# ASSESSMENT OF TOXICOLOGY (RESPIRATORY RISK) ASSOCIATED WITH AIRBORNE FIBROUS COTTON-RELATED DUST

**Robert R. Jacobs**
**Department of Environmental Health Sciences**
**School of Public Health**
**University of Alabama at Birmingham**
**Birmingham, AL**
**P. J. Wakelyn**
**National Cotton Council**
**Washington, DC**

## Abstract

Recently the U. S. Environmental Protection Agency (EPA) has identified naturally occurring and man-made fibers of respirable size, including cotton, as priority substances for review of health effects. The basis for this is a concern that respirable natural and synthetic organic fibers may cause lung diseases similar to those caused by asbestos and other mineral fibers. This paper reviews the literature linking man-made and natural organic fibers with 'fibrogenic lesions' and lung cancer; and summarizes the relevant data with respect to cotton-related dust. Conclusions regarding the risk of developing fibrogenic lesions or lung cancer from exposure to cotton dust/fibers are offered: Epidemiological studies of textile workers and chronic inhalation studies have not shown that exposure to cotton-related dust can cause or is a risk for fibrosis or cancer; pathology studies (postmortem studies of long-term cotton mill workers) have shown no evidence of fibrosis or cancer and are consistent with chronic bronchitis.

## Introduction

Naturally occurring (including cotton) and man-made (synthetic) fibers of respirable size are substances that have been identified by the U.S. Environmental Protection Agency (EPA) as priority substances for toxicity evaluation (the Prioritized Chemicals List, U.S. EPA, EPA 530-D-97-002, April 1997, Draft; and "Assessment of the Potential Health Effects of Natural and Man-Made Fibers and Their Testing Needs: Perspectives of the U.S. Environmental Protection Agency") under the Toxic Substances Control Act (TSCA). Fibers of respirable size as defined by WHO are of length >5 microns and diameter <3 microns with an aspect ratio >3:1 (M. Meldrum ref. 5). The health concern for respirable fibers is based on the link of occupational asbestos exposure and environmental erionite fiber exposure to the development of chronic respiratory diseases, including interstitial lung fibrosis, lung cancer, and mesothelioma in humans. There is also considerable laboratory evidence indicating that a variety of fibers of varying physical and chemical characteristics can elicit fibrogenic and carcinogenic effects in animals under certain exposure conditions. For example, recent studies have reported: 1) the isolation of cellulosic and plastic fibers from tissue sections of lung specimens from cancer patients; and 2) that man-made organic fibers may induce fibrotic lesions in animals.

Reprinted from the *Proceedings of the Beltwide Cotton Conference*
Volume 1:213-220 (1998)
National Cotton Council, Memphis TN

### Asbestos Pulmonary Toxicity

The association between exposure to mineral fibrous dust and development of lung disease has a long history. From ancient literature, Pliny the Elder reported on the pulmonary toxicity of asbestos. But perhaps a greater indicator of the risk associated with asbestos was the action taken in 1918 by both U.S. and Canadian companies of refusing to insure asbestos workers based on data from actuarial risk (1). Asbestosis was described medically in the 1920s as a pneumoconiosis, similar to black lung and silicosis, and in the 1930s, an increased incidence of lung cancer was observed in workers who survive asbestosis. The definitive evidence linking asbestos to lung cancer came from the epidemiology work by Doll in the 1950s, which demonstrated a 10-fold increase in lung cancer among asbestos workers (2). Later, Selikoff et al, using Union records, demonstrated that lung cancer risk in asbestos workers was strongly associated with smoking, but that non-smokers were at substantial risk as well (3). Finally, mesothelioma, a rare cancer of the pleura, was shown to be increased risk among asbestos workers, however there was no synergy with smoking.

The types of disease outcomes associated with asbestos exposure include:

- **Asbestosis**, a pulmonary fibrosis characterized by the presence of macrophages, neutrophils and irregular areas of increased collagen, most prominent in the lung bases and subpleural locations. A characteristic feature of asbestosis is the presence of asbestos bodies which are asbestos fibers coated with hemosiderin. Asbestos bodies account for fewer than 1% of all asbestos fibers retained in the lung but because of the universal use of asbestos, asbestos bodies are found in the lungs of persons both with and without occupational exposure.

- **Asbestos-induced lung cancer**: Exposure to asbestos increases the incidence of all common histological types of lung cancer (squamous cell carcinoma, small cell carcinoma, and adenocarcinoma). Asbestos related bronchogenic cancers have a long latency period, ranging from 15-30 years after onset of exposure. These is some question as to whether asbestosis is a risk factor for asbestos related bronchogenic lung cancer, however, the International Agency for Research on Cancer (IARC) concluded that the mechanisms of production of asbestos-related lung cancer are unknown and that asbestosis is

not a biologically effective dose marker of lung cancer susceptibility (4).

