〈Review〉

Biological effects of refractory ceramic fiber

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ABSTRACT Refractory ceramic fibers (RCFs) are one of the many man-made mineral fibers (MMMFs) / synthetic vitreous fibers (SVFs) used as alternative products to asbestos fibers. The Japanese Ministry of Health, Labour and Welfare began to regulate the manufacturing and handling of RCFs under specific chemical disorder prevention rules to reduce the risks of exposure to RCFs since November 1st, 2015. In fact, the International Agency for Research on Cancer (IARC) categorized RCFs as group 2B, being possibly carcinogenic to humans, according to results obtained from animal experiments. Thus, given the biological effects of RCFs previously reported in the literature, it is necessary to consider further monitoring in addition to the development of measures to prevent adverse health effects caused by exposure to RFCs. In this review, a summary of the biological effects of refractory ceramic fibers (RCFs) is presented and discussed with respect to toxicity, animal models and epidemiological studies, and a comparison is made with asbestos exposure to outline and clarify the current status pertaining to the biological effects of RCFs. doi:10.11482/KMJ-E41(2)57 *(Accepted on October 6, 2015)*

Key words: Refractory ceramic fiber, Toxicity, Animal model, epidemiology, carcinogenesis, mesothelioma

INTRODUCTION

Asbestos fibers cause various human diseases such as lung fibrosis, pleural plaque, pleural thickening, and cancers (lung cancer and malignant mesothelioma)[1－5]. Thus, the use of asbestos has been banned in many countries including Japan. However, since the latency period for the occurrence of malignant mesothelioma (MM) is assumed to be 30 to 50 years, and the prognosis of MM is poor, with a median survival time of less than one year, it is necessary to develop better tools for early diagnosis and treatment, in addition to strategies that prevent the occurrence of MM[6－9].

On the other hand, many man-made mineral fibers (MMMFs) / synthetic vitreous fibers (SVFs) have been used in the industrial field as alternative products to asbestos[10－13].

Among the MMMFs, refractory ceramic fibers (RCFs; CAS no. 142844-00-6), also referred to as aluminosilicate wools (ASWs), are amorphous

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fibers that possess several features such as high-temperature insulation, resistance to thermal shock, light weight, and corrosion resistance. The chemical composition comprises 30-60% Al_2O_3, 40-60% SiO_2 and 0-20% R_nO_m (R is Cr or Z)[14-16]. However, the safe usage and production of RCFs should be considered since there is a fear of adverse biological effects given the fibrous characteristics. In fact, the International Agency for Research on Cancer (IARC) categorized RCFs as group 2B, being possibly carcinogenic to humans, according to results obtained from animal experiments[17]. Moreover, the Japanese Ministry of Health, Labour and Welfare regulates the manufacturing and handling of RCFs under the specific chemical disorder prevention rules to reduce the risks of exposure to RCFs since November 1st, 2015[18].

At this point, it will be important to summarize the biological effects of RCFs to establish a better understanding for the prevention of excess exposure to RCFs in workers involved in the RCF manufacturing industry.

Biopersistence

Several reports have described the biopersistence of SVFs and amosite asbestos in the rat lung following inhalation, since the toxicity of fibers is mainly dependent on the concentrations in the body, dimension of the fibers (length, width, thickness and aspect ratio) and biopersistence[15, 19-21]. From these reports, the durability of RCFs expressed as K_{dis} (ng/cm^2/h); kinetic constant for dissolution) was reported as 8.0[15, 21]. Since the durability of crocidolite was reported as 0.3, RCFs possess relatively lower durability than asbestos fibers, however, they possess higher durability than other SVFs such as rockwool and glasswool. Additionally, although many reports have shown results with respect to biopersistence, detailed methods of exposure such as duration are lacking. However, taken together with the many reports[15, 19-22], it is clear that RCFs possess significantly lower bioresistence compared to asbestos fibers, but greater bioresistence compared to other SVFs.

Toxicological bioassays in animals

Bioassays using animals are usually performed by intraperitoneal implantation[23-25], intrapleural implantation[16, 25], intratracheal instillation[26] and chronic inhalation[23-29]. Although the length and doses of fibers and experimental animals (Wistar rats, Osborne-Mendel rats and Syrian golden hamsters) varied, the intraperitoneal[23-25] and intrapleural implantation[16, 25] methods yielded mesothelioma, sarcoma and adenoma. Intratracheal studies also showed the occurrence of lung tumors such as adenoma, carcinoma and mesothelioma, even though the incidence was lower than that observed with the implantation studies[26]. Additionally, results of studies involving chronic inhalation varied, from no pulmonary tumors being observed to the occurrence of tumors including pulmonary adenoma, carcinoma, and pleural mesothelioma[23-29].

