released after activation of macrophages/monocytes via LPS, for example, IL-1β and IL-6. A test, which is based on the quantification of released cytokines after blood cell stimulation is the so-called in-vitro pyrogen test (IPT), a modification of the “whole blood assay” concept. Therefore peripheral blood cells (whole blood without cell separation) are incubated with aliquots of sample material potentially containing endotoxin, for example, filter extracts and for standard endotoxin in various concentrations. The amount of the released cytokines IL-1β or IL-6 is quantified in the cell-free supernatant. Extrapolation in the semi-quantitative way of cytokines released by incubation with the endotoxin standard concentration is possible. In the IPT, cytokines are measured which are directly involved in pyrogen reaction in humans. However, the test is difficult to standardize because fresh blood from healthy subjects has to be collected and this varies from donor to donor and the ability to release cytokines is individually different [Wouters et al., 2002]. So far LAL-Test and especially IPT are not internationally standardized and results vary between different labs. However, a European norm for measurement of endotoxin is based on LAL-Test [BGIA-Arbeitsmappe, 1989; DIN EN 14031, 2003]. Environmental monitoring of endotoxins is usually performed by sampling airborne dust and subsequent aqueous extraction. An airflow is constituted by pumps and dust sampled on filters. Several types of filter materials are commonly used for endotoxin sampling: cellulose, polyvinylchloride (PVC), glass fiber, Teflon, or polycarbonate.

Chromogen kinetic or turbidimetric LAL-test using glass fiber filters and Tween buffer (0.05%) for extraction are recommended by DECOS [1998]. However, several working groups avoid Tween as the detergent induces side effects influencing the measurement with LAL-reagent.

ENDOTOXIN EXPOSURE IN DIFFERENT ENVIRONMENTS

Although endotoxins are nearly ubiquitous, not each dusty area has high endotoxin levels. Several workplaces have been studied and Table I summarizes mainly data concerning endotoxin exposure at the workplace and health effects. Studies indicating information about study population, dust-, and endotoxin-measurement were preferentially integrated. Endotoxin measurement in all studies mentioned was performed with LAL-test. However, different protocols of this test were used. Additional differences arise by dust sampling, dust filter, and flow rates during sampling and dust extraction.

Agricultural Work

Agricultural environments are characterized by high concentrations of endotoxin exposures [Schwartz et al., 1995; Baur et al., 2003]. From these areas results arise, indicating that the time point of endotoxin exposure during development of the immune system plays an important role with regard to health effects. Studies by von Mutius et al. [2000] revealed that children living in traditional farmhouses in Bavaria, Switzerland, and Austria with high endotoxin exposure are protected against allergies later in their life. However, studies focusing on the working population showed predominantly adverse health effects induced by endotoxin (Table I). Within a 3-year follow-up study in 171 pig farmers a high decrease of forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) was found which is associated with endotoxin exposure. Total dust exposure was associated with decreased FVC only. These results did not differ between symptomatic and asymptomatic workers [Vogelzang et al., 1998].

