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Health Effects of Biological Agents: The Role of Endotoxins

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Gram-negative bacteria and their endotoxins are commonly found in agricultural settings, yet they can be quantified also in environmental/occupational situations that are considered traditionally to be nondusty, such as office buildings or libraries. Endotoxins are biologically active agents that can induce respiratory and systemic reactivity after inhalation of airborne dusts which contain relatively small quantities of the toxin. Research studies with strong and compelling results are needed to lead to the prevention of lung disease caused by the inhalation of endotoxins. Olenchock, S.A.: Health Effects of Biological Agents: The Role of Endotoxins. Appl. Occup. Environ. Hyg. 9(1):62–64; 1994.

KEY WORDS: **agriculture; gram-negative bacteria; lung; endotoxin, occupations; respiratory disease**

Introduction

Endotoxins are heat stable, lipopolysaccharide-protein complexes that are integral parts of the outer membrane of gram-negative bacteria.[1] They are released into the environment after lysis of the bacterial cell or during active cell growth[2] and intact bacterial cells can be phagocytized by macrophages, processed, and the endotoxins released with increased toxicity.[3] Gram-negative bacteria and their endotoxins are ubiquitous. They can be found in the soil, water, and in other living organisms throughout the world. They are found commonly in various materials in agricultural work sites where large amounts of organic dusts are generated.[4] However, they can also be found in many other occupational environments, including office buildings and libraries where humidification systems are operative.[5]

In agricultural environments, endotoxins have been quantified in such diverse materials as stored grains, silage, hays, straw, and animal bedding material;[6] composted wood chips[7] and stored timber;[8] tobacco (unpublished data); bulk cottons;[9] mushrooms, including processing materials such as manure, compost, and spawn;[10] bulk and airborne dusts in swine confinement units[11] and poultry confinement and processing facilities;[12] and in horse and dairy cow barns.[13,14] Endotoxins have been quantified in other industrial settings as well, including those associated with humidifiers, air conditioners, cooling towers, and other water-associated processes;[5,15,16] dusts generated during processing of cotton, wool, and flax;[17–20] machining fluids;[21] waste disposal, sewage, and sewage composting;[22,23] animal feed production;[24] and biotechnology.[25,26]

Health Effects

Because of the ubiquitous nature of endotoxins, it is not surprising that exposures to these agents are commonplace. Endotoxins are biologically active materials and profoundly affect both humoral and cellular host mediation systems.[2,27,28] Complement and coagulation systems are affected and direct interaction of endotoxins has been reported with a myriad of human cell types, including basophils, mast cells, endothelial cells, macrophages, platelets, polymorphonuclear leukocytes, and T and B lymphocytes. Research related to environmental exposures to endotoxins focuses on respiratory exposures to airborne dusts containing endotoxins. The primary cell responsible for initiating pulmonary reactions after inhalation of organic dusts laden with endotoxins is the pulmonary macrophage,[29] and human alveolar macrophages are extremely sensitive to the effects of endotoxins *in vitro*.[30] Systemic signs and symptoms that are suggestive of exposure to airborne endotoxins have been reported. Chest tightness, cough, shortness of breath, fever, and wheezing have been found in workers in sewage treatment facilities,[22] swine confinement buildings,[31] and poultry units.[32]

Few large studies of endotoxin effects on lung function are reported. Controlled exposures of human volunteers to cotton dusts laden with endotoxins resulted in the observation of an association between decreased acute pulmonary function and the airborne level of endotoxins in the dusts.[17,33,34] In these studies of acute pulmonary function effects, as measured by the forced expiratory volume in 1 second, the threshold for zero pulmonary function change was defined for cotton workers who smoke as 33 ng/m^3,[34] whereas the results from a larger study of a mixed population (with reference to prior cotton mill work and smoking history) indicated a calculated zero-charge threshold of as little as 9 ng/m^3.[17]

