HUMAN HEALTH AND CELLULOSE DUST EXPOSURE

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Abstract

One of the most ubiquitous polysaccharides cellulose, possesses physical and chemical properties suiting it to a variety of industrial applications. There has been a long history of safe occupational exposure to wood derived cellulose in the pulp and paper industries. In all industrialized countries, wood derived-cellulose is treated as a nuisance dust. Several epidemiology studies of the pulp and paper industry indicate that, in general, workers are at lower risk of lung disease than the general population. Elevations of lung disease noted when comparing one employee subgroup to another, have been largely attributed to smoking. The largest epidemiology study currently conducted by Johns Hopkins University, is a case cohort analysis to designed to determine if there is any potential for specific chemical exposures to be linked to lung disease, and to confirm the effect of smoking. Animal studies conducted to date have examined the effect of high dose lung exposure to different cellulose containing compounds (e.g., microcrystalline cellulose, cellulose insulation) in the lung. All studies used high dosed levels (>2mg/g lung), likely to exceed the lungs capacity to clear cellulose, and subsequently showed nonspecific inflammatory effects. Similar responses can be demonstrated for a variety of insoluble nuisance dusts at high exposure, whereas at sub-overload doses persistent inflammatory effects are not observed. Importantly, in a recent study we have examined the effects of low doses of various cellulose containing materials in the rat lung. The results show minimal transient inflammatory effects consistent with the effects of innocuous nuisance dusts.

Introduction

The use of cellulose spans beyond its fundamental role in the paper products and textile industries, to such important uses as food additives for thickening, binding and emulsifiers. It is also widely used in the cosmetics, personal care, pharmaceutical and paint industries. Occupational exposure to cellulose dust has been managed under OSHA nuisance dust limits of 15mg/m3 total dust and 5mg/m3 respirable dust. Other groups such as the American Conference of Governmental Industrial Hygienists (ACGIH) have proposed limits of 10mg/m3 total dust and 3mg/m3 respirable dust.

Despite a long history of safe use of bleached cellulose, effects of respirable cellulose dust on the pulmonary system have been questioned in recent years. Several reports have suggested cellulose respirable dust may cause persistent inflammation in the lungs of rats. In addition some morbidity studies have suggested that there is a potential for loss of lung function in paper mill employees. Also some mortality studies have suggested that there may be elevations of lung cancer in some subgroups of the paper mill employee population. However, these databases have limitations which do not necessarily support the conclusion that exposure to respirable bleached cellulose dust increases risk of persistent lung injury.

Epidemiology

Over the past 20 years there have been numerous studies of mortality and morbidity in the Pulp and Paper industry. Several studies have reported elevations of lung cancer (Menck et al., 1976, Jappinen et al., 1987, Jarvholm et al., 1988, Solet et al., 1989, Band et al., 1997). However, there are considerable inconsistencies between these studies. Most data analyses were based on vital statistics, and occupation was usually abstracted from death certificates. Data obtained from these types of records are often inaccurate for cause of death and for accurate job description. Also, they do not take into account work history but rely only on last job, which may inaccurately reflect the types of exposures which were predominant during employment. Furthermore, most of these studies were limited to small employee cohorts, and most did not examine the confounding effect of smoking. None of these studies have examined the influences of individual chemical exposures on risk of lung cancer. The evidence concerning the carcinogenic risk in workers employed in the Paper Industry was judged inadequate in a 1987 International Agency for the Research on Cancer (IARC) review (IARC 1987).

A subsequent study of the U.S. Paper Industry, which is the most comprehensive mortality study to date, examined a cohort of over 63,000 employees with at least 10 years employment in the industry (Matanoski et al., 1998). This study concluded that compared to the U.S. population, and several other U.S. regional populations such as state and county, there were no observed increases in the rate of lung cancer. However, the internal analysis comparing one sub-group of employees versus another indicated there may be some elevations of lung cancer (RR=135). However, the authors indicate that this is likely due to smoking which was examined by incorporating a lifestyles component to the study.

Equally, there have been several morbidity studies of the Pulp and Paper industry, examining effects of mixed chemical exposures on lung function (Ferris et al., 1979, Heederick et al., 1987, Ericsson et al., 1988, Thoren et al., 1989a, Thoren et al., 1989b, Thoren et al., 1996). Again

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results of these studies are inconsistent. Most indicate that in cross-sectional analysis there is little effect on lung function, and a couple indicate some loss of FEV_1 (Heederick et al., 1987, Ericcson et al., 1988). However, these effects were noted only in smokers in the study of Heederick et al., (1987), and the Ericsson study (1988) did not account for smoking. In all cases these studies examined only small cohorts of employees, and only in cross-sectional analysis, which does not provide a robust ability to detect changes between sub-cohorts. No studies have looked at longitudinal changes in lung function, which is a more sensitive model for detecting effects of exposure on lung function over time.