A longitudinal study [Nieuwenhuijzen et al., 1999] with workers of 10 California farms revealed that the level of exposure to dust and endotoxin varied dependent on the type of working activity. Measurement was performed when farmers harvest fruits and vegetables, are engaged in poultry farming, or in the agricultural environment.
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<td>Baur et al. [2003]</td>
<td>Review of two cases and current literature to gain dust-induced asthmatic reactions; report</td>
<td>Two case reports</td>
<td>n.i.</td>
<td>LAL-test</td>
<td>5 – 935 EU/m³</td>
<td>50 EU/m³</td>
<td>A remarkable reduction of exposure to dust with high levels of airborne endotoxin in agriculture has to be achieved since in many workplaces corresponding exposures are still rather high.</td>
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<td>Nieuwenhuisen et al. [1999]</td>
<td>To measure personal related dust, ET- and silica-exposure during agricultural exercises</td>
<td>Dust sampling</td>
<td>Workers of 10 farms in California, in each case 8 times tested 142 samples (inhalable), 144 samples (respirable)</td>
<td>Personal sampling: 10 11 dust sampler with PVC-filter (5 μm pores), air flow ca. 2 L/min LAL-test (Kinetic QCL, Whittaker)</td>
<td>1.5 – 103 EU/m³ (mean values)</td>
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<td>Level of exposure varied dependent on workplaces (highest exposure at cotton cleaning and vegetable harvest), duration of exposure plays an important role.</td>
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<td>NIOSH [1994]</td>
<td>To describe risk for OOTs in farmers</td>
<td>Dust samples/medical examination</td>
<td>Case reports with OOTs (n = 29)</td>
<td>—</td>
<td>244 – 16,300 EU/m³</td>
<td>Preventive measures recommended</td>
<td>Limit values, which are suggested for cotton workers, farmers or woodworkers are not appropriate for workers who handle organic dust; to lower the risk for workers different proposals are given, for example, to use ventilation.</td>
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<td>Reynolds et al. [2002]</td>
<td>To evaluate the execution of the LAL-test in six different laboratories using dust from three agricultural companies</td>
<td>Dust samples from poultry farms, pig farms and animal food production</td>
<td>Six laboratories are involved for testing</td>
<td>3 g dust + 30 ml PBS, 1hr shake Three laboratories used the QCL-1000 end point test, three the kinetic QCL-test (each with one Lot)</td>
<td>37.19 – 76.4 EU/m³</td>
<td>n.i.</td>
<td>Different results arise between the laboratories, probably because of the different extraction and analytical methods.</td>
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<td>Simpson et al. [1999]</td>
<td>To operate valid data regarding dust- and ET-exposure</td>
<td>Dust sampling</td>
<td>259 samples of 9 different workplaces (textile branch, agriculture, animal industry)</td>
<td>Personal sampling, gravimetric analysis of the dust exposure, water extraction from the dusts LAL-test (quantitative turbidimetric method)</td>
<td>50 – 6,936 ng/m³ (5 – 63,360 EU/m³)</td>
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<td>Dust exposure in many industries is higher than the “set exposure standards;” highest exposures are found during cleaning activities and animal handling.</td>
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<td>Vogelzang et al. [1998]</td>
<td>To identify the relationship between long-term ET-exposure and lung function decline</td>
<td>Questionnaire, lung function; 171 pig breeder</td>
<td>Long-term-average exposure to ET 105 ng/m³ (1050 EU/m³)</td>
<td>Within a 3-year follow-up a high decrease of FEV₁ and FVC is found which is associated with ET-exposure</td>
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<td>Schwartz et al. [1995]</td>
<td>To identify the role of ET in grain-dust induced lung disease</td>
<td>Population-based cohort study, health evaluation by questionnaire and spirometry; 410 grain worker, 201 postal worker</td>
<td>LAL-test (chromogen) 83.2 ± 2779 EU/m³ (respirable) 2858.7 ± 7208 EU/m³ (total)</td>
<td>Grain workers had a significantly higher prevalence of work-related respiratory symptoms (concentration of ET in the bioaerosol may be important)</td>
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<td>Donham et al. [2000]</td>
<td>To determine dose-response relationships between bioaerosol-exposure and airways</td>
<td>Questionnaire, spirometer, lung function, measurement of ammonia exposure; 257 poultry worker, controls: 111 post officers, 39 employees</td>
<td>LAL-end point determination (QCL-1000) 614 EU/m³</td>
<td>Significant dose-response relationships between bioaerosol exposure and decrease of lung function during work shift</td>
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<td>Hagmar et al. [1990]</td>
<td>To investigate changes of exposure to organic dust and ET in poultry slaughterhouses during work shift</td>
<td>Questionnaire, lung function, blood collection pre- and post-shift; measurement of complement factors in the sera; 23 poultry slaughters</td>
<td>LAL-test 0.02 – 1.50 µg/m³ (200 – 15,000 EU/m³)</td>
<td>Increase of respiratory symptoms during shift; significant association between poultry dust and ET</td>
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<td>Heederik et al. [1991]</td>
<td>To clarify relationship between airway disease, lung function and ET levels in pig farms</td>
<td>Spirometry; determination of ammonia; cross-sectional study; 183 pig breeder of 136 farms</td>
<td>LAL-test (KabiVitrum) Divided into three groups: under 100 ng/m³, 100 – 200 ng/m³, &gt; 200 ng/m³ (1000 – 2000 EU/m³)</td>
<td>Negative correlation between ET-exposure and FEV₁ in a subgroup of 62 farmers</td>
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<td>Smid et al. [1992]</td>
<td>To analyze the relationship between organic dust exposure, airway disease and chronic lung function changes</td>
<td>Questionnaire, lung function</td>
<td>315 animal food workers in 14 animal food mills, therefrom 50 internal controls from the animal food mills but without dust exposure as well as 125 external control persons (other areas without dust exposure)</td>
<td>Personal sampling; 8-hr dust measurement</td>
<td>LAL-test</td>
<td>0.2  — 470 ng/m$^3$(2 — 4,700 EU/m$^3$)</td>
<td>n.i.</td>
<td>Higher correlation of ET to lung function decrease than to dust-exposure; ET is an important factor in the development of airway diseases</td>
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<td>Bueng er et al. [2000]</td>
<td>To clarify the correlation of immunological markers, health problems and biowaste exposure</td>
<td>Biowaste samples concerning actinomycetes (ELISA)/ sera concerning antibodies against fungal antigens (specific IgG)</td>
<td>151 biowaste worker/40 controls (new employed workers)</td>
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<td>While no difference between biowaste workers and controls regarding health effects exists, compost worker reveal significantly more symptoms and airway diseases; furthermore they showed significant increased antibody concentrations against fungi (aspergillus, penicillum) and actinomycetes</td>
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<td>Gladding et al. [2003]</td>
<td>To determine health effects among recycling workers</td>
<td>Total dust, ET, b-glucan, blood (cell count, total IgE)</td>
<td>159 employees from nine material recovery facilities</td>
<td>Personal sampling; total dust measurement for 4 hr; 2 L/min air flow; polycarbonate filter (37 mm/0.8 μm)</td>
<td>LAL-test (kinetic)</td>
<td>0.19  — 198 ng/m$^3$(19 — 1,980 EU/m$^3$)</td>
<td>&quot;no-effect-level&quot; of 10 ng/m$^3$(100 EU/m$^3$)</td>
<td>Workers exposed to higher levels of ET and b-glucan at their workplaces exhibit various work-related symptoms; the longer a worker is in this environment, it is more likely that he becomes affected by various symptoms</td>
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<td>Hansen et al. [1997]</td>
<td>To clarify the risk of respiratory symptoms among waste collectors</td>
