STANDARD Proposal Science Case Template

1. Abstract

The proposed experiment aims to reveal the fine details of the interfaces between the asbestos fibers, the ferruginous coating they develop after long resident time in the lungs, and the surrounding biological tissue. This will be achieved by exploiting cutting-edge x-ray ptychographic imaging in tomographic mode (ptychotomography). The proposed experiment is complementary to a recent successful microtomography experiment performed at I13-2 at Diamond, which allowed determining the spatial density of the asbestos fibres and possible preferential accumulation regions in the biological tissue.

2. Scientific context

In the lungs, asbestos irritates the tissue causing minerals and proteins to cluster around the inhaled asbestos fibres. These clusters are known as asbestos bodies (*AB)*, and are the product of a biomineralization process carried out by alveolar macrophages (Fig. 1a). The coating developing on the fibres after long residence time in the lungs was long believed to be a protective mechanism deposited by macrophages trying to segregate the cytotoxic fibres from the organic tissue[1]. However, other authors suggested that the coating material itself might enhance the cytotoxic properties of asbestos by increasing the generation of free radicals[2]. These studies also demonstrated that the iron contained in the coating is catalytically active[3] and can induce modification in the DNA[4]. Earlier studies[5] suggested that the coating contained crystalline particles of the same order of size of the inorganic iron core of the ferritin molecule. On this basis, it was assumed that the crystalline material comprising the major part of the *AB* is composed of ferritin. Today, it is widely accepted that the coating consists of a protein (ferritin or hemosiderin) and mucopolysaccharides.

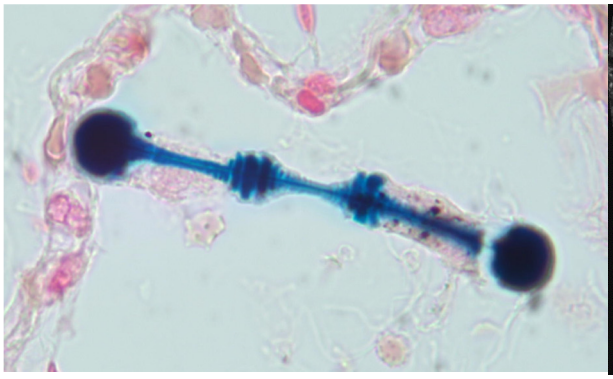

Fig. 1a. Optical microscopy image (1000x) of an Asbestos Body in a histological section of lung tissue impacted with asbestos fibres.

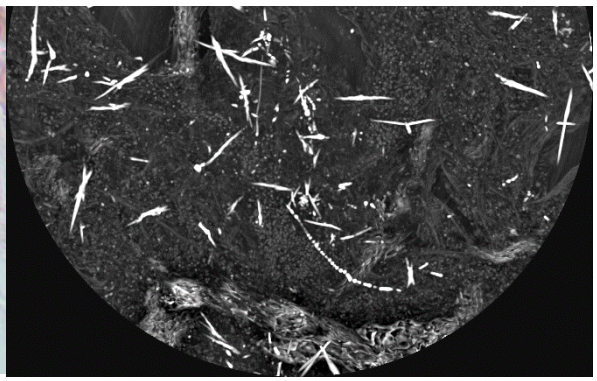

Fig. 1b. Microtomography of lung tissue impacted with asbestos fibres acquired at I13-2 (resolution ~0.8μm; FOV 2.1x1.8 mm^2).

Asbestos bodies usually do not exceed 100 μm in length and 5 μm in diameter. The majority of the studies on *AB* suffers from the fact that suitable micro or nanoprobe techniques required to study small objects became widespread only recently. Synchrotron radiation microprobe tools have spatial resolution far superior to that of laboratory X-ray tomography, and have started to be exploited only recently to study the present topic, and only in 2D acquisition mode[6,7]. Conversely, phase-contrast microtomography has the potential to reveal the fine details of the

AB, and ptychography, a relatively new technique, can reveal information of the interface with the biological tissue with unprecedented level of detail in unaltered bulk lung samples[8]. With the proposed experiment we intend to investigate the interface between the asbestos fibres and their coating, and between the coating and the surrounding biological tissue. This can be achieved by exploiting ptychographic imaging combined with tomography (ptychotomography), a relatively new technique that is available at the I13-1 branch at Diamond. The results obtained will complement the results of a successful microtomography experiment performed in mid-September 2017 at the I13-2 branch at Diamond (Fig. 1b), which allowed determining the spatial density of the asbestos fibres and revealing possible preferential accumulation regions in the biological tissue.

3. Experiment proposed

To investigate the interface between the asbestos fibres and their coating, and between the coating and the biological tissue, we request ptychographic imaging combined with tomography (ptychotomography). Ptychotomography will be performed at the highest resolution achievable on the beamline (~100nm). The preferred working energy will be in the range 15-20keV. We plan to use a detector to sample distance of ~7m. Since this technique is relatively new and the experiment is potentially challenging, we request 15 shifts at the I13-1 branch.

4. Results expected

A deeper knowledge of the interaction between asbestos fibres, their coating, and the surrounding biological tissue, can lead scientists in their effort to better understand the carcinogenic mechanism and develop more effective medical treatments for highly deadly asbestos-induced diseases, such as malignant pleural mesothelioma.

5. Publications

[1] A B Kane. Asbestos bodies: clues to the mechanism of asbestos toxicity? *Human Path.* 34, 735 (2003);

[2] H Pezerat *et al.* Man-made mineral fibers and lung cancer. *Toxic. and Ind. Health* 8, 77 (1992);

[3] A J Ghio *et al.* Ferruginous bodies: implications in the mechanism of fiber and particle toxicity. *Toxic. Path.* 32, 643 (2004);

[4] L G Lund *et al.* Iron associated with asbestos bodies is responsible for the formation of single strand breaks in φ X174 RFI DNA. *Occupat. & Environ. Medicin* 51, 200 (1994);

[5] F D Pooley. Asbestos bodies, their formation, composition, and character. *Environ. Res.* 5, 363 (1972);

[6] L Pascolo *et al.* The interaction of asbestos and iron in lung tissue revealed by synchrotron-based scanning X-ray microscopy. *Sci. Rep. 3*, 1123 (2013);

[7] F Bardelli *et al.* New insights on the biomineralisation process developing in human lungs around inhaled asbestos fibres. *Sci. Rep.* 7, 44862 (2017);

[8] S H Shahmoradian *et al.* Three-Dimensional Imaging of Biological Tissue by Cryo X-Ray Ptychography. *Sci. Rep.* 7, 6291 (2017).