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Physiologically based pharmacokinetic modeling of metal nanoparticles for risk assessment of inhalation exposures: a state-of-the-science expert panel review

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ABSTRACT

A critical review of the current state-of-the-science for the physiologically based pharmacokinetic (PBPK) modeling of metal nanoparticles and their application to human health risk assessment for inhalation exposures was conducted. A systematic literature search was used to identify four model groups (defined as a primary publication along with multiple supplementary publications) subject to review. Using a recent guideline document from the Organization for Economic Cooperation and Development (OECD) for PBPK model evaluation, these model groups were critically peer-reviewed by an independent panel of experts to identify those to be considered for modeling and simulation application. Based upon the expert panel input, model confidence scores for the four model groups ranged from 30 to 41 (out of a maximum score of 50). The three highest-scoring model groups were then applied to compare predictions to a different metal nanoparticle (i.e. not specifically used to parameterize the original models) using a recently published data set for tissue burdens in rats, as well as predicting human tissue burdens expected for corresponding occupational exposures. Overall, the rat models performed reasonably well in predicting the lung but tended to overestimate systemic tissue burdens. Data needs for improving the state-of-the-science, including quantitative particle characterization in tissues, nanoparticle-corona data, long-term exposure data, interspecies extrapolation methods, and human biomonitoring/toxicokinetic data are discussed.

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PBPK; nanoparticles; state-of-the-science; expert panel; systematic peer-review model application

1. Introduction

Metal nanoparticles, such as those comprised of cerium dioxide, gold, iridium, silver, and titanium dioxide, represent a group of particulate materials that have a variety of uses including in the manufacture of solar cells, as a catalyst for fuel oxidation, chemical–mechanical polarization, corrosion protection, control of bacterial growth, and in a variety of potential medical applications (diagnostic, therapeutic, and pharmacologic) (Huynh et al. 2020; Khan, Saeed, and Khan 2019). Human populations may be exposed to these nanoparticles during their manufacture and formulation (i.e. occupational exposures), use, disposal, and environmental pathways (i.e.

workers and general population). Risk assessment for metal nanoparticles requires an understanding of processes for deposition, absorption, tissue distribution, clearance, and mode of action, all of which can be affected by differences in chemical composition, particle size, surface area, surface chemistry, differences between test species (e.g. laboratory rodents) and humans, nonlinear dose-dependencies (e.g. saturable processes), and internal exposure specificities (e.g. particle-protein corona formation).

Physiologically based pharmacokinetic (PBPK) models serve as the preferred method for characterizing tissue dosimetry and provide a means for performing many of the extrapolations (interspecies,

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route-to-route, high-to-low concentrations) required for human health risk assessment. Several PBPK models have been developed to describe the kinetics of inhaled metal nanoparticles that are insoluble (e.g. Carlander et al. 2018; Lin, Monteiro-Riviere, and Riviere 2016; Lin et al. 2016; Sweeney et al. 2015), and some have included dissolution pathways for soluble nanoparticles (e.g. Bachler, von Goetz, and Hungerbühler 2013; Chen et al. 2015).

The goals of this work are: (1) to perform a critical review of the scientific literature to identify PBPK models developed for metal nanoparticles; (2) to characterize the extent to which the published models have been developed according to good modeling practices and to further describe criteria for assessing the reliability and utility of these models; and (3) to provide examples of the application of currently available PBPK models for use in assessing worker exposures to metal nanoparticles, for quantitative risk assessment, and to describe limitations and research needs.

2. Methods

To achieve the goals of this work, three tasks were performed: (1) a systematic literature search was conducted to identify available PBPK models for metal nanoparticles and potentially useful publications; (2) an expert panel was assembled and engaged to critically review available models identified from the literature search; and (3) selected panel members applied the highest rated PBPK models to a recently published toxicokinetic data set and estimated corresponding internal doses in humans following occupational exposures.

2.1. Literature search

A literature search and review were conducted following systematic review concepts (Moher et al. 2009), including transparency, documentation of search strategy and terms, and specification of selection and exclusion criteria (Supplement 1). Metal nanoparticle PBPK modeling and exposure publications identified in this search were organized into four categories based on their relevance to the goals of this project: A) metal nanoparticle PBPK models with an inhalation/dermal/oral route; B) metal nanoparticle PBPK models with a non-inhalation/dermal/oral route, nanoparticle PBPK models not specific to nano-metals, or more focused models such as the respiratory tract only without accounting for other organs or systems in the body;

C) supporting information; and D) not likely to be helpful. Key PBPK model publications from the first two categories were divided into four PBPK model groups, based upon a consideration of similarity in PBPK model structures (i.e. visual inspection and comparison of model structure figures), author's citing of earlier model publications as the basis for their model (i.e. refinement/expansion of a previously published model), and recurring collaborating authors. This grouping of models reflects the publications available at the time the literature search was conducted. For each model group, a publication that was considered the most recent or complete for risk assessment purposes was designated as the primary publication for the group. Publications that included earlier versions of the models and/or extensions of the model were designated as supplementary for each group, as listed below.

- **Group 1** – Group 1 was defined to include Carlander et al. (2018) as the primary publication to be considered along with the following supplementary publications: Carlander et al. (2016), Li et al. (2014, 2016).
- **Group 2** – Group 2 was defined to include Bachler, von Goetz, and Hungerbühler (2013) as the primary publication to be considered along with the following supplementary publications: Bachler et al. (2015), Bachler, von Goetz, and Hungerbühler (2015), Juling et al. (2016), Rosário et al. (2022).
- **Group 3** – Group 3 was defined to include Chou et al. (2022) as the primary publication to be considered along with the following supplementary publications: Lin, Monteiro-Riviere, and Riviere (2016), Lin et al. (2016), Lin et al. (2017).
- **Group 4** – Group 4 was defined to include Gakis et al. (2022) as the primary publication to be considered along with the following supplementary publications: Krikas et al. (2022), Sweeney et al. (2015), MacCalman, Tran, and Kuempel (2009), MacCalman and Tran (2009).

2.2. Model review

2.2.1. Expert panel

For the model review and application tasks, an expert panel was engaged utilizing the methods described in. Multiple design elements were included in this review to minimize potential sources of bias. These elements include the following (Kirman et al.