When these data from vertically elutriated dust samples are mathematically converted to contemporary endotoxin units (EU), and a conversion factor of 10 EU/ng is used, the thresholds are 330 EU/m^3 and 90 EU/m^3, respectively. To put these calculated thresholds in perspective, Table I lists typical environmental endotoxin exposures in several occupational settings. It can be seen from Table I that airborne endotoxin exposures can be very high in many situations. Associations between endotoxin concentration in the air and chronic lung disease have been reported as well. In a study of 443 cotton textile workers from two mills, a dose–response trend was observed between current endotoxin levels in vertically elutriated dusts and chronic bronchitis.[18] This association was not observed with the concentration of vertically elutriated dust alone. Analysis of data from that study indicated that exposures from 1 to 20 ng/m^3 (approximately 10 to 200 EU/m^3) constituted an adverse respiratory health effect in the exposed workers. In a separate epidemiologic study of 315 animal feed workers, symptoms and lung function changes were related more to present and historic endotoxin exposures than to inspirable dust exposures.[35] These investigators reported that lung function changes occurred at levels of endotoxin which ranged from 0.2 to 470 ng/m^3.

Other systemic and respiratory effects are thought to be the result of endotoxin inhalation, or at least, to the inhalation of endotoxin-contaminated organic dust. The International Committee on Occupational Health, through its Committee on Organic Dusts, reported that endotoxin may provoke different reactions when the exposure occurs at different levels.[36] As an example, the report states that organic dust toxic syndrome (ODTS) is elicited at a level of 1000 to 2000 ng/m^3, while acute bronchoconstriction occurs at levels of 100 to 200 ng/m^3, and mucous membrane irritation (MMI) at levels of 20 to 50 ng/m^3. These levels may be lower for sensitive subjects. Confirmation of the endotoxin-induced effects in such conditions as ODTS and MMI require the same rigorous exposure–response criteria that support the role of endotoxins in eliciting the acute pulmonary function change after exposure to cotton dusts. Endotoxin inhalation has been associated also with eliciting inflammation. Although not a common environmental agent or typical respiratory exposure, inhalation of purified lipopolysaccharide (a component of endotoxin), was shown to induce local bronchial inflammation and a systemic inflammatory response in a small group of asthmatic subjects.[37]

TABLE I. Airborne Endotoxin Levels in a Variety of Occupational Environments

Activity	Dust	Endotoxin (EU/m^3)
Bedding chopping, dairy farm	T	20944.95
Silo unloading, farm	T	88502.50
Opening area, Shanghai cotton mill	T	16604.12
Opening area, Shanghai cotton mill	VE	5172.96
Hulling area, Shanghai rice commune	T	13412.80
Hulling area, Shanghai rice commune	VE	4501.10
Shackling line, poultry processing	T	6340.00*

*Mean time-weighted average.
T = Total.
VE = vertically elutriated.

Discussion

Throughout actual workplace studies and controlled dust exposure studies, it must be remembered that endotoxins are a part of a mixed and complex dust that contaminates the air and breathing zone of subjects. As additional worker related epidemiologic studies are completed, the contribution of endotoxin exposure to the development of acute and chronic lung impairment should become more clear. Exposure-response relationships between airborne endotoxins found in different occupational environments would aid in understanding the health impact of respiratory insults with endotoxin-containing dusts. However, several questions remain unanswered concerning that role that endotoxins play in the health effect of exposure to airborne dusts containing biological agents.[38] Among them, the relative toxicity of different endotoxins, those produced by different species/strains of gram-negative bacteria, has not been properly addressed in exposure-response studies. Likewise, the role of endotoxins as adjuvants to the toxicity of other inhaled agents/dusts should be clarified. In addition, do endotoxin exposures in one setting, such as during the uncapping of a tower silo on a farm, equate in quality and quantity to endotoxin exposures in other situations, such as in a cotton textile mill? These questions and others, when addressed with strong and compelling data, will lead research toward the prevention of lung disease caused by the inhalation of gram-negative bacterial endotoxins.

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