<td>Questionnaire/job exposure matrix (JEM)</td>
<td>1,515 Danish waste collectors; 423 controls (civic employees in parks)</td>
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<td>Waste collectors show a slightly increased prevalence of airway disease compared to controls; increased concentrations of microbiological parameters were accompanied of an increased prevalence of bronchitis</td>
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<td>Laitinen et al.</td>
<td>To evaluate exposure of waste water workers to bacteria and ET</td>
<td>Sampling of airborne bacteria and ET; questionnaire</td>
<td>Sampling at nine waste water treatment plants; investigation of 16 male waste water workers</td>
<td>High levels of exposure to bacteria and ET are related to certain phases of the treatment process; in these fields it is necessary to control and reduce exposure to bacteria and ET</td>
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<td>Mahar et al.</td>
<td>To evaluate workers exposure in refuse-derived fuel plants</td>
<td>Measuring of particulates, ET and bioaerosols</td>
<td>Seven workers/shift at two plants (total n = 35)</td>
<td>The tasks of cleaners and mechanics should receive priority for periodic air monitoring as they had large exposures</td>
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<td>Marth et al.</td>
<td>To determine heath risk to employees of waste treatment facilities</td>
<td>Spirometry, total IgE, blood sugar</td>
<td>117 employees from five different companies, control group from the office (25 women, 18 men)</td>
<td>No significant correlation between duration of employment, IgE and lung function; the highest risk for disturbances existed for the mucosa of the airways (OR 2.938), the lowest for asthma (OR 0.817)</td>
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<td>Prazmo et al.</td>
<td>To measure the exposure to fungi, bacteria and ET in a sewage treatment plant</td>
<td>Stationary dust sampling, measurement of bacteria and fungi</td>
<td>12 air samples in a Polish sewage treatment plant</td>
<td>20 pathogenic fungi- and bacteria-species were found; mentioned limit values for bacteria and ET were not exceeded</td>
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<td>Smit et al.</td>
<td>To investigate work-related symptoms</td>
<td>Questionnaire, measurement of personal ET-exposure</td>
<td>468 employees from 67 sewage treatment plants</td>
<td>ET seems to play a causal role for work-related symptoms</td>
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<td>Thorn et al.</td>
<td>To evaluate different measurement strategies for determination of ET</td>
<td>Measurement of airborne ET</td>
<td>Working sewage plants in three municipalities in Sweden</td>
<td>ET exposure in sewage plants is complex, level of exposure depends on activities</td>
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<td>Thorn et al.</td>
<td>To clarify the relationship of β-glucan, ET and airway inflammation in household waste collectors</td>
<td>Questionnaire, sera and sputum collection, dust samples</td>
<td>17 waste worker (household), 8 waste worker (organic waste), 24 controls (office)</td>
<td>Dusts from household waste can cause airway inflammations, the effects are associated with higher (1–3) β-glucan exposures</td>
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<td>Wouters</td>
<td>To investigate health effects in association with bioaerosol exposure</td>
<td>Determination of dust, endotoxin and β-glucan; questionnaire</td>
<td>166 compost workers from 57 composting plants</td>
<td>Respiratory symptoms were more prevalent in compost workers than in general population</td>
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<td>Castellan et al. [1984]</td>
<td>To investigate cotton dust exposure and lung function (FEV₁)</td>
<td>Cotton exposure, fungi-, bacteria-dust-, ET-determination, spirometry, questionnaire</td>
<td>54 volunteers (simulation of workplace-related conditions)</td>
<td>37 mm PVC-filter in the exposure chamber; filter-elution with pyrogen-free water</td>
<td>LAL-test (spectrophotometric modified, Pyrostat)</td>
<td>n.i. (just correlations ET/FEV₁ quoted)</td>
<td>n.i.</td>
<td>Correlation between FEV₁ modification and fungi/bacteria dust/ET (highest correlation for ET); ET plays an important role in the acute lung reaction to cotton dust exposure</td>
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<td>Castellan et al. [1987]</td>
<td>To clarify relationship between ET-exposure, airway disease and cotton dust</td>
<td>Cotton exposure, spirometry (workplace simulation)</td>
<td>108 sittings with each 32 different cotton species and each 24 to 35 persons</td>
<td>Dust-air sampling for 6 hr continuously</td>
<td>LAL-test modified</td>
<td>6–779 ng/m³ (60–7790 EU/m³)</td>
<td>9–33 ng/m³ (90–330 EU/m³)</td>
<td>Significant dose-response relationship between ET-concentration and median modification of FEV₁; stronger correlation in the high exposure group compared to the low exposed group</td>
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<td>Christiani et al. [1999]</td>
<td>To identify the relationship of long-term cotton dust exposure, ET and lung function in Chinese textile workers</td>
<td>Questionnaire, lung function</td>
<td>374 cotton and 392 textile workers from Shanghai</td>
<td>Stationary sampling</td>
<td>LAL-test (chromogen, kinetic-QCL; Bio-Whittaker)</td>
<td>27–12,038 EU/m³</td>
<td>n.i.</td>
<td>Chronic airway disease is more associated with cotton dust exposure than with ET exposure; significant effects of cotton dust exposure on FEV₁ decrease</td>
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<td>Kennedy et al. [1987]</td>
<td>To study relationship of ET-exposure and lung function of cotton textile workers</td>
<td>Questionnaire, lung function</td>
<td>443 cotton workers from 2 factories, 439 controls from silk factories</td>
<td>Stationary sampling; sampling for 3–7 hr; particle &lt;15 µm are collected</td>
<td>LAL-test (Pyrostat-50); extraction with sterile, pyrogen-free water</td>
<td>0.002–0.55 µg ET/m³ (20–5,500 EU/m³)</td>
<td>Health effects at &lt;20 ng/m³ (200 EU/m³)</td>
<td>Dose-response relationship between ET-exposure and FEV₁, prevalence of bursitis and chronic bronchitis (except for highest exposure group)</td>
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<td>Nordness et al. [2003]</td>
<td>To report the development of EAA and humidifier fever in workers of a nylon factory after ET exposure; to investigate the correlation of humidifier antigens, ET and lung function</td>
<td>Lung function, IgE, questionnaire, specific provocation with ET</td>
<td>55 exposed symptomatic patients, 19 asymptomatic workers, five controls</td>
<td>Biomass from the humidifier extracted with phenol</td>
<td>LAL-test</td>
<td>Inhalation of the patients with 2 ng/ml Endotoxin for 10–15 min (20 EU/ml)</td>
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<td>Inhalation challenge with Cytophaga-ET isolated from the air-conditioning system caused fever and leukocytosis in all subjects tested</td>
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<td>Rylander et al. [1985]</td>
<td>To compare lung function before and after work shift and identify the relationship to dust and ET-levels</td>
<td>ET-extracts from cotton samples/lung function, Three groups with each four to six persons, One gram of the cotton samples of different workplaces extracted, LAL-test</td>
<td>0.28–8 μg/m³ (2.800–80000 EU/m³) — Dose-response relationship between ET-exposure and symptoms of byssinosis, increase of neutrophils</td>
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<td>Wang et al. [2002]</td>
<td>To clarify the correlation of textile dust and lung diseases at non-smokers</td>
<td>Questionnaire, spirometry, 225 textile workers, Stationary sampling: 27 mm PVC-filter, 6-hr sampling, LAL-test (chromogen)</td>
<td>0.25–759 ng/m³ (25–7590 EU/m³) n.i. Respiratory symptoms are the first answer to cotton exposure; 1 year after exposure changes in lung function are detectable</td>
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**Wood processing industry**