2019): (1) a double-blinded process was adopted for panel recruitment and engagement to minimize potential participation bias; (2) objective expertise metrics were used to guide panel selection decisions to minimize potential selection bias; (3) individual responses and comments from the panelists are provided in their entirety (see [Supplement 2](#)) to ensure transparency and minimize potential reporting bias; and (4) these responses and comments are not attributed to the individual reviewers to allow panel members to participate anonymously. (e.g. to Expert 1, Expert 2, etc.).

Nine topic experts were identified to participate in the model review and/or application tasks for this work. The panelists provide a broad variety of perspectives including those associated with the development of PBPK models for metal nanoparticles, the application of these models to human health risk assessment, and the establishment of regulatory policies for these compounds. The process for recruiting, selecting, and engaging the expert panel is described in [Supplement 3](#). The demographics and expertise metrics for the nine-panel members:

- Country of residence: Canada (1), Germany (1), Spain (1), United States (6)
- Advanced degrees: PhD (9)
- Mean (\pm SD) years of experience: 17 ± 11 years
- Mean (\pm SD) number of publications: 55 ± 27

2.2.2. Review material and charge questions

Review material was defined to include the models/publications for the four model groups listed in [Table 1](#), along with the Organization for Economic Cooperation and Development's guidance document for use of PBPK models for regulatory purposes (OECD 2021). This guidance document was selected since it appears to be thorough and complete and considers previous guidelines and guidance documents from other agencies in their preparation (e.g. EMA 2018; FDA 2018; Loizou et al. 2008; Tan et al. 2020; USEPA 2006; WHO 2010). The model checklist developed by OECD (see [Table 3.2](#) in OECD 2021) served as the primary basis for the charge questions used in this model review. Charge questions were developed to characterize the presence or absence of specific model attributes, as well as to collect scores for reviewer confidence (scale = 1 to 5, with 5 corresponding to the highest confidence). The OECD checklist was converted a web-based application and was made available online to the

reviewers. Some additions and modifications to the checklist were made to include charge questions addressing model application to risk assessment. Final charge questions used in this review are provided in [Supplement 2](#). Model scores were tallied by summing all confidence scores provided by each reviewer (10 confidence score questions; maximum score = 50), and then calculating the arithmetic mean and standard deviation across reviewers.

2.2.3. Model review and application

For the model review task, each reviewer was tasked with reviewing a subset of the models/publications in [Table 1](#). Specifically, eight experts were each assigned three of the four model groups subject to this review (1 of 9 experts was only engaged in the model application task described below). Because some of the experts engaged are also authors of publications under review, this design prevented any experts being tasked with critically reviewing their own publication(s). Using this design, each model group received six reviews. Experts reviewed the material and answered the charge questions independently in a single round of engagement ([Supplement 2](#)).

The three highest scoring models (Groups 2–4) were carried through to the model application task. One model group (Group 1) was removed from the model application work, primarily because it lacked a corresponding human model needed to complete this task. Three modelers from the nine recruited experts were selected and assigned a single model for the application effort. Unlike the model review task, model publications' authors were permitted to perform the model application task (i.e. apply their own models). Model code was retrieved from either publicly available sources or by contacting model authors and made available to the three modelers as needed. Experts were given flexibility on how to best implement the model code provided (e.g. apply in the model language as written, or convert to a more accessible language prior to application when the language platform is either obsolete or proprietary; addressing conflicting model parameter values in publications and model code), and in determining what model predictions are feasible given the current state of the model (see [Supplement 2](#)). The three modelers were also provided a recent publication that characterizes the toxicokinetics of nanoceria (CeO₂ nanoparticles) in female Wistar rats exposed over a 2-year period (Tentschert et al. 2020). This study assessed multiple exposure

Table 1. Comparison of PBPK models for metal nanoparticles.

	Model group			
	Group 1	Group 2	Group 3	Group 4
Primary Model Publication	Carlander et al. (2018)	Bachler, von Goetz, and Hungerbühler (2013)	Chou et al. (2022)	Gakis et al. (2022)
Supplemental Model Publications	Carlander et al. (2016), Li et al. (2014, 2016)	Bachler, von Goetz, and Hungerbuhler (2015), Bachler et al. (2015), Juling et al. (2016), Rosário et al. (2022)	Lin, Monteiro-Riviere, and Riviere (2016), Lin et al. (2016), Lin et al. (2017)	Krikas et al. (2022), Sweeney et al. (2015), MacCalman, Tran, and Kuempel (2009), MacCalman and Tran (2009)
Nanoparticle(s)	Cerium dioxide, Gold, Titanium dioxide	Silver, Titanium dioxide, Gold	Gold	Iridium, Silver, Gold
Consider particle size	Yes	Yes	Yes	Yes
Species*	R	H, R, M	H, R, M, P	H, R
Routes of exposure**	I, O, IT, IV	I, O, IT, IV, Dermal	I, O, IT, IV	I, IT
Track solubilized metal	No	Yes	No	No
Tissue compartments	Blood (venous, arterial), Lung Bone marrow, Brain, Heart, Kidney, Liver, Spleen, Other	Blood, Lung, Brain, Heart, Kidney, Liver, Spleen, Intestines	Blood (venous, arterial), Upper respiratory tract, Lung (tracheobronchial, pulmonary, interstitium), Brain, Kidney GI Tract, Liver, Spleen, Other	Blood (venous, arterial), Olfactory, Lung (alveolar, tracheobronchial, interstitium), Brain, Kidney, GI Tract, Liver, Spleen, Heart, Lung associated lymph nodes, Other
Nonlinear toxicokinetics	Saturation of phagocytic cells	No	Saturation of phagocytic cells	No
Toxicokinetic data sets used	R: Yokel et al. (2012, 2013, 2014), Li et al. (2016), He et al. (2010), Park, Park, and Park (2009), Kumari et al. (2014)	H: ICRP (1960), DiVincenzo, Giordano, and Schriever (1985), Bader (1966) R: Klaassen (1979), Lankveld et al. (2010), Kim et al. (2008), Loeschner et al. (2011), Takenaka et al. (2001), Ji et al. (2007), Juling et al. (2016), Kreyling et al. (2014), Xie et al. (2011), Fabian et al. (2008) M: Wang et al. (2007), Rosário et al. (2022)	H: Libutti et al. (2010) R: Hirn et al. (2011), Schleh et al. (2012), Kreyling et al. (2014, 2018), Morais et al. (2012) M: Cho et al. (2009, 2010); Zhang et al. (2009) P: Fent et al. (2009)	H: Miller et al. (2017) R: Kreyling et al. (2018), Han et al. (2015)
Modeling software	acslX, Berkeley Madonna	MatLab, R	acslX, Berkeley Madonna, MatLab, R	MatLab
Code available	Provided by author (available upon request)	Provided by author (available upon request)	Available online: primary model (https://github.com/UFPBPK/Nano-iPBPK); supplemental models (https://iccm.k-state.edu/models/pbpbk/index.html)	Provided by author (available upon request)

