Physiologically-based Pharmacokinetic (PBPK) Model of TiO_2 Nanoparticles' Bio-distribution in Rat Tissues

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ABSTRACT

The emerging of nanotechnology has increasingly gained expansions and applications in various materials science research and development. However, the exposure to nanoparticles and engineered nanomaterials can lead to adverse biological effects because the small sizes of nanoparticles can enter the human body and deposit in the organs or translocate from the intake area to the secondary organs and can cause inflammation. One of the most used nanoparticles is TiO_2, which is commonly found in skin care and household products. It is still unclear how TiO_2 nanoparticles are remained in human bodies after exposing. In the present study, we develop a physiologically-based pharmacokinetic (PBPK) model to predict the bio-distribution of TiO_2 concentrations in rat tissues. The model is validated with an existing in-vivo study in rats. We also extend our PBPK model to predict cell death caused by TiO_2 nanoparticles in the rat liver using a dose-response model. The dose-response model accounts for the interplay between the cellular accumulation of TiO_2 due to cell's particle uptake and the dilution of TiO_2 due to cell division. Our developing framework, which can be scaled-up to understand the effects in human system, has a potential to provide the health risk data and to help regulate the human exposure to TiO_2 nanoparticles.

Keywords: PBPK model; TiO_2 nanoparticles; bio-distribution; nanotoxicology; health risk

1 INTRODUCTION

Nanoparticles are generally classified as ultrafine particles when at least one of their dimensions is in the size range <100 nanometers. Unlike the larger particles, products derived from engineered nanomaterials are very fascinating, as the particles' properties are known to change, which can be useful and result in more effective medical and industrial applications. However, the exposure to nanoparticles and engineered nanomaterials may lead to adverse biological effects [1-3]. The most at-risk population is the group of people working in the engineered nanomaterial production industry especially for those who have to handle nanomaterials. As a result, risk assessment to the exposure of these nanomaterials is now becoming an emerging trend in the field of nanotoxicology [1, 2, 4].

One of the most used nanoparticles is TiO_2 which is commonly found in cosmetic products, clothes, pigments, food, paper, toothpaste, skin care products, household products, etc. TiO_2 nanoparticles offer greater relative surface area leading to much better properties such as catalytic activity and UV absorption. Sufficient evidence in the literature has shown that TiO_2 nanoparticles may be very harmful and can promote tumors by interfering with the immune cells [5].

Due to the complexity of nanoparticle's screening in experiments, it has raised the issues and brought to the modeling of nanoparticles' bio-distribution, toxicity, etc. The methods include physiologically-based pharmacokinetic (PBPK) model, data modeling and molecular modeling (e.g., molecular docking and molecular dynamics). Data modeling is typically based on quantitative structure activity relationship (QSAR - a statistical tool used to identify the properties of studied molecules based on a set of molecules whose properties are already known). Another pharmacokinetic model is related to the absorption, distribution, metabolism, and excretion (ADME) of pharmaceuticals to describe nanomaterial kinetics in the body [6, 7].

PBPK modeling is an alternative approach based on physiology of compartmental tissues and the knowledge of blood transport to and from organs and tissues throughout the body. This model can be used to study time series profiles of particles' concentrations in each tissue and in the plasma [8, 9]. PBPK modeling has been used in nanoparticle research since 2006 and has gained more efforts for the advancement of nanoparticle research. One great advantage of PBPK models is that it enables the interspecies extrapolation which allows the animal model to be scaled up to represent the human system because in many cases the tissue concentration data cannot be obtained from humans directly [10].

The literature relevant to using PBPK models for the nanoparticles' bio-distribution predictions includes: Pery *et al*. [11] developed a PBPK model for carbon nanoparticle

exposure by inhalation, using imaging data collected from humans. A recent published article by Lankveld *et al.* [12] revealed the development of a PBPK model of the kinetics of silver nanoparticles of different sizes. It is concluded that the kinetics can be also governed by surface charge in addition to sizes. In the present study, our aim is to develop a PBPK model to predict bio-distribution of TiO_2 nanoparticles in rat tissues. In addition, the distribution of TiO_2 nanoparticles predicted from the PBPK model is treated as an input for a dose-response model, which is implemented to estimate cell viability of rat liver cells after the nanoparticles' exposure.

2 METHODOLOGY

PBPK model composed of a set of coupled differential equations is used to derive the mass transport of the nanoparticles in the body. The equations can be solved numerically using available software and the solutions are the time-series profile of the nanoparticle concentration in each tissue after an exposure. Due to limitation of available data in humans, the model will be built based on experimental data in rats. A PBPK equation for basic mass transport is shown as follows:

$$V_T \cdot \frac{dC_T}{dt} = Q_T (C_A - \frac{C_T}{P_T}), \quad (1)$$

where C_T is the concentration of the particle in the tissue, C_A is the concentration of the particle in the blood reaching the tissue, Q_T is the blood flow to and from the tissue, V_T is the volume of the tissue, and P_T is the partition coefficient of the particle between the tissue and the blood leaving the tissue.

