Doc S1 A Brief Discussion of the Fiber Pathogenicity Paradigm and Carcinogenicity Studies of POT Fibers

The fiber pathogenicity paradigm identifies three critical factors that dictate whether or not an inhaled fiber is potentially pathogenic.[1] These factors are width, length, and biopersistence. Width is the main factor in determining the aerodynamic diameter and deposition pattern of a fiber. Length affects the ability of macrophages to physically remove fibers that are deposited beyond the ciliated airways. Biopersistence is a measure of the physical stability of deposited fibers. POT fibers have a long needle-like shape, similar to asbestos, and consequently, they have aerodynamic diameters that allow deposition beyond the ciliated airways and lengths that inhibit clearance by macrophages. POT fibers are also biopersistent: POT fibers administered to rats by inhalation can be recovered 12 months after administration without any erosion on their surface.[2] Thus, the fiber pathogenicity paradigm identifies these fibers as potential carcinogens.[1]

The carcinogenicity of POT fibers was confirmed by an initial study that administered POT fibers by application of hardened gelatin containing 40 mg POT fibers directly to the pleural surface of Osborne-Mendel rats. This study followed the treated animals for up to 2 years and found that approximately 70% of the rats developed pleural sarcomas.[3, 4] A later 2-year study using intraperitoneal injection of rats with POT fibers found that injection of 5 mg and 10 mg POT fibers suspended in saline resulted in cululative incidences of peritoneal mesothelioma of 20% and 77%, respectively.[5] Based in part on the biopersistence of POT fibers and the fact that intraperitoneal injection of POT fibers resulted in the development of mesothelioma in rats, the WHO Workshop on Mechanisms of Fibre Carcinogenesis and Assessment of Chrysotile Asbestos Substitutes concluded that potassium titante fibers pose a high hazard to humans after inhalation exposure.[6, 7]

Two recent studies infused 3 mg POT fibers suspended in saline directly into the pleural cavity of mice and rats. One study followed the treated animals for 52 and 65 weeks,[8] and the other study followed the treated animals for 52 weeks.[9] Although, none of the treated animals had developed mesothelioma by the time the study was terminated, all mice and rats treated with POT fibers exhibited pleural thickening. These studies suggest that the carcinogenic effect of POT fibers may require extended exposure of susceptible tissues to the fibers.

Four studies exposed animals to POT fibers by inhalation and followed the exposed animals for up to 2 years: there are no studies that followed exposed animals for 1 year or less that report the development of exposure-related proliferative lesions. Lee et al. (1981) exposed rats, hamsters, and guinea pigs to up to 370 mg/m^3 (fibers longer than 5 μM and less than 10 μM were approximately 41.8 x 10^3 fibers/cm^3) POT fibers for 6h/day, 5 days/wk for 3 months and followed the animals for an additional 15 - 24 months.[10, 11] Yamato et al. (2003) exposed rats to 2.2 mg/m^3 (111 fibers/cm^3) POT fibers for 6 h/day, 5 days/wk for 1 yr and followed the animals for up to 1 year after the end of the exposure period.[12] Oyabu et al. (2004) exposed rats to POT fibers obtained from two different manufacturers, 1.9 mg/m^3 (manufacturer 1) and 2.2 mg/m^3 (manufacturer 2) for 6 h/day, 5 days/wk for 1 yr and followed the animals for up to 1 year after the end of the exposure period.[13] The calculated amount of POT fibers inhaled in the Yamato, 2003, and Oyabu, 2004, studies was 30 mg.[13] Ikegami et al. (2004) exposed rats to up to 200 POT fibers/cm^3 for 6 h/day, 5 days/wk for 24 months.[14]

Yamato et al. (2003), Oyabu et al. (2004), and Ikegami et al. (2004) report that POT fiber exposed rats did not develop exposure related malignant neoplasms. Yamato et al. (2003) did report the development of non-malignant neoplasms in POT fiber exposed rats: 2 of 5 rats had developed lung adenomas 6 months after the end of

the one year exposure period and 1 of 11 rats developed a lung adenoma and 1 rat developed squamous metaplasia at 12 months after the end of exposure. In contrast, rats exposed to POT fibers in the studies reported by Oyabu et al. (2004) and Ikegami et al. (2004), studies using very similar conditions to those of Yamato et al. (2003), did not develop any exposure related proliferative lesions. Only Lee et al. (1981), a study that used much higher levels of POT fibers than the other inhalation stidues, report the development of a maligant neoplasm in POT fiber exposed animals. In this study, 1 hamster in the group exposed to 2.9 x 10^3 fibers/cm^3, 1 hamster in the group exposed to 13.5 x 10^3 fibers/cm^3, and 1 hamster in the group exposed to 41.8 x 10^3 fibers/cm^3 developed mesothelioma. No mesotheliomas were observed in POT fiber exposed rats or guinea pigs. A few other pulmonary tumors developed in exposed animals, but the incidence was not higher than in the control groups. These studies are summarized below.

Summary of Two-Year Inhalation Studies

	Fiber Concentration (mg/m^3)	Fiber Number ($fibers/cm^3$)	Exposure	Malignant Tumor Development
Lee 1981	370	2900 13500 41800	6 h/day, 5 d/wk 3 months	Hamsters - Yes Guinea pigs - No Rats - No
Yamato 2003	2.2	111	6 h/day, 5 d/wk 1 yr	No
Oyabu 2004	1.9 & 2.2	Not Stated	6 h/day, 5 d/wk 1 yr	No
Ikegami 2004		Up to 200	6 h/day, 5 d/wk 2 yr	No

Overall, the studies cited above indicate that POT fibers are carcinogenic, but that a high amount of POT fibers in prolonged contact with susceptible tissue is required for induction of malignant neoplasia. Importantly, as can be seen in the summary table, the 2-year inhalation studies using a maximum of 100 - 200 fibers/cm^3 did not give rise to malignant lung or pleural tumors. Even the study by Lee et al., which exposed test animals to 2,900, 13,500, or 41,800 fibers/cm^3 (fiber number represents fibers between 5 and 10 μM in length) did not find any exposure-related neoplasms in rats or guinea pigs. These studies suggest that inhalation of POT fibers is not carcinogenic in rats and that low level exposure may not be carcinogenic in humans.[14]

References

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