*Species: H=human, R=rat, M=mouse, P=pig.

**Routes: I=inhalation, O=oral, IT=intratracheal instillation, IV=intravenous injection.

concentrations (0, 0.1, 0.3, 1, 3 mg/m³), over multiple time points (3, 12, and 24 months), and provides tissue burden data for more than ten different tissues. It is important to note that none of the three models used in the application task had been specifically parameterized for nanocerium, so these models are being applied to a new data set and new nanoparticle, in the hopes of assessing the generalizability of these models. Experts were provided a spreadsheet that contained tissue burden data from Tentschert et al. (2020). In addition, the spreadsheet contained template tables for collecting model predictions in rat and human tissues. Experts were tasked to use their assigned model, unadjusted (i.e. with no or minimal code changes), to make as many

predictions as feasible for rat tissues under the conditions of the Tentschert et al. (2020) study to support comparisons to the data. Model predictions for an additional exposure concentration (10 mg/m³) was also included to evaluate potential lung overload. For human model predictions, exposures were defined to correspond to a chronic occupational exposure scenario (e.g. 8 hours/day, 250 days/year, 45 years) for the same exposure concentrations (0.1–10 mg/m³). Internal dose-ratio plots (human:rat) were prepared as described in Kirman et al. (2003) for the chronic exposure model simulations (24 months in rats; 45 years in humans) to assess the potential impact of model predictions to human health risk assessment.

3. Results

3.1. Literature search

After initial eligibility criteria were applied, 255 publications were retained for evaluation and sorted into priority categories (Supplement 1). Ten publications on PBPK models were included in the highest priority (Category A). These publications include PBPK models developed for silver, gold, iridium, titanium dioxide, and cerium dioxide nanoparticles, some of which were parameterized with multiple exposure routes, including intratracheal instillation, endotracheal instillation, inhalation, oral, dermal, and intravenous (IV). The models were primarily parameterized with biodistribution data from rats or mice, and in some cases extrapolated to humans with limited data. Full details on these models are provided in Supplement 1 (Appendix B, Table B2). There were 64 publications included in Category B, which included those for PBPK models parameterized for exposure routes other than inhalation (e.g. IV). There were 142 publications containing data that may be useful for evaluating/refining available PBPK models which were placed in Category C. Lastly, in Category D, there are 39 publications that were deemed unlikely to be helpful in evaluating PBPK models for metal nanoparticles.

3.2. PBPK model review

The four model groups identified from the literature search were scored using charge questions based primarily on OECD's model checklist (OECD 2021). Based on the mean confidence scores from six independent reviewers (maximum score of 50), the resulting scores were as follows (in descending order): Group 3 model (mean score = 41.0); Group 2 model (mean score = 39.3); Group 4 model (mean score = 37.8); and Group 1 model (mean score = 30.2) (Table 2; Figure 1). Scores across reviewers were reasonably consistent, with mean coefficient of variation in scores across models and charge questions of 26%. The Group 3 model scored highest (compared to other models) in the categories for model documentation, biological basis, theoretical basis, sensitivity/uncertainty analysis (tie), route-to-route extrapolation (tie), and risk assessment for nanoparticles in general. The Group 2 model scored highest in the categories for route-to-route extrapolation (tie) and for risk assessment of the specific nanoparticle for which the model was intended. The Group 4 model scored highest in the

categories for sensitivity/uncertainty analysis (tie), fit/predictivity, and interspecies extrapolation. In general, the Group 1 model scored the lowest, but only slightly so for many of the OECD checklist categories. For specific rationales that underly individual reviewer scores please refer to Supplement 2.

3.3. PBPK model application

Three unadjusted models (model Groups 2–4, which were not specifically parameterized for predicting the toxicokinetics of nanocerium) were applied to new toxicokinetic data for nanocerium in rats (Tentschert et al. 2020). Rat tissue burden data and predictions from these three models generally increase linearly with increasing exposure concentration [example data for three tissues (lung, liver, and kidney) provided in Figure 2]. Visual inspection of the predictions from the models indicates that for rat lung burden, the three models perform reasonably well at the 3-month time period but tend to underpredict tissue burden at 12 and 24 months. For rat liver burden, the models perform reasonably well at 12 and 24 months and at 3 months for one of the models (Group 3), but two of the models (Groups 2 and 4) tended to overestimate at 3 months. For rat kidney burden, all three models tend to overestimate at 3 and 12 months, and two models performed reasonably well at 24 months (Groups 2 and 4) while the third model (Group 3) tended to underestimate tissue burdens.

When model predictions are considered together with the data for all tissues, time points, and exposure concentrations (Figure 3), based on visual inspection the three models were found to be generally consistent with one another despite being developed for different nanometal particles and toxicokinetic data sets (Table 1). However, all three models generally tend to underestimate rat tissue burdens above 100 ug/organ or ug/g (e.g. high concentration data for lung and lung-associated lymph nodes), with mean ratios for predicted:observed burdens ranging from 0.26–0.78. Poor prediction results are not unexpected given that available models are largely developed from acute exposure studies that likely do not reflect conditions for long-term, repeated exposures. For rat tissue burdens between 1 and 100 ug/organ or ug/g (e.g. low and medium concentration data for lung, lung-associated lymph nodes, and high concentration data for some systemic tissues such as the liver), the models perform reasonably well (mean

Table 2. Summary of PBPK model scoring results.