However, there are certain criticisms regarding animal studies. For example, although the intraperitoneal and intrapleural implantation methods may be useful in exploring fiber-related carcinogenic mechanisms, the relevance to human exposure conditions has not been delineated. Additionally, there is the possibility of over-loading animals with the fibers. As mentioned above, since the durability and biopersistence of fibers are important factors in the evaluation of toxicity, it is very difficult to apply the results of animal models to the occupational exposure of humans to fibers.

Given that regulatory rules need to be implemented to protect the health of workers, and due consideration be given to the variety of occupational sites and exposure situations that exist, it is inappropriate to simply wait for the appearance of adverse effects in workers before

regulations are formulated and enacted. Thus, the results from animal models investigating fibers and various chemicals should be considered in the categorization of harmful effects, especially in terms of carcinogenesis.

Epidemiological studies

RCFs were initially commercialized during the 1950s in the United States, late 1960s in Europe, middle of the 1970s in South Africa and Australia, and then spread to the rest of the world[30]. As mentioned above, in addition to the results of animal model studies demonstrating the carcinogenic effects of RCFs, some epidemiological studies were performed.

The initial cross-sectional study in the U.S. showed that significantly higher pulmonary symptoms such as dyspnea were present in production workers compared to non-production workers in the RCF handling and manufacturing industries[31]. The incidence of pulmonary symptoms was 29.6% in production workers and 11.3% in the non-production population with a significant odd ratio of 2.9 (Confidence interval (CI) : 1.4-6.2). Other studies also represented the relationship between recent exposure and dry cough, nasal obstruction and stimulatory symptoms in eye and skin, a positive relationship between RCF exposure and dyspnea, and a relationship between accumulative exposure and various pulmonary disorders including chronic bronchitis, dyspnea, recurrent respiratory diseases, and pleural pain. Regarding pulmonary function examinations, although forced expiratory volume in one second ($FEV_{1.0}$) was the same for production workers and the non-production population, forced vital capacity (FVC) was lower in RCF production workers compared to present or past smokers. The decrease in FVC in fiber-handling workers was not specific for RFCs. It has also been reported in the asbestos-handling population[32]. Additionally, one report using a rat model demonstrated that RCFs and tobacco smoke additively induced cellular toxicity in the lung[33].

Regarding pleural plaque and fibrotic changes in the lung interstitium, although insufficient epidemiological studies have been performed, accumulative exposure to RCFs seemed to induce pleural changes diagnosed by radiological examination every three years[34]. However, these reports failed to detail the interstitial changes of the lung. Another study also showed the occurrence of pleural plaque in workers handling RCFs[35].

What about carcinogenesis?

Relatively few studies have demonstrated the occurrence of lung cancers in workers exposed to RCFs, and no statistically significant relationship was found between the occurrence of lung cancer and exposure to RCFs[36-40].

However, there is one report of interest regarding the mortality of workers that handled RCFs[39]. Among the deaths, heart disease, respiratory system diseases, digestive system diseases, accidents, violence, and cancers including total cancers, digestive, respiratory, urinary and other sites, only cancer in urinary organs showed significant high mortality with a 344.8 standardized mortality ratio (SMR; 95% CI: 111.6-805.4), although there were no excess mortality in all deaths, cancers, and respiratory diseases including mesothelioma. There is no immediate explanation to account for the excess death involving urinary cancer in the RCF-exposed population, and further studies are required.

Other biological effects of RCFs

Regarding other cellular and molecular biological effects of RCFs, there are some reports that have focused on the immune system, since the immune system particularly in the lung is important as the initial response to recognize foreign substances entering the body.

