INHALED ENDOTOXIN AND DECREASED SPIROMETRIC VALUES

An Exposure–Response Relation for Cotton Dust

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Abstract The early stages of byssinosis, the chronic lung disorder caused by the inhalation of cotton dust, are characterized by repeated episodes of mild and reversible obstruction of airways on exposure to cotton dust. To define the relation between exposure to endotoxin and the airway response to inhaled cotton dust, we pooled and analyzed data from several previous studies of experimental exposure. The pooled data set involved a total of 108 separate sessions of exposure to dust and 32 different cottons. Each dust-exposure session had involved exposing a group of 24 to 35 prescreened healthy subjects to dust from one of the cottons for six hours. The following data were obtained for each session: average concentrations of airborne dust (range, 0.12 to 0.55 mg per cubic meter) and endotoxin (range, 6 to 779 ng per cubic meter) as determined in air samples collected by vertical elutriators, and group mean percentage change in forced expiratory volume in one second (range, +0.5 to −9.1 percent), as determined by preexposure and postexposure spirometry.

When data from the 108 exposure sessions were pooled, the dust concentration was not correlated with the group mean percentage change in forced expiratory volume in one second ($r = -0.08$; $P = 0.43$). In contrast, a clear exposure–response relation was observed between endotoxin concentration and group mean percentage change in forced expiratory volume in one second ($r = -0.74$; $P<0.0001$). Logarithmic transformation of endotoxin values clarified this relation at low-exposure concentrations and improved the correlation ($r = -0.85$; $P<0.0001$).

Our observations strongly support the hypothesis that endotoxin has a causative role in the acute pulmonary response to inhaled cotton dust. (N Engl J Med 1987; 317:605-10.)

BYSSINOSIS, an occupational lung disorder observed most commonly in textile workers, is caused by the inhalation of cotton, flax, or hemp dust. Within cotton mills, cardrooms have been the areas posing the highest risk, since much airborne dust is released when cotton is mechanically carded (brushed) before being spun into yarn. The early stage of byssinosis is characterized by a distinctive temporal occurrence of chest tightness, which is most notable during the first work shift of the week after a weekend away from cotton dust.[1] This "Monday chest tightness" is typically accompanied by a moderate and reversible decrease in ventilatory function,[2,3] but after many years of exposure to cotton dust, a chronic and irreversible impairment of lung function may result.[4]

Although the widespread occurrence of byssinosis among British textile workers was well documented more than a century ago,[1] byssinosis was not generally recognized in U.S. cotton-textile workers until the 1960s.[5,6] Despite this late recognition, much progress has been made toward the prevention of byssinosis in this country.[7,8] In 1978, the Occupational Safety and Health Administration (OSHA) issued regulations that limit worker exposure to cotton dust.[9] That standard, which remains in effect with modifications,[10] is based primarily on epidemiologically defined relations between exposure to dust and the prevalence of byssinosis among workers in cotton-textile mills.[11,12] However, several different permissible exposure limits for dust currently apply to various cotton industries and work areas.[10] In addition, because byssinosis can occur even at permissible dust levels,[12] the regulations require periodic medical surveillance to identify affected workers. In recommending the cotton-dust-exposure limit to OSHA in 1974,[13] the National Institute for Occupational Safety and Health recognized these shortcomings and stated that "Research . . . should be vigorously pursued with the eventual goal of developing scientific data that will enable development of a better occupational health standard for cotton dust."

One principal research objective has been the identification of the etiologic agent or agents within the complex mixture of plant, soil, and microbial particles that constitutes cotton dust. We have reported the results of an experimental study indicating that the acute ventilatory response to cotton dust is related to the concentration of endotoxin in the inhalable dust.[14] To extend those results, we combined and analyzed available data from several previous studies.[14-22]

METHODS

The methods used for the selection of subjects, the generation and scheduling of exposures to dust, and the assessment of the ventilatory response to exposures have been described in detail elsewhere.[14] These methods and particular aspects of the selection of data for this analysis are summarized below.