OECD group	Charge question	Models								
		Group 1		Group 2		Group 3		Group 4		
		Y/P/N*	Score**	Y/P/N	Score	Y/P/N	Score	Y/P/N	Score	
Documentation	Clear indication of the chemical, or chemicals, to which the model is applicable?	5/1/0	3.5+/-0.8	5/1/0	3.7+/-0.5	6/0/0	4.5+/-0.5	6/0/0	3.3+/-1.2	
	Is the model being applied for the same scientific purpose as it was developed, or has it been repurposed for a different application?	5/1/0		5/0/1		5/1/0		4/2/0		
	Have all model assumptions been adequately described and supported?	5/1/0		5/1/0		6/0/0		3/3/0		
	Graphical representation of the proposed mode of action, if known?	2/0/4		2/2/2		2/1/3		2/3/1		
	Graphical representation of the conceptual model?	4/2/0		6/0/0		6/0/0		6/0/0		
	Supporting tabulation for parameters (names, meanings, values, mean and standard deviations, units, and sources)?	3/3/0		5/1/0		5/0/1		3/2/1		
	Relevance and reliability of model parameters?	2/4/0		2/3/0		5/1/0		3/3/0		
	Uncertainty and sensitivity analysis?	2/4/0		5/1/0		4/2/0		4/2/0		
	Mathematical equations available?	2/2/2		6/0/0		4/1/1		4/1/1		
	PBPK model code available?	1/0/5		0/0/5		4/2/0		0/1/5		
Validity	Software algorithm to run the PBPK model code reported?	4/2/0		0/2/3		6/0/0		3/0/3		
	Qualification of PBPK software platform?	4/0/2		4/0/2		5/0/1		4/0/2		
	Underlying PK data available?	3/3/0		5/1/0		4/2/0		5/1/0		
	Is the biological basis for the model structure provided?	3/2/0	3.3+/-1	5/1/0	4.0+/-0.6	5/1/0	4.2+/-0.8	5/1/0	4.0+/-0.9	
	Is the complexity of the model structure appropriate given the biological information?	3/2/1		5/0/1		5/1/0		5/1/0		
	Are assumptions concerning the model structure and parameters clearly stated and justified?	2/4/0		5/1/0		5/1/0		4/2/0		
	Is the choice of values for physiological parameters justified?	5/1/0		5/1/0		5/1/0		6/0/0		
	Is the choice of methods used to estimate chemical-specific ADME parameters justified, including for saturable kinetics processes (e.g. using Km and Vmax for metabolism)?	2/4/0		1/5/0		3/3/0		4/2/0		
	Are the underlying equations based on established theories, e.g. Michaelis-Menten kinetics, Fick's laws of diffusion?	3/2/1	3.0+/-0.9	5/1/0	3.8+/-1	4/2/0	4.0+/-0.6	6/0/0	3.7+/-0.8	
	Theoretical Basis	In the case of PBK models for particles, does the model take into consideration the properties of particles, e.g. particle size ranges, (poor) solubility, aggregation, partitioning, and diffusion/sedimentation behavior?	0/5/1		4/2/0		3/3/0		2/4/0	
Has the uncertainty (individual variability, experimental reproducibility, and reliability) of test conditions on the outcome of the study) in the input parameters been characterized?		0/4/2	2.8+/-0.8	2/3/1	3.0+/-0.6	3/2/0	3.5+/-0.8	2/1/3	3.3+/-1	
Are there particular parameters you have low confidence in? If so, which model parameters, and why?		3/2/0		3/1/1		2/2/1		3/1/1		
Has the impact of uncertainty (individual variability, experimental reproducibility, and reliability) in the parameters on the chosen dose metric been estimated, including (i) Local sensitivity analysis, and (ii) Global sensitivity analysis?		2/2/1		3/1/1		3/3/0		4/1/0		
Is confidence in influential input parameter estimates (i.e. based on comparison of uncertainty and sensitivity) reasonable (within expected values; similar to those of analogs) in view of possible application in quantitative risk assessment?		5/1/0	2.8+/-1.5	5/1/0	3.7+/-0.5	6/0/0	3.8+/-0.8	5/1/0	4.2+/-0.4	
Are goodness-of-fit metrics/statistics provided?		3/3/0		3/0/3		6/0/0		5/1/0		
Has the model been applied to make predictions where data are limited or lacking (e.g. dose measures in humans)?		0/0/6		4/1/1		3/1/1		5/0/0		
Additional questions (not specifically tied to OECD 2021 checklist)		Please rate your degree of confidence that this model could be used to support interspecies extrapolation (e.g. test species to humans) (1=lowest, 5=highest). Please explain your rating below.	NA	1.8+/-0.8	NA	3+/-1.3	NA	3.5+/-0.8	NA	4+/-0
		Please rate your degree of confidence that this model could be used to support route-to-route extrapolations (1=lowest, 5=highest). Please explain your rating below.	NA	2.2+/-1	NA	3.8+/-0.8	NA	3.8+/-0.8	NA	1.7+/-0.8
		Please rate your degree of confidence that this model could be used to extrapolate across doses or exposure scenarios, including to support high-to-low dose extrapolations (1=lowest, 5=highest). Please explain your rating below.	NA	2+/-0.9	NA	3.5+/-0.8	NA	3+/-0.6	NA	3+/-0.6
	Please rate your degree of confidence that this model can be used to support human health risk assessment for the specific metal nanoparticle evaluated, to predict biologically-relevant doses at target tissues (1=lowest, 5=highest). Please explain your rating below.	NA	2.8+/-1.2	NA	4+/-0.9	NA	3.5+/-0.8	NA	3.7+/-0.8	
	Please rate your degree of confidence that this model could be adapted and applied to risk assessment for metal nanoparticles in general, to predict biologically-relevant doses at target tissues (1=lowest, 5=highest). Please explain your rating below.	NA	2.2+/-1	NA	3.2+/-0.4	NA	3.3+/-0.8	NA	3.2+/-1	
	Overall Score		30.2 ± 1.0		39.3 ± 0.8		41.0 ± 0.7		37.8 ± 0.8	

*Charge question response: Y=Yes; P=Partially; N=No; values reflect the frequency of each response; shading reflects the response mode (Yes=green; Partially=yellow; No=red).

