Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment:

A Preliminary Approach to Deriving Dose-Exposures of Inhaled Aerosols using PBPK Modeling

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1. INTRODUCTI ON

Prediction of dose-exposures following inhalation of a self-administered aerosol is central for performing risk assessment whereby of physiologically based pharmacokinetic (PBPK) models provide a mechanism for the determination of predicting the absorption, distribution, metabolism and excretion of the inhaled aerosol compounds. Developing validated inhalation PBPK modeling methods for dose-exposure estimations including aerosol physics, inhalation and dosimetry, would not only support risk assessment but also help achieve (1) precise delivery of the compound, (2) optimal and consistent deposition in the lung, (3) high reproducibility, and (4) improved safety. Therefore, this case study is set forth to discuss development of advanced methodologies for PBPK modeling of inhaled evolving liquid aerosols considering existing methods and outlying key considerations for future developments. The case study is not intended to advocate for, or to oppose any of the existing methods. Rather, it attempts to understand the key considerations and requirement needs for PBPK modeling for complex inhaled aerosol mixtures.

2. PROVIDE A FEW SENTENCES SUMMARIZING THE METHOD ILLUSTRATED BY THE CASE STUDY.

The incorporation and coupling of aerosol transport dynamics including dosimetry with PBPK models represents a unique opportunity for more realistic deposited dose predictions during and following aerosol inhalation. Aerosols are continuously evolving (through ongoing condensation, evaporation and coalescence processes) prior to deposition on the respiratory tract. The physical process of aerosol evolution has a direct impact on the delivered dose. Figure 1 presents a hierarchical sketch of modeling approaches for aerosol dosimetry with increased level of complexity. A more detailed description of the aerosol physics, processes and dosimetry approaches are supplied in the Appendix. In the subsequent sections we highlight a few preliminary inhalation PBPK models which have been developed based on published clinical trial data for inhalation of nicotine. Finally, we would like to highlight opportunities for developing the state-of-the-art PBPK models including recommendations for the incorporation of aerosol dosimetry models.