Q_T and V_T for each tissue can be obtained from physiological parameters of rats from literature (Table 1). The values of P_T's are not known for TiO_2 nanoparticles and will be estimated to fit the simulations to experimental data.

Table 1 Physiological parameters for rats.

Organ	Weight (Fraction of body weight)	Blood flow (Fraction of total blood flow)
Liver	0.037 [13]	0.18 [14]
Kidney	0.0073[13]	0.12 [14]
Spleen	0.0020 [13]	0.0085 [14]
Lung	0.0050 [13]	0.021 [13]
Gut	0.0330 [15]	0.10 [14]

Rat body weight = 0.3 kg and rat total blood flow = 15 L/(h-kg) [15]

The diagram of tissues and mass transport routes considered in the present work is illustrated in Figure 1.

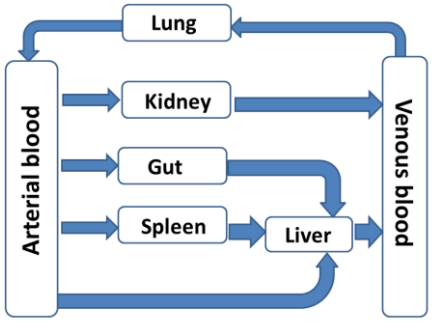

Figure 1: Tissues and transport routes of TiO_2 nanoparticles in the model.

We include only major tissues and organs (Figure 1) reported to have substantial amounts of TiO_2 particles deposited after exposures. The PBPK model is developed in 3 steps: 1) model building, 2) parameter estimation, and 3) scenario implementation. The aim of the PBPK model is to estimate time series profiles of TiO_2 nanoparticles remaining in major organs after the exposure. However, the use of the PBPK model may not be suffifient to describle cellular behavior that likely plays a role in determining adverse effects of the cells exposed to TiO_2 nanoparticles. To quantitatively assess health risks, we further incorporate a dose-response model to predict cell viability. Our goal is to develop a modeling framework suitable to predict cell toxicity based on different exposure scenarios.

3 RESULTS AND DISCUSSIONS

It is important to understand how TiO_2 nanoparticles are taken up and distributed throughout the body. We apply the PBPK model to investigate TiO_2 nanoparticles distributed in the major organs, such as, liver, spleen, lung, and kidney after a single intravenous injection of TiO_2 nanoparticles to a rat body with weight of 0.3 kg. The model is validated by comparing the time course of the nanoparticle levels in the major organs to experimental values [16].

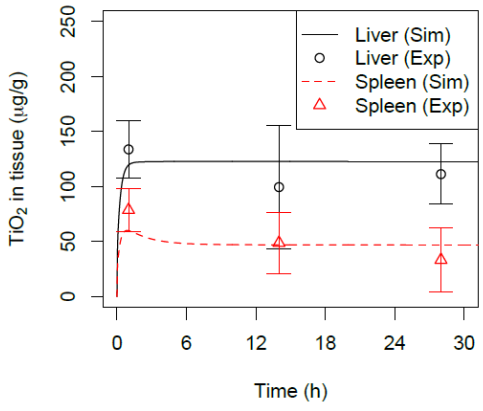

Figure 2: Simulation results (Sim) of TiO_2 nanoparticles' bio-distribution in liver and spleen compared with experimental data (Exp).

Figures 2 and 3 show a comparison of TiO_2 concentrations from our simulation and the experimental results in liver, spleen, lung, and kidney tissues after different exposure time. It can be observed that the model is in good agreement with experimental results. The estimated values of P_T's used in the simulation are given as such: 340 for liver, 0.8 for kidney, 130 for spleen, 8 for lung, and 1 for gut.

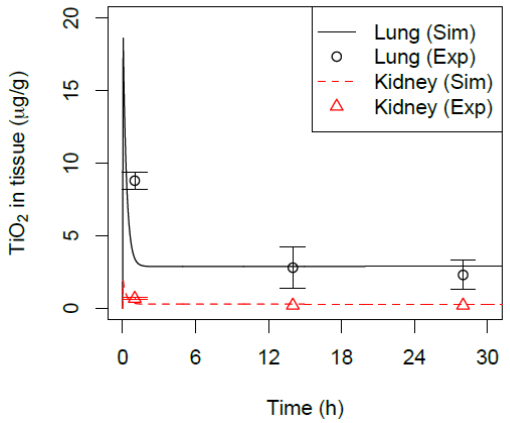

Figure 3: Simulation results (Sim) of TiO_2 nanoparticles' bio-distribution in lung and kidney compared with experimental data (Exp).