**Values reflect the mean confidence score (±SD) from the panel based upon a consideration of the responses to OECD group of charge questions.

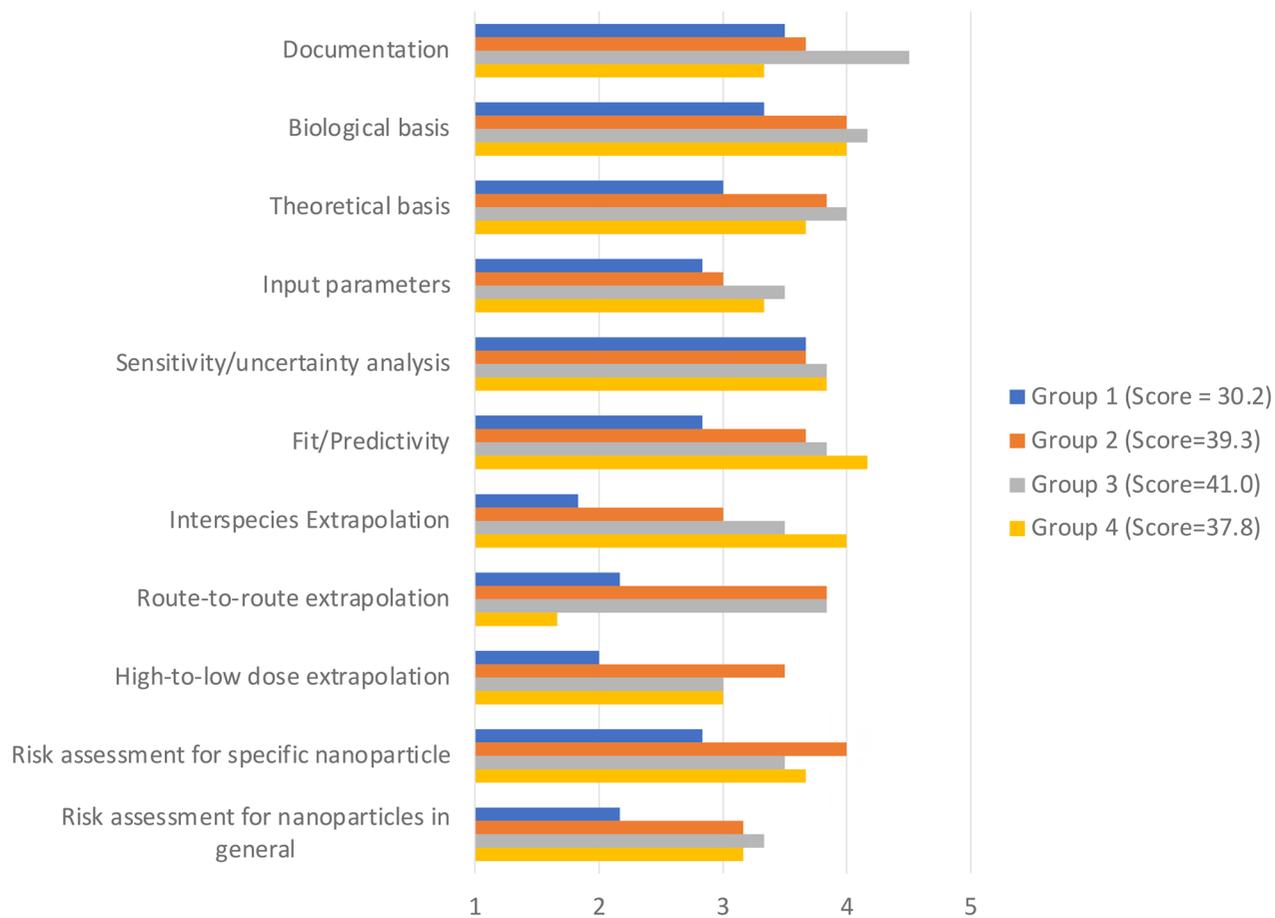


Figure 1. Results for model Scoring (maximum score = 50).

