PULMONARY TOXICITY STUDIES OF SYNTHETIC ORGANIC FIBERS: PARA-ARAMID RFP AND CELLULOSE RESPIRABLE FIBERS

DB Warheit and MA Hartsky
DuPont Haskell Laboratory
Newark, DE

Abstract

The purpose of this study was to assess the toxicity of 2 organic fiber-types. The study has two components . First, one study compared the pulmonary effects of inhaled para aramid (p-aramid) vs. size-separated aerosolized chrysotile asbestos fibers in rats. In another study, the effects of inhaled cellulose in rats were investigated. For both studies, the parameters assessed were clearance/biopersistence of inhaled p-aramid or cellulose RFP relative to asbestos fibers, as well as cell proliferation in the lungs of rats following 2-week exposures. Rats were exposed nose-only to asbestos at concentrations of 459 and 782 f/cc, or to p-aramid RFP at 419 or 772 f/cc, or to an aerosol of 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 at several times postexposure. Lung clearance/biopersistence studies in p-aramid-exposed rats showed biodegradation of inhaled p-aramid, as evidence by breakage and progressive shortening of inhaled fibrils (with increased residence time in the lung). In contrast, clearance of short chrysotile fibers was rapid, but slow or insignificant for long chrysotile fibers, as evidenced by a progressive increase over time in the mean lengths of fibers recovered from the lungs of exposed rats. Cellulose RFP were also cleared slowly and appeared to be more biopersistent than the p-aramid RFP. Two week, high-dose exposures to p-aramid or cellulose in rats produced transient increases in pulmonary cell proliferation parameters. In contrast, asbestos exposure produced sustained cell proliferative responses. These results demonstrate differences in the pulmonary responses to these two inhaled organic respirable fiber-types when compared to chrysotile asbestos.

Introduction

Para-aramid RFP are used as asbestos fiber substitutes in friction products such as gaskets and brake lining. One component of this inhalation toxicity study was designed to evaluate the pulmonary effects of size-separated p-aramid vs. chrysotile asbestos inhalation exposure in rats. Additional studies were conducted with cellulose respirable fibers. Also, we introduce a new term to characterize the respirable component of para-aramid and cellulose fibers. Respirable-sized, fiber-shaped particulates (RFP) have recently been described as the respirable component of para-aramid fibers (ECETOC). Para-aramid fibers are nonrespirable-sized, having a diameter of 12 - 15 mm. The new term, p-aramid RFP, can be used interchangeably with the term "p-aramid fibrils", and these denote the respirable-sized fraction of para-aramid fibers, which can be found in a commercial preparations of p-aramid pulp.

Methods Groups of male Crl:CDBR rats (7-8 weeks old, Charles River Breeding Laboratories, Kingston, New York) were exposed nose-only 6 hrs/day, 5 days/week for two weeks to at 419 or 772 f/cc p-aramid RFP or to chrysotile asbestos fibers at concentrations of 459 and 782 f/cc. After completion of exposures, the lungs of p-aramid or chrysotile-exposed animals and aged-matched sham controls were assessed for terminal bronchiolar, parenchymal, subpleural and mesothelial cell proliferation and clearance at 0 hrs, 5 days 1, 3, 6, and 12 months postexposure. The experimental design, RFP preparation, aerosol exposure methods, and techniques for pulmonary lavage, biochemical assays, cell proliferation and lung digestion/biopersistence studies are described elsewhere (Warheit et al., 1995, 1996). For the cellulose studies, rats were exposed 6 hrs/day, 5 days/week for two weeks to an aerosol of Thermocell mechanical wood pulp (Laxa Bruks AB, Rofors, Sweden) cellulose fibers at target concentrations of 300 and 575 fibers/cc. Following exposures, the lungs of rats were assessed at 3 and 10 days, as well as 1 and 3 months postexposure by a BrdU cell proliferation assay and for biopersistence/clearance studies.

Results and Discussion
p-Aramid and Chrysotile Asbestos

Lung retention/biopersistence studies in p-aramid-exposed rats and hamsters showed biodegradation of inhaled p-aramid, as evidenced by breakage and progressive shortening of inhaled fibrils (with increased residence time in the lung) in both species. In contrast, clearance of short chrysotile fibers was rapid, but slow or insignificant for long chrysotile fibers, as evidenced by a progressive increase over time in the mean lengths of fibers recovered from the lungs of exposed rats (see Table 1). Two week, high-dose exposures to p-aramid in rats produced transient increases in pulmonary cell proliferation parameters. In contrast, asbestos exposure produced sustained cell proliferative responses in terminal bronchiolar, pulmonary parenchymal, and subpleural regions, measured through a period of 1-3 months postexposure (only the terminal bronchiolar cell proliferation results are presented here - see Table 2). To summarize these findings, pulmonary cell proliferation results demonstrated substantial increases in lung parenchymal, airway, pleural/subpleural, and mesothelial cell proliferation effects following chrysotile exposures, suggesting that chrysotile produces a potent proliferative response in the airways, lung parenchyma, and subpleural/pleural regions. In contrast, p-aramid RFP

Reprinted from the *Proceedings of the Beltwide Cotton Conference*
Volume 1:157-158 (1999)
National Cotton Council, Memphis TN

exposures produced only transient effects in airway and subpleural regions. Based on these comparisons, we conclude that the proliferative effects and enhanced biopersistence of chrysotile asbestos fibers that are associated with the induction of chronic disease do not occur with para-aramid fibrils.

Cellulose. Two week high dose inhalation exposures to cellulose fibers produced lung burdens in the range of 3 x 10 E7 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. Analysis of mean lengths of cellulose recovered from the lungs of exposed rats indicate that these fibers did not break down to any large extent (Table 1). Using BrdU cell proliferation techniques, it was demonstrated that inhaled cellulose fibers produced a transient terminal bronchiolar cell proliferative response, and this was not significantly different from controls at 10 days postexposure (Table 2).

Despite the fact that cellulose fibers would appear to be widespread in the environment, very few toxicity studies have been conducted with these materials.Tatrai (1996), and Adamis and coworkers (1997) have reported that a single intratracheally instilled dose of 15 mg cellulose (Cellulosepulver MN 33 for TLC) produced inflammation and a fibrosing granulomatous alveolobronchiolitis which showed moderate progression over time. Milton et. al. (1990) reported that intratracheally instilled cellulose fibers (Whatman CC41 microgranular cellulose) produced granulomata and fibrosis after repeated instillations. Muhle et al. (1997) concluded that cellulose fibers were more biopersistent in the lungs of rats when compared with ceramic fibers at similar protocols and concentrations. In summary, 2-week inhalation exposures to 300 and 575 f/cc of Thermocell cellulose fibers produced minimal cell proliferative effects. The fibers appeared to be rather biopersistent, as clearance was slow and the length dimensions of retained fibers were not significantly altered at 3 months postexposure. Two key issues related to cellulose toxicity are derived from this 2-week study. First, it is unclear whether the Thermocell wood pulp cellulose preparation tested herein are representative of other wood pulp/cellulose samples; and second, the biopersistence of this fiber may be a concern and thus the potential chronic following repeated exposures should be investigated in a longer term inhalation study.

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Table 1. Mean lengths of fibrils recovered from the lungs of rats

	Time after 2-week exposure					
	0hr	5 or 10D	1M	3M	6M	12M
Cellulose	15.2 um	12.0 um	13.6 um	10.6 um	-----	-----
Chrysotile	5.2 um	5.6 um	8.4 um	------	9.8 um	10.8 um
p-Aramid	12.7 um	------	9.5 um	8.1 um	6.4 um	5.7 um

0 hr = immediately after exposure; 5 or 10D = 5 or days after exposure 1M, 3M, 6M and 12M = 1,3,6 or 12 months postexposure

Table 2. Terminal Bronchiolar Cell Proliferation in Fiber-Exposed Rats

	Time after 2-week exposure % Labeled Terminal Bronchiolar Cells					
	0hr	5 or 10D	1M	3M	6M	12M
Sham	0.17	0.21		0.25	0.22	
Cellulose (300 f/cc)	0.88	0.23		0.44	0.17	
Cellulose (575 f/cc)	1.12*	0.44		0.47	0.26	
Sham	0.7	0.7	0.7	0.6	0.5	0.3
Chrysotile (459 f/cc)	2.21*	1.5*	1.1	0.7	0.7	0.3
Chrysotile (782 f/cc)	2.9*	1.8*	1.9	0.7	0.6	0.3
Sham	0.7	0.8	0.7	0.5	0.3	0.2
p-Aramid (419 f/cc)	0.7	0.8	0.6	0.7	0.6	0.5
p-Aramid (772 f/cc)	1.26*	0.8	0.7	0.9	0.6	0.3

*p = <0.05

0 hr = immediately after exposure; 5 or 10D = 5 or days after exposure 1M, 3M, 6M and 12M = 1,3,6 or 12 months postexposure