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PBPK models in risk assessment—A focus on chloroprene☆,☆☆

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Abstract

Mathematical models are increasingly being used to simulate events in the exposure-response continuum, and to support quantitative predictions of risks to human health. Physiologically based pharmacokinetic (PBPK) models address that portion of the continuum from an external chemical exposure to an internal dose at a target site. Essential data needed to develop a PBPK model include values of key physiological parameters (e.g., tissue volumes, blood flow rates) and chemical specific parameters (rate of chemical absorption, distribution, metabolism, and elimination) for the species of interest. PBPK models are commonly used to: (1) predict concentrations of an internal dose over time at a target site following external exposure via different routes and/or durations; (2) predict human internal concentration at a target site based on animal data by accounting for toxicokinetic and physiological differences; and (3) estimate variability in the internal dose within a human population resulting from differences in individual pharmacokinetics. Himmelstein et al. [M.W. Himmelstein, S.C. Carpenter, P.M. Hinderliter, Kinetic modeling of beta-chloroprene metabolism. I. In vitro rates in liver and lung tissue fractions from mice, rats, hamsters, and humans, Toxicol. Sci. 79 (1) (2004) 18–27; M.W. Himmelstein, S.C. Carpenter, M.V. Evans, P.M. Hinderliter, E.M. Kenyon, Kinetic modeling of beta-chloroprene metabolism. II. The application of physiologically based modeling for cancer dose response analysis, Toxicol. Sci. 79 (1) (2004) 28–37] developed a PBPK model for chloroprene (2-chloro-1,3-butadiene; CD) that simulates chloroprene disposition in rats, mice, hamsters, or humans following an inhalation exposure. Values for the CD-PBPK model metabolic parameters were obtained from in vitro studies, and model simulations compared to data from in vivo gas uptake studies in rats, hamsters, and mice. The model estimate for total amount of metabolite in lung correlated better with rodent tumor incidence than did the external dose. Based on this PBPK model analytical approach, Himmelstein et al. [M.W. Himmelstein, S.C. Carpenter, M.V. Evans, P.M. Hinderliter, E.M. Kenyon, Kinetic modeling of beta-chloroprene metabolism. II. The application of physiologically based modeling for cancer dose response analysis, Toxicol. Sci. 79 (1) (2004) 28–37; M.W. Himmelstein, R. Leonard, R. Valentine, Kinetic modeling of β-chloroprene metabolism: default and physiologically-based modeling approaches for cancer dose response, in: IISRP Symposium on Evaluation of Butadiene & Chloroprene Health Effects, September 21, 2005, TBD—reference in this proceedings issue of Chemical–Biological Interactions] propose that observed species differences in the lung tumor dose–response result from differences in CD metabolic rates. The CD-PBPK model has not yet been submitted to EPA for use in developing the IRIS assessment for chloroprene, but is sufficiently developed to be considered. The process that EPA uses to evaluate PBPK models is discussed, as well as potential applications for the CD-PBPK model in an IRIS assessment.
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Keywords: PBPK model; Chloroprene; Risk assessment; Toxicokinetic; IRIS

1. Introduction

The mission of the EPA to protect human health and the environment depends on the availability of quality data for quantitative characterization of the dose–response relationship. Biologically based mathe-

