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Development and specification of physiologically based pharmacokinetic models for use in risk assessment

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Abstract

Risk assessments are performed to estimate the conditions under which individuals or populations may be harmed by exposure to environmental or occupational chemicals. In the absence of quantitative data in the human, this process is often dependent upon the use of animal and *in vitro* data to estimate human response. To reduce the uncertainty inherent in such extrapolations, there has been considerable interest in the development of physiologically based pharmacokinetic (PBPK) models of toxic chemicals for application in quantitative risk assessments. PBPK models are effective tools for integrating diverse dose–response and mechanistic data in order to more accurately predict human risk. Yet, for these models to be useful and trustworthy in performing the necessary extrapolations (species, doses, exposure scenarios), they must be thoughtfully constructed in accordance with known biology and pharmacokinetics, documented in a form that is transparent to risk assessors, and shown to be robust using diverse and appropriate data. This paper describes the process of PBPK model development and highlights issues related to the specification of model structure and parameters, model evaluation, and consideration of uncertainty. Examples are provided to illustrate approaches for selecting a "preferred" model from multiple alternatives.

Keywords: Physiologically based pharmacokinetic modeling; PBPK; Physiological modeling; Pharmacokinetics; Toxicokinetic modeling; Biokinetic modeling; Risk assessment

1. Introduction

Pharmacokinetics is the study of the time course for the absorption, distribution, metabolism, and excretion of a chemical substance in a biological system. In pharmacokinetic modeling, established descriptions of chemical transport and metabolism are employed to simulate observed kinetics *in silico* (Andersen et al., 1995a). Implicit in any application of pharmacokinetics to toxicology or risk assessment is the assumption that the toxic effects in a particular tissue can be related in some way to the concentration time course of an active form of the substance in that tissue. Moreover, absent pharmacodynamic differences between animal species, it is expected that similar responses will be produced at equivalent tissue exposures regardless of species, exposure route, or experimental regimen (Andersen, 1981; Monro, 1992; Andersen et al., 1995b). Of course the actual nature of the relationship between tissue exposure and response, particularly across species, may be quite complex.

Classic compartmental modeling is largely an empirical exercise, where data on the time course of the chemical of interest in blood (and perhaps other tissues) are collected. Based on the behavior of the data, a mathematical model is selected which possesses a sufficient number of compartments (and therefore parameters) to describe the data. The compartments do not generally correspond to identifiable physiological entities but rather are abstract concepts with meaning only in terms of a particular calculation. The advantage of this modeling approach is that there is no limitation to fitting the model to the experimental data. If a particular model is unable to describe the behavior of a particular data set, additional compartments

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can be added until a successful fit is obtained. Since the model parameters do not possess any intrinsic meaning, they can be freely varied to obtain the best possible fit, and different parameter values can be used for each data set in a related series of experiments.

Once developed, these models are useful for interpolation and limited extrapolation of the concentration profiles which can be expected as experimental conditions are varied. They are also useful for statistical evaluation of a chemical's apparent kinetic complexity (O'Flaherty, 1987). However, since the compartmental model does not possess a physiological structure, it is often not possible to incorporate a description of these non-linear biochemical processes in a biologically appropriate context. For example, without a physiological structure it is not possible to correctly describe the interaction between blood-transport of the chemical to the metabolizing organ and the intrinsic clearance of the chemical by the organ.

Physiologically based pharmacokinetic (PBPK) models differ from the conventional compartmental pharmacokinetic models in that they are based to a large extent on the actual physiology of the organism (Teorell, 1937a,b). A number of excellent reviews on the subject are available (Himmelstein and Lutz, 1979; Gerlowski and Jain, 1983; Fiserova-Bergerova, 1983; Bischoff, 1987; Leung, 1991). Fig. 1 illustrates the structure of a simple PBPK model for a volatile, lipophilic compound—styrene. The model equations represented by the diagram are described in the original publication (Ramsey and Andersen, 1984), which is an Institute for Scientific Information "citation classic".