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<td>Alwis et al. [1999a]</td>
<td>To review exposure to organic dust in wood industry (Australia)</td>
<td>Dust sampling, questionnaires, 195 lumberjacks of four different lumberjack places; 34 controls (office), 6–8 hr personal dust sampling; polycarbonate filter (25 mm, 0.8 μm); [β-glucan determination; filter elution in 2.5–20 ml ET-free water for 60 min at room temperature, centrifugation 10 min/1000 g, LAL-test (quantitative chromogen end point), standard E.coli 011B4</td>
<td>1.3–91.1 EU/m³ 20 ng/m³ (200 EU/m³) Respiratory symptoms were significantly increased in workers compared to controls; ET-exposure was associated with lung and β-glucan exposure; mean ET-exposure was lower than the suggested limit value of 20 ng/m³</td>
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<td>Alwis et al. [1999b]</td>
<td>To review wood dust exposure in New South Wales (Australia), evaluation of control strategies to lower dust exposure</td>
<td>Dust monitoring at different workplaces, Four different, randomized wood processing companies, overall 182 dust samples collected, Personal dust sampling (inhalable); 6–8 hr collection with flow rate of 2 L/min, LAL-test (quantitative chromogen)</td>
<td>— — n.i. The overall geometric mean of personal inhalable dust exposure was 2.1 mg/m³, 62% of exposures exceed standards; equipments for protection are used insufficiently</td>
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<td>Dennekamp et al. [1999]</td>
<td>To determine if lumber mill workers were exposed to hazardous levels of airborne ET</td>
<td>Dust sampling, 216 personal ET samples in four lumber mills, Personal sampling, 3.5 L/min, Teflon filter extraction in 20 ml buffer for 1 hr; centrifugation 1000 g for 10 min, LAL-test (quantitative chromogen Bio-Whittaker), standard: E.coli 011B4</td>
<td>0.25–347.5 ng/m³ (2.5–347.5 EU/m³) n.i. Factors related to the personal ET-exposure are job-type, use of compressed air, dust concentration and time period, spent in a booth or cab during a shift</td>
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TABLE I. (Continued)