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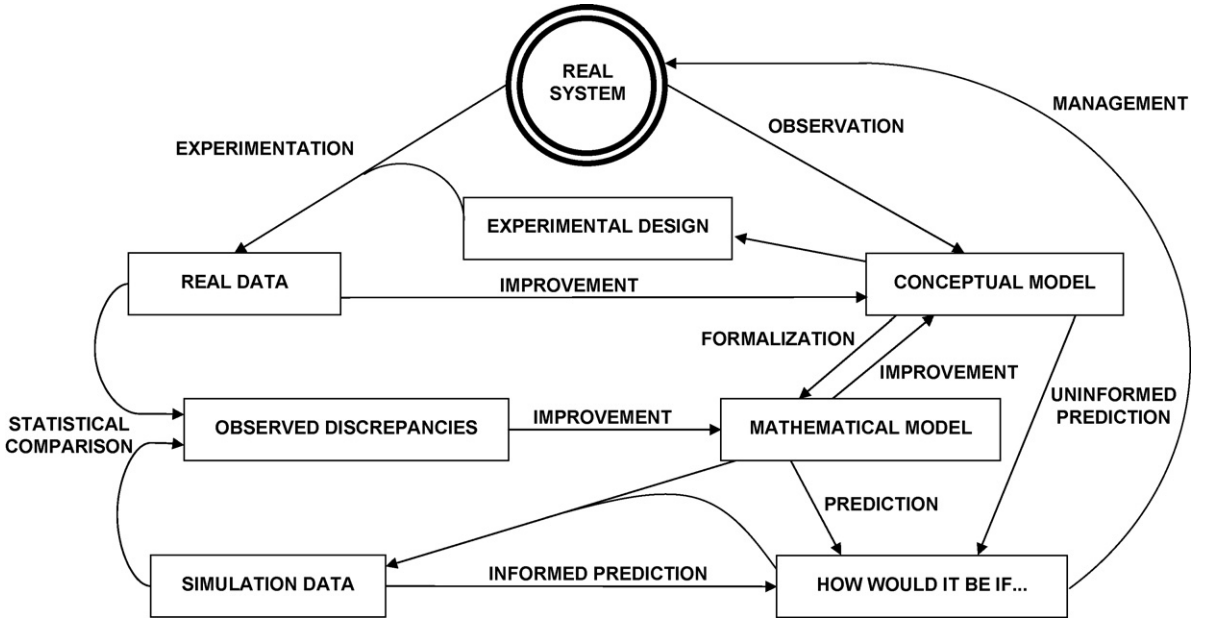

Fig. 1. The role of quantitative modeling and simulation in research is illustrated in this schematic of the relationship between a real system, a conceptualization of the system (the theoretical model), and the data. A BBDR model evolves from a qualitative (conceptual) model to a quantitative (mathematical) model of the mode of action, and therefore serves the role of both of these compartments in the figure. [Reprinted with permission from John Wiley & Sons, Inc. from the book [1], Copyright© 1992 Wiley-Liss, Inc.].

matical models are increasingly being used to maximize the utility of the available data for this characterization, and to identify data gaps. This presentation provides a brief overview of the development, use, and evaluation of physiologically based pharmacokinetic (PBPK[1]) models in risk assessment, and potential applications of a PBPK model for chloroprene.

2. Development and use of PBPK models in risk assessment

Computer models of biological systems begin with a conceptual (i.e., qualitative) representation of the components and behaviors of a real system. In an iterative process, this qualitative conception is progressively replaced with mathematical representations (i.e., the quantitative model) that simulate system behavior for comparison with experimental observations. Keen and Spain [1] illustrate this iterative process in model development in Fig. 1.

In risk assessment, the "system" behaviors to be simulated are the spatial and temporal sequence of events from the release of a chemical in the environment to an adverse effect in humans. For practical reasons, this continuous sequence is somewhat arbitrarily divided into discrete stages, each represented by a different subset of computer models, as illustrated in Fig. 2. The dosimetry models in Fig. 2 of interest here are called physiologically based pharmacokinetic (PBPK, see footnote

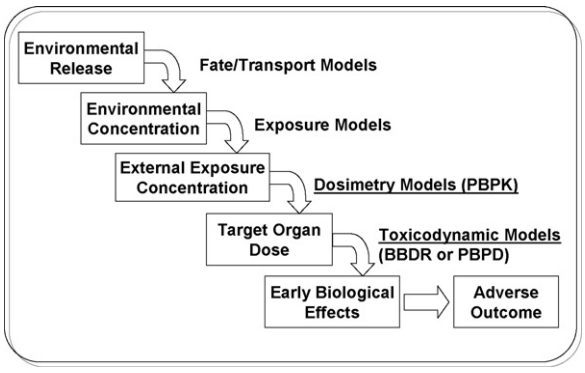

Fig. 2. Computer models for various subgroupings of the risk assessment events from release of a toxin to the environment to an adverse effect in humans.

[1] Some people prefer the acronyms PBTK and PBTD, replacing "pharmacokinetic" and "pharmacodynamic" terms with "toxicokinetic" and "toxicodynamic" to distinguish models for toxic substances from those for pharmaceuticals. The Greek root "pharmakon", however, means either poison or drug, and although contemporary use associates the prefix "pharmaco-" most commonly with a medicine, both PBPK and PBTK monikers are correct, and the choice of which to use is a matter of personal preference.

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