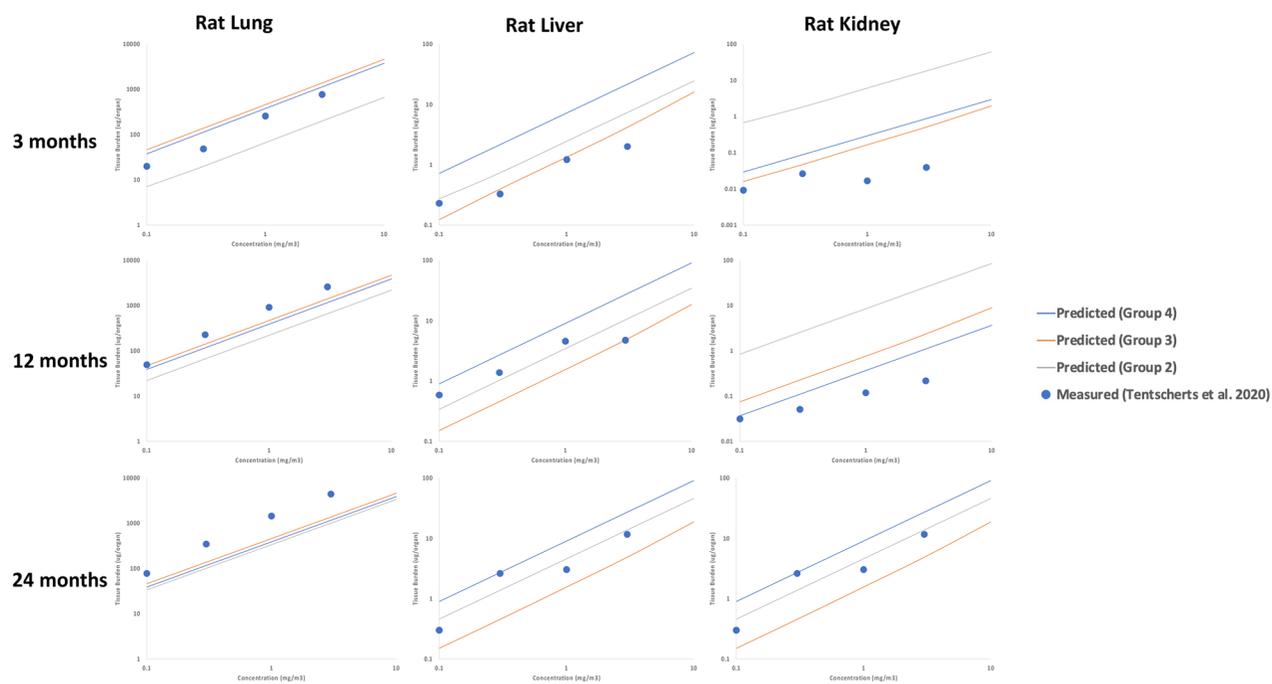
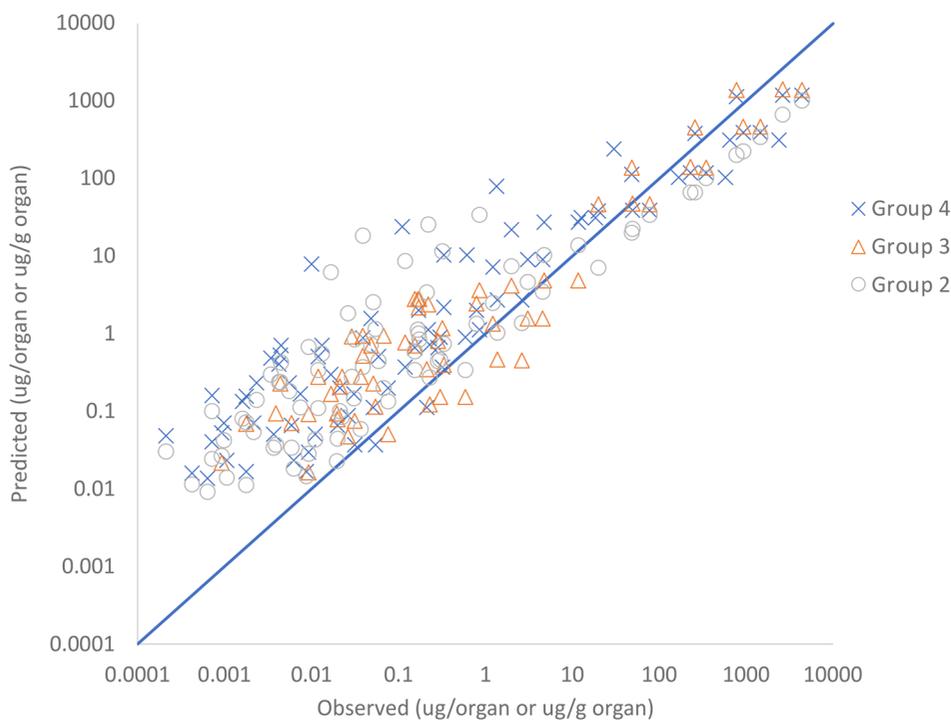


Figure 2. Model applications to new rat data (Tentschert et al. 2020).



	Model	<0.01*	0.01-1*	1-100*	>100*
Mean Ratio (Predicted: Observed)	Group 2	41.4	38.6	1.2	0.26
	Group 3	23.1	8.6	1.1	0.78
	Group 4	68.5	41.1	6.9	0.55

*Observed organ concentration ranges, units of ug/organ or ug/g organ)

Figure 3. Observed vs predicted tissue Levels for nanoceria in rats (across available exposure Levels, time points, and tissues); solid line=perfect concordance between observed and predicted concentrations.

ratios for predicted:observed burdens ranging from 1.2–6.9). For rat tissue burdens ranging from 0.01–1 ug/organ or ug/g (e.g. systemic tissues, small intestines), the models tend to overestimate measured values (mean ratios for predicted:observed burdens ranging from 8.6–41.1). The degree of overestimation by the models was even larger for rat tissue burdens less than 0.01 ug/organ or ug/g (mean ratios for predicted:observed burdens ranging from 23.1–68.5). Of the three models applied to the rat tissue data, the ratios for predicted:observed tissue burdens from the Group 3 model were closest to a value of 1 (i.e. perfect prediction) across all exposure ranges. The relatively better performance of this model group may reflect several possible factors, including the robustness of the modeling approach used by Group 3 model authors (as reflected in the higher model confidence scores from the reviewers), similarities between the nanoparticles used to develop the model (gold) and the data to which it is applied (cerium), similarities between the rat

studies used to develop the model (see Table 1) and Tentschert et al. (2020), and/or other possible factors. Together, the pattern exhibited in Figure 3 suggest there is greater lung retention (and consequently lesser systemic delivery) of nanoceria at the higher exposure levels than is predicted by available models. When the variation in the measured data of Tentschert et al. (2020) is considered, the percentage of model predictions (across all tissues, time points, and exposure concentrations) that are within 1 and 2 standard deviations are as follows: Group 2 (6%, 14%), Group 3 (8%, 20%), and Group 4 (6%, 12%). Model predictions for human tissue burdens are only feasible for two of the models evaluated (Groups 2 and 4). Although a human model is available for the Group 3 model, it has only been parameterized for acute intravenous exposures, and would require additional parameterization for application to chronic inhalation exposures. Human model predictions for tissue burden (simulation for 8 hours/day, 250 days/year, like those for the rat, increase