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<td>Dutkiewicz et al. [2001]</td>
<td>To evaluate exposure to airborne microorganisms in polish saw mills</td>
<td>Dust sampling</td>
<td>Four sawmills</td>
<td>Stationary sampling, 20 L/min; PVC filter, extraction in 10 ml pyrogen-free water, heating 100°C/15 min</td>
<td>LAL-test (Pyrotell)</td>
<td>0.24 and 4 ng/m³ (2,880 and 48,000 EU/m³; 1 ng = 12 EU)</td>
<td>n.i.</td>
<td>Workers in saw mills maybe exposed at some workplaces to airborne microorganisms (including ET-producing bacteria) posing respiratory hazards</td>
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<td>Mandryk et al. [1999]</td>
<td>To determine the wood dust exposure effects to lung function, ET, [3]-glucan, bacteria and fungi within the scope of wood processing</td>
<td>Lung function; questionnaire pre- and post-shift</td>
<td>Employees of four sawmills, five joineries and one woodchipping mill (in total 168 men), 30 controls from the office</td>
<td>Personal sampling; dust collection 6—8 hr; polycarbonate filter (25 mm, 0.8 μm Millipore)</td>
<td>LAL-test (chromogen quantitative end point), standard E.coli 0111:B4</td>
<td>Median 0.37—9.1 ng/m³ (3.7—91 EU/m³)</td>
<td>n.i.</td>
<td>Significant association of decreased FVC and nose obstruction/phlegm; compared to controls, the lung function decrease after work was higher in wood workers; wood dust is a possible health risk and should be controlled</td>
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<td>Carvalheiro et al. [1994]</td>
<td>To investigate brewery worker with respect to ET exposure</td>
<td>Dust sampling at workplaces, investigation of workers</td>
<td>28 male brewery worker, 42 non-exposed office workers</td>
<td>Stationary sampling</td>
<td>n.i.</td>
<td>0.06—0.927 μg/m³ (600—9,270 EU/m³)</td>
<td>n.i.</td>
<td>Mucous membrane irritation and OATS are more prevalent in brewery workers and may be caused by ET</td>
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<td>Forster et al. [1989]</td>
<td>Investigation of organic aerosols generated during sugar beet slicing</td>
<td>Dust sampling; specific IgG determination</td>
<td>Three dust samples; 15 workers</td>
<td>Stationary sampling, extraction in 5 ml pyrogen-free water</td>
<td>LAL-test (Sigma)</td>
<td>2.5—32 ng/m³ (25—320 EU/m³)</td>
<td>n.i.</td>
<td>There was a considerable contamination by biologically active material in the atmosphere around the beet slicers; installation of exhaust ventilation reduced the airborne concentration of microorganisms remarkably</td>
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<td>Kullman et al. [1988]</td>
<td>To characterize exposure to organic dust during work in dairy barns</td>
<td>Dust sampling</td>
<td>101 farmers in 85 barns</td>
<td>Personal and stationary sampling</td>
<td>LAL-test (chromogen-kinetic)</td>
<td>254—34,800 EU/m³</td>
<td>n.i.</td>
<td>Dairy farmers are exposed to organic dusts containing many toxic and immunogenetic constituents, which may be risk factors for respiratory diseases</td>
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<td>Larinen et al. [1999]</td>
<td>To evaluate workers exposure to microbes and bacterial ET during the use of metal-working fluids</td>
<td><strong>Air and bulk sampling</strong> 18 workplaces; 25 workers <strong>Personal and stationary sampling</strong> 37 mm glass fiber filter; 2 L/min, extraction in 10 ml pyrogen-free water for 60 min; centrifuged at 1000 rpm for 10 min <strong>LAL-test (KabiVitrum Diagnostica)</strong> 0.03 – 25,000 ng/m³ (0.03 – 30,000 EU/m³); 1 ng = 12 EU</td>
<td>In occupational hygiene measurements ET serves as excellent indicators of exposure to the microbial contaminations of machine working fluid</td>
<td>Low dust and ET-values are found; prevalence of 7.7% for occupational asthma</td>
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<td>Monso et al. [2002]</td>
<td>To determine the prevalence of work-related asthma and sensitization against work place-allergens for arborium-flower breeder</td>
<td><strong>Dust sampling</strong> 39 plant breeder in arboriums <strong>Personal sampling with glass fiber filters and constant air flow</strong>  <strong>LAL-test (KabiVitrum)</strong> 0.03 – 0.89 ng/m³ (ET in the total dust) (1.7 to 8.9 EU/m³)</td>
<td>n.i.</td>
<td>The reduction of “tramp oil” the use of synthetic fluids and the control of temperature and pH could contribute to reduce the ET-exposure in catchment tanks of metal work fluids</td>
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<td>Park et al. [2001]</td>
<td>To measure ET-concentrations in metal processing fluids, identification of interacting factors</td>
<td><strong>Sampling from the machine fluid</strong> 140 machines <strong>Supernatant of metal working fluids transferred to pyrogen-free water</strong>  <strong>LAL-test (kinetic turbidimetric; BioWhittaker, pyrogen-5000)</strong> 6.791 EU/ml (median)</td>
<td>n.i.</td>
<td>The highest ET and dust concentrations are found during handling and weighing of raw tobacco; humidifier were a higher source of microbes than tobacco; in summary, microbial contamination was not as high as described to induce EAA</td>
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<tr>
<td>Reiman and Uitti [2000]</td>
<td>To determine the risk of respiratory symptoms in cigarette factories caused by microbes and ET</td>
<td><strong>Air samples, total dust-, microbial determination</strong> One cigar and two cigarette-factories <strong>Stationary sampling (20 – 30 cm of the respiratory zone of the workers). Flow rate 29 L/min; sterile Millipore-filter, pore size 0.45 μm</strong>  <strong>LAL-test (modified spectrophotometry; KabiVitrum)</strong> Cigar production max 38 ng/m³ (380 EU/m³); cigarette production max 1060 EU/m³</td>
<td>4.5 or 10 ng/m³ (45 or 100 EU/m³)</td>
<td>The reduction of “tramp oil” the use of synthetic fluids and the control of temperature and pH could contribute to reduce the ET-exposure in catchment tanks of metal work fluids</td>
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<td>Sigsgaard et al. [2004]</td>
<td>To reveal if lung function decrease was associated with work at a paper mill</td>
<td><strong>Examination of workers; measurement of dust, ET, microorganisms</strong> 97 male paper workers, 55 control workers <strong>7 hr personal dust sampling, 37 mm filter (8 μm pore size)</strong>  <strong>LAL-test (chromogen-kinetic)</strong> 6 – 370 EU/m³</td>
<td>200 EU/m³</td>
<td>Annual loss of lung function in exposed workers does not increase if workers have ET-exposures below 200 EU/m³</td>
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<tr>
<td>Teeuw et al. [1994]</td>
<td>To evaluate the role of Gram-negative bacteria and ET in sick building syndrome</td>
<td><strong>Microbiological assessment; questionnaire</strong> 1,355 employees in 19 governmental office buildings <strong>Stationary sampling: samples heated for 30 min (100 °C)</strong>  <strong>LAL-test (CapeCod)</strong> 27 – 800 ng/m³ (270 – 8,000 EU/m³); 9 – 33 ng/m³ (90 – 330 EU/m³)</td>
<td>Airborne microbial contaminations including ET may play a role in the causation of sick building syndrome</td>
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farming, or work with dairy cows. The highest average of inhalable endotoxin levels was measured during cleaning of poultry houses. The respirable endotoxin levels were generally low and mostly under the limit of detection. The highest respirable endotoxin levels were measured during the machine harvest of vegetables. The authors pointed out that the development of adverse health effects is generally not only dependent on the level of exposure, but also on the duration of exposure. In general, preventive measures are recommended for workers who handle organic dust since farmers are at high risk to develop organic dust toxic syndrome (ODTS) [NIOSH, 1994].