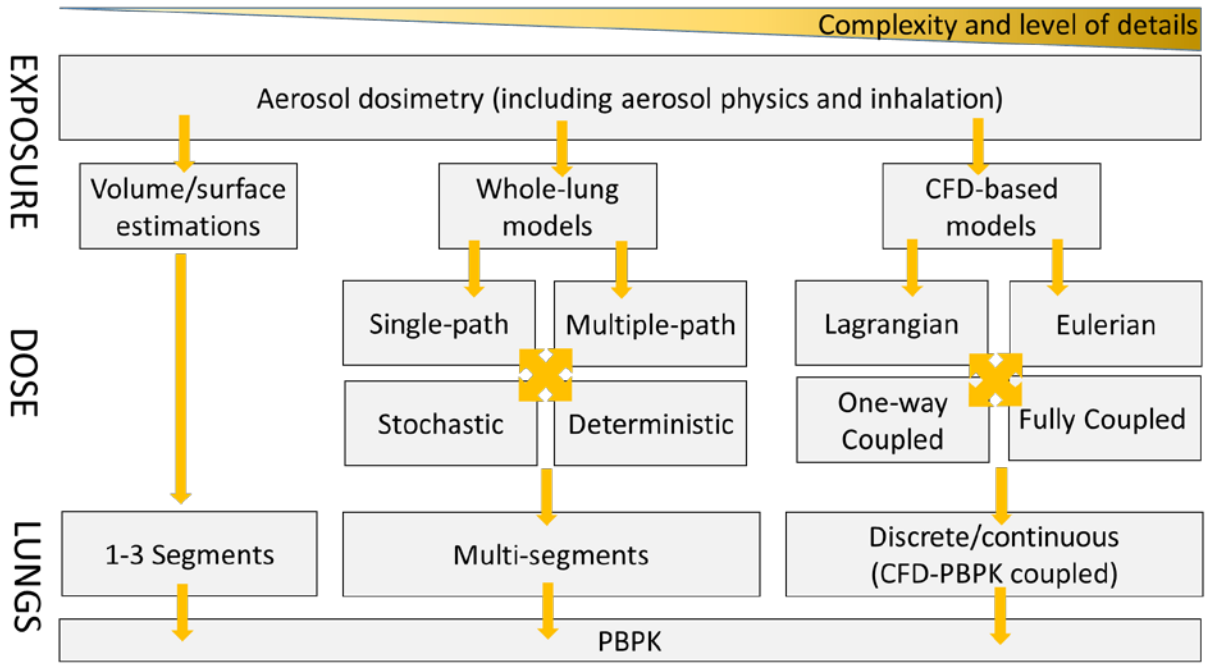

Figure 1: Dosimetry models for inhaled aerosols - a hierarchical view

A. Preliminary PBPK models for inhaled aerosols

A.1. Towards an advanced inhalation human PBPK model

To address development of simplified aerosol dosimetry approaches for PBPK models, we are in process of developing a PBPK model that includes aerosol deposition in each generation of the human respiratory tract. The respiratory tract descriptions were obtained from Weibel's airway model [1]. Particle deposition modeling is being implemented in a simplified manner as described by previous work of Asgharian and colleagues (Figure 2) [2, 3]. The model currently accounts for particle deposition by impaction [4], sedimentation [5] and diffusion [6], and will be improved by the inclusion of changes in particle sizes and phases (liquid/gas) during aerosol evolution, taking into account filtration in the mouth and throat. Such an approach coupled to a PBPK model at varying levels of granularity could predict the delivered/deposited dose. A description of aerosol properties and earlier developed PBPK models is detailed in the Appendix.

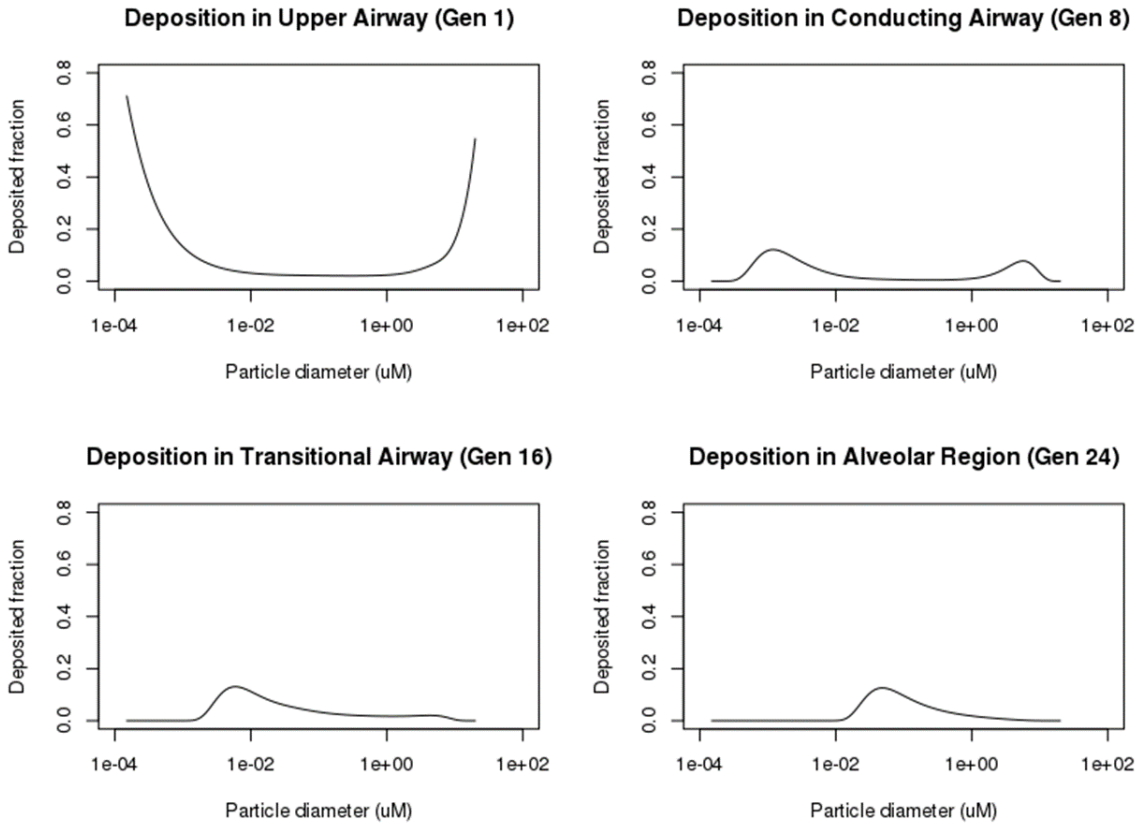

Figure 2: Predicted aerosol deposited fractions upon particle impaction [4], sedimentation [5] and diffusion [6] for a breathing cycle in airway generation 1, 8 16 and 24.

