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Bayesian evaluation of a physiologically-based pharmacokinetic (PBPK) model of long-term kinetics of metal nanoparticles in rats

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ABSTRACT

Biomathematical modeling quantitatively describes the disposition of metal nanoparticles in lungs and other organs of rats. In a preliminary model, adjustable parameters were calibrated to each of three data sets using a deterministic approach, with optimal values varying among the different data sets. In the current effort, Bayesian population analysis using Markov chain Monte Carlo (MCMC) simulation was used to recalibrate the model while improving assessments of parameter variability and uncertainty. The previously-developed model structure and some physiological parameter values were modified to improve physiological realism. The data from one of the three previously-identified studies and from two other studies were used for model calibration. The data from the one study that adequately characterized mass balance were used to generate parameter distributions. When data from a second study of the same nanomaterial (iridium) were added, the level of agreement was still acceptable. Addition of another data set (for silver nanoparticles) led to substantially lower precision in parameter estimates and large discrepancies between the model predictions and experimental data for silver nanoparticles. Additional toxicokinetic data are needed to further evaluate the model structure and performance and to reduce uncertainty in the kinetic processes governing *in vivo* disposition of metal nanoparticles.

1. Introduction

The use of nanoparticles in commerce has expanded rapidly, with an increase from 803 products in 2008 to 1628 products as of October 2013 in a nanotechnology consumer products database (Project on Emerging Nanotechnologies, 2013). As consumer exposure increases, concerns about toxicity have also been raised, based on effects identified in laboratory animals. As in other areas of chemical toxicology, the development of physiologically based pharmacokinetic (PBPK) dosimetry models has the potential to improve understanding of concerns identified in rodents and the potential relevance to humans, based on comparative internal dosimetry. The fate of nanoparticles is an active area of research.

A biomathematical model was previously developed for the disposition of nanoparticles in rats (MacCalman et al., 2009; MacCalman and Tran, 2009) based on calibration to three data sets (Semmler et al., 2004; Takenaka et al., 2001; Fabian et al., 2008). In the preliminary model, adjustable parameters were calibrated for each data set using least squares methods, with varying values for a given parameter obtained for the different data sets. Some of these parameter values differed radically among data sets. For example, the estimates of fractional translocation from the liver capillaries to the venous blood (λ_3^2) were 0.9786 (Semmler), 0.5 (Takenaka) and 0.0001 (Fabian). As these data sets describe the disposition of three different types of nanoparticles, it is unclear whether the parameter differences were due to material-specific differences in disposition, inadequate data to unambiguously identify model parameter values, or an inappropriate model structure.

In the current model, Bayesian population analysis using

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Markov chain Monte Carlo (MCMC) simulation was performed to provide estimates of the parameter distributions (rather than point estimates), which also allowed for subsequent uncertainty and variability analysis. Bayesian population analysis is an appropriate method for calibrating the rat nanoparticle PBPK model (Bernillon and Bois, 2000; Lunn et al., 2009; Jonsson and Johanson, 2003; Hack, 2006; Hack et al., 2006; Péry et al., 2009). Using this technique, the model parameters were calibrated to one or more data sets simultaneously. Data from one of the three previously-identified studies were used; additional data useful for model calibration were extracted from one of these previously identified studies (described in more detail in the "Methods" section) and from a newly published study of nanoparticle toxicokinetics. The previously-developed model structure was modified and some physiological parameter values modified to improve physiological realism or simplify the model structure, based on published PBPK modeling of nanoparticles in rats and humans.

A sensitivity analysis of the adjustable model parameters was conducted to assess the impact of uncertainty/variability in model parameter values to predictions of output, using the population posterior distribution as inputs for Monte Carlo simulations.

2. Materials and methods

2.1. Key data sets

The preliminary rat PBPK model for nanoparticles (MacCalman et al., 2009; MacCalman and Tran, 2009) was based on calibration to three data sets (Semmler et al., 2004; Takenaka et al., 2001; Fabian et al., 2008). (Key characteristics of these studies and others used in the model calibration are summarized in Table 1). For the preliminary model, the iridium data initially reported in Semmler et al. (2004) (with additional detail reported by Semmler-Behnke et al., 2007) constituted the key data set for understanding rat whole-body disposition of nanoparticles due to the extended follow up time (longer than Takenaka et al., 2001) and the measurement of nanoparticles in most of the tissue regions of interest (particles were not observed in the brain, olfactory, alveolar, and upper airway regions in the i.v. study by Fabian et al., 2008; which was also reported in van Ravenzwaay et al., 2009).