### Poultry Farming

During poultry farming workers are exposed to high levels of dust, bacteria, endotoxin, and ammonia. Investigations of 257 poultry farmers showed that concentrations of 2.4 ng/m$^3$ total dust and 614 EU/m$^3$ might result in a decline in lung function [Donham et al., 2000]. Ammonia exposure may be important for the lung function changes.

In addition, increased respiratory symptoms during the work-shift as well as association between poultry dust and endotoxin was detected by Hagmar et al. [1990]. They measured endotoxin values between 200 and 15,000 EU/m$^3$ (Table I) and found no association between decrease of lung function and total dust or endotoxin measured during the work-shift.

### Waste Collection

Waste collectors and compost workers are currently exposed to a variety of respiratory irritants and sensitizers, such as molds, endotoxin, β-glucan, mites, and rats. The exposure to these agents for long periods has been considered a risk factor for respiratory symptoms [Thorn et al., 1998]. Gladding et al. [2003] found that workers exposed to endotoxin and β-glucan at their workplaces exhibit various work-related symptoms. The longer a worker is in this environment, the more likely he is to become affected by various symptoms. Personal dust measurement revealed endotoxin levels of 1.9–1,980 EU/m$^3$ in the nine recovery facilities investigated.

In a cross-sectional study of Bünger et al. [2000], work-related health complaints and diseases of 58 compost workers and 53 biowaste collectors were investigated and compared with 40 control subjects (Table I). The control subjects were newly employed compost workers and biowaste collectors. Biowaste collectors did not differ from control subjects regarding health problems, but compost workers showed significantly more symptoms and airway disorders. In addition, they revealed significantly increased IgG-antibody concentrations against fungi and actinomycetes.

### Table I.

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<td>Walters et al.</td>
<td>Total dust sampling and analyzing techniques</td>
<td>66 different air samples</td>
<td>cyclonic filter; glass disc filter</td>
<td>LAL-test (chromogen-kinetic, Bio-Whittaker)</td>
<td>0.05–62.27 EU/m$^3$</td>
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<td>n.i.</td>
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<td>Zocket et al.</td>
<td>Time-integrated dust and dust sampling</td>
<td>Four potato factories</td>
<td>Personal sampling, flow rate of 0.4 L/min</td>
<td>LAL-test (kinetic)</td>
<td>0.5–62.27 EU/m$^3$</td>
<td>n.i.</td>
<td>n.i.</td>
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The focus of literature selected from Medline was on studies reporting endotoxin exposure at workplaces and providing data to endotoxin levels. If endotoxin-values were not given in EU, the indicated values (data in brackets) were converted. If not otherwise mentioned, 1 ng is calculated as 10 EU. n.i., no detailed information given in the paper. ET, endotoxin.
Hansen et al. [1997] demonstrated that Danish waste collectors (n = 1515) show a slightly increased prevalence of airway disease compared to controls (423 park workers). As presumably reasons exhaust fumes of cars and bioaerosols contaminated with microorganisms are mentioned. The increased concentration of microbial contaminants was accompanied by an increased prevalence of bronchitis.

Data of Marth et al. [1997] described no significant correlation between duration of employment in waste treatment facilities, total IgE, and lung function exists. The highest risk existed for mucosal problems of the airways, the lowest for asthma.

None of these studies determined the special role of endotoxins. However, it can be assumed that endotoxins are part of the microbial burden.

In the study of Neumann et al. [2002], exposure to microbes, endotoxins, and fungi was determined. The medical examination of 220 waste collectors showed only a low number of employees with respiratory symptoms. A correlation between microbial exposure and health status could not be proved. However, the healthy-worker effect has to be taken into account: People developing symptoms may cancel the job prematurely whereas healthy, resistant workers rest. Consequently the low number of employees suffering from respiratory symptoms would not reflect a low risk to develop these symptoms at this workplace in general. Nevertheless, they reported that endotoxin concentrations, which do not exceed 50 EU/m³ may be easily obtained. Protection measures were recommended by the authors.

Exposure to bioaerosols in a municipal sewage treatment plant was reported by Prazmo et al. [2003] and 20 pathogenic fungi and bacteria species are described. However, measurement of endotoxin revealed values below the potential threshold limit value of 50 EU/m³. Thorn et al. [2002] and Laitinen et al. [1994] noticed that endotoxin exposure fluctuates due to activity. High levels of exposure are mainly related to certain phases of the working process. Smit et al. [2005] detected a wide range of symptoms that may be work-related in wastewater treatment workers.

