氏　　　　名	AVRAMESCU MAYA LILIANA
授与した学位	博　士
専攻分野の名称	理　学
学位授与番号	博甲第　　　６７２０　　　号
学位授与の日付	２０２２年　９月　２２日
学位授与の要件	自然科学研究科　　　　地球惑星物質科学専攻 （学位規則第４条第１項該当）
学位論文の題目	The aetiology of mesothelioma: morphological and chemical analyses of asbestos ferruginous bodies （中皮腫の病原：アスベスト小体の形態学的および化学的分析）
論文審査委員	准教授　国広　卓也　　教授　小林　桂　　教授　田中　亮吏　　教授　牧嶋　昭夫 教授　Mark Rehkamper

学位論文内容の要旨

Mesothelioma (MM) is an aggressive cancer that has no cure and the mechanisms behind its progression remain unclear. MM is mainly associated with inhaled asbestos fibres and the ferruginous (iron-rich) coat that forms around them. Together, the asbestos and coat are referred to as asbestos ferruginous bodies (AFBs). During my PhD, I studied the role of AFBs in the onset and progression of MM. Previously, my research institute analysed lung tissue samples and discovered high concentrations of some rare earth elements and radium, the latter being a radioactive element capable of damaging DNA. However, this previous study was undertaken on bulk lung samples, which included AFBs and other lung components. Therefore, I extracted the AFBs from the lung samples to individually analyse them for their true concentrations of the rare earth elements and radium.

In my study, the bulk major, minor and trace elements of MM lung tissue samples were obtained via inductively coupled plasma mass spectrometry (ICP-MS). The in-situ major element composition and structure of AFBs were determined by scanning electron microscopy (SEM), transmission electron microscopy (TEM) and energy-dispersive X-ray spectroscopy (EDS). Ra and some trace elements in the AFBs were investigated by secondary ion mass spectrometry (SIMS).

For TEM analysis, I cut the AFBs using the FIB-SEM system to expose their internal structure and achieve a thickness of less than 150 nm, so that the electrons can pass through the very thin sample. I observed the internal morphology, crystallography, and chemical composition of the AFBs. With such data, an accretion model for AFB formation was developed.

Subsequently, I developed a protocol for creating ferrihydrite standards and an AFB sample mounting protocol for SIMS analysis. After SIMS analyses, radium calibration curves were drawn for the ferrihydrite standards which showed linearity between the intensities obtained in SIMS and the concentrations obtained in ICP-MS. Furthermore, background values for radium were obtained by using ferrihydrite standards without radium.

By detecting radium within the AFBs at certain concentrations using SIMS, it can be determined whether the ionizing radiation, from the radium accumulated in their ferruginous coat, could cause sufficient DNA damage to increase a given patient's risk of developing cancer. Damaged DNA leads to gene mutations that allow the proliferation of faulty cells, leading to cancerous tumours.

論文審査結果の要旨

Asbestos is a fibrous mineral and after its inhalation into the human lung, the asbestos is coated by an iron-rich material, togheter the coat and fibre are termed an asbestos ferruginous body (AFB). It is considered that AFBs in the lung environment generate reactive oxygen species, which lead to the onset of a cancer known as malignent mesothelioma (MM). Nakamura et al. (2009) *PJAB* **85** detected Ra in bulk lung samples and proposed a novel model, in which the radioactive decay of Ra in AFBs leads to MM. To further elucidate the role of AFBs in the aetiology of MM, she described the internal morphology of AFBs and determined their Ra concentrations. Since the size of a typical AFB is 10 μm, she applied microbeam techniques to the AFBs, expanding Nakamura et al. (2009).

She replicated the detection of Ra from bulk lung samples using ICP-MS. She described the internal morphology of AFBs a focused-ion beam and transmission-electron microscopy. She found that AFBs are mainly composed of ferrihydrite (Fh) and smokers and non-smokers have significantly different morphologies and Fe concentrations. She speculated that Fe complexation from cigarette smoke will increase the deposition of Ra.

She also developed a micro-meter-sized Ra-detection technique. She optimized the conditions for SIMS analysis of Ra and synthesized Fh reference materials with varying Ra concentrations and a variety of trace elements. The concentrations of each element were determined by ICP-MS and the ion yield of Ra during SIMS analysis estimated.

With the background condition of [Ra] being 0.2 ng/g, she detected Ra from three AFBs and their average concentration was estimated to be 5 ng/g. Based on the abundance, she quantitatively estimated the impact to the human body from radioactivity. She demonstrated that cells around AFBs receive radiation at a million times more than the safe public exposure limit.

After considering the candidates work, the dissertation committee recommended that Avramescu Maya-Liliana be awarded the degree of Doctor of philosophy in Science.