CONCORDANCE OF RAT AND HUMAN DATA-BASED RISK ESTIMATES FOR LUNG CANCER FROM CHRYSOTILE ASBESTOS

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Introduction: Risk assessment often relies on animal bioassay data to predict risks in humans, requiring extrapolation from animals to humans and usually from higher animal doses to lower human doses. Few human exposure-response data are available for assessing the validity of these assumptions. In this study, we use existing data in both rodents and humans to quantitatively compare the exposure, dose, and response relationships in humans and animals.

Methods: In the first phase of this study, we used a quantal multistage model to compute the toxic doses (TDs) associated with a 0.01, 0.1, 1, and 10% excess risk of lung cancer in two studies of male rats (Wistar-derived strain AF/HAN; inhalation exposure, 2 and 10 mg/m3, 7 hr/day, 5 day/week, 12 months, killed at approx. 30 months). The rat-based TDs were extrapolated to humans using allometric and lung surface area scaling approaches. Human-based TDs were derived from three human studies (two of Canadian miners/millers and one of U.S. textile workers), using Poisson regression modeling and lifetable analyses. Ratios of the rat- and human-based TDs were computed to evaluate concordance of the risk estimates.

Results: The TD ratios from the studies in rats and Canadian miners/millers varied from 0.3 to 3 for the scaling approaches of body surface area, metabolic rate, and air intake; while the TD ratios for body weight and lung surface area were more variable (1.5 to 20). The TD ratios comparing rats to the textile workers were all higher, ranging from approximately 20 to 800. Overall, the rat-based risk estimates for lung cancer in humans were reasonably concordant to those from the Canadian miners/millers studies, suggesting similar sensitivity in rats and humans. In contrast, the risk estimates were much higher from the textile workers study, suggesting humans are more sensitive. It is unknown how the airborne fiber size distributions compared between the rat studies and either human study; however, there is some evidence that the textile workers may have been exposed to longer fibers than the Canadian cohorts.

Discussion: The next phase of this study includes the development of lung dosimetry models, using existing data in rodents, cynomolgus monkeys, and humans, to compare the kinetics of chrysotile clearance and retention across species. Exposure, dose, and response relationships will be examined for both neoplastic and nonneoplastic lung responses, using statistical and biologically-based models. Fiber dimension will be investigated as a potential factor in lung fiber retention and response. The kinetic and mechanistic findings from this study may be especially useful for extrapolating from animal bioassay data to predict disease risk in humans exposed to airborne fibers.

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May 24-25, 2001