- **Asbestos-induced pleural diseases**: Pleural abnormalities include areas of plural thickening, focal pleural plaques and pleural and diaphragmatic calcifications. There is generally no pulmonary impairment associated with these pleural disorders and their significance is that they indicate a previous history of exposure to asbestos and therefore a risk for other related disorders. However, their presence is not an indicator of risk for developing asbestosis or bronchogenic lung cancer.

- **Asbestos-induced Mesothelioma**: Mesothelioma is an extremely rare tumor originating in the cell lining of the plural space or peritoneum. Approximately 75% of the patients with malignant mesothelioma have a history of exposure to asbestos.

Asbestos is a general term for a group of mineral silicates that are fibrous. There are two basic forms, Serpentine (chrysotile or white asbestos) and Amphibole (Amosite, Crocidolite, Tremolite, Anthophylite and Actinolite). Both are hydrated magnesium silicates ($Mg_6Si_4O_{10}$ $(OH_8)$), but differ in their chemical structure and properties. In the U.S., the majority of asbestos used is Chrysotile, a fiber made up of fibrillar subunits arranged in pseudo hexagonal arrays of silicon sheets .

**Structure and Fiber Characteristics and Disease Mechanisms**

It is generally accepted that the carcinogenic potential of any fiber is related to its **dimension** and its **biopersistence.** Only fiber particles of length > 5 microns ($\mu$m) and diameter <3 $\mu$m, and with an aspect ratio (length to diameter) of >3:1 are able to reach the periphery of the lung. In addition to the traditionally considered variables of **particle size and shape** (dimension), and number of fibers present, characteristics such as chemical composition, dissolution behavior, ion exchange, sorptive properties, surface area, and the nature of the surface (e.g., surface reactivity) play important roles in determining the toxicity and carcinogenicity of a particle. (5). All of these variables are likely to be related to fiber biopersistence which can be defined as the fiber retention in a tissue. Biodegradability refers to the breakdown and/or dissolution of fibers within the lung or other tissues; mechanical, chemical and/or enzymatic factor may be involved (5a).

Fibers residing in the lung milieu will be attacked and modified chemically, structurally, and physically (size and shape) (6). Because of surface reactivity, the toxicity of solids is not predictable from the chemical composition and molecular structure, as with water soluble compounds. Thus, particles having the same bulk composition may have different toxicities due to their micromorphology, which determines the kind and abundance of active surface sites, thus modulating reactivity toward cells and tissues (7). Ultimately asbestos fibers are thought to induce DNA damage by oxidoreduction processes that originate from cells during attempted fiber phagocytosis. Oxidoreduction reactions originating from cells can induce mutations, chromosomal damage, alteration of cell cycle progression, formation of aneuploid and polyploid cells, and nuclear disruption. Therefore, asbestos fibers may act at multiple stages of the carcinogenic process by both genetic and epigenetic mechanisms (8,9). The question remains, do other fibers with similar particle sizes and shapes endure a similar toxicity?

**Other Fibrous Mineral Materials and Pulmonary Toxicity**

The increasing knowledge about the carcinogenic properties of asbestos have given rise to an extensive research on possible adverse health effects of alternative materials. Especially man-made mineral fibers (MMMF), i.e., glass fibers, but also glass-, stone- and slag wools. In rodent studies, inhalation of MMMF, except refractory ceramic fibers, did not provoke tumors, whereas the intratracheal, intrapleural and intraperitoneal instillation induced a carcinogenic effect for most kinds of MMMF. Compared to asbestos, MMMF clears out much faster from the lung tissue. There is no consistent epidemiological evidence for an increased in standardized mortality ratios for malignant tumors of the airways and malignant mesotheliomas in individuals formerly exposed to MMMF. Therefore, there appears to be no clear-cut cancer risk, when one is handling glass fibers and wool; however, the potential risk of exposure to refractory ceramic fibers has to be evaluated with more caution (10-13).

Taken together, the data indicate that among those occupationally exposed, glass fibers do not appear to increase risk of respiratory system cancer. Of six studies that specifically examined rock and slag wool workers, three reported excesses in respiratory system cancer among such workers. Two of these three studies, however, did not control for cigarette smoking, a powerful predictor of such cancers. There are no published studies, in humans, of refractory ceramic fibers (14,15).