Using rat alveolar macrophages exposed *in vitro* to

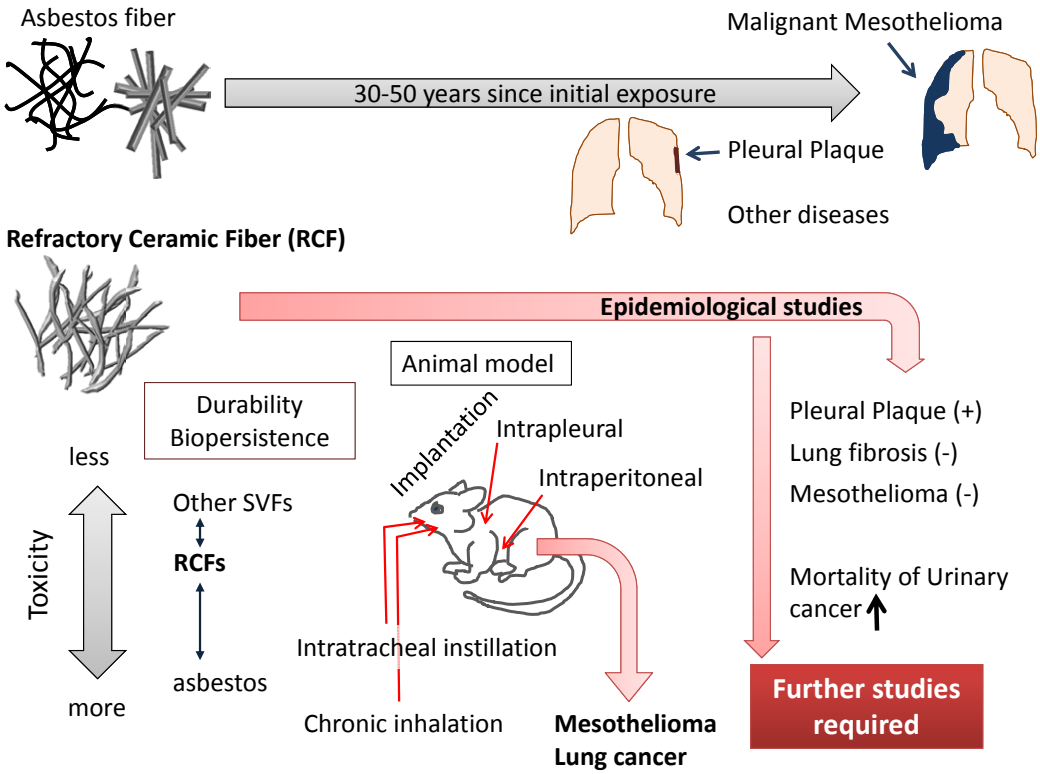

Fig. legend
Summary of biological effects of refractory ceramic fibers (RCFs), in terms of toxicity, animal models and epidemiological studies, and a comparison with asbestos exposure.

various fibers including crocidolite, RCF, silica and titanium dioxide (TiO_2) as the control, Leikauf *et al.* studied the release of eicosanoids and cytokines[41]. RCF induced the release of eicosanoids and tumor necrosis factor (TNF), although the extent of the release was lower compared to that of macrophages exposed to crocidolite.

Morimoto *et al.* examined mRNA expression in rat alveolar macrophages exposed to various mineral fibers and tobacco smoke[42]. They showed an enhancement in mRNA expression of interleukin (IL)-1α by cigarette smoke, IL-1α, IL-6 and TNF α by chrysotile asbestos, inducible nitric oxide synthase (iNOS), IL-6 and basic fibroblast growth factor (bFGF) by chrysotile with cigarette smoke, in addition to IL-1α and TNFα by RCF, and IL-1α and bFGF by RCF with cigarette smoke. Since cytokines such as IL-1α, iNOS and bFGF are known to play an important role in remodeling of the lung, these cytokines may be important in cases of lung injury and remodeling caused by exposure to mineral fibers.

Additionally, Tulnska *et al.* performed intratracheal instillation of RCF (1 mg/animal) using male Sprague Dawley rats[43]. They showed a proliferative response in spleen T cells caused by mitogen, and T cell-dependent B cell activation induced by mitogen was lower compared to control animals.

Moreover, we also reported apoptosis in human peripheral blood mononuclear cells (PBMCs) caused by various MMMFs including RCF[44]. This report showed that apoptosis in PBMCs was caused

by chrysotile asbestos as well as other MMMFs such as RCF, rockwool, glasswool and wollastorite, with overexpression of apoptosis-related genes. The degree of occurrence and level of gene expression induced by RCFs were lower compared to chrysotile, but greater than other fibers.

Taken together with these studies, the immunological effects of RCFs may be intermediate, although lower than that of asbestos and greater than in the case of other SVFs. Our laboratory has been investigating the immunological effects of asbestos fibers and found a reduction in anti-tumor immunity in T cells, natural killer cells, and CD8-positive cytotoxic T cells. Further studies are needed to elucidate the alteration in anti-tumor immunity caused by exposure to RCFs.

CONCLUSION

Given the impending enforcement of the law regarding the specific chemical disorder prevention rules to reduce the risks of exposure to RCFs from November 1st, 2015, the biological effects of RCFs should be carefully monitored and explored since we have to avoid the same disaster that occurred as a result of exposure to asbestos. For example, radiological monitoring of workers handling RCFs for manufacturing needs to be performed, in addition to checking the past chest X-P taken in standard medical check-ups from the viewpoint of pneumoconiosis monitoring. Moreover, cellular and molecular studies should be performed to detect any adverse effects of RCFs, and if present, facilitate the development of strategies that prevent carcinogenesis caused by exposure to RCFs.

ACKNOWLEDGEMENTS

This review was written based on the symposium lecture presented by Takemi Otsuki (corresponding author) at the third annual meeting of the Japan Association for the Study of Fiber Materials, on August 7th, 2015 at the Buddhism Conduction Center Building, Minato-ku, Tokyo, Japan.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare regarding the contents of this review.

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