A.2. A semi-descriptive human inhalation PBPK model

Prior to developing a coupled flow and deposition model for the aerosol, we developed and implemented a semi-descriptive inhalation model based on the styrene gas inhalation PBPK model proposed by Sarangapani et al [7]. The model consisted of the upper airways (nose, mouth and larynx), conducting airways (airway branching from generations 0–10), transitional airways (airway branching from generations 11–16) and pulmonary regions (airway branching from generations 17–24) representing the respiratory tract. Further each region included mucus and epithelial layers. The fraction of compound being delivered in each region was varied to fit a PK curve (Figure 3). The underlying assumption for directly varying the delivered fractions (fUA, fCA, fTA and fPA) in the respiratory region was based on the fact that inhalation patterns and aerosol mixture properties influence deposition of aerosol particles and absorption of gases throughout the respiratory tract.

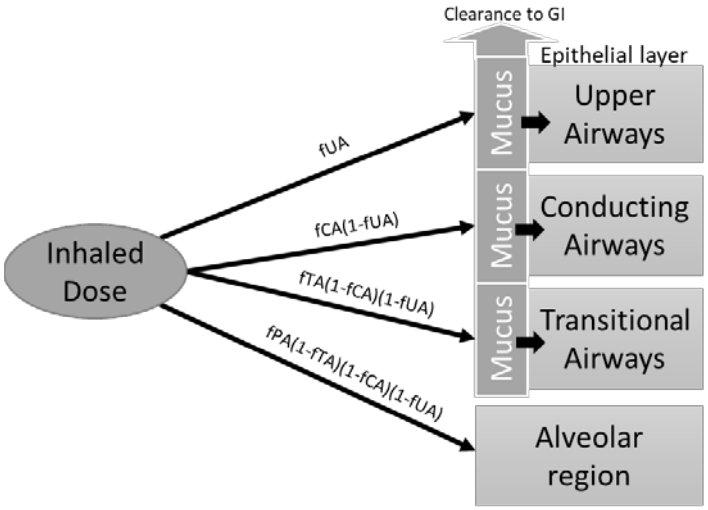

Figure 3 Inhalation PBPK model for nicotine based on fractions absorbed on the surface of respiratory tract. fUA = fraction in upper airways; fCA = fraction in conducting airways; fTA = fraction in transitional airways; fPA = fraction entering pulmonary alveolar region. (Rest of PBPK model not shown).

In order to test and verify this proof of concept, we extracted the plasma nicotine concentrations for cigarette smoke (JPS Silver King Size, 0.6mg) and electronic vapor product (menthol flavored e-liquid containing 2.0% nicotine – brand unknown) from Walele et al. [8]. The dose-exposures for nicotine delivered by different means (cigarette and vapor products) were compared as the pharmacokinetics of nicotine vary based on route of administration (oral, dermal and pulmonary routes) and product formulation (chewing gum, dermal patch, oral snus, smoke) [9]. A detailed

description of nicotine pharmacokinetics is described in the Appendix. The study conducted by Walele et al. was randomized, controlled, with four-way crossover trial in which the participants were administered four product inhalation cycles at one-hour intervals. Further, each inhalation cycle consisted of 10 inhalations with a 4–second puff and 10–second interval [8]. In the developed semi-descriptive human inhalation PBPK model, the nicotine metabolism and elimination rates were kept constant for both products because the study was a cross-over design, so the same set of participants received both products. The model was fitted to nicotine plasma concentrations resulting from inhaling cigarette smoke and electronic vapor product by varying the fractions absorbed on the surface of the respiratory tract (Figure 4).