Subjects

After they gave informed consent to participation, volunteers solicited from the general public gave answers to a standardized questionnaire and were assessed by spirometry. Subjects were excluded on the basis of the following criteria: a history of asthma, chronic bronchitis, or dyspnea while walking; nonrespiratory medical conditions precluding safe participation; frequent use of medications or current occupational exposure known to affect airway response; or forced expiratory volume in one second (FEV_1) below 80 percent of the predicted value.[23]

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The remaining subjects were further screened on the basis of ventilatory responses during two exposures to airborne dust generated by carding cotton consisting of a blend of 50 bales. The screening exposure concentrations were approximately 1 mg of dust per cubic meter and 100 ng of endotoxin per cubic meter. As a precaution, persons with reductions in FEV_1 greater than 30 percent on their first exposure to dust were excluded from further exposure.

Subjects who completed the initial screening exposures and who had individual mean decreases in FEV_1 of at least 5 percent attributable to exposure to cotton dust were further screened with 10 additional exposures to dust from the blended cotton. From among the subjects who completed these exposures, 61 who had consistent ventilatory responses to dust were selected as participants in the subsequent series of studies from which data were pooled.[14-22]

Over the 20-month period covered by the study exposures, the number of participating subjects gradually decreased to 33 for a variety of reasons, none of which were related to responsiveness to cotton dust. In fact, those who remained in the study for the entire period of the exposure sessions did not differ from those who dropped out in terms of mean ventilatory responses to the initial screening exposures (Table 1).

Cottons

Nine study cottons were purchased from commercial brokers in bale form[14-17]; 22 were grown and prepared as bales for the exposure studies with use of standard commercial methods,[18,19] and one was a rebaled composite blend of cotton samples from hundreds of individual bales processed in a commercial yarn-production mill.[22]

Exposures

The exposure system consisted of a commercial carding machine in a cardroom, an exposure room, and connecting duct work. To generate dust, each of the selected cottons was carded while filtered and conditioned air (24°C; 55 percent relative humidity) was supplied to the cardroom at a rate of 18.4 m^3 per minute. Constant dust concentrations were maintained during the exposure sessions by adjusting the proportion of dust-contaminated exhaust air from the cardroom that entered the exposure room. Airborne dust concentrations were monitored with a continuous aerosol monitoring system (Model CAM-A, ppm, Inc., Knoxville, Tenn.) and with approximately hourly mean gravimetric measurements of the inhalable fraction of airborne dust, as collected by four vertical elutriators,[13] one in each quadrant of the room. All facilities were cleaned after each exposure.

Exposures were six hours long and occurred between 7 a.m. and 3 p.m. Each of the 108 separate sessions of dust exposure followed at least two full days without dust exposure, and each of the 66 sessions of exposure to clean air (during which no cotton was carded) followed at least one full day without exposure. Subjects and spirometry technicians were blinded in regard to which, if any, cotton was being carded on any given day.

For each exposure session, the mass airborne concentration (milligrams per cubic meter) of dust was calculated as a time-weighted average with use of the weights of all dust samples collected by vertical elutriators during that session. The endotoxin concentration (nanograms of U.S. reference endotoxin per cubic meter) was calculated as a time-weighted average with use of the same dust samples, extracted and assayed for endotoxin activity with a modification of the limulus amebocyte lysate test.[24]

Spirometry

Spirometry, performed immediately before and after each exposure, met published specifications.[9] Each subject's change in FEV_1 during an exposure session (percentage change in forced expiratory volume in one second) was expressed as a percentage of the value before exposure as follows:

$$\Delta FEV_1\% = \frac{(FEV_{1\ \text{after exposure}}) - (FEV_{1\ \text{before exposure}})}{(FEV_{1\ \text{before exposure}})} \times 100.$$

For each exposure session, the group mean percentage change in FEV_1 was calculated for the subjects (n = 24 to 35) exposed during that session.

Analysis

To justify the pooling of data from separate studies, a preliminary linear regression analysis was done with a subset (81 percent) of the pooled data. Included were data from individual studies that each involved a series of at least 10 sessions of dust exposure.[14,18,19] The model used the group mean percentage change in FEV_1 as the dependent variable and the dust concentration, log endotoxin concentration, and "study" as independent variables. For the preliminary analysis, the values for group mean percentage change in FEV_1 were calculated with use of spirometric results only from subjects who were present for all exposures in a particular study. No significant "study" differences were found for the effects of dust or endotoxin on the values for group mean percentage change in FEV_1.