Animal Studies

There are far less data available on the effects of respirable cellulose dust in the lung in animal models, than there is epidemiology data. There has only been one inhalation study reported by (Hadley et al., 1992) examining the effects of respirable cellulose insulation in the lungs of rats. While the results of the 21 day exposure indicated severe inflammatory responses, and the potential for long term damage, it should be pointed out that exposures were unrealistically high (80-718mg/m3), and would likely have resulted in overloading the lungs normal clearance mechanisms. More recently Warheit (1998) reported that inhalation to a bleached cellulose respirable dust (300-575 fibers/cc) resulted in a transient mild inflammatory response in rats, with no evidence for long term effect.

In several other studies samples of respirable dust containing various types of cellulose, were instilled directly into the lungs of animals (Milton et al., 1990, Tatrai & Ungvary 1992, Tatrai et al., 1995, Muhle & Bellman 1997, Adamis et al., 1997). In most cases the cellulose used was derived from cotton, with secondary processing to achieve a high purity microcrystalline material for chromatography filtration. Tatrai and others (1992, 1995) reported severe inflammatory responses with granulation, collagen deposition, and persistent inflammatory effects, which would likely lead to chronic lung damage. However, the dose used in these studies was 8mg/g lung, which is well above the burden needed to exceed the protective clearance mechanism of the lung (Morrow 1992).

It is now well established that if an insoluble particle lung burden exceeds 2mg/g lung, there is a non-specific inflammatory response, which is independent of the type of particulate. These types of responses have been demonstrated for a variety of insoluble particulates which fall under the general Nuisance Dust category, such as TiO2, carbon black, and aluminum oxide. Clearly, cellulose containing particulate being insoluble, demonstrates similar effects to other insoluble particulates, as has been demonstrated (Milton et al., 1990, Tatrai & Ungvary 1992, Tatrai et al., 1995, Muhle & Bellman 1997, Adamis et al., 1997).

In a study by Muhle and Bellman (1997), it was reported that bleached cellulose respirable dust was highly persistent in the lungs of rats, with an estimated retention half life of >1000 days. In comparison cellulose insulation had a retention half life of approximately 72 days. The typical half life for insoluble particulate in the rat lung is about 60 days. A similar result was noted in the inhalation study of Warheit (1998), with a slow particle clearance rate for cellulose respirable dust. It is unlikely that lung overload phenomenon confounded the results in either study, as doses did not result in lung burdens exceeding 2mg/g lung.

In a recent study by Adamson and others (1999), low doses of respirable dust, of either bleached wood cellulose pulp, microcrystalline cotton cellulose, or recycled cellulose insulation, were instilled into the lungs of rats. At low doses of 0.25 and 1mg/animal there was no adverse response noted with any of the samples. At the high dose of 4mg/animal, which is likely to cause lung overload, only microcrystalline cotton cellulose and cellulose insulation elicited any effects. These were limited predominantly to mild cytotoxicity, macrophage activation and some minimal inflammation. These responses were persistent through the recovery period. This persistence is most likely a result of an inability of the lung to clear particulate from the broncho-alveolar region. Therefore, it was concluded that at low exposures, which do not exceed the lungs clearance capacity, regardless of cellulose type, there is little potential for any adverse effect. However, at levels which would likely cause lung overload, there appears to be some small but significant differences between bleached wood cellulose, microcrystalline cotton cellulose and recycled cellulose insulation. Therefore, this may suggest that a single cellulose type cannot be used to represent the broad spectrum of cellulose respirable dust types, to characterize effects in the lungs at high dose.

Conclusions

While there has been speculation that organic respirable dusts such as cellulose may pose some health risk in the occupational setting, the weight of the evidence does not appear to support this conclusion. Both mortality and morbidity studies while sporadically reporting some small but significant increases in lung cancer or decrease in lung function, are most likely due to confounding effects of smoking. Furthermore, the epidemiology has only examined effects in relationship to multiple chemical (and particulate) exposures, and not specifically to cellulose respirable dust. Moreover, given the inconsistent and small changes reported, in small cohort sizes, it is unlikely that the power of these studies is sufficient to delineate between any small effect of a mixed particulate exposure, versus the effects of smoking. Potential chemical associations to diseases will be examined in an on-going case-cohort analysis of the Pulp and Paper Industry in the U.S. Matanoski and others at Johns Hopkins University will examine the relationship between potential differences in disease rates within Pulp an Paper Industry workers, to specific chemical exposures.

In addition, while animal studies do show inflammatory effects of cellulose containing respirable dusts, and that there appears to be persistence of particulate in the lung, these studies are compromised by the confounding issue of lung clearance overload. The overload phenomenon may in-fact produce a non-specific inflammatory response unrelated to cellulose. Indeed this seems to be the case, as a study of the effects of low exposures, where lung overload would not occur, showed no inflammatory effects of three different cellulose containing respirable dusts.

In conclusion, the weight of the evidence in either man or animal does not appear to provide strong support that exposure to respirable cellulose dusts are of significant health concern, beyond that of other insoluble particulate nuisance dusts.

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