**Natural Organic Fibers/Cotton and Other Cellulosic Toxicity Data**

The effects of exposure to vegetable fiber dust were described among dressers of flax and hemp as early as 1713 by Bernardo Ramazzini. In the 19th century, two Belgian physicians, Maresta and Heyman, in interviews of 1000 men and 100 women in the textile mills of Gent, described acute symptoms on Mondays. Thus the association of Monday illness with exposure to cotton dust was established over 150 years ago. The disease associated with work in the cotton textile industry was named Byssinosis, a phrase first used by the Parisian Physician A. Proust in 1877. Byssinosis, also

described in lay terms as "Brown Lung", is an occupational lung disease associated with exposure to airborne dust from textile processing of vegetable fibers (e.g. cotton, flax, and hemp), and is seen primarily in workers who are in the early phases of fiber processing (opening, blending, carding) (16). Cotton dust is regulated by the US Occupational Safety and Health Administration (OSHA), the UK Health and Safety Executive (HSE) and other countries because it can cause Byssinosis, an obstructive respiratory disease, similar in its chronic state to chronic bronchitis (16a), not as a cause of fibrosis (restrictive disease) or cancer like asbestos is. The acute and chronic respiratory effects of cotton dust were the subject of almost 15 years of rulemaking by OSHA and have been intensively reviewed (16a, 16b).

The diagnosis of Byssinosis has been difficult in that there are few unique markers of disease. Currently, for regulatory purposes, Byssinosis is diagnosed through a combination of questionnaire responses and objective measures of respiratory function. These diagnostic criteria are thought to have had their origins in a government committee established in 1932 in Great Britain to determine "whether and if so to what extent dust in card rooms in the cotton industry is a cause of ill-health or disease". The report stated that "the medical witness who came before us could not suggest any clinical features whereby the respiratory disease which so frequently occurred among card room operatives could be differentiated from that which occurred in the general population." The report concluded that the "continued effect of inhaling dust is progressive" and that this progression could be identified to occur in three "stages", namely, a) stage of initiation, b) stage of temporary incapacity and c) stage of total incapacity. This sequence was based on the appearance of eight textile operatives that appeared as examples of the natural history of Byssinosis (17). There was no mention of other types of respiratory disorders, specifically lung cancer. Richard Schilling later expanded the three stage clinical classification of Byssinosis in a series of papers, the first of which was published in 1950, and which cites HMHO document, in a clinical classification scheme known as the "Schilling Classification". Shilling later added the objective measures of respiratory function. At no point in this sequence of papers nor in subsequently published studies is any reference made to chronic pulmonary diseases that are similar to those that occur on exposure to asbestos or dust that cause pneumonociosis.

In 1987, a panel of scientist, including Richard Schilling, met in Manchester, England to discuss the acute and chronic risk associated with exposure to cotton dust (18). This meeting resulted in the formation of the "Manchester Criteria". These criteria are shown in the Table 1. In the literature reviewed by this group, no evidence for cancer or pre-cancer lesions were presented.

Table 1. Pulmonary Reactions to Cotton Dust

| The Manchester Criteria |
|---|
| • Mill Fever |
| • Acute Change in Pulmonary Function |
| • Chest Tightness |
| • Increased Airway hyper-reactivity |
| • Chronic Bronchitis |
| • Byssinosis |

## Is There Evidence for an Association Between Exposure to Cotton Fibers and Lung Cancer?

Most of the epidemiology studies evaluating the acute and chronic effects of exposure to cotton dust served as the basis of the Manchester Criteria. None of these studies have indicated an elevated risk for the development of respiratory cancers, and most have reported a reduced mortality odds ratio.

Table 2 summarizes the observed numbers of deaths from all causes and for all cancer and respiratory cancer in male and female cotton textile workers.

Table 2. Deaths from all causes, for all cancer and respiratory cancer in textile workers

| Study | All Causes Obs. | SMR | All Cancers Obs. | SMR | Respiratory Cancers Obs. | SMR |
|---|---|---|---|---|---|---|
| Enterline, 1965 (19) | 486 | 88 | 55 | 60 | 7 | 27 |
| Henderson and Enterline, 1973 (20) | 824 | 79 | 91 | 70 | 20 | 55 |
| Datum et al 1975 (21) | | | | | | |
| Years worked | 102 | 109 | 14 | 106 | 6 | 163 |
| <20 | 177 | 85 | 22 | 73 | 6 | 67 |
| Years worked >20 | | | | | | |
| Berry and Molyneaux, 1981 (22) | 48 | 70 | 11 | 64 | na | na |
| Merchant and Ortmeyer, 1981 (23) | | | | | | |
| Lightly exposed | 320 | 103 | 47 | 89 | 18 | 101 |
| Highly exposed | 51 | 98 | 18 | 41 | 5 | 40 |