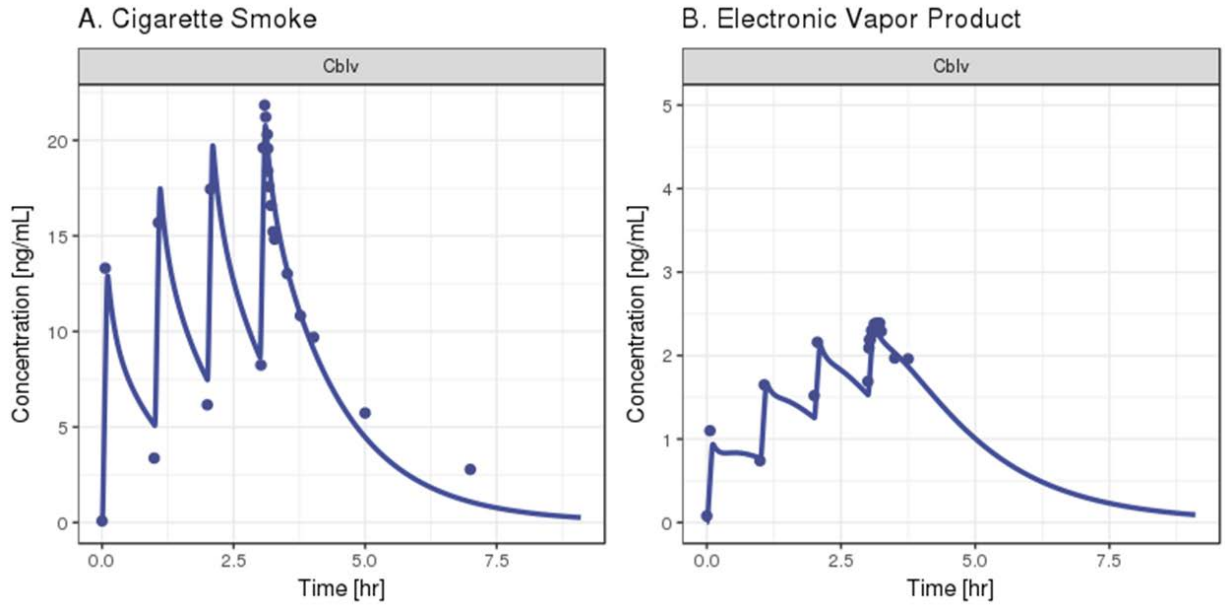

Figure 4: Plasma nicotine concentration-time profiles for cigarette smoke (A) and electronic vapor product (B). Data from Walele, *et al.* [8]. Note: Electronic vapor product described is not a Philip Morris Products PMP S.A. product.

The model predicted increased nicotine uptake for electronic vapor product in the upper airways compared to the cigarette smoke (Figure 5) [10]. Around 96% of the nicotine in cigarette smoke was predicted to be absorbed from the pulmonary alveolar region in line with other observations in the literature [9]. This increased absorption from pulmonary alveolar region enables plasma nicotine concentrations to rise rapidly. Although the model is able to predict deposited dose fractions and tissue exposures after obtaining plasma concentrations, it lacks a detailed description of aerosol physiochemical properties including flow with transport of gas and liquid

phases. Incorporation of aerosol characteristics and evolution mechanisms would allow us to predict changes in pharmacokinetics for varying exposure conditions.

