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Review Article

Biopersistence of Man-Made Fibers by Animal Inhalation Experiments in Recent Reports

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Abstract: Biopersistence of man-made fibers by animal inhalation experiments was mainly reviewed. This report showed that the biopersistence and maximum tolerated dose are significantly important factors for hazard assessment for man-made fibers as well as fiber size (diameter/length), chemical compositions and surface properties.

Key words: Hazard assessment, Biopersistence, Man-made fiber, Magnesium sulphate whisker, Fiberglass, Refractory ceramic fiber, Potassium octatitanate whisker, Graphite whisker

Introduction

Risk assessment is the process by which the nature and magnitude of the risk is determined. Risk assessment consists of hazard assessment and exposure condition. The hazard is recognized that the fiber is likely to cause an adverse effect under the conditions in which it is produced and used. There should be an indication that exposure to the fiber may be significant, and that adverse effect may be occurring from such exposure. Even if a fiber is inherently hazardous, if there is no exposure there will be no risk.

Inhalation is a very important route of exposure to hazardous fibers, especially in the workplaces. For the evaluation of the health effect of fibers in animal study, inhalation exposure follows the physiological route by which humans are exposed and could, therefore, be considered superior to the other routes.

For airborne fibers, aerodynamic diameter is the critical factor determining how far down the respiratory tract the fibers will go. The aerodynamic diameter is defined as diameter of sphere having unity in specific gravity and the same gravitational settling velocity as that of a fiber. Inhaled fibers are deposited all along the respiratory tract depending on the aerodynamic diameter and interruption. The fiber penetrated into the deep lung (alveoli) is called respirable fiber (the aerodynamic diameter is below 10 μm). However, the health effect does not occur, immediately, when the fibers are penetrated into lungs because of the lung defense mechanisms, that is, mucociliary clearance for respiratory tracts and immune system in the respiratory system. When the fibers become longer and thicker, they deposit upper part in the respiratory tracts (nose, throat, trachea, bronchioles and bronchi) and may be cleared by mucocilliary clearance. Respirable fibers in the alveoli may be cleared by immune cells (macrophages) that ingest the fibers.

Changes observed in the lung as a result of inhalation of hazardous fibers depend upon the concentration of inhaled fibers, duration of exposure and hazard potential of the fibers. Despite the defenses of lung, chronic injury can occur from repeated chronic exposure to low levels of the substance in the workplaces. Types of chronic damage include cancer and fibrosis. The results of the inhalation experiments are most important evidences in animal studies for hazard assessment.

In case of fibers, hazard assessment was started from asbestos. Asbestos is a representative fiber and has been one of the most useful fibers for construction materials (roofing, flooring, siding and cements) and friction materials. However, it has been shown that occupational exposure to

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various types of asbestos may lead to asbestosis, bronchial cancer, and pleural and peritoneal mesotheliomas. Recently, the production of man-made fibers (MMFs) has increased instead of asbestos. As MMFs is also fiber shape like asbestos, the health effect of MMFs may be suspected.

Hazard assessment of fibers is known to depend on the dose (fiber exposure concentration), fiber size (diameter/length), chemical compositions, biopersistence and surface properties. Kohyama *et al.*[1] and Yamato *et al.*[2] proposed that the characteristic standard reference samples of MMFs for biological experiments. The standard reference samples are very useful for comparing and assessing results between different researchers.

In this paper, results of our previous inhalation studies and resent reports of inhalation studies in animal experiments for MMFs are introduced.

Magnesium Sulphate Whisker

Magnesium sulphate whisker (MSW) is used a reinforcement for plastics and rubbers and a thickener of paint materials and epoxy adhesives.

For investigating the effect of fiber length on histopathological examination, two different lengths (12 μm and 4.9 μm) were used. Fiber size is well known to be one of the most important factors for fiber toxicity. The thinner and longer the fiber is, the more the toxicity increases. However, the experimental results show that there were no significant difference of histopathological findings among the short whisker exposure group, long whisker exposure group and controls for 1 month and 12 months inhalation study. On the other hand, the biopersistence of these whiskers were measured by instillation method instead of the inhalation study because of quick clearance in rat lung. The result showed that the biological half time (BHT) was only 17.6 min for MSW. This experimental result shows that the biopersistence is more important factor rather than the fiber size (diameter/length)[3].

Fiberglass

Fiberglass (FG) is the largest productions of MMFs. Many types of FG are produced for specific uses, that is, building insulation, filtration and sound absorption.

Before biopersistence study, the fiber properties (chemical compositions and fiber size) must be made clear. Especially, the chemical compositions of fiberglasses are large difference among them. The main chemical compositions are SiO_2 (50–70%), Al_2O_3, Na_2O. CaO, MgO and B_2O_3.

The Wistar rats were exposed to FG for 1month (6 h/day, 5 d/wk). The lungs of the exposed rats were treated by a modified Kjeldahl method with microwaves for recovering the deposited FG. The biological half time in the rat lungs for longer fiber than 20 μm was 1.4 months for the clearance time up to 3-month and 3.2 months after 3-month clearance time. The size distribution was shown as no change remarkably during 6-month clearance time[4].

The lung deposition and clinical observations were investigated by 78-week nose-only inhalation to two kinds (MMVF10a and MMVF33) of FG[5]. MMVF33 is a relatively durable glass composition. The results showed that MMVF10a was nontoxic and MMVF33 should be considered as potentially fibrogenic and carcinogenic under conditions of high exposure. The faster the dissolution, the lower were the lung burdens and the less severe the effects.