In general, the SMRs for all cancers and for respiratory cancers specifically were lower than those observed in the general population. The smoking patterns for those studies that accounted for smoking within the textile industry were no different than for the general population suggesting that other factors would account for the reduced prevalence of lung cancer. One of the postulated factors is endotoxin from Gram-negative bacteria. Endotoxin, a known immunomodulator is a common naturally occurring contaminant of cotton and most plant materials and is a

suspected causative of Byssinosis (23a). It has been suggested that the low prevalance of cancer in cotton textile mill workers is associated with the chronic low level of exposure to endotoxins (24). This postulate has been evaluated in animal studies. Lange injected BL/6J mice with Lewis lung carcinoma (LL/2) and exposed them to aerosolized endotoxin prepared from *E. agglomerans* isolated from cotton dust. Animals treated with inhaled endotoxin exhibited reduced lung cancer involvement compared to positive controls not exposed to endotoxin (25). In a follow-up study, mice injected with Lewis Lung carcinoma were exposed to endotoxin (25). In a follow-up study, mice injected with Lewis Lung carcinoma were exposed to aerosolized endotoxin and an inert cellulose dust (26). The cotton dust exposed mice had a significantly reduced pulmonary tumor involvement when compared to non-treated and cellulose dust controls (27).

A more recent epidemiology study from a different occupational environment with exposure to organic dust has also postulated that endotoxin may account for the lower cancer incidence. From two areas in the Province of Padova, cancer mortality was evaluated in 2,283 male farmers who worked either in cattle raising or in crop/orchard cultivation. There were 422 cohort deaths from 1970 to 1992. Using the regional population as a reference, the cancer mortality was significantly reduced among the 1,561 farmers (SMR = 0.65; CI = 0.53-0.81); there was a significant decrease in lung cancer (SMR = 0.49; CI = 0.31-0.74. Neither overall cancer mortality nor the lung cancer SMR was reduced for the 722 crop/orchard farmers. Among dairy farmers, lung cancer SMRs showed a significant downward trend with an increasing load of work. This decrease was not attributed to either a selection (healthy worker effect) or a confounding (lower percentage of smokers) bias. The authors postulated that since dairy farmers are known to be exposed to higher airborne endotoxin concentrations, they may be protected against lung cancer through the tumor necrosis factor produced by alveolar macrophages (28).

More recent studies evaluating the mortality and disability of cotton mill workers have shown similar trends. In a study of five Finnish cotton mills, the respiratory health of 1065 women, exposed to raw cotton dust for a minimum of five years between 1950 and 1971, was evaluated. The follow up period for the mortality analysis was from 1950 to 1985. Comparison of incidence rates between cotton mill workers and the Finnish female population showed excessive rates for both respiratory diseases ($p<0.001$) and musculoskeletal diseases ($p<0.01$), with an excess of new cases of rheumatoid arthritis ($p<0.001$). By the end of 1985 the number of person years was 31,678 and the number of deaths 95. The SMRs for the total period of follow up (1950-85) showed no excess for respiratory diseases, and a lower than expected mortality from cardiovascular diseases (29).

To evaluate the effectiveness of the current workplace standards in preventing chronic health effects from cotton dust exposure, a 5-yr. longitudinal study of a large multi-mill population of cotton textile and synthetic process workers, employed at a major US textile company, was conducted. The analysis was limited to those 1,817 subjects who worked exclusively in cotton yarn manufacturing or slashing and weaving, or in synthetic textile mills. The expected effect of smoking on average annual change in lung function was demonstrated for both cotton and synthetic workers. Despite lower overall dust exposure, cotton yarn workers exhibited steeper annual declines in lung function than did workers in slashing and weaving; this difference persisted within each smoking category, indicating a dust potency effect. There were mill differences in annual change in lung function among cotton workers, potentially masking an exposure effect. A smoking-work area interaction persisted after adjusting for mill differences, with the largest annual declines observed in cotton yarn workers who smoke. A significant dose-response relationship was seen in cotton yarn manufacturing between annual declines in $FEV_1$, FVC, and FEF25-75 and average exposure by mill, and the larger declines were found in mills using the highest percentage and lowest grade of cotton. No data regarding respiratory cancers were presented (30).

In a study comparing respiratory effects cotton dust and asbestos, 63 spinners exposed to cotton dust and 75 spinners exposed to asbestos dust were examined. In the women working in asbestos spinning rooms the prevalence on chronic nonspecific respiratory tract disease was 30%. For the cotton exposed group it was 15%. Mean FVC values were within the predicted values, although they were statistically significantly lower in asbestos exposed spinners ($p<0.001$). However, the $FEV_1$was significantly lower ($p<0.01$) in those exposed to cotton dust (31). These data reinforce the difference between dust which causes restrictive diseases (asbestos), and those which cause obstructive diseases (cotton-related).