Once the model is formed, the nanoparticles' distributions in rat tissues with different scenarios of exposure doses are simulated. Figure 4 shows predicted levels of TiO_2 in the rat liver tissue at different time after an intravenous injection of TiO_2 with 1, 50, 500, and 5000 mg per kg of body weight.

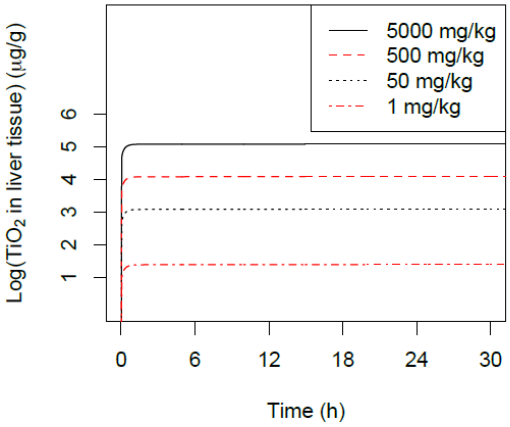

Figure 4: Predicted levels of TiO_2 distributed in rat liver tissues after an intravenous injection with different TiO_2 exposure doses (1, 50, 500, and 5000 mg/kg).

Though PBPK model can calculate TiO_2 levels in the internal organs, the risk assessment from the remained nanoparticles inside the tissues remains unclear. Therefore the behavior of the cellular uptake must be taken into account. Several studies have suggusted that the cellular uptake of nanoparticles depend on many factors, including, size and/or shape of the nanoparticle. In addition, it has been shown that cell division can dilute the cellular nanoparticles' concentration [17]. We determine the cellular uptake kinetics and cell death using a dose-response model, which takes into account the interplay between the accumulation of TiO_2 due to cell's particle uptake and the dilution of TiO_2 due to cell division. (details are in another manuscript preparation). The model can be used to calculate cell viability of the liver tissue based on different exposure doses of the nanoparticles. We use predicted levels of TiO_2 in the liver tissue of rats exposed to different TiO_2 doses (Figure 4) as input parameters for the dose-response model in order to predict cell viability of the liver tissue as shown in Figure 5. The resulting simulations show nonlinear behavior of the timescale of viability in cell population receiving different TiO_2 concentrations.

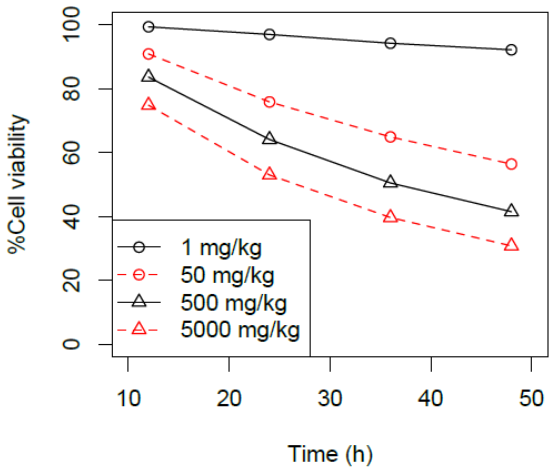

Figure 5: Predicted cell viability of rat liver cells after the rat is exposed intravenously to different TiO_2 doses.

4 CONCLUSIONS

Wide applications of TiO_2 lead to substantial human exposure and environmental release. Therefore it is inevitable to avoid potential health risks to humans. The negative health and environmental effects of engineered nanomaterials arise because their sizes are so small that they can pass through the skin, lungs, intestinal tract, and possibly can reach to the brain. Subsequently, nanoparticles can cause inflammation when they are inhaled and later deposited in the organ or translocate from the intake area to the secondary organs. This fast expansion of the nanotechnology-based consumer products, especially TiO_2, raises the issues of potential harms when humans are exposed to them. Yet the health risks and the potential health effects are poorly understood.

We develop a modeling framework to assess the risk of cell toxicity quantitatively upon TiO_2 exposures. The model is performed in two subsequent steps. First, the PBPK model is implemented to predict the TiO_2 distribution in

different tissues based on different exposure levels of the nanoparticles. Then the TiO_2 levels deposited in the tissue are used to estimate cell viability based on cellular uptake kinetics and cell division activity.

For the future works, more data on bio-distribution of TiO_2 concentrations in tissues based on different exposure routes, exposure doses, exposure intervals and particle sizes are needed to validate and revise the PBPK model. In addition, the current animal model needs to be scaled up to represent the human system to benefit human health risk assessment.

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