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A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan

Rémy Beaudouin, Sandrine Micallef [1], Céline Brochot *

INERIS, Institut National de l'Environnement Industriel et des Risques, Unité Modèles pour l'Ecotoxicologie et la Toxicologie (METO), Parc ALATA, BP2, 60550 Verneuil en Halatte, France

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ABSTRACT

Physiologically based pharmacokinetic (PBPK) models have proven to be successful in integrating and evaluating the influence of age- or gender-dependent changes with respect to the pharmacokinetics of xenobiotics throughout entire lifetimes. Nevertheless, for an effective application of toxicokinetic modelling to chemical risk assessment, a PBPK model has to be detailed enough to include all the multiple tissues that could be targeted by the various xenobiotics present in the environment. For this reason, we developed a PBPK model based on a detailed compartmentalization of the human body and parameterized with new relationships describing the time evolution of physiological and anatomical parameters. To take into account the impact of human variability on the predicted toxicokinetics, we defined probability distributions for key parameters related to the xenobiotics absorption, distribution, metabolism and excretion. The model predictability was evaluated by a direct comparison between computational predictions and experimental data for the internal concentrations of two chemicals (1,3-butadiene and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin). A good agreement between predictions and observed data was achieved for different scenarios of exposure (e.g., acute or chronic exposure and different populations). Our results support that the general stochastic PBPK model can be a valuable computational support in the area of chemical risk analysis.

1. Introduction

Humans are exposed daily to a multitude of xenobiotics at environmental or occupational levels. The typical residence times of these xenobiotics in the human body is usually relatively short compared to the human lifetime, but notable exceptions arise for persistent substances (Kerger et al., 2006). In those cases, it may be necessary to follow the fate of these xenobiotics in the body over a long-term period in order to prevent toxic or adverse effects. Thus the determination of internal effective concentrations, i.e., in the target tissues where toxic effects arise, is required to characterize accurately the link between an external exposure and the internal dosimetry that may be associated with the observed effects (Andersen and Dennison, 2002).

Internal dosimetry depends on the biokinetics (toxicokinetics for chemicals and pharmacokinetics for therapeutic compounds) of the substance that are governed by its absorption, distribution, metabolism, and excretion (ADME). Biokinetic models are dedicated tools to describe mathematically these ADME processes. Such processes are essentially influenced by physiological, physicochemical and biochemical factors that may vary over lifespan. For example, some of these factors (e.g., the tissue volumes, or the quantity of metabolic enzymes) are known to vary continually throughout the growth and the development of a child. The combination of the age-dependent changes in these factors may lead to adult-children differences in toxicokinetics. In adulthood, the physiology and the anatomy of the body are usually supposed stable, except during gestation, lactation period or old age. For example, during pregnancy, the pace of organogenesis and remodelling, which can be measured in days, becomes commensurable with the scale of persistence of many chemicals in the body.

A class of biokinetic models, the physiologically based pharmacokinetic (PBPK) models, is based on the physiology and the anatomy of the individuals (Andersen, 1991; Brochot et al., 2007; Nestorov, 2003). Typically, most of the model parameters are directly linked to a physiological process or to an anatomical entity. For this reason, PBPK models are often considered as being more realistic compared to empirical models. These models are a tool well-suited for integrating available information on age- or gender-dependent changes and then evaluating the influence of

* Corresponding author. Fax: +33 (0) 3 44 55 68 00.
E-mail addresses: Remy.Beaudouin@ineris.fr (R. Beaudouin), Sandrine.Micallef@sanofi-aventis.com (S. Micallef), Celine.Brochot@ineris.fr (C. Brochot).
[1] Present address: Clinical Biostatistics Oncology, Sanofi-Aventis R&D, 20 Avenue Raymond Aron, 92165 Antony Cedex, France.

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these changes on the chemical pharmacokinetics (Yang et al., 2006). Literature reviews have been performed to gather experimental data on the human physiology and anatomy at different ages for males and females and to develop quantitative relationships linking the physiological variations to the age during childhood and adolescence (Haddad et al., 2001; Price et al., 2003). Several PBPK models have been developed for specific compounds or classes of compounds integrating the time evolution of the human body during the prenatal period, i.e., foetus's development (Luecke et al., 1994; Young et al., 1997), during childhood (Edginton et al., 2006; Verner et al., 2009) or the whole life (Clewell et al., 2004; Gentry et al., 2003a; Nong et al., 2006). However, the latter do not include pregnancy or lactation for women, and specific models have been developed for these issues (Gentry et al., 2002, 2003a; Luecke et al., 1994). In that context, several models have to be used to predict tissue levels for the same individual during the whole life time.

