THE ACUTE PULMONARY RESPONSE TO INHALED PARTICULATE CELLULOSE AND REGENERATED CELLULOSIC FIBER DUST RELATIVE TO COTTON DUST

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Previous studies evaluating the pulmonary response to cotton dust have used different types of exposures as negative controls. These have included particulate cellulose, carded rayon dust (regenerated cellulose fiber dust) and carded scoured and bleached cotton. This paper will review the acute pulmonary response associated with these dusts relative to different types of cotton dust.

Introduction

Cellulose $(C_6H_{10}O_5)n$ is a polymer consisting of 4-$-D-glucosido-D-glucose units. In its purest form its physical and chemical properties resembles cellulose derived from cotton. Recently studies have suggested that inhalation of cellulosic fibers is associated with adverse pulmonary responses and suggestions have been made that cellulose be regulated with a substance specific standard (1). Currently, OSHA regulates cellulose under its total particulate limit of 15 mg/m^3 or its respirable fraction limit of 5 mg/m^3. The ACGIH has a TLV-TWA of 10 mg/m^3 (total dust) applicable to cellulose dust. To date much of the research on cotton dust has focused on defining the etiology and pathogenesis of Byssinosis. A basic assumption associated with this research is that the cotton fiber is pure cellulose and therefore biologically inert. The toxicity associated with cotton dust is considered to be from the accumulation of bioactive components on the fiber; either from natural products produced by the plant or from external contamination that occurs during growth, harvest, or processing of the fiber. Many of the studies designed to evaluate the toxicity of cotton dust have used either cellulose or regenerated cellulosic fibers as an inert particulate control. Since there are questions regarding the biologic reactivity of cellulose, this paper reviews some of the studies that have used either pure cellulose or regenerated cellulose fiber as a negative control relative to the response to cotton dust.

Animal Studies

Several different animal models have been used to evaluate the effects of inhaled cotton dust however only a few have used a cellulose as a particulate control. In a sub-chronic study, Milton *et al* exposed hamsters, intratrachaelly, to respirable cotton dust (0.75 mg/100-g animal), endotoxin (255 micrograms/100-g animal), or cellulose (0.75 mg/100-g animal) twice weekly for 6 weeks (1). A saline-instilled group was the negative control. Endotoxin-treated animals had increased lung distensibility, reduced surface-to-volume (S/V) ratios, and morphologically apparent mild centrilobular emphysema. Cellulose-treated animals had decreased distensibility, normal S/V ratios, and significant numbers of granulomata with patchy areas of thickened interalveolar septa; however there were no emphysema like lesions. Cotton-dust-instilled animals had normal distensibility, reduced S/V ratio, significant numbers of granulomata, and mild centrilobular emphysema. These data suggest that the response to cellulose, while not as severe as the response to cotton dust or endotoxin, did produce histopathologic effects relative to the saline controls. A possible confounder of this study was that the high dose of cellulose used for the exposure might have overloaded the animals clearance mechanisms thus inducing an abnormal pathologic outcome (2).

In another subchronic animal study, guinea pigs were exposed to aerosols of a purified particulate cellulose (Whatman CC41) at 76 mg/m^3, cotton dust at 27 mg/m^3 , and endotoxin on cellulose at 29 mg/m^3 for 6 hours and respiratory effects measured immediately after exposure and at 18 hours post-exposure (3). Both, the cotton dust and cellulose-endotoxin exposures caused an increase in the breathing frequency, a decrease in tidal volume and a decrease in plethysmograph pressure immediately after exposure and at 18 hours post-exposure. There was no change in any of the measured parameters for animals exposure to the cellulose aerosols, suggesting no acute physiologic pulmonary effects of cellulose at these levels. In a follow-up study, guinea pigs were exposed to aerosols of cotton (24 mg/m^3), endotoxin on cellulose (34.6 mg/m^3), and cellulose (20 mg/m^3) for 6 hours on two successive Mondays (4). A Monday response, as determined by an increase in breathing frequency, decreased tidal volume, airflow interruptions, and increased numbers of apneic periods was observed in animals exposed to either cotton dust or endotoxin on cellulose. No effects were seen for any of these parameters for pure cellulose. These data suggest that there are no acute respiratory effects associated with inhaled cellulose, but in subchronic exposure studies there were mild changes in pulmonary tissue.

Human Exposure Studies

A number of studies have been done in which human volunteers have been exposed to cotton dust using regenerated cellulose fiber (rayon) as the negative particulate control. Table 1 shows studies done in a controlled exposure chamber in which rayon was used as the control exposure (5). Other exposures included an unwashed cotton from Texas, the Texas cotton with an oil overspray added to reduce dust, and the Texas cotton washed according to the protocol

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approved by the 1985 amendments to the Cotton Dust Standard. Specifically focusing on the overall response, there was no change in FEV_1 of subjects exposed to either rayon or the washed cotton, however, there was a significant decrease, pre to post-exposure, for both the Texas unwashed and Texas cotton with overspray. There was an increase in FEV_1 over the shift for both the Texas washed and Rayon suggesting no dust effect because the subjects exhibited the expected diurnal increase during the exposure period.

