COMMENTS ON THE RAT LUNG AS A HUMAN SURROGATE IN INHALATION STUDIES

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INTRODUCTION

The laboratory rat is often used as a surrogate to estimate the hazard to human health following inhalation exposure to ambient aerosols. Extrapolation of rat deposition data to humans depends, however, on the similarities and differences between the morphometric structures of the two airway systems. The main structural difference between the lungs of the two species, aside from dimensions per se, is their respective airway branching pattern: while the human lung is a rather symmetrically, dichotomously dividing system, the rat network is a more monopodial branching structure (Yeh et al. 1979).

In our stochastic modeling approach (Koblinger and Hofmann 1986) to defining suitable morphologies for human and rat lung, we utilize measured morphometric dimensions as the data base upon which a rigorous statistical analysis is performed, instead of forcing them into a formalized, average pathway scheme. This stochastic approach allows us, therefore, to account for structural irregularities, such as asymmetric branching, monopodial structure, and inter- and intra-subject variability.

STATISTICAL ANALYSIS OF MORPHOMETRIC DIFFERENCES

Our comparison between the human and rat lung will focus on the symmetry/asymmetry aspect of the branching pattern in the tracheobronchial (TB) region and on the applicability of the generation concept to characterize properly the position and physiologic function of each airway in the respective system of bifurcating generations. Morphometric data for both tracheobronchial regions have been derived from measurements on silicon rubber replica casts at the Lovelace Inhalation Toxicology Research Institute (Raabe et al. 1976). The common origin of both data sets, i.e., using the same laboratory techniques for the human and rat lung, facilitates the interspecies comparison of data.

For a symmetric branching scheme of airways of circular cross section, the theoretical ratio of the parent-to-daughter (both daughters) cross section is 0.794 (D'Arcy Thompson 1942). Our calculated average value for fuman bronchial generations 6-17 of 0.82 (Koblinger and Hofmann 1985) is close to the symmetric value, suggesting that the human TB tree is reasonably approximated by a dichotomous, symmetric airway system.

A distinct asymmetry of the TB branching pattern, however, is found in the rat lung. In Fig. 1 the cumulative distribution functions for the ratios of the major daughter-to-parent and minor daughter-to--parent diameters are plotted for different parent airway diameters. A consistent difference between major and minor daughters is apparent for all parent diameters, illustrating a more asymmetric structure of the rat TB region relative to the human. An additional indicator of structural asymmetry is the distribution of branching angles for major and minor daughters, shown in Fig. 2. In the rat lung, in most cases, major daughters deviate from the parent by only a small angle, whereas minor daughter branching angles are much larger. This is a clear indication of the monopodial structure of the rat tracheobronchial region. There is another important interspecies difference in the respective branching patterns: in the rat lung the branching angles are practically independent of the generation number, while in the human lung branching angles decrease with increasing generation number.

