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A Review of Chronic Inhalation Studies with Mainstream Cigarette Smoke in Rats and Mice*

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ABSTRACT

In this paper, I review the results of a representative selection of chronic inhalation studies with rats and mice exposed to mainstream cigarette smoke and describe the inhalation exposures and the histopathological changes reported by various authors. Many of the studies used nose-only exposure systems, whereas others simply used large whole-body chambers. Smoke-induced epithelial hypertrophy, hyperplasia, and squamous metaplasia were reported in the conducting airways in most of the studies, along with increased numbers of intra-alveolar macrophages that were occasionally associated with alveolar metaplasia. Lung adenomas and adenocarcinomas were reported in only a few of the studies. No statistically significant increase in the incidence of malignant lung tumors was seen in either species as a result of smoke exposure, a finding that does not agree with the results of epidemiological studies in humans. Possible reasons for this lack of correlation are given.

Keywords. Cigarette smoke; inhalation toxicology; rodent respiratory tract

INTRODUCTION

Rats and mice are used routinely in studies of experimental carcinogenesis (12, 30, 33), leading others (11) to consider that "these laboratory results are the main source of information that is used to set regulatory standards for potential human exposures." The (unstated) presumption is that the rodent carcinogenic responses accurately predict human carcinogenic responses (27). The present review was performed to verify whether the measured response to cigarette smoke in rodents reflects the strong epidemiological findings in human smokers (19, 31).

This paper is a critical review of the scientific literature relating to the pulmonary pathology of rats and mice exposed by inhalation to cigarette smoke. There is a large amount of published literature on this subject, so for space reasons only a selection of the major papers is presented: the reviewed findings are similar to those in papers not so selected. Although there are numerous reports on smoke inhalation studies with other small animals (e.g., hamsters and rabbits) and larger animals (e.g., dogs and primates), these species will be considered in future reviews. Rigorous criteria by which to evaluate the results were selected in accord with accepted standards of toxicology, pathology, and carcinogenesis.

Reviews of the earlier literature are available (32, 36), so the present review includes only the more recent work on animal inhalation studies with cigarette smoke. Criteria for inclusion of such studies were (a) an overall duration consistent with the induction of cancer, including those studies where details on gross pathology, subsequent histopathology, or both were lacking, and (b) detailed histopathological descriptions, no matter what the duration of the experiment.