Table 2 shows the methocholine challenge results from the same study. These data differ from the response in Table 1. For subjects exposed to Rayon, there was no change in methacholine responsiveness during the exposure, however for the three cottons there was a significant increase in methacholine responsiveness. The response was dependent on the type of exposure, with unwashed cotton showing a significantly larger increase in responsiveness than either the oversprayed or washed cotton; and the oversprayed cotton showing a significantly larger increase in responsiveness over the washed cotton. These data suggest that methocholine responsiveness is either a more sensitive indicator than change in FEV_1 or that the mechanism inducing changes in FEV_1 differs from the mechanism causing increases in airway responsiveness. While these data indicate that washing has not removed all the biological activity of the cotton they also show that exposure to rayon causes no change in two measures of pulmonary responsiveness (FEV_1 and methocholine responsiveness).

In a follow-up study, unwashed and washed Texas cotton was compared to cotton grown in California and to Rayon. These data are summarized in Table 3. For FEV_1, there was no difference between the Rayon, the Texas washed, and the California cottons. However, the change observed for the Texas unwashed cotton was significantly larger than that for the other exposures. For methacholine, the response to rayon was no different that the response to the California cotton, however both the Texas unwashed and Texas washed showed significantly larger increases in responsiveness. These data again demonstrate a difference in response between methacholine and FEV_1 and also show that rayon, in these acute studies, does not cause any adverse pulmonary effects.

Figure 1 shows the results of an acute exposure study in which volunteers were exposed four hours on day one to either Rayon (0.5 mg/m^3), a blend of a California cotton and Texas cotton (1 mg/m^3), the California cotton (1 mg/m^3), and the Texas cotton (1 mg/m^3). The following day volunteers were again exposed to Rayon (0.5 mg/m^3) for 4 hours. There was a significant decrease in FEV_1 for each of the cottons over the first day of exposure, however there was no significant response to the rayon dust. These data again confirm the lack of an acute respiratory response to rayon. In summary, there is no evidence from acute exposure studies using human volunteers that cellulose based dust have any effects on respiratory function or methacholine responsiveness.

Epidemiological Studies

A number of epidemiology studies have compared the pulmonary health of workers in cotton textiles with those in man-made fiber mills (6). Berry et al. evaluated bronchitis in cotton mills and man-made fiber mills. Although the type of man-made fiber mill was not identified, they observed that bronchitis was higher in cotton mills than in man-made fiber mills. There was no association of bronchitis with dust level or length of exposure. More recent epidemiological studies have shown different patterns in that synthetic mill workers have shown greater declines for selected respiratory parameters than cotton workers. Again, for these studies the type of fiber used by the man-made fiber mills was not identified. Glindmeyer et al, compared the annual decline in FEV_1 between cotton mill workers and synthetic mill workers. After controlling for smoking, steeper declines were observed for the synthetic mill workers than the cotton mill workers (-24.7 vs -36.6 ml/yr, respectively) (7). Fishwick et al, reported a greater prevalence of respiratory symptoms in man-made fiber mills (8) and that the percent of perdicted FEV_1 was significantly less in man-made fiber mills than cotton mills (9). These data suggest that workers in man-made or synthetic fiber mills may be at an increased risk of adverse for adverse respiratory health effects. If these mills had a history of using regenerated cellulose fiber, then these observations could suggest an association between adverse respiratory effects and chronic exposure to cellulose. However, while biologically plausible, this conclusion cannot be confirmed by these studies because they were not specifically designed to evaluate the hypothesis that chronic exposure to man-made fibers increase risk for adverse respiratory outcomes. They can however be used to generate hypothesis about respiratory risk in man-made fiber environments and to regenerated cellulose specifically and could serve as the basis for a well designed prospective study to address these questions about cellulose in these environment.

In conclusion, there is no evidence that either cellulose or dust from regenerated cellulose fiber causes any acute respiratory effects in either animals or man. However, there is suggestive evidence from a subchronic animal study and from epidemiology studies of man-made fiber environments, that long-term exposure may cause specific pathological changes and alterations in respiratory function.

Literature Cited

1. Adamson, G.M., Human Health and Cellulose Dust Exposure, In: Proceedings of the 23th Cotton Dust Research Conference, pp:151-153. R. Rylander, P.J.

Wakelyn and R.R. Jacobs, eds. Memphis, TN:National Cotton Council, 1999.