The mathematical biopersistence model was generally consisted of translocation by phagocytes of macrophages or mucociliary elimination, dissolution by body fluid and disintegration (breakage)[6–8]. By using the model, they found that the effects of dissolution and disintegration are important factors as well as translocation for FG[6].

The biological half time in a single exponential model was 8.7 months in a chronic inhalation study much longer than 1.5 month in short-term inhalation study. However, there were no severe histopathological changes both experiments. The rat lung burden was 1.49 mg just after the chronic inhalation. This value was estimated to be over the maximum tolerated dose (MTD)[9]. This result showed the biopersistence depended on the dose (lung burden), especially, MTD. Hesterberg *et al.*[10] showed that the exposure conditions were 6 h/d, 5 d/wk for 13 wk and 30 mg/m^3 exceeded the estimated MTD.

We should always check that the dose level is under the dose of MTD, because the clearance rate is different and then the mechanism to get the health effect is different between over and under MTD.

The chronically inhaled FG showed no apparent promoting effects of lung fibrosis or tumor genesis under 2.2 mg/m^3 for 12 month exposure in rats[11].

Cullen *et al.*[12] showed the different result that was markedly different phathogenicity in rats for the two FG of similar dissolution rates. The numbers of long fibers and the surface properties were suggested to play an important role.

Refractory Ceramic Fiber

Refractory ceramic fiber (RCF) is an energy-efficient, high-temperature insulation, used principally in industrial

furnaces, heaters.

The main chemical compositions of RCF are SiO_2 (50–54%) and Al_2O_3 (46–50%). The Wistar rats were exposed to RCF for 2 weeks (20.7 mg/m^3, 6 h/day, 5 d/wk) and were sacrificed at 1 d,1mo, 3 mo and 6mo after the termination of exposure[13–15].

The exposed rats were treated by a low temperature ashing on a plasma asher for recovering the deposited RCF. The fiber numbers and dimension (diameter and length) were measured with a scanning electron microscope. The results showed that there were no significant difference in the number and geometric mean length at each clearance time. The geometric mean diameter decreased linearly with clearance time. The surface of fibers recovered from the lungs had an eroded appearance with the long clearance time. This fact showed signs of dissolution of the RCF remained in rat lungs. The theoretical dissolution model was coincided with the experimental data.

The effect of exposure period (1 mo, 3 mo, 6 mo and 12 mo) on the biological half time (BHT) of RCF was examined by inhalation studies[16]. Ashed lung samples were digested with phosphoric acid, and the silicon and aluminum were measured by an inductively coupled plasma atomic emission spectroscopy. Based on a single compartment model, the BHTs of all groups had almost the same value (2.8–3.8 mo) in spite of the difference in the exposure period (1 mo, 3 mo, 6 mo and 12 mo).

From the relationship between BHT and the deposited amounts of fibers just after the termination of exposure periods (1, 3, 6 and 12 mo), the BHTs show almost the same level (1, 5–4 mo) when the lung burden is lower than 0.65 mg per rat lungs. The BHTs increased significantly with over 1.5 mg. The MTD was estimated over 1.5 mg in this study[16].

For biochemical effect of RCF, the matrix metalloproteinases and tissue inhibitors of metalloproteinases from rat lungs were investigated with adding passive smoke[17]. The long-term exposure to cigarette smoke inhibited the stimulating effect of RCF on production of tumor necrosis factor from alveolar macrophages of rats stimulated by RCF[18, 19]. Message levels of IL-1, iNOS, and bFGF increased by exposure to RCF and enhanced by combined exposure to RCF and cigarette smoke[20].

Mast *et al.*[21] introduced the recent review of toxicology, epidemiology and risk analyses on RCF.

Potassium Octatitanate Whisker

Potassium octatitanate whisker (PT1) was mainly used car's brake pad.

The rats were exposed to PT1 for 4 weeks (1.1 mg/m^3). The BHT was 3.3 months for the rapid clearance stage and 6.1 months for the late stage. No surface change due to fiber dissolution was detected over the 12 months observation period. Macrophage-mediated clearance was thought to be main mechanism for the clearance of PT1. The longer fiber was, the stronger the biopersistence[22].

For biochemical effect of PT1, gene expression of cytokines, IL-1, TNF and IL-6 were investigated. The results showed that these gene expressions increased by exposure to PT1 but there was no change for iNOS[23].

From inhalation study of PT1 for 12 months (2.2 mg/m^3, 110 fiber/cc), bronchiolization and mildfibrotic change were observed around fiber laden macrophages and pleural thickening was observed[24].

Graphite Whisker

The biopersistence of graphite whisker (length: 6.8 μm, diameter: 0.86 μm) was investigated by inhalation study. The deposited graphite whisker in rat lungs was determined by the X-ray diffraction method after microwave ashing with acid solutions. The biological half time was 4 months[25, 26].

There are no results of biological and histopathological examination in this stage.

Other MMFs

Para-aramid fiber[27–29], cellulose fiber[30] and fibrous gypsum[31] have been investigated, but there is no enough experimental data for a review.

Future Study

For inhalation study in animals, next factors must be recognized step by step.

1. fiber size(diameter and length, respirable fiber).
2. chemical composition of fibers.
3. constant fiber and mass concentrations during the exposure period.
4. biopersistence and maximum tolerated dose.
5. biological and histopathological findings.

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