A multi-cancer site, multi-factor case control study, undertaken to generate hypotheses about possible occupational carcinogens observed the following elevated risk: lung-wood dust (odds ratio (OR)=1.5), stomach-wood dust (OR=1.5), colorectal-synthetic fiber (OR=1.5), bladder-synthetic fiber (OR=1.8), non-Hodgkin's lymphoma-cotton dust (OR=1.9), colon-grain dust (OR=2.6), prostate-grain dust (OR=2.2), and prostate-paper dust (OR=2.0). Only the associations with wood dust, synthetic fibers and cotton dust showed some evidence of "dose-response" with duration of exposure (32). No data were given on exposure levels in the associated industry, job function or other potential hazardous exposures.

A retrospective study evaluating cause specific mortality patterns in male workers from 1968-1978 identified a significantly elevated PMR (110; CI 102-120) for nonmalignant respiratory disease. This was related to areas with higher dust exposures including carding, lapping and combing operatives (PMR 166; CI 114-243) and cotton

manufacturing (PMR 137; CI 104-179). PMRs were also significantly elevated for diseases of the circulatory system (PMR 103; CI 101-105). There was a statistically significant PMR deficit observed for malignant neoplasm (PMR 89, CI 85-94) and PMRs for lung cancers were low across all textile manufacturing (PMR 80, CI 72-88). When textile manufacturing was stratified by type: wool and worsted; cotton, synthetic, and silk; synthetic and silk only; dyeing and finishing; knitting; and undetermined, the PMRs were significantly reduced for all categories except cotton, synthetic and silk (PMR 100, CI 78-127) and for synthetic and silk (PMR 130, CI 67-251). For these two categories the PMRs were no different than expected values (33).

The mortality of 3458 cotton industry workers, originally enrolled in a study of respiratory symptoms (1968-1970), was followed to the end of 1984. Both the total mortality and the mortality from respiratory disease was less than expected, and both decreased as length of service increased. However, for the subjects who initially reported byssinotic symptoms, the mortality from respiratory disease was slightly raised overall, together with a long-term effect reflected in respiratory mortality on the health of those workers susceptible to the effects of cotton dust. The mortality from lung cancer was lower than expected, and it decreased with length of service. This finding is consistent with other observations that exposure to cotton dust may reduce the risk of lung cancer (34).

Data from a case-control study conducted at 27 hospitals in France in 1986-1988 were analyzed to examine the association between exposure to textile dust and sinonasal cancer. The study included 207 cases and 409 controls. Exposure to textile dust was assessed by an industrial hygienist. Among women, exposure to textile dust was associated with an elevated risk of squamous cell carcinoma (odds ratio (OR) = 2.45, 95% CI = 0.85-7.06) and adenocarcinoma (OR=3.70, 95% CI=0.56-24.4). For squamous cell carcinomas, the risk increased with the duration and the level of exposure ($P<0.05$): the ORs for the low, medium and high level of cumulative exposure were 1.00 (95% CI=0.10-9.43), 2.43 (95% CI = 0.54-11.1), and 3.57 (95% CI = 0.92-13.8), respectively. There was also a limited evidence of an excess risk of squamous cell carcinomas among men exposed to high levels of textile dust (OR=2.18, 95% CI=0.65-7.30, four exposed cases). The risks associated with the different types of textile fibers (cotton, wool, and synthetic fibers) were similar (35). No data were given on exposure levels to "textile dust", job function or other potential hazardous exposure.

The relationship between lung cancer risk and work in the cotton textile industry was investigated in 1405 newly diagnosed lung cancer cases and 1495 controls in urban Shanghai. A significantly low risk of lung cancer was associated with cotton textile employment [(OR) = 0.7, 95% CI = 0.6-0.9)]. In men, the decreased risk was observed among both smokers (OR = 0.7, 95% CI = 0.5-1.1) and nonsmokers (OR = 0.3, 95% CI = 0.1-1.0). In women, the risk also decreased regardless of smoking status (OR = 0.8, 95% CI =0.4-1.6 among smokers; OR = 0.9, 95% CI = 0.6-1.2 among nonsmokers). Low risks were found regardless of occupations within the cotton textile industry. The OR for workers in textile processing who potentially had greater dust exposure was 0.8 (95% CI = 0.6-1.2), whereas the OR for those in other industry jobs was 0.7 (95% CI = 0.4-1.0). There was little difference in risk according to self-reported exposure to textile dust, and no clear trend with duration of employment or dust exposure. The findings are consistent with prior epidemiological studies and support the possible role of bacterial endotoxins as tumor-inhibitory factors, that are found in dusts from cotton and other fiber crops (36).