2. Milton DK. Godleski JJ. Feldman HA. Greaves IA . Toxicity of intratracheally instilled cotton dust, cellulose, and endotoxin. American Review of Respiratory Disease. 142(1):184-92, 1990 Jul.
3. Karol, M., Ellakkain, M., Barnett, M., Alarie, Y., and Fischer, J. , Comparison of the Respiratory Response of Guinea Pigs to Cotton Dust and Endotoxin From Enterobacter agglomerans. In: Proceedings of the 23th Cotton Dust Research Conference, pp:151-153. R. Rylander, P.J. Wakelyn and R.R. Jacobs, eds. Memphis, TN:National Cotton Council, 1999.
4. Ogundiran, N., M. Ellakkani and M.Karol. Pulmonary Response of Guinea Pigs to Repeated Inhalation of Pseudomonas Syringae/Cellulose Powder, In: Proceedings of the 23th Cotton Dust Research Conference, pp:151-153. R. Rylander, P.J. Wakelyn and R.R. Jacobs, eds. Memphis, TN:National Cotton Council, 1999.
5. Jacobs,R. and B. Boehlecke, United States Department of Agriculture Cooperative Agreement 58-43YK-0-0025
6. Berry G. Molyneux MK. Tombleson JB. Relationship between dust level and byssinoise and bronchitis in Lancashire cotton mills. British Journal of Industrial Medicine. 31(1):18-27, 1974 Jan.
7. Glindmeyer, H.W., J.J. Lefante, R.N. Jones, R.J. Rando, and H. Weill; Cotton Dust and Across Shift Change in FEV1 and predictors of annual change in fev1. Am Rev Respir Dis 1991; 149:584-590 (1994)
8. Fishwick, D., Fletcher, A.M., Pickering, C.A.C., Niven, R. Farageher, E. Respiratory symptoms and dust exposure in Lancashire cotton and manmade mill operatives; Am J Respir Crit Care Med 1994; 150:441-7
9. Fishwick D. Fletcher AM. Pickering CA. McL Niven R. Faragher EB. Lung function in Lancashire cotton and man made fibre spinning mill operatives. Occupational & Environmental Medicine. 53(1):46-50, 1996 Jan.

Table 1. Acute Percent Changes in FEV_1 in Response to Exposures to Different Cotton Dust and Rayon

	Percent Change in FEV_1					
Exposure	**Overall**	**LS mean ⑤ 0**	**Non-Atopic**	**LS mean ⑤ 0**	**Atopic**	**LS mean ⑤ 0**
Tx Washed	0.49 (0.9)^{A}	N	1.52 (1.3)	N	-0.3 (1.2)	N
Tx Unwashed	-4.21 (0.9)^{B}	Y	-4.2 (1.4)	Y	-4.3 (1.2)	Y
Rayon	0.86 (1.0)^{A}	N	2.3 (1.5)	N	-0.07 (1.2)	N
Tx Additive	-3.36 (0.9)^{B}	Y	-4.0 (1.2)	Y	-2.7 (1.2)	Y

Means within a column with different letters are significantly different (P < 0.05).
Negative values indicate a decrease from pre-exposure values

Table 2. Exposure Related Change in Methacholine Responsiveness Using HCD.

Exposure	Overall Mean (SEM)	LS mean ⑤ 0	Non-Atopic	LS mean ⑤0	Atopic	LS mean ⑤ 0
Tx Washed	0.23 (0.08)^{A}	Y	0.21	N	0.25	Y
Texas Unwashed	0.76 (0.08)^{B}	Y	0.67	Y	0.84	Y
Rayon	-0.05 (0.08)^{C}	N	-0.14	N	0.02	N
Texas Additive	0.53 (0.07)^{D}	Y	0.50	Y	0.57	N

Means within a column with different letters are significantly different (P < 0.05).
Positive number means an increase in responsiveness

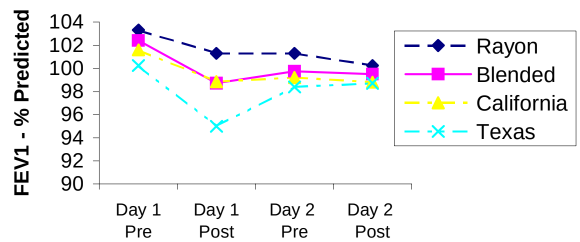

Figure 1. Pre and Post % Predicted over Two Sequential Exposure Days.

Table 3. Mean Drop in FEV_1 and Methacholine Response By Exposure Type.

Exposure ^{a}		FEV_1 Total	Methacholine TOTAL^{c}
California Cotton	Mean	-32^{A}	0.61^{A}
	SD	123	2.82
	p value^{a}	0.02	0.21
Texas Cotton	Mean	-147^{B}	2.36^{B}
	SD	166	3.90
	p value^{a}	0.0001	0.0009
Texas Washed Cotton	Mean	-75^{A}	1.98^{B}
	SD	142	3.18
	p value^{a}	0.0001	0.0007
Rayon	Mean	-37^{A}	0.21^{A}
	SD	118	0.73
	p value^{a}	0.10	0.092
p value ^{c}:			
exposure		0.0001	0.0026
exposure * atopic		0.08	0.99