TISSUE DOSIMETRY, PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING, AND CANCER RISK ASSESSMENT

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Chemical risk assessment is a complex process that requires integration of various biological data from test species, ultimately producing a prediction of the expected outcome of anticipated human exposure. There are two aspects of this process in which pharmacokinetic (PK) modeling can play an important role: in dosimetry, the process of estimating target tissue dose in the test species, and in extrapolation, the process of generalizing beyond the test species to predict human target tissue dose for various ambient exposure conditions. Mechanistic information on the cancer process is crucial in selecting the appropriate measure of target tissue dose: i.e., is it tissue exposure to parent chemical, tissue exposure to stable or reactive metabolite(s), occupancy of critical cellular receptors by parent or metabolite, or some measure of cytotoxicity with concomitant reparative hyperplasia? (This is not intended, by the way, to be an exhaustive list of the potential measures of tissue dose associated with cancer induction.) With a presumed carcinogenic mechanism and its appropriate measure of tissue dose in mind, a pharmacokinetic model can then be developed to quantitate this measure of target tissue dose for various exposure conditions. Physiologically based pharmacokinetic (PB-PK) modeling is the preferred modeling strategy since it is more readily amenable to the interspecies extrapolation necessary to calculate human tissue dose. This essay focuses on the issues of what constitutes an appropriate measure of tissue dose and of how PB-PK models can be developed to estimate tissue dose for chemicals which cause cancer by differing mechanisms. It outlines preliminary attempts to
include information on cytotoxicity into a quantitative risk assessment process. Quantitative, extrapolable cytotoxicity models are necessary to conduct biologically valid risk assessments for those chemicals whose primary effect is overt cellular toxicity instead of direct chemical interaction with cellular DNA. Rational, comprehensive risk assessments will only be possible with the advent of descriptions which combine information on both pharmacokinetics and pharmacodynamics into a single integrated model.

INTRODUCTION

The overall risk assessment process integrates hazard assessment data on chemical toxicity with exposure assessment information. PK modeling is useful in the hazard assessment process where it can be used to support extrapolations outside the range of toxicity testing conditions examined in the experimental animals. The basis for these pharmacokinetically based extrapolations is the assumption that an equivalent "tissue dose" will have the same effect regardless of dose route or of species. PK models, then, are tools to allow estimation of tissue dose for varying exposure conditions and in various species. Physiologically based (PB) PK models (Fig. 1) are constructed based on the physiological, biochemical, and physical chemical properties of the animal and test chemical. They are readily amenable to extrapolation and can be readily generalized to describe the kinetics of a large number of chemicals within the same conceptual framework. Physiologically based (PB) PK modeling readily supports the four important extrapolations: high dose-low dose, dose route, interspecies, and altered exposure patterns. The use of PB-PK in this arena has been extensively discussed by Clewell and Andersen, 1985.

DOSIMETRY WITH CARCINOGENS

The use of a PB-PK model for risk assessment sounds straightforward enough: determine the toxic tissue dose in the test species and calculate under which conditions this dose is likely to be achieved in humans (Fig. 2). It's a simple recipe, but it's not always easy to define all the ingredients. The main ingredient in the recipe is "tissue dose." An appropriate measure of tissue dose is some measure of the intensity of chemical exposure that is directly linked to the biological processes leading to tumor formation. With this definition, it is clear that some presumption of mechanism of tumor formation is necessary before we can define tissue dose. This presentation discusses which measure of dose is most appropriate for particular mechanisms of carcinogenicity. I must add a caution for the reader at this point. The comments in this essay are preliminary in the sense that toxicologists have not reached consensus on what constitutes the correct tissue dose for each proposed cancer mechanism. My goal here is to consider cancer mechanism from my personal