

## TITLE

### **CIGARETTE SMOKE INHALATION STUDY FOR LUNG TUMORIGENICITY IN A/J MICE**

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Cigarette smoking is a major cause of lung cancer; however, it has been difficult to reproduce the tumorigenicity of cigarette smoke in preclinical animal models. Increased lung tumorigenicity has been reported in A/J mice exposed for 5 months to an environmental tobacco smoke surrogate or to cigarette mainstream smoke (MS) followed by 4 months without further exposure. Here, we report on MS-induced lung tumor formation in male A/J mice after 18 months of exposure to a continuous flow of MS (6 h/day, 5 d/wk) at total particulate matter concentrations of 150 and 300 mg/m<sup>3</sup>. Animal health, housing conditions, test atmosphere characterization, and markers for MS exposure (e.g., carboxyhemoglobin) were carefully monitored over the 18-month period to ensure the stability of the experimental conditions. Body weight gain was reduced dose-dependently in MS-exposed groups. An influx of neutrophils (up to 33% of leukocytes) and lymphocytes (up to 21%) into the bronchoalveolar space, indicating severe inflammation, was seen in MS-exposed groups. Classical histopathological evaluation of step-serial sections identified nodular alveolar hyperplasia, bronchiolo-alveolar adenoma, and carcinoma in all groups. Lung tumor multiplicity was increased in MS-exposed groups: up to 5-fold for adenomas and 2-fold for carcinomas. The data show that under these long-term, carefully controlled conditions, the A/J mouse is a promising model for cigarette-smoke-related lung tumorigenicity.