Next, data from all 108 sessions of dust exposure were analyzed with use of spirometry results from all subjects exposed. Correlation analyses were performed for associations between the group mean percentage change in FEV_1 and the dust concentration, endotoxin concentration, and log endotoxin concentrations, and for an association between dust and endotoxin concentrations. Weighted and unweighted linear regression analyses were performed with the group mean percentage change in FEV_1 as the dependent variable, the log endotoxin concentration as the independent variable, and the variable number of subjects present at the exposure sessions as the weights. Because the results were identical, only those from the unweighted analysis are reported.

The data on group mean percentage change in FEV_1 from the sessions of exposure to clean air were used to define a 95 percent confidence interval for the mean re-

Table 1. Characteristics of Subjects at the Beginning and End of the Period during Which Exposure Sessions Were Conducted.*

Characteristic	Subjects Initially Enrolled (N = 61)	Subjects Who Remained (N = 33)	Subjects Who Dropped Out (N = 28)	P Value†
Age (yr)	33.6±11.2	35.1±11.7	31.8±10.5	0.26
Sex				
Male	25	8	17	<0.01
Female	36	25	11	
Ethnic group				
White	52	31	21	0.08
Black	8	2	6	
Hispanic	1	0	1	
Smoking status				
Never	23	14	9	0.40
Current	34	16	18	
Former	4	3	1	
Previous job in the cotton industry				
Yes	32	18	14	0.72
No	29	15	14	
Mean screening $\Delta FEV_1\%$	−9.4±4.6	−9.4±4.4	−9.4±4.8	0.99

*$\Delta FEV_1\%$ denotes the percentage change in forced expiratory volume in one second. Plus–minus values are means ±SD.
†For the comparison, by t-test or chi-square test, between subjects who remained and subjects who dropped out.

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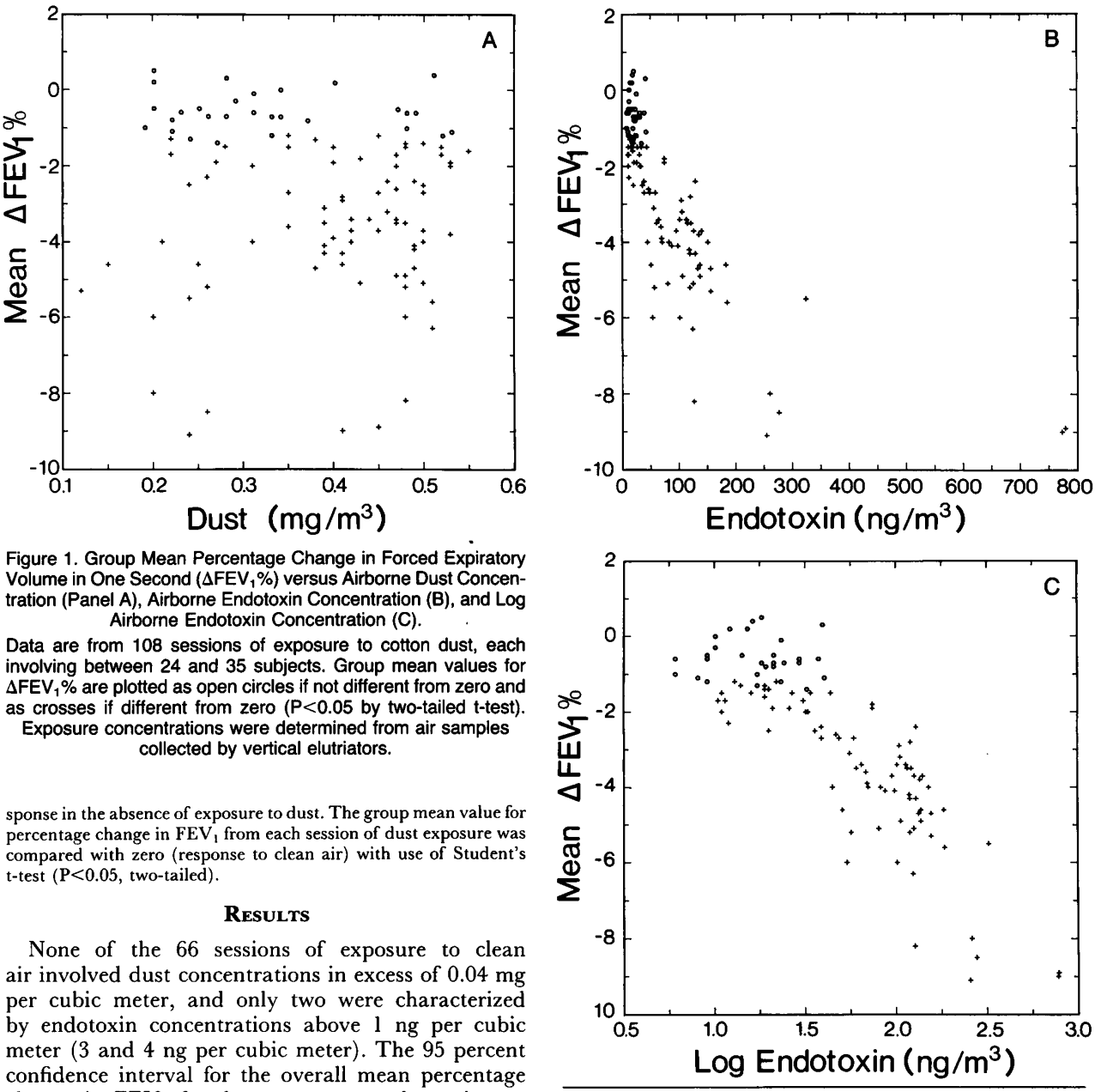