The aim of our study is to propose a single general PBPK model able to simulate the body burden of various xenobiotics throughout the entire human lifespan (including childhood, pregnancy, lactation and advanced age). Unlike the models previously developed, the model we propose is based on a detailed description of the body anatomy and includes a substantial number of tissue compartments. The integration of additional organs in the structure of our model enables the analysis of toxicokinetics for diverse chemicals that induce multiple effects in different target tissues. The availability of physiological and anatomical data (International Commission on Radiological Protection, 2002) that are used to parameterize PBPK models, combined with the possibility to measure internal concentrations in different tissues (Kreuzer et al., 1997) allows the validation of detailed models such as the one we developed. New quantitative relationships for age- or gender-dependent variables are derived and the associated inter-individual variability is assessed in order to encourage the use of such a model in risk assessment for the general human population. To demonstrate the suitability of our approach, the general PBPK model is tested on two chemicals: 1,3-butadiene (BD), a volatile organic compound, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a persistent organic compound. These two chemicals are commonly present in the environment, and may be quite representative of different contaminants since their toxicokinetics properties (e.g., metabolism, bio-persistence) and mode of exposure differ. The PBPK model predictions are compared to experimental data, when available.

2. Materials and methods

2.1. Model structure

The lifetime PBPK model used in this study is presented Fig. 1. The model structure is identical for men and women, although an exception arises in case of pregnancy. This model proposes a detailed compartmentalization of the human body with 22 organs. Two compartments integrate several entities. The urinary tract compartment includes the bladder, the ureters and the urethra, and the sexual organs compartment includes the testes, the epididymes and the prostate for men, and the ovaries, the fallopian tubes and the uterus for women. All tissue compartments are assumed to be well-mixed and blood flow-limited. We also separate the lungs to distinguish the pulmonary functions from the lungs anatomy (the tissues). Nineteen compartments are added to the general PBPK model to describe a woman's pregnancy and foetal development. They correspond to the placenta, the amniotic fluid and the foetus organs. Pregnancy also impacts the parameterization of four permanent compartments: adipose tissues, breast, sexual organs and blood. During pregnancy, the weight of the ovaries and the fallopian tubes was assumed negligible in the sexual organs compartment compared to the weight of the uterus, so exchanges with the foetus occur via the whole sexual organs compartment.

Elimination occurs via metabolism, urinary and faecal excretion, exhalation and, in case of lactation, milk production. Four sites of metabolism are modelled: liver, lungs, gut and placenta.

The mathematical description of the general PBPK model is detailed in the Appendix.

2.2. Model parameterization

Quantitative relationships linking bodyweight, tissue volumes, or other physiological parameters with age have already been developed for childhood or for the whole life (Clewell et al., 2004; Haddad et al., 2001; Price et al., 2003). However, these relationships are not well-suited for our model, since they have not been established for all the organs of our PBPK model, and since our model is parameterized with relative tissue volumes (as a fraction of body weight) instead of tissue volumes.

Four different models were used to describe the changes related to age: the Preece–Baines model (Preece and Baines, 1978), the von Bertalanffy equation (von Bertalanffy, 1938), a sigmoid function and a polynomial function. These functions are, respectively:

$$\text{Parameter} = H_1 - \frac{H_1 - H_\theta}{e^{(s_0(\text{Age}-\theta))} + e^{(s_1(\text{Age}-\theta))}} \quad (1)$$

$$\text{Parameter} = y_{\text{inf}} + (y_0 - y_{\text{inf}}) \times e^{-\lambda \times \text{Age}} \quad (2)$$

$$\text{Parameter} = y_{\text{inf}} \times \frac{1}{1 + e^{-\lambda \times \text{Age} + \rho}} \quad (3)$$

$$\text{Parameter} = \alpha \times \text{Age}^n + \beta \times \text{Age}^{n-1} + \ldots + \zeta. \quad (4)$$

The Preece–Baines growth model (Eq. (1)) is a family of curves that conforms to the shape of the human growth curve. It combines two different exponential growth phases to represent the gradual growth of infants followed by a faster growth of adolescents, but becoming rapidly asymptotic. In von Bertalanffy model (Eq. (2)), growth is the fastest at the outset, gradually diminishes, and finally reaches zero. Size cannot exceed the horizontal asymptote of the curve (y_{inf}) and y_0 is the parameter's value at birth. In the sigmoid or logistic function (Eq. (3)), the initial stage of growth is approximately exponential, then, as saturation begins, the growth slows, and at y_{inf} (parameter's value at infinity set to the adult values) growth stops. If none of the von Bertalanffy or the sigmoid models fitted the data correctly, a polynomial function (Eq. (4)) was used. For few parameters, it has not been possible to define a single function for the whole life, so several functions were defined on different time ranges.

Notable effects of aging on the bodyweight and tissue volumes, that are modelled, include skeletal muscle atrophy and variations of the adipose tissues. We assumed that all the organ volumes, except those two, do not evolve during adulthood. Aging atrophy of the muscle begins around 24 years old and thereafter accelerates (Lexell et al., 1988), and the adipose volume starts to increase around age 20. Before the increase of adipose volume during adulthood, the volume of adipose tissues is determined as the difference between 96% of bodyweight minus the volume of the other compartments. Separable connective tissues, non-perfused bones and certain lymphatic tissues account for most of the remaining 4% of body mass. In adulthood, we model the increase in the adipose volume as the difference between the adult asymptotic value of the bodyweight (parameter H_1 in the Preece–Baines model) and the polynomial model which describes the bodyweight variations during the adult period.