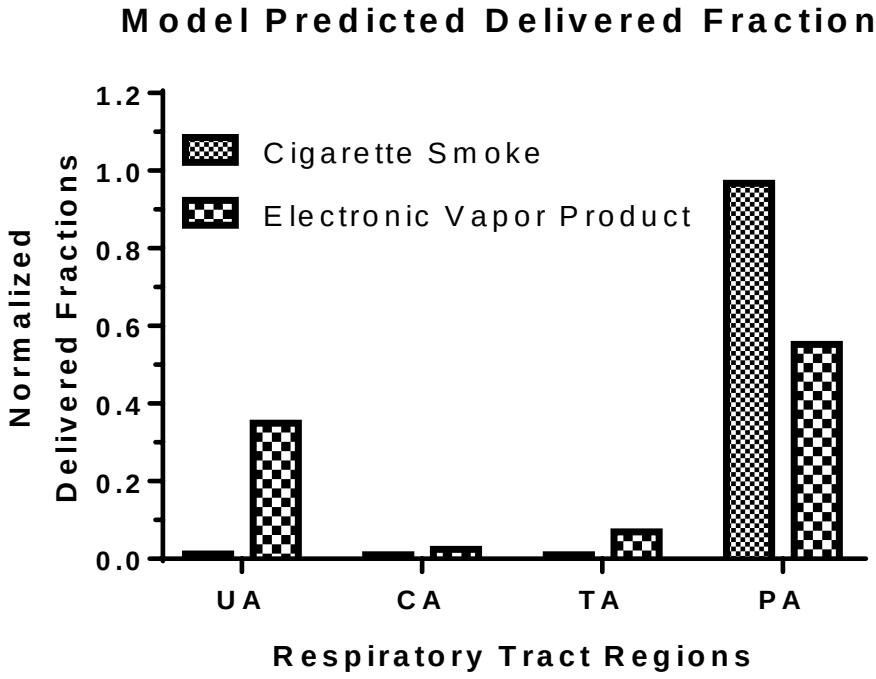

Figure 5: Model predicted (cigarette smoke and electronic vapor product) delivered fractions in various respiratory tract regions: UA = upper airways (nose, mouth, larynx); CA = conducting airways (airway branching from generations 0-10); TA = transitional airways (airway branching from generations 11-16); PA = pulmonary alveolar region (airway branching from generations 17-23).

A.3. A semi-descriptive rat inhalation PBPK model

Predicting dosimetry for inhaled aerosol exposures in rodents is as challenging as in humans due to differences in anatomy and respiratory physiology. For example, many preclinical species such as rats and mice are nose only breathers with high frequency breathing cycles and significantly different and smaller airways geometries. Depending on the aerosol particle size distribution, there can be significant aerosol deposition in the upper airways followed by absorption from gastrointestinal tract. To capture this phenomenon, we built a preliminary inhalation PBPK model with the compound fractions entering the respiratory tract before, reaching the alveoli and gastrointestinal tract (Figure 6).

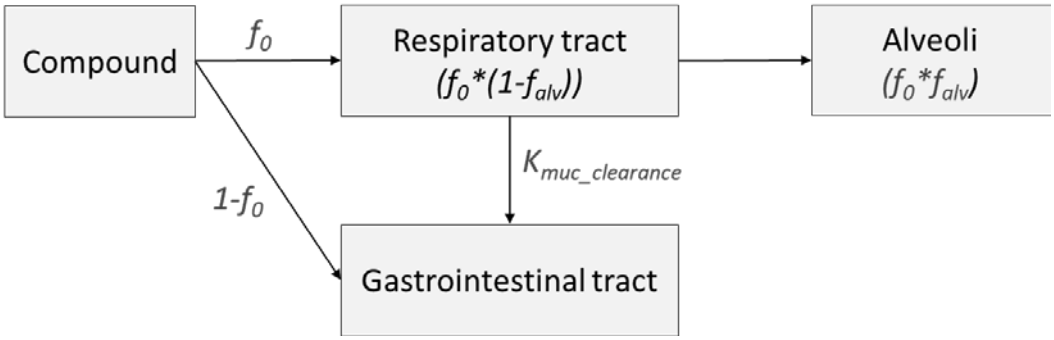

Figure 6: Rat Inhalation PBPK model capturing aerosol fractions absorbed from the respiratory tract and gastrointestinal tract: f_0 (fraction inhaled), $1-f_0$ (fraction entering gastrointestinal tract), f_{alv} (fraction reaching alveoli), $K_{muc\_clearance}$ (mucocilliary clearance). (Coupled to traditional PBPK model – not shown).

A two-week nose-only inhalation study of aerosol containing nicotine in Sprague-Dawley rats[1]. A solution containing 50 µg/mL of nicotine (nicotine dissolved in deionized water) was nebulized and administered for up to six hours/day, for five days/week during two weeks. Blood samples were collected and the respiratory minute volumes measured. For the PBPK model development, the metabolism and clearance parameters were obtained from Plowchalk et al [11]. The PK curve for day 11 was fitted (Figure 7) after adjusting for respiratory minute volumes to estimate the fraction of nicotine deposited and absorbed through the respiratory tract and gastrointestinal tract. The model predicted a 39.6% absorption of inhaled aerosol via the gastrointestinal tract. Although, the model was able to predict the absorption of the inhaled compound, it is challenging to perform any translation due to the lack of any aerosol characterization or species-specific anatomical descriptions. The obtained result indirectly infers that a significant amount of compound was delivered to the upper respiratory tract and eventually absorbed through the gastrointestinal tract. These results are in line with general aerosol dosimetry predictions for rodents using the whole-lung approach (e.g., MPPD model [2]).