Figure 1. Group Mean Percentage Change in Forced Expiratory Volume in One Second ($\Delta FEV_1\%$) versus Airborne Dust Concentration (Panel A), Airborne Endotoxin Concentration (B), and Log Airborne Endotoxin Concentration (C).

Data are from 108 sessions of exposure to cotton dust, each involving between 24 and 35 subjects. Group mean values for $\Delta FEV_1\%$ are plotted as open circles if not different from zero and as crosses if different from zero ($P<0.05$ by two-tailed t-test). Exposure concentrations were determined from air samples collected by vertical elutriators.

sponse in the absence of exposure to dust. The group mean value for percentage change in FEV_1 from each session of dust exposure was compared with zero (response to clean air) with use of Student's t-test ($P<0.05$, two-tailed).

Results

None of the 66 sessions of exposure to clean air involved dust concentrations in excess of 0.04 mg per cubic meter, and only two were characterized by endotoxin concentrations above 1 ng per cubic meter (3 and 4 ng per cubic meter). The 95 percent confidence interval for the overall mean percentage change in FEV_1 for the exposures to clean air was −0.16 to +0.20, justifying statistical comparison of the mean response in each dust-exposure session with zero.

For the 108 sessions of dust exposure, dust concentrations ranged from 0.12 to 0.55 mg per cubic meter, and endotoxin concentrations from 6 to 779 ng per cubic meter. There was no correlation between concentrations of dust and endotoxin ($r = 0.07$; $P = 0.46$). As shown in Figure 1A, no correlation existed between group mean percentage change in FEV_1 and dust concentration ($r = -0.08$; $P = 0.43$). Several exposure sessions resulted in substantial mean responses at approximately 0.2 mg per cubic meter, the current OSHA-permitted exposure limit in carding areas of cotton mills. Other exposure sessions resulted in little or no response, even at dust concentrations nearly three times the OSHA limit.

Figure 1B reveals an obvious exposure–response relation between the group mean percentage change in FEV_1 and endotoxin ($r = -0.74$; $P<0.0001$). The linear correlation was enhanced ($r = 0.85$; $P<0.0001$) when values for the endotoxin concentration were logarithmically transformed in order to clarify the low-dose part of the relation (Fig. 1C). All group mean decreases in FEV_1 were significant at endotoxin concentrations above 50 ng per cubic meter, and many were significant at concentrations between 10 and 50 ng per cubic meter. The linear regression model developed from these data [percentage change in

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$FEV_1 = 3.84 - (4.02)(\log \text{endotoxin})]$ yielded a zero percentage change in FEV_1 at 9 ng per cubic meter.

As shown in Figure 2, the proportion of subjects within an exposed group who had an individual decrease in FEV_1 of at least 5 percent increased from approximately 10 percent at the lower concentrations of endotoxin to more than 75 percent at the highest concentrations. Among these subjects, the effective concentration required for 50 percent of the exposed population to achieve a specified effect (EC_{50}) was approximately 100 ng per cubic meter for a 5 percent or larger decrease in FEV_1. Similarly, although no subjects had decreases as large as 10 percent at endotoxin concentrations below 10 ng per cubic meter, as many as 45 percent had this degree of response at the highest endotoxin concentration (data not shown), suggesting an EC_{50} for a 10 percent decrease in FEV_1 of approximately 1000 ng per cubic meter.