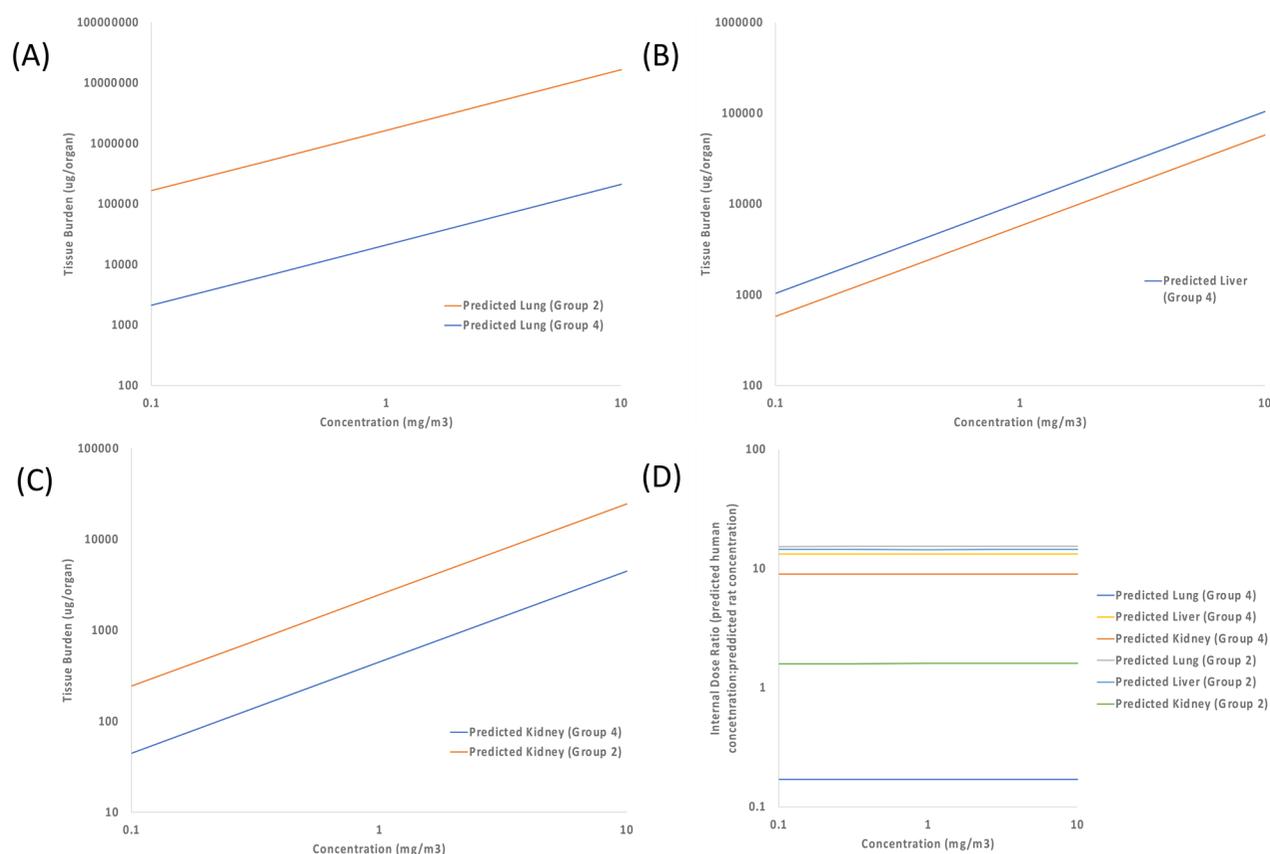


Figure 4. Human model predictions: (A) lung burden; (B) Liver burden; (C) Kidney burden; (D) Internal dose ratios (predicted tissue concentration in humans:predicted tissue concentration in rats).

linearly with exposure concentration (depicted for human lung, liver, and kidney in Figure 4A-C). Using model Groups 2 and 4, predicted internal dose-ratio plots (human:rat; Figure 4D) describe linear toxicokinetics (i.e. constant as a function of exposure concentration) across all exposures considered (up to 10 mg/m³). The potential impact of PBPK modeling to human health risk assessment is highly dependent upon the internal dose measure used, which is subject to target tissues and mode of action determinations for metal nanoparticle risk assessment. As such, the resulting interspecies extrapolation may vary by approximately an order of magnitude in either direction (i.e. human tissues experiencing higher or lower burdens than corresponding rat tissues for a given external exposure). The modelers' confidence in the human model predictions was considered to be medium (confidence score of 3–4 on a scale of 1 to 5) for the Group 2 and 4 models, and low (confidence score of 1 out of 5) for the Group 3 model following chronic inhalation exposure. The Group 2 model incorporated the International Commission on Radiological Protection (ICRP 1994) inhalation model that can account for particle size-dependent deposition

fraction as well as breathing pattern and exertion of the subject. The Group 2 model also included the Monte Carlo simulation to characterize the individual variability. For the Group 4 model, some technical difficulties were experienced for the human model simulations. Specifically, simulations longer than 16 years in duration resulted in an out-of-memory error. However, tissue burden concentration predictions at 16 years were approaching steady-state levels and estimates of tissue burdens (based on annual increases in tissue burdens) would be only slightly higher if the model could have been successfully run for the full 45-year exposure (up to approximately 12% higher for most tissues). For the Group 3 model, while the confidence in predicting internal dosimetry for humans was low following chronic inhalational exposure, its confidence was considered medium (confidence score of 3–4 out of 5) in predicting internal dosimetry for humans following intravenous injection.

4. Discussion

To assess the current state-of-the-science for the PBPK modeling of nanometal particles a systematic

literature search was conducted to identify available models, which were then critically reviewed and applied to new toxicokinetic data by a panel of experts. Based on this review, the development of a generalized model (i.e. one that could be used for any metal nanoparticle) is considered to be feasible but will require additional data before model predictions can be made across materials, tissues, exposure durations, and air concentrations with reasonable confidence (see data needs below). During the review task, model reviewers expressed medium confidence (mean confidence scores of 3.2–3.3) in the ability to adapt and apply model Groups 2–4 to the risk assessment of metal nanoparticles generally. Upon completion of the model application task, 2 of 3 modelers considered a general model to be feasible. The third modeler indicated they could not answer this question on feasibility but expressed interest in seeing the work for model Group 3 extended further toward this goal.

The disparity between model predictions and the measured rat data (Tentschert et al. 2020) are not unexpected and serve to indicate the challenges faced when attempting to extrapolate model predictions outside of their original domains (i.e. to different nanoparticles, to long-term exposures). Experimental and measurement variability can also contribute to this disparity.