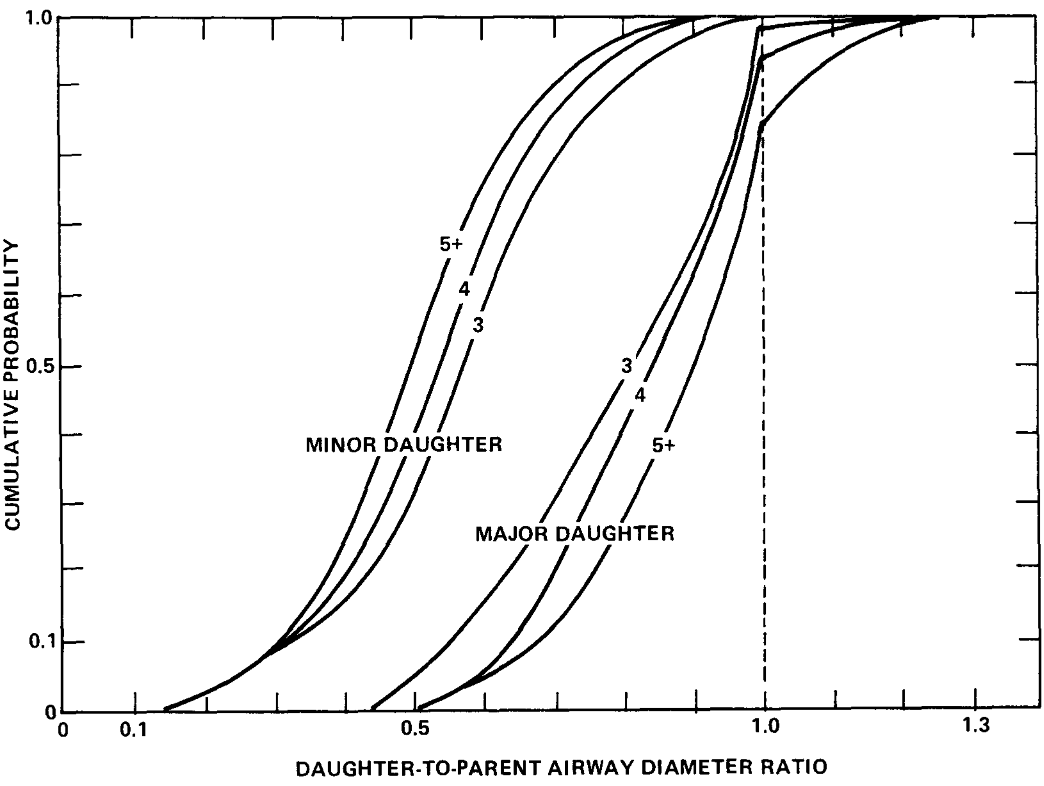

Figure 1 Cumulative distribution functions for major daughter-to-parent and minor daughter-to-parent diameter ratios for different parent diameters (in 0.1 mm units) in the rat lung. The curves denoted by 5+ contain all parent diameters >0.5 mm, for curves do not change significantly above 0.5 mm.

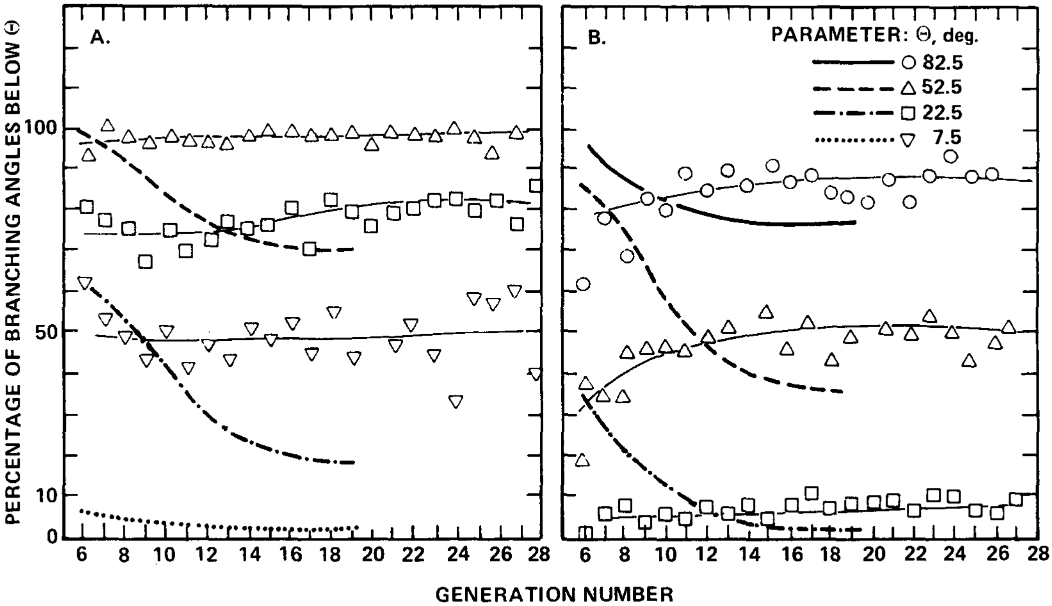

Figure 2 Cumulative branching angle distributions for major (panel A) and minor (panel B) daughters plotted versus generation number for arbitrarily selected branching angles. Solid lines denote rat lung, broken lines signify human lung.

Let us now investigate the termination probability, i.e., the probability that an airway of given linear dimensions or generation number is the terminal bronchiole and that the following airway belongs already to the alveolated, acinar region of the lung. For the human lung the termination probability depends on diameter and generation number: at a given diameter, it increases with increasing generation number and, for a given generation, it increases with decreasing diameter (Koblinger and Hofmann 1985).

In the rat lung the termination probability depends practically only on airway diameters but not on generation numbers; thus, the generation concept provides an inadequate description of the monopodial structure of the rat lung.

Considering all the arguments above, we propose to classify bronchial airways in the rat lung by their diameters (or diameter classes), and not by their generation numbers.

CONCLUSIONS

The statistical analysis has shown the above mentioned structural differences. The question, whether the rat lung is an applicable surrogate for human lungs for inhaled particles deposition calculations can be answered after comparing results calculated by the use of the two airway geometries.

We intend to carry out such comparative calculations with our stochastic lung model, in the near future.

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