Discussion

Endotoxin is a component of the cell walls of gram-negative bacteria, which commonly colonize cotton plants grown in fields.[14] Endotoxin is known to cause effects (e.g., alveolar-macrophage activation, complement activation, neutrophil chemotaxis, and mast-cell release of histamine) that make it highly suspect as a possible causative agent of byssinosis.[25-27]

Cinkotai et al., in a survey of workers in cotton-spinning mills, observed a good correlation of the prevalence of byssinotic symptoms with airborne gram-negative bacteria but not with airborne dust.[28,29] Other epidemiologic studies have also implicated gram-negative bacteria or endotoxin as a possible cause of the pulmonary-function abnormalities or respiratory symptoms of textile workers exposed to cotton dust.[30,31] The results of several experimental studies of human exposure have likewise supported the association between endotoxin or gram-negative bacteria and the acute respiratory response to cotton dust.[14,32-37] Thus, there is an increasing body of evidence to support the hypothesis, first suggested by Neal et al. in 1942,[32] that endotoxin is responsible for the acute respiratory response to inhaled cotton dust.

We have been able to extend our previous findings[14] by pooling a large amount of data that more clearly describe an association between decreases in FEV_1 and exposure to endotoxin in the absence of an effect due to dust. A key to this effort was the lack of correlation between dust and endotoxin in our exposure data — an observation more likely to be made in an experimental setting (in which relatively small quantities of individual cottons can be separately carded) than in commercial mills (in which large quantities of blended cottons are carded).

Rylander and associates, in assessing a smaller pooled set of their own similarly analyzed data, calculated a threshold level of 33 ng of endotoxin per cubic meter for a mean FEV_1 response of zero.[35] That our calculated threshold (9 ng per cubic meter) was lower

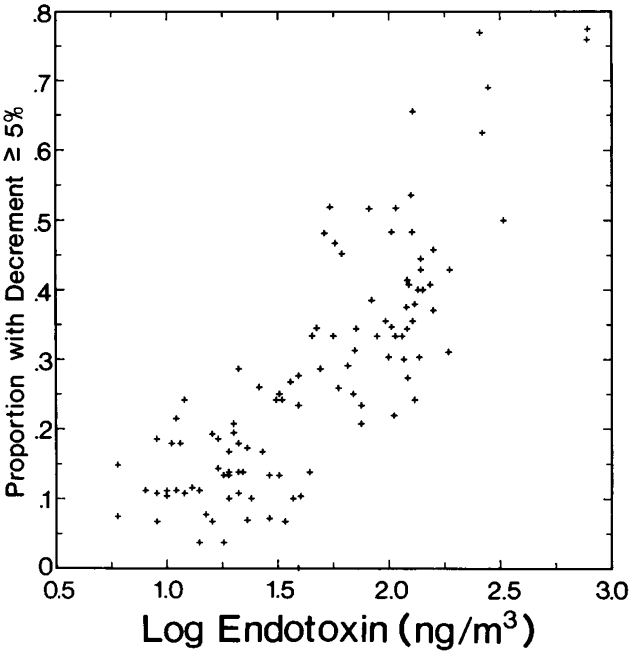


Figure 2. Proportion of Subjects in Exposed Group with an Individual Decrease in Forced Expiratory Volume in One Second of ≥5 Percent versus Log Airborne Endotoxin Concentration.

Data are from 108 sessions of exposure to cotton dust, each involving between 24 and 35 subjects. Exposure concentrations were determined from air samples collected by vertical elutriators.

is consistent with the fact that our exposure sessions were two hours longer than those in the study by Rylander et al. Thus, at any given airborne concentration, our subjects should have had more cumulative deposition of inhaled agent in their airways. Furthermore, we intentionally enhanced the sensitivity for assessment of acute airway responses by selecting subjects on the basis of airway responsiveness during preliminary screening exposures to dust from a blended cotton.