The only report identifying an association between lung cancer and exposure to cotton dust was a case-control study of 141 newly cytologically or pathologically diagnose cancer patients in Tiawan. The comparison between cases and age- and sex-matched hospital and neighborhood controls showed lung cancer was significantly associated with cigarette smoking, keeping doves, prior chronic bronchitis, occupational exposure to cotton dust, asbestos and radiation, low frequency of burning incense, and low intake of vitamin A derived from vegetables and fruits (37). No data were given on exposure levels and there are many confounding factors in this study.

## Is There Pathological Evidence Suggesting a Potential for Lung Cancer?

In a 1997 report **Pauly** et al. “observed cellulosic and plastic fibers in the lungs of patients with lung cancer (83% of non-lung cancer specimens and 97% of lung cancer specimens)" (38). The results of this study implied an association of cellulose and plastic based fibers and lung cancer and suggested that more research is needed to evaluate this association. This observation also raises the question regarding the biopersistence of cellulose based fibers. The method of fiber-detection used by Pauly et al. in this study was developed to isolate macrophages from lung tissue and is not a standard method for determining fibers. The lung samples of patients with lung cancer or lung metastases of other cancers were collected and examined without an appropriate control group. In their study Pauly et al. found fibers >250 $\mu$m (i.e., standard size textile fibers); such fibers are not inhalable and, therefore, can not reach the alveoli. Such fibers could be from contamination during the removal of the lung tissue by a swab and there are many possibilities in a hospital to expose and contaminate patients lung tissue with cellulosic and plastic fibers. Thus, it is not known if the fibers that were found are actually inhaled or due to contamination. Further work by Pauly et al. may answer this and other questions.

Several studies have evaluated the pathology associated with exposure to cotton dust. K. Schilling, in 1925 described morphologic findings in cotton spinners and determined that

the lungs showed none of the changes seen after inhalation of other fibrotic dust (39). Also in 1925, Landis reported being unable to detect any distinctive lesions in the lung autopsy of 50 cotton-workers (40). In another autopsy study, Gough reported the presence of chronic bronchitis and emphysema in the lungs of cotton workers but indicated they were not distinguishable from the same lesions in non-cotton workers (41). **Ruttner et al** reported on the presence of cellulose "cotton" fibers in the lungs of a single cotton operative that had severe fibrosis (42). The authors eliminated tuberculosis as an confounding exposure, and differentiated the fibrosis from silicosis since neither quartz nor silicated could be demonstrated. They concluded that exposure to cotton dust causes not only byssinosis, but can lead to depositing of cotton fibers in the lung parenchyma and subsequent foreign body reactions and progressive fibrosis. They speculated that similar observations had not been reported because of the lack of post-mortem investigations in cases of byssinosis. However, subsequent evaluation of this case suggested a diagnosis of sarcoidosis in a cotton worker.

Postmortem studies of compensated byssinotics and long-term cotton mill workers have demonstrated that the airways are affected by cotton dust exposure (43, 43a, 44, 45). Findings attributable to the effects of cotton dust inhalation are essentially those of chronic bronchitis and include mucous gland hypertrophy and globlet cell hyperplasis, as well as smooth muscle hypertrophy.

Edwards reported a post-mortem study of patients being compensated for byssinosis in the United Kingdom (43). Forty-three cases were evaluated for pathological changes. Sputum and wheeze while living and gland hyperplasia and smooth muscle hypertrophy on autopsy were observed regardless of smoking status and degree of ventilatory impairment. Emphysema was not routinely observed in non-smoking byssinotic subjects and no other parenchymal disease, including fibrosis was observed. Byssinosis bodies were observed in 7 of 43 subjects, but was not a routine occurrence. There was no evidence that these have diagnostic or pathogenetic significance. Cotton fibers were not observed in the lungs.

A review of 2895 consecutive autopsies from 1962 to 1980 showed no significant differences in the prevalence of emphysema or other chronic lung disease between 282 active and retired employees of a cotton textile mill and the non-textile population. There was no statistical evidence that exposure to cotton dust, even after many years, produced emphysema, interstitial fibrosis, or cor pulmonale. The prevalence of emphysema in the series was highest in white males (22.0%), followed closely by black males (18.3%). In white females it was 7.5%, in black females, 5.5%. The prevalence in subjects under age 50 yr was 4.5%; in the age group 60-64 yr, 14.6%; and in subjects 65 yr of age and older, 21.9% (44).