[1] Study performed at Charles River Laboratories, Ashland, OH under the sponsorship of Philip Morris Products S.A., Switzerland.

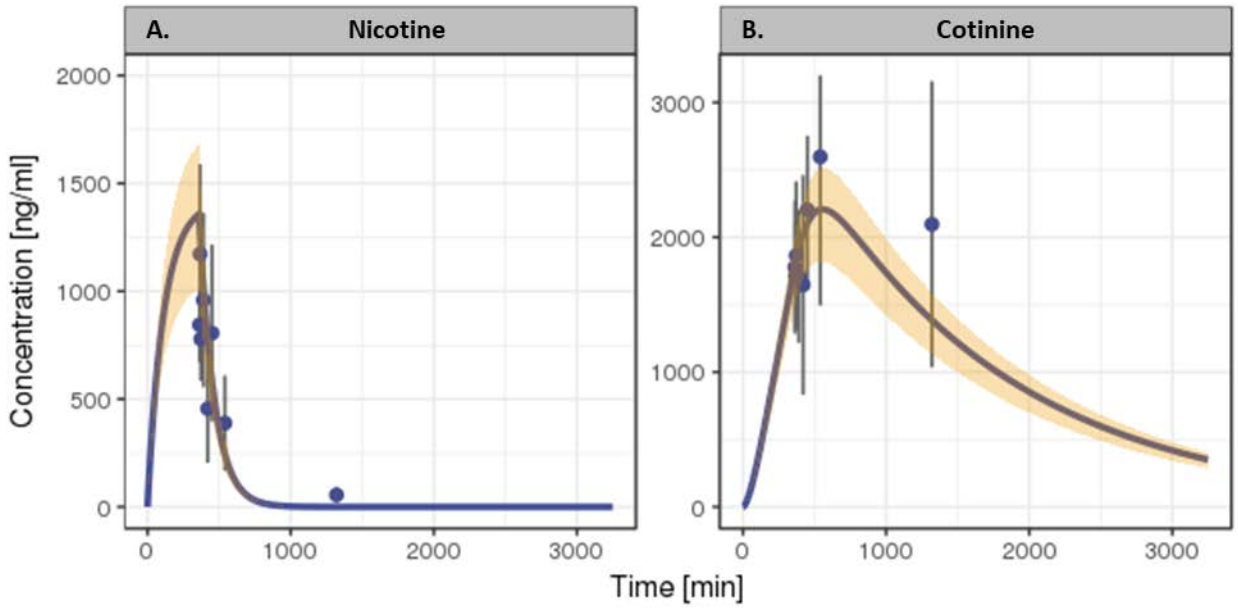

Figure 7: Pharmacokinetics of nicotine (A) and cotinine (B) in rats exposed to nicotine-containing aerosol for six hours.

B. Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?

Over the past years significant efforts have been dedicated towards understanding aerosol dosimetry with respect to tissue exposures; however, the challenges of predicting and understanding the key processes that determine pulmonary exposure to inhaled compounds remain [12]. One of the key challenges in developing and validation of an evolving aerosol model for nicotine, as well as other compounds, is the lack of experimental tools available for measuring aerosol characteristics and deposition in living subjects. Understanding how the chemical composition and physical characteristics of aerosols influences deposition, drug absorption (permeability, tissue affinity) and their impact on physiological processes (including mucociliary clearance and metabolism) would be beneficial. Computer-based mechanistic modeling and aerosol dosimetry provide an opportunity to explore these questions, but significant gaps still exist. The method/approaches described in the previous section are based on preliminary modeling efforts and needs to be further developed and validated to be applicable for inhaled aerosols. The challenges are broadly grouped into various categories as shown in Figure 8 and although not exhaustive, the list of potential gaps shown in Table *2* should warrant a workshop discussion.