The Tentschert et al. 2020 dataset is relatively unique for metal nanoparticles in that it provides data for multiple exposure groups, time points, and tissue doses needed for PBPK model development and evaluation. The biodistribution of nanoparticles is sure to be affected by nanoparticle-specific parameters such as distribution coefficient, phagocytosis-related parameters, and other pharmacokinetic parameters (e.g. clearance). As noted by the authors of the reviewed research, these parameters may be impacted by physicochemical properties of nanoparticles that are difficult to measure *in situ*, including size, shape, surface chemistry, and corona formation. To improve the predictive power of PBPK models, a computational model that can predict the nanoparticle-specific parameters based on their physicochemical properties is needed, as was recently explored by Chou et al. (2023). Duration of exposure is also an important factor, since many data sets on which the rat models were developed are for acute exposures to metal nanoparticles, whereas the data from Tentschert et al. (2020) reflect chronic exposures. One modeler noted that at every duration, the brain predictions were the least accurate. These experimental data always

demonstrated greater-than-linear increases with increasing dose, whereas the model predictions were strictly linear with dose. Furthermore, departures from linearity in the lung data from Tentschert et al. (2020) suggests the need for including a saturable process in the models. As depicted in Figures 2 and 4, none of the models predicted non-linear toxicokinetics for rat and human lung, even at concentrations (i.e. 10 mg/m³) above those tested by Tentschert et al. (2020).

To advance the science for PBPK modeling of metal nanoparticles, the following list of data needs were identified by the expert panelists during model review or application tasks.

- *Quantitative Particle Characterization in Tissues* – Changes in particle size (e.g. through agglomeration or dissolution), surface chemistry, and composition (e.g. through dissolution and reformation of particles) may occur and are noted in the reviewed research as potential sources of error. Quantitative characterization of particle size and chemistry, as afforded by labor-intensive methods such as ToF-SIMS used in Tentschert et al. (2020), is needed to bridge the gap between whole organ metal analysis data commonly used in PBPK studies and any influential transformations that may occur at the nanoscale.
- *Nanoparticle-Corona Data* - Nanoparticles can interact with proteins within the body, generating nanoparticle-protein coronas, which may affect particle properties (e.g. size, surface charge) and ultimately determine the fate of nanoparticles in the body. Bachler, von Goetz, and Hungerbühler 2013 noted that protein coronas have very similar composition among different kinds of metallic nanoparticles, however, the corona may be route-dependent such that traditional route-to-route extrapolation approaches of PBPK models may be inappropriate (Chou et al. 2022). The role of nanoparticle-protein coronas in the toxicokinetics and tissue distribution remains to be characterized and encoded within a PBPK model.
- *Long-Term Exposure Data* - Existing PBPK models for metal nanoparticles are largely based on single or short-term exposures that characterize short-term toxicokinetics. For this reason, additional long-term studies (such as Tentschert et al. 2020) are needed to refine PBPK models so that can reliably simulate

long-term toxicokinetics of nanoparticles in animals and humans. In addition, studies that include a post-exposure clearance/recovery phase would be useful for model refinement.

- *Interspecies Extrapolation Methods* - Because existing PBPK models for metal nanoparticles are primarily based on rodent data (with limited human data), additional studies are needed to investigate the across species extrapolation methodology of PBPK models for nanoparticles from rodents to humans.
- *Human Data* - Although it is currently possible to extrapolate a PBPK model for a metal nanoparticle from rodents to humans, the lack of human data precludes the application of any such model with reasonable confidence. Additional human data, such as human biomonitoring and/or toxicokinetic studies for different metal nanoparticles, are needed to validate human PBPK model for metal nanoparticles.
- *Standards for Data Sharing* - Establishing standardized protocols for data collection, analysis, and reporting to facilitate comparisons and integration of findings across studies are important needs. Encouraging data sharing among researchers and institutions can lead to comprehensive databases useful for meta-analyses and model development. This applies to PBPK model code as well as data. For this review model code was readily available for one model (Group 3), which could be accessed through a GitHub repository and as a web-based application, but access was more limited for the other three model groups (i.e. available upon request to the authors). Wherever possible, model code should be included as part of the [supplemental material](#) for all PBPK model development publications.
- *Computational Modeling* - Upon the availability of comprehensive databases, computational models that simulate the behavior, interactions, and toxicological effects across different metal nanoparticles can be further developed, refined, and possibly generalized. The computational models are crucial to facilitate the establishment of the next generation of risk assessment for metal nanoparticles.
- *Risk Assessment Frameworks* - By integrating experimental data (including newly generated

data to fill data needs) and a mechanistic computational model, robust risk assessment frameworks that consider exposure routes, doses, exposure scenarios, and mechanisms of toxicity specific to various types of metal nanoparticles can be developed. These frameworks should integrate data from physicochemical characterization, toxicological studies, and environmental assessments.

- *Interdisciplinary Collaboration* - Encouraging collaboration among experts from diverse fields including chemistry, biology, toxicology, material science, environmental science, and risk assessment. This collaborative effort enables a more holistic understanding of the complexities surrounding metal nanoparticles. By integrating these approaches and fostering collaboration among researchers and institutions, advancements in understanding, modeling, and risk assessment of metal nanoparticles can be achieved. This comprehensive approach will lead to more informed decisions regarding the safe and responsible use of nanotechnology.

Publications that were identified during the systematic literature search (e.g. from Categories B and C) as potentially useful for improving the available models, including those for the toxicokinetics of zinc nanoparticles (Alsmadi et al. 2022); biomonitoring equivalents, exposure assessment, and risk assessment for silver nanoparticles for silver nanoparticles (Aylward et al. 2016; Yang et al. 2019); toxicokinetics, occupational exposures, and risk assessment for titanium nanoparticles (Heringa et al. 2016; Koivisto et al. 2018; Liao, Chiang, and Chio 2008); nanoparticle distribution coefficients (Kumar et al. 2023), PBPK modeling of carbon nanoparticles (Péry et al. 2009), gold nanoproboscopes for chemotherapy (Zhang et al. 2019), and recent studies published after the systematic review (Chou et al. 2023; Kumar et al. 2023; Lin et al. 2022) may help to fill some of these data gaps.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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