A collection of 565 unselected inflation-fixed lungs was divided into three groups: (1) normal (209 lungs); (2) centrilobular emphysema (231 lungs); and (3) "other" (125 lungs), the last including examples of fibrosis, tuberculosis, cancer, and other forms of emphysema. Clinical hospital records were reviewed to ascertain smoking history [no smoking (105 lungs); greater than 0.5 pack cigarettes per day (427 lungs); or pipe/cigar (33 lungs)] and occupation [non-textile (521 lungs), or textile (44 lungs)]. Lungs were subjected to morphometric determination of the extent of centrilobular emphysema, mucus gland hyperplasia in large bronchi, and goblet cell metaplasia in bronchioles. Extent of tissue pigmentation in normal lungs was also measured. Associations between morphologic data and background factors were examined by covariance analysis. As in many previous studies, data show highly significant cigarette smoking effects on all factors measured. Significant pipe smoker effects were also found, and when the cigarette group was excluded, a significant association was found between cotton dust exposure and both mucus gland hyperplasia and goblet cell metaplasia, but not emphysema. The results suggest that centrilobular emphysema is not associated occupationally in the textile industry, although bronchitis and bronchiolitis may be (45).

In summary, these human pathologies do not support the development of fibrotic lesion, fiber biopersistence or cancer in the lungs of textile workers.

**Chronic Animal Inhalation Studies**

A chronic study which exposed guinea pigs to aerosols of cotton dust for 52 weeks used the following parameters to indicate chronic effects: respiratory measurements, weight gain, lung volume and weight, and histopathological evaluation. In the first 3 months, experimental animals displayed an increase in breathing frequency and a decrease in breathing volume measured as whole-body plethysmographic pressure. These effects were pronounced on the "Monday" of each week. During months 3-6, similar reactions occurred on each day of exposure, although Monday responses were most severe. After 6 months, respiratory reactions were pronounced daily. Other indications of a chronic effect of exposure were increased lung volume, measured by water displacement, 15.0 +/- 3.3 ml (mean +/- SD) vs 9.8 +/- 2.0 ml for the controls; increased lung weight 9.4 +/- 1.5 g vs 7.0 +/- 0.8 g; and bronchiolar epithelial hyperplasia and hyperplasia of alveolar type II cells. Additionally, a histomorphometric study of the lungs performed by others detected changes in the peripheral conducting airways, including increased thickness of bronchiolar epithelium and increased thickness of septa at the alveolar level, denoting chronic exposure. No fibrotic lesions or cancer were described and the presence of cellulose fibers were not indicated by histopathologic evaluation (46).

**Acute Animal Inhalation Study with Cellulose Fiber Particles**

Warheit et al. conducted a study to access the toxicity of inhaled cellulose fibers and to compare the pulmonary effects with other organic fiber-types (46a). Male rats were exposed to an aerosol on Thermocell mechanical wood pulp (Laxa Bruks AB, Rofors, Sweden) cellulose fibers for 2 weeks at target concentrations of 300 and 575 fibers/cc. Following exposures, the lungs of rats were evaluated 3 and 10 days, as well as 1 and 3 months postexposure by lavage and immediately after, as well as 10 days, 1 and 3 months for biopersistence/clearance studies. The parameters that were evaluated were pulmonary clearance, retention and durability of inhaled cellulose fibers, pulmonary inflammation, as measured by bronchoalveolar lavage indices and a BrdU method for cellular proliferation of airway and alveolar cells. Two week high dose inhalation exposures to cellulose fibers produced lung burdens in the range of 3 x 10E7 fibers. Clearance of cellulose fibers was moderate to slow with mean values in the high dose group of 2.84 x 10E7 reduced to 1.55 x 10E7 after 3 months postexposure. Preliminary data indicate that the median lengths of fibers recovered from digested lungs of exposed rats were the following: 13$\mu$m (2wk/0); 10 $\mu$m (2wk/10D); 11 $\mu$m (2wk/1M); and 10 $\mu$m (2wk/3M); using bronchoalveolar lavage techniques, it was demonstrated that inhaled cellulose fibers produced a mild but transient pulmonary inflammatory response, and this returned to control levels within 10 days postexposure. The results suggest that inhaled cellulose fibers have a slow clearance pattern but do not produce sustained pulmonary inflammatory effects.

**Evidence That Cellulose Can Cause Pre-Cancerous Lesions (Intratracheal and Other Impantations)**

Several studies have reported the effects of pure cellulose placed either in the lung or in other tissues. Cellulose, after a single intratracheal dose (15 mg per animal), caused fibrosing granulomatous alveobronchiolitis and an increase of IgA production in the bronchoalveolar lavage. Fibrosing alveolitis showed moderate progression with time and injury of type I pneumocytes and the incomplete repair of type II pneumocytes were detected. The damage of the alveolar epithelium initiated and activated a series of processes that led to definite pulmonary alterations including pulmonary fibrosis leading to the disintegration of the alveolo-capillary morphological functional unit (47).

The lung-damaging effect of intratracheally administered cellulose was examined in bronchoalveolar lavage fluid 1, 3 and 7 days after instillation. Histological tests were performed after days 1, 3 and 30. Interstitial edema as well as the initial signs of inflammation were observed in the lung after the first day., Protein, lactate dehydrogenase, acid phosphatase, phospholipid and cell count were elevated in the bronchoalveolar lavage fluid after days 1 and 3. At one month a fibrotic like bronchioalveolitis was observed (48).

