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Physiologically Based Pharmacokinetic Modeling

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Editorial

Physiologically based pharmacokinetic modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion of synthetic or natural chemical substances in humans and other animal species. PBPK modeling is used in pharmaceutical research and drug development, and in health risk assessment for cosmetics or general chemicals. PBPK models strive to be mechanistic by mathematically transcribing anatomical, physiological, physical, and chemical descriptions of the phenomena involved in the complex ADME processes [1]. A large degree of residual simplification and empiricism is still present in those models, but they have an extended domain of applicability compared to that of classical, empirical function based, pharmacokinetic models. PBPK models may have purely predictive uses, but other uses, such as statistical inference, have been made possible by the development of Bayesian statistical tools able to deal with complex models. That is true for both toxicity risk assessment and therapeutic drug development [2]. PBPK models try to rely a priori on the anatomical and physiological structure of the body, and to a certain extent, on biochemistry. They are usually multi-compartment models, with compartments corresponding to predefined organs or tissues, with interconnections corresponding to blood or lymph flows more rarely to diffusions. A system of differential equations for concentration or quantity of substance on each compartment can be written, and its parameters represent blood flows, pulmonary ventilation rate, organ volumes etc., for which information is available in scientific publications. Indeed, the description they make of the body is simplified and a balance needs to be struck between complexity and simplicity [3].

Besides the advantage of allowing the recruitment of a priori information about parameter values, these models also facilitate inter-species transpositions or extrapolation from one mode of administration to another e.g., inhalation to oral. An example of compartment PBPK model, suitable to describe the fate of many solvents in the mammalian body, is given in the Figure on the right. The first pharmacokinetic model described in the scientific literature was in fact a PBPK model. It led, however, to computations intractable at that time [4]. The focus shifted then to simpler models, for which analytical solutions could be obtained such solutions were sums of exponential terms, which led to further simplifications. The availability of computers and numerical integration algorithms marked a renewed interest in physiological models in the ear For substances with complex kinetics, or when inter-species extrapolations were required, simple models were insufficient and research continued on physiological models by hundreds of scientific publications have described and used PBPK models, and at least two private companies are basing their business on their expertise in this area. The model equations follow the principles of mass transport, fluid dynamics, and biochemistry in order to simulate the fate of a substance in the body. Compartments are usually defined by grouping organs or tissues with similar blood perfusion rate and lipid content i.e. organs for which chemicals' concentration vs. time profiles will be similar [5]. Ports of entry lung, skin, intestinal tract, ports of exit kidney, liver and target organs for therapeutic effect or toxicity are often left separate. Bone can be excluded from the model if the substance of interest does not distribute to it. Connections between compartment follow physiology e.g., blood flow in exit of the gut goes to liver, etc. Drug distribution into a tissue can be rate-limited by either perfusion or permeability. Perfusion-rate-limited kinetics apply when the tissue membranes present no barrier to diffusion. Blood flow, assuming that the drug is transported mainly by blood, as is often the case, is then the limiting factor to distribution in the various cells of the body.

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