Instead of compartments defined solely by mathematical analysis of the experimental kinetic data, compartments in a PBPK model are based on realistic organ and tissue groups, with weights and blood flows obtained from experimental data. Moreover, instead of compartmental rate constants determined solely by fitting data, actual physicochemical and biochemical properties of the compound, which can be experimentally measured or estimated by quantitative structure–property relationships, are used to define parameters in the model. To the extent that the structure of the model reflects the important determinants of the kinetics of the chemical, the result of this approach is a model that can predict the qualitative and quantitative behavior of an experimental time course without having been based directly on it. In recent years, there has been an enormous expansion of uses of PBPK modeling in areas related to environmental chemicals and drugs (Reddy et al., 2005).

In particular, a properly validated PBPK model can be used to perform the high-to-low dose, dose-route, and interspecies extrapolations necessary for estimating human risk on the basis of animal toxicology studies (Clewell and Andersen, 1985, 1994; Andersen et al., 1987, 1991; O'Flaherty, 1989; Reitz et al., 1990; Gerrity and Henry, 1990; Johanson and Filser, 1993; Corley et al., 1990, 1994; Corley, 1996; el-Masri et al., 1995; Mann et al., 1996a,b; Fisher, 2000; Barton and Clewell, 2000; Clewell et al., 2000, 2001a,b). The physiological structure of PBPK models is also useful for examining the effects of changing physiology on target tissue dosimetry, as in the case of early life exposure (Fisher et al., 1989, 1991; O'Flaherty, 1995; Clewell et al., 2001a,b, 2007; Corley et al., 2003; Sarangapani et al., 2003; Gentry et al., 2003, 2004; Clewell et al., 2004; Barton, 2005). Target tissue dosimetry provided by PBPK modeling is also a essential component in models of pharmacodynamics, such as acetylcholinesterase inhibition (Gearhart et al., 1994) or mixture interactions (el-Masri et al., 1995), as well as in biologically based dose–response models of cancer (Clewell and Andersen, 1989).

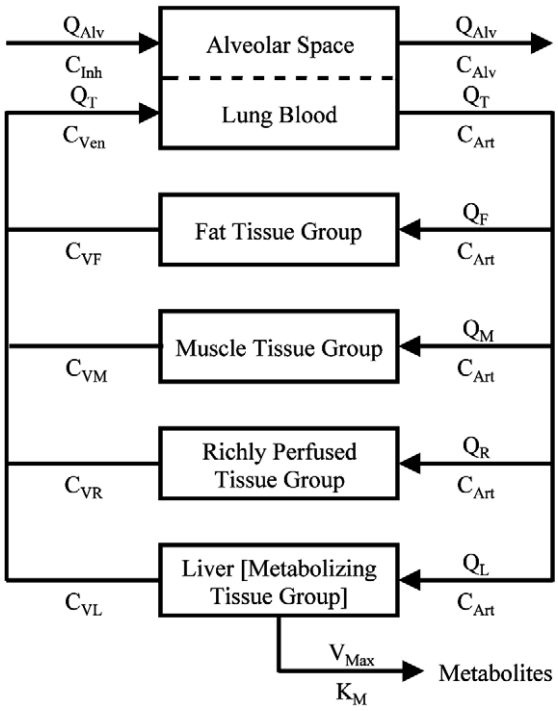

Fig. 1. Diagram of a physiologically based pharmacokinetic model for styrene. In this description, groups of tissues are defined with respect to their volumes, blood flows (Q), and partition coefficients for the chemical. The uptake of vapor is determined by the alveolar ventilation (Q_{ALV}), cardiac output (Q_T), blood:air partition coefficient (P_B), and the concentration gradient between arterial and venous pulmonary blood (C_{ART} and C_{Ven}). The dashed line reflects the fact that the lung compartment is described by a steady-state equation assuming that diffusion between the alveolar air and lung blood is fast compared to ventilation and perfusion. Metabolism is described in the liver with a saturable pathway defined by a maximum velocity (V_{max}) and affinity (K_M). The mathematical description assumes equilibration between arterial blood and alveolar air as well as between each of the tissues and the venous blood exiting from that tissue. (Adapted from Ramsey and Andersen, 1984).

2. Model development process

The basic approach to PBPK model development is illustrated in Fig. 2. The process of model development begins with the identification of the chemical exposure and toxic effect of concern, as well as the species and target tissue in which it is observed. Literature evaluation