In a negative study, Anderson et. al. reported that the chronic ingestion of purified cellulose over the entire life spans in rats and mice did not result in any increase in spontaneous disease or neoplasia. Further, purified cellulose did not display promotional activity in the mammary gland, the colon, or the bladder of rats nor did it significantly alter the absorption or the metabolism of dietary components. No adverse effects were found on reproduction or neonate development in rats and mice (49).

In a study evaluating cotton dust and purified cellulose, Milton et al exposed hamsters intratracheally with respirable cotton dust particles (0.75 mg/100-g animal), endotoxin (255 micrograms/100-g animal), and cellulose (0.75 mg/100-g animal)twice weekly for 6 weeks. A saline-instilled group was the control. Hamsters were killed 8 wk after the last instillation. Endotoxin-treated animals had increased lung distensibility, reduced surface-to-volume (S/V) ratio, and morphologically apparent mild centrilobular emphysema. Cellulose-treated animals had decreased distensibility, normal S/V ratio, and significant numbers of granulomata with patchy areas of thickened interalveolar septa. Cotton-dust-instilled animals had normal distensibility, reduced S/V ratio, significant numbers of granulomata, and mild centrilobular emphysema. These data suggest that intratracheally introduced cotton dust produces a significant parenchymal lesion with elements similar to both the emphysematous response to endotoxin and the fibrotic nodular response to cellulose (50).

Tissue biocompatibility of cellulose and its derivatives was examined in two *in vivo* tests, one for absorbance by living tissue and one for foreign body reaction. The samples included: regenerated celluloses and cellulose derivatives: methyl cellulose, ethyl cellulose, aminoethyl cellulose, hydroxyethyl cellulose, and cellulosic polyion complexes. The *in vivo* absorbance by living tissue was found to depend on the degree of crystallinity and the chemical structure of the sample. The foreign body reaction was relatively mild for all the samples examined, showing that cellulose can be converted to biocompatible materials by physical and/or chemical transformation (51).

Since the 1950s a number of implantable substances have been used to study granulation tissue formation: steel mesh, polyvinylalcohol (PVA), polytetrafluoroethylene (PTFE), polyurethane, and viscose cellulose sponges (VCS). The side effects of these materials on granulation tissue formation vary considerably. An ideal material does not interfere with the normal wound-healing process and collects as many cells as possible for further analysis. Viscose cellulose sponge has been shown to be one of the most inert materials for this purpose. In this study Pajulo et al. examined the correlation between changes in the structure of the sponge and the number of cells harvested and the synthesis of granulation tissue after subcutaneous implantation in rats. It was discovered that it is possible to control the structure of the sponge and by certain changes in this structure increase the

number of invading cells and the production of granulation tissue in the sponge. There is, however, a distinct plateau after which changes in structure do not increase the number of invading cells and the production of granulation tissue in the sponge (52).

Finally, a case report indicated that fine cotton fibers originating from the cotton gauze pads used during surgery caused a rare case of intracranial foreign body granuloma. The patient presented with headache and right hemiparesis. CT scan demonstrated a large enhanced tumor in the left temporal lobe. The brain surface was covered with oxidized cellulose (Oxycell) after the tumor was subtotally removed. The histological diagnosis was astrocytoma. A CT and MRI on the 40th day after the operation, showed a large tumor in the left temporal lobe. A second operation disclosed a mass which was a foreign body granuloma containing fine cotton fibers suggesting that cotton fibers caused the foreign body granuloma (52).

These data suggest that cellulose can cause fibrotic-like lesions in the lungs or granuloma in other tissues when implanted. However, they also suggest that the physical/chemical characteristics of the cellulose (including size of the fibers which are too big to be cleared from the lung, for example) are important determinants of its biological activity and biopersistence. This may account for differences seen in the pathology of workers exposed to cotton dust in the workplace and the pathology after implanting cellulose. The different health effect/toxicity of implantation of cellulosic fibrous material into issues as opposed to inhalation has also been observed with MMMF where intratracheal instillation induced carcinogenic effects whereas inhalation did not provoke tumors (14,15).

## Conclusions

1. There is no epidemiological evidence from the literature that cotton fibers can cause cancer

2. Chronic inhalation studies with cotton dust have not shown a risk for fibrosis or cancer

3. Postmorteum pathology studies of long-term cotton mill workers have shown no evidence of fibrosis and are consistent with chronic bronchitis.

4. There is some suggestion that implanted cellulose can cause granuloma formation but this has not been demonstrated in postmorteum pathology studies on cotton textile workers.

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