Based on literature searches, additional data sets that could potentially be used to further the development of this model were identified. The studies under consideration were limited to a narrow range of particles sizes (15–30 nm) (Table 1) due to findings that particles of approximately 20 nm diameter behave differently *in vivo* than larger (80–100 nm) particles (Sarlo et al., 2009; Lankveld et al., 2010). Furthermore, nanoparticles between 6 nm and 34 nm are expected to result in the greatest internal tissue exposure, relative to other particle sizes (Choi et al., 2010). Additional desirable characteristics for candidate studies were the availability of time course data (vs. disposition at a single sampling time) and potential for mass balance (extensive tissue sampling and/or excretion data). Studies with a duration of 7 days or more, and the use of non-functionalized metal particles were preferred due to greater comparability to the key data (Semmler et al., 2004). Potentially applicable new data sets included studies by Zhu et al. (2009) (ferric oxide), Lankveld et al. (2010) (silver), Dziendzikowska et al. (2012) (silver), and Shinohara et al. (2014) (titanium dioxide); the data of Sarlo et al. (2009) could not be used because nanoparticle recovery for most tissues was reported in semi-quantitative form (i.e., 0.005–0.05% of dose). In addition, another study of iridium nanoparticles from the same laboratory as the Semmler et al. (2004) study (Kreyling et al., 2002, 2009) was identified and the additional data deemed useful for the development of this model. The data of Zhu et al. (2009) were not used due to uncertainty regarding the distribution of intratracheally instilled particles within the airway. A portion of the study of Lankveld et al. (2010) was conducted using particles similar in size to the previously identified data, the study duration was similar, and the data were provided in a convenient tabular form, so these data were also used in model development (Table 1). The Dziendzikowska et al. (2012) concentration data were reported in terms of dry weight of tissue or feces; conversion factors were not provided, so this data set could not readily be used for model development. In the Shinohara et al. (2014) study, titanium dioxide was measured as titanium metal (Ti); since Ti in excreta were not elevated above the substantial levels in controls, mass balance could not be adequately characterized.

The data of Semmler et al. (2004), reported in graphical form, were digitized. Whole body retention and fractional excretion rate

Table 1
Summary of key studies used in rat nanoparticle PBPK model calibration and testing.

Study	Dosing information	Particle characteristics	Study duration	Available dosimetry information	Animal characteristics
Semmler et al. (2004); Semmler-Behnke et al. (2007) [a,b,c]	Controlled ventilation via endotracheal intubation of the upper trachea for 60–100 min, 0.7 mg/m^3 (single exposure)	^{192}Ir, count median diameter (CMD) 15–20 nm	168 days	Lung, liver, spleen, and brain burdens, fecal excretion rate	Young adult male Wistar-Kyoto rats
Kreyling et al. (2002, 2009) [b]	Controlled ventilation via endotracheal intubation of the upper trachea for 60 min, 0.2 mg/m^3 (single exposure)	^{192}Ir, CMD 15 nm, geometric standard deviation 1.6	7 days	Lung, liver, kidney, heart, spleen, brain, feces (cumulative), blood, carcass (skeleton and muscle)	Young adult male Wistar-Kyoto rats
Lankveld et al. (2010) [b]	Five daily iv injections of 23.8 μg	Ag, 20.3 ± 1.9 nm	17 days	Blood, lung, liver, spleen, brain, heart, kidney, testes burdens	6 week-old male Wistar rats
Fabian et al. (2008); van Ravenzwaay et al. (2009) [a,b]	Single iv injection 5 mg/kg	TiO_2 20–30 nm	28 days	Lung, liver, spleen and kidney concentration	Male Wistar rats (200–300 g)

[a] Data used in earlier model (MacCalman and Tran, 2009).
[b] Data used in current model development and testing.
[c] Feces data and detailed lung time course data from Semmler et al. (2004) (Figs. 3 and 4) were not previously used by MacCalman et al. (2009).