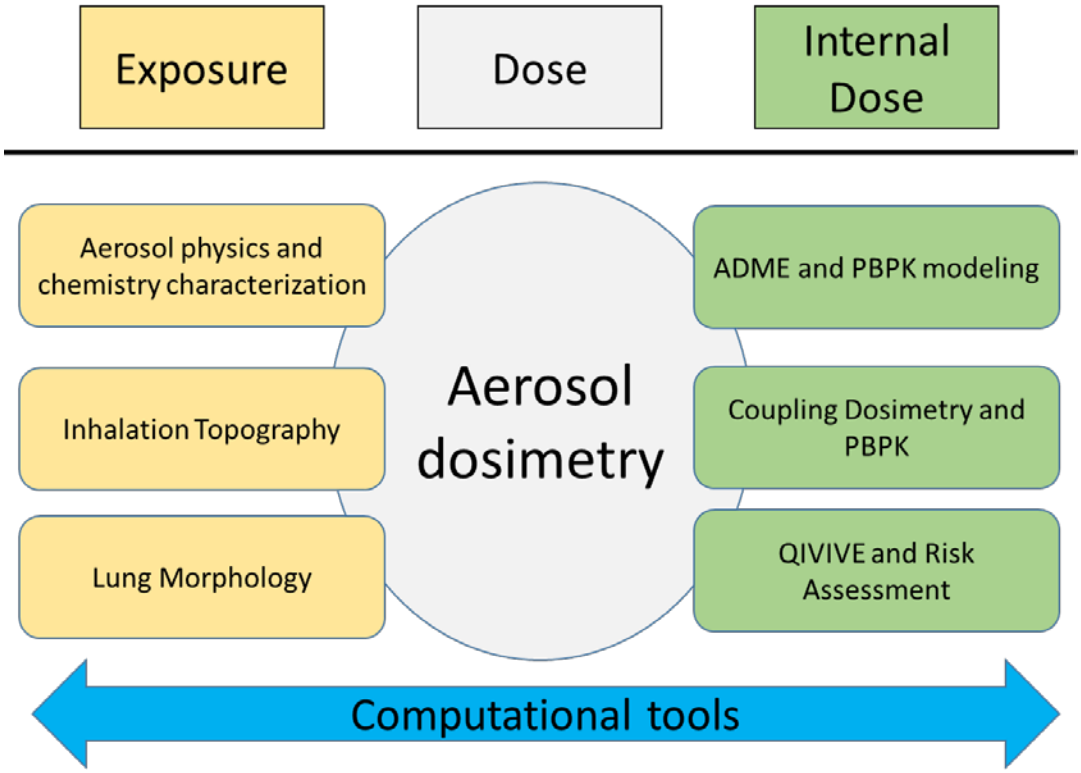

Figure 8: Main categories related to challenges involved in developing evolving aerosol inhalation PBPK models. Internal dose refers to tissue concentrations.

Table 1: Scientific challenges for the advancement of aerosol inhalation PBPK models.

Aerosol physics and chemistry characterization - Chemical composition of aerosol formulation impacts transport, evolution and deposition of aerosol mixture in respiratory tract. - Partitioning of the aerosol mixture phases influences deposition and absorption, which subsequently impacts dose response of the compound under investigation. - Transport of an evolving aerosol is influenced by several factors including changes in pH, influence of spatio-thermal and humidity conditions along the respiratory tract.
Inhalation Topography and Lung Morphology - Inhalation topography (breath hold, mouth hold and deep/shallow inhalation) effects the pharmacokinetics of short interval exposure. - There is a limited knowledge on the influence and deposition of mouth and nose

geometries on the delivery of aerosols for rodents and humans.

- Current data on rodent and human lung geometries are limited. They are not representative for the population differences.
- Inhalation patterns vary across individual subjects resulting in different exposures, thus there is a requirement to analyze and benchmark patterns of absorption, distribution, metabolism and excretion following aerosol exposures for development of population-based PBPK modeling.

Aerosol Dosimetry (and coupling to PBPK)

- The outcomes of a PBPK model show the actual deposited dose in the lung (respiratory tract) and gastrointestinal (swallowed directly) vary due to dependence on the aerosol inhalation process.
- Various methodologies were developed to determine and validate regional deposition of aerosol in the respiratory tract, but they lack generalization concerning dependence on chemical and aerosol physical properties.
- There is limited knowledge concerning the partitioning coefficients of compounds in various regions of the respiratory tract (e.g., extra-thoracic, thoracic, bronchiolar and alveolar regions) especially considering the varied tissue thickness and transfer rates.
- The aerosol exposure to delivered dose calculations as per Association of Inhalation Toxicologists [13] does not account for aerosol physics with an inclusