Histopathological findings

The inflammatory reaction seen with the different exposures was comparable, and the extent (i.e., degree) of reaction correlated with the dose of the fibers being administered.

Changes were characterized by multifocal intra-alveolar macrophages aggregation, associated with hyperplasia of the lining epithelium, and interstitial fibrosis. The fibrotic reaction was consistent with interstitial fibrotic granulomas. The changes were located at the centri-acinar regions (i.e., surrounding the terminal bronchioles). Asbestos-like fibers were seen within the macrophages. The increase of dose was also associated with aggregates of multinucleated giant cells located within the peribronchial lymphoid tissue (BALT).

Sporadically (see incidence table), cases of bronchiole-alveolar carcinomas were noted, occasionally associated with presence of metastases into the thoracic cavity. No lung tumors were noted in the concurrent control group.

Also, sporadically (see incidence table), focal fibrosis, with/or without chronic inflammation were noted on the diaphragm. In a typical case (see photo 2D), the reaction was composed of mixed mononuclear cells, associated with fibroblastic proliferation and collagen deposition.

**Legend for figures:**

**FIGURE 4:**

All photos are from masson’s trichrome stained sections of the lung.

**A**: DM #159 (x20) – No abnormality detected.

**B**: 0.5 LA #187 (x20) – Changes were characterized by multifocal intra-alveolar macrophages aggregation, associated with hyperplasia of the lining epithelium, and interstitial fibrosis. The changes were of minimal degree, and located at the centri-acinar regions (i.e., surrounding the terminal bronchioles). Asbestos-like fibers were seen within the macrophages.

**C**: 1.5 LA #202 ( x20)

Changes were characterized by minimal (grade 1), multifocal, intra-alveolar macrophages aggregation, associated with minimal hyperplasia of the lining epithelium, and mild (grade 2) interstitial fibrosis (arrows). The fibrotic reaction was consistent with interstitial fibrotic granulomas. The changes were located at the centri-acinar regions (i.e., surrounding the terminal bronchioles). Asbestos-like fibers were seen within the macrophages. In addition, mild degree of multinucleated giant cells aggregates were seen within the peribronchial lymphoid tissue (BALT).

**D**: 0.5 ON #229   (x20) – No abnormality detected.

**E**: 1.5 ON #249 (x20) – No abnormality detected

**F**: 0.5 SM #277 (x20)

Changes were characterized by minimal, multifocal, intra-alveolar macrophages aggregation, associated with minimal hyperplasia of the lining epithelium, and mild interstitial fibrosis (arrows). The fibrotic reaction was consistent with interstitial fibrotic granulomas. The changes were located at the centri-acinar regions (i.e., surrounding the terminal bronchioles). Asbestos-like fibers were seen within the macrophages.

 **G**: 1.5 SM #301 (x20)

Changes were characterized by minimal, multifocal, intra-alveolar macrophages aggregation, associated with minimal hyperplasia of the lining epithelium, and moderate (grade 3) interstitial fibrosis (arrows). The fibrotic reaction was consistent with interstitial fibrotic granulomas. The changes were located at the centri-acinar regions (i.e., surrounding the terminal bronchioles). Asbestos-like fibers were seen within the macrophages.

**H**: 0.5 ED #324 (x20) – No abnormality detected.

**I:** 1.5 ED #344 (x20)

Changes were characterized by minimal (grade 1), multifocal, intra-alveolar macrophages aggregation, associated with minimal hyperplasia of the lining epithelium, and mild (grade 2) interstitial fibrosis (arrows). The fibrotic reaction was consistent with interstitial fibrotic granulomas. The changes were located at the centri-acinar regions (i.e., surrounding the terminal bronchioles). Asbestos-like fibers were seen within the macrophages. In addition, mild degree of multinucleated giant cells aggregates were seen within the peribronchial lymphoid tissue (BALT).

Figure 5

All photos are from H&E stained sections.

        **A**: LA #178 H&E carcinoma (x2)

Poorly circumscribed bronchiolo-alveolar carcinoma occupying peribrochial regions of the lungs (arrows). The gland-like structures were embedded within stromal tissue. Multiple irregular metastatic nodules were identified on the pericardial fat tissue, thymus and on the diaphragm.

        **B**: LA #216 H&E –(x8) minimal focal fibrosis in diaphragm, composed of small aggregates of fibroblasts, embedded within mature collagen.

**C**: ED #337 H&E (x2)

Poorly circumscribed bronchiolo-alveolar carcinoma occupying perivascular regions of the lungs (arrows). The neoplastc cells were forming solid and papillary structures. No metastasis was identified.

        **D**: ED #365 – H&E – (x8) A single large plaque of chronic inflammation located on the diaphragm. The reaction was composed of mixed mononuclear cells, associated with fibroblastic proliferation and collagen deposition.