These calculated threshold values should be interpreted cautiously, since they are derived from linear statistical models that cannot be expected to represent precise estimates of the exposure–response relation at either very high or very low doses. In fact, in a manner consistent with the sigmoidal semilog plots characteristic of many typical biologic dose–response relations, a curvilinear character is evident at the lower exposures to endotoxin shown in Figure 1C. Thus, no true threshold can be assumed to exist. In addition, as in many studies of dose–response relations based on experimental data from human subjects, we did not have the information needed to describe an upper limit of the graded response curve. Consequently, no clear evidence of a maximal response is evident in Figure 1C.

Despite our selection process, the relevance of our results should not be considered to be restricted to a small minority of the general population. The degree of airway response required for inclusion in the ses-

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sions of cotton exposure in our study was observed in approximately one third of the volunteers who completed the initial screening exposures.[38] This proportion would have been larger had we exposed subjects for eight hours (the length of a typical work shift), had the subjects exercised during the exposure sessions to achieve a level of ventilation corresponding to that of working textile workers, or had we not excluded subjects with asthma, chronic bronchitis, low baseline FEV_1 values, or marked responses to screening exposures.[39]

Our current findings do not prove that inhaled endotoxin is the cause of the observed airway response to cotton dust. However, other dusts known to cause byssinosis (e.g., flax and hemp) have been shown to contain substantial quantities of endotoxin, in contrast to vegetable dusts, which are not associated with byssinosis.[28,40] Also, the respiratory response of guinea pigs to inhaled endotoxin prepared from *Enterobacter agglomerans*, a common cotton contaminant known to botanical scientists as *Erwinia herbicola*,[41] has been shown to mimic the respiratory response to cotton dust.[42] The results of limited challenges of humans with inhalation of endotoxin have been disparate, but the reported absence of an airway response to a nebulized endotoxin solution[43] may be misleading with regard to an occupational exposure involving particulate endotoxin.[36]

Even if endotoxin is not itself the causative agent, our results suggest that measuring its concentration in air is a much more reliable means of assessing the risk of an acute airway response to exposure to cotton dust than measuring the mass concentration of dust. In our study, 4 of 8 sessions of dust exposure involving dust concentrations below the current OSHA limit resulted in substantial ventilatory responses, and only 8 of 11 exposures above 0.5 mg per cubic meter resulted in statistically significant responses. In comparison, none of the 8 sessions of exposure with endotoxin concentrations below 10 ng per cubic meter resulted in a significant response, whereas all 51 sessions with concentrations above 50 ng per cubic meter yielded significant mean responses. It follows that limiting exposures to endotoxin in work environments may eventually prove to be an appropriate strategy for protecting workers from respiratory hazards associated with cotton dust. Of course, before an endotoxin-based revision of the current OSHA regulations regarding cotton dust could be recommended, it would be important to determine and consider the ranges and correlation between endotoxin and dust concentrations in actual work areas in the cotton industry. As an additional caution, even if a limit were imposed on occupational exposure to endotoxin, it might be considered unwise to permit higher exposures to cotton dust until more is understood about the cause and pathogenesis of the chronic ventilatory impairment associated with the inhalation of cotton dust. The hypothesis that disabling obstructive airways disease results from repeated acute airway responses to cotton dust, although controversial,[44] remains a fundamental premise underlying OSHA-mandated medical surveillance of textile workers exposed to cotton dust.[9]

Finally, it has been suggested that humidifier fever, a disorder that shares clinical features with byssinosis, is caused by endotoxin from humidification–ventilation systems that are heavily contaminated with gram-negative bacteria.[45] Inhaled endotoxin may also be responsible for the adverse respiratory effects associated with the grain industry,[46] swine and poultry confinement,[47,48] poultry processing,[49] composting,[50] sewage processing,[51] and silo unloading.[52] Thus, the potential effect on health of inhalational exposure to endotoxin extends far beyond its probable role in the pathogenesis of byssinosis and related disorders in cotton workers.

The data analyzed were collected under the auspices of a government–industry–union task force with representatives from the National Institute for Occupational Safety and Health, the Agricultural Research Service (U.S. Department of Agriculture), Cotton Incorporated, the Cotton Foundation (National Cotton Council), the American Textile Manufacturers Institute, and the Amalgamated Clothing and Textile Workers Union. We are indebted to C.K. Bragg, J.B. Cocke, H.H. Perkins, Jr., P.E. Sasser, and R.R. Jacobs for acquiring cottons and providing exposure facilities and to M.D. Attfield for assisting in the preliminary analysis.

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