**Textile Industry**

Moist cellulose-rich materials favor the development of moulds as well as of Gram-negative bacteria. In consequence, occupational airway disease in the textile industry may be due to endotoxins [Pernis et al., 1961]. Christiani et al. [1999] found that chronic airway disease is more associated with cotton dust exposure than with endotoxin exposure. Their data revealed that cumulative cotton dust, more strongly than cumulative endotoxin exposure predicts long-term loss of ventilatory lung function. Significant effects of cotton dust exposure on FEV₁-decrease are found. The authors point out that the mechanisms of the byssinosis syndrome may involve stimulation of the same inflammatory processes via endotoxin or cotton dust (Table I).

A correlation between FEV₁ modification and exposure to fungi, bacteria, dust, and endotoxin (highest correlation for endotoxin) was measured in a study of Castellan et al. [1984] examining 54 healthy volunteers in an exposure chamber. The results indicate that endotoxin plays an important role in acute lung reactions to cotton dust. The correlation was more pronounced in the high exposure group [Castellan et al., 1987].

A dose-response relationship between endotoxin-exposure and FEV₁ according to cotton dust was measured by Kennedy et al. [1987] as well. They investigated 443 cotton textile workers from China. Endotoxin values measured by LAL-test reached up to 5,500 EU/m³ (Table I). Workers were divided into four groups based on the median endotoxin-exposure level in their current work area. A dose-response trend was seen with the current endotoxin level and FEV₁ and the prevalence of byssinosis and chronic bronchitis. Except for the highest exposure level group in which a reversal of the trend was seen.

A dose-response relationship between endotoxin exposure and symptoms of byssinosis and an increase of neutrophils was detected in cotton workers by Rylander et al. [1985]. They compared lung function parameters pre- and post-work shift and identified a relationship of their changes to dust and endotoxin levels (0.28–8 µg/m³) (Table I).

Wang et al. [2002] investigated newly hired female cotton textile worker in Shanghai (China). The follow-up study revealed respiratory symptoms as the first response induced by cotton exposure. One year after exposure, changes in lung function are measurable.

A study of Nordness et al. [2003] concerning workers in a nylon factory revealed that the endotoxin from the air-conditioning system might cause fever and leucocytosis.

**Wood Processing Industry**

Wood chips and dust are generated when wood is processed. The largest portion of the wood dust is inhalable (82%–90%) that remains in the mouth and nose. Carcinogenic effects as well as (allergic) asthma may occur in relationship to wood dust exposure. However, it is not clarified whether wood dust itself or competing factors like mould spores, bacteria and other causes the health problems [Dutkiewicz et al., 2001; Schulze et al., 2003].

Significant association of decrease of FVC and nose obstruction/phlegm was measured in 168 wood workers by Mandryk et al. [1999]. Compared to controls, decrease of lung function after work was more pronounced in wood workers. Endotoxin exposure at wood-related workplaces reached from 0.37 to 91.1 EU/m³ (Table I). According to this study wood dust (including biohazards associated with wood
dust-like endotoxins, fungi, etc.) is a possible health risk and should be controlled.

In a study of Alwis et al. [1999a] exposure to biohazards like bacteria, fungi, and endotoxins were evaluated at different wood-working sites. The authors refer to a suggested threshold-limit value for endotoxin of 20 ng/m³. Although mean endotoxin levels were lower, some personal exposures at sawmills and joinery exceeded the standard. In their study, personal inhalable endotoxin exposures were significantly associated with exposure to Gram-negative bacteria $(P < 0.0001)$ and $(1-3)\beta$-glucan $(P < 0.0003)$. Although personal exposure levels of respirable dust, β-glucan, and endotoxins were very low, they still had significant relationships with respiratory symptoms, throat irritation, and ear problems in joinery and sawmill workers [Alwis et al., 1999a,b]. Dennekamp et al. [1999] pointed out that type of job and time of work in the dusty area are of importance for personal endotoxin exposure.

Other Workplaces

Endotoxin exposure was also described at the following workplaces (Table I): cigarette factories [Reiman and Uitti, 2000], fiberglass production [Walters et al., 1994], potato industry [Zock et al., 1995], brewery [Carvalheiro et al., 1994], sugar beet slicing [Forster et al., 1989], paper mills [Sigsgaard et al., 2004], dairy barns [Kullman et al., 1998], and during plant breeding [Monso et al., 2002] or metal working [Laitinen et al., 1999; Park et al., 2001; Olten et al., 2003].

In some companies the main source of endotoxin is the water of ventilation and humidifier equipment. Regularly cleaning of ventilators is of main importance to avoid high endotoxin loads in such ventilated rooms [Raulf-Heimsoth et al., 2003]. In this context endotoxin may also contribute to sick-building syndrome [Teeuw et al., 1994].

DISCUSSION AND SUMMARY

Dust and endotoxin exposure occur in many industries (Table I). Highest exposures are found in workplaces with animal breeding and handling and during cleaning activities [Mahar et al., 1999; Simpson et al., 1999]. However, there are only a few working facilities with continuous high airborne exposures exceeding 50 EU/m³. Furthermore, describing endotoxin exposure, differences in airborne concentrations dependent on the activity at the workplace have to be taken into consideration. For example, in sewage treatment plants airborne endotoxin concentrations varied dependent on whether mud is shifted or rested. Similar differences occur at other workplaces. For farmers it is especially difficult to distinguish between private and occupational exposure since they mostly live on their own farms. The healthy-worker effect, which may play an important role in many industrial high-exposure areas, does not exist for farmers as it is usual for children in Europe to inherit farms from their parents. To compare endotoxin levels in different environments and to establish health-based threshold limit values standardized measurements has to be implemented and evaluated.

In general, the chromogen-kinetic Limulus amoebocyte lysate test (LAL-test) is an international accepted method for quantification of airborne endotoxin [DECOS, 1998]. It is a very sensitive method, which is able to detect even very low exposures. Unfortunately, the sensitive system is vulnerable: minute variations in the instructions may cause changes in the results already [Reynolds et al., 2002; Jacobs and Chun, 2004]. In Germany, the BG-Institute for Occupational Safety and Health (BGIA) has published a national instruction for the LAL-test [BGIA-Arbeitsmappe, 1989].

Further endotoxin measurement methods are possible, but not established so far. Processing of all these methods is still going on.

Although measurement of endotoxin is not completely standardized to date, it is clear that endotoxin exposure may cause acute and chronic health effects [Kennedy et al., 1987; Smid et al., 1992; Christiani et al., 1999]. Important for individual endotoxin effects are the level and the duration of exposure as well as individual susceptibility, including for example the individually different expression of CD14 [Alexis et al., 2001; Vercelli, 2003]. Time point of exposure seems to be important as well since low exposure in childhood contributes to protection for asthma and atopy [Gereda et al., 2000; von Mutius et al., 2000; Riedler et al., 2001; Schwartz, 2001; Trujillo and Erb, 2003]. Gehring et al. [2004] reported that even in adults the exposure to higher levels of house-dust endotoxin might be associated with decreased odds ratio of allergic sensitization. Their analysis of 350 adults and their living rooms showed a negative association between exposure to house-dust endotoxin and severe allergic sensitization. This indicates that kind of exposure is important and that decrease in lung function following endotoxin exposure is mainly not due to allergic sensitization [Walusiak et al., 2004]. However, Alexis et al. [2004] showed that healthy people inhaling endotoxin reveal increased IL-13 and decreased IFN-γ levels in sputum. Consequently, authors assume that low-dose endotoxin challenge skews airway inflammation in a Th2 response in vivo. This points out that the immune system has different possibilities to react to endotoxin. Exposure due to workplace, home living or challenge experiments may lead to different results. Investigations of metropolitan home living conditions showed that households with detectable allergen levels but low endotoxin levels might provide a pre-disposing environment for animal allergen sensitization [Gereda et al., 2001]. In general, pets and vermin are associated with high-endotoxin levels in house dust [Heinrich et al., 2001]. Eduard et al. [2004] concluded that exposure to endotoxins and fungal spores may have a protective effect on atopic asthma...
but may induce non-atopic asthma in farmers. However, endotoxins may be a surrogate marker, which is correlated with other factors, responsible for asthma and atopy protection. In addition, the impact of endotoxins may differ dependent on the kind of dust. This hypothesis is supported by results of Palmberg et al. [1998] who found swine dust but not LPS to be a strong stimulus for IL-8 production in epithelial cells and alveolar macrophages of humans.

Acute endotoxin effects are characterized by inflammatory reactions or systemic effects (ODTS). Decrease in lung function (FEV1) during shift and increase of proinflammatory cytokines in bronchoalveolar or nasal lavage fluids can be diagnosed [Castellan et al., 1987; Vogelzang et al., 1998]. The relevance of subjective irritations is unclear up to now. Exposed subjects may become adapted to these irritations. Longitudinal studies are necessary to clarify these aspects.

Endotoxin exposure at the workplace over a long period contributes probably to irreversible chronic bronchitis with or without obstruction. Hitherto published epidemiological studies did not admit to define whether these effects rise preliminary from endotoxin or from other components of the complex inhalative bioaerosol exposure [Rylander, 2002].

The implementation of a general health-based threshold limit value for endotoxins at workplaces seems to be not suitable at the moment. In agricultural workplaces, for example, compliance with such threshold limit values is technically impossible. In addition, it has to be considered that bioaerosols are very heterogeneous and differ from area to area. Results concerning a “No-effect-level” (NOEL) range from 90 to 1,800 EU/m³. This broad variance emphasizes that measurement is not standardized and multiple factors influence the effects of endotoxins [Linsel and Kummer, 1998]. Therefore, if any control value is established it should be specific for industrial sectors, graded procedures of protection should be adopted. As the adverse health effects of endotoxins are known and some workplaces have very high exposures, primary, and secondary prevention has to be arranged independent of threshold limit values [Baur et al., 2003]. Exposures should be minimized, for example, by ventilation, cleaning, special animal keeping, and other procedures. Regular medical surveillance should be established especially in high-exposure areas. Intervention studies should be performed, controlling the development and effect of endotoxin and glucan exposure. In such investigations it should be considered that measurements are always performed with the same method in the same lab. Endotoxin values could be evaluated only in the context of a detailed study protocol. However, sampling strategies have to be harmonized and standardized. Stationary sampling, for example, may underestimate the personal burden. However, the advantage of individual monitoring measurements has to be proven. In addition, time of sampling and filter size should be defined [Thorne et al., 2004]. Under these premises results of the LAL-test may be comparable [Lane et al., 2004]. Finally, for a sufficient characterization of working conditions endotoxin measurement should be used in concert with determination of microorganisms (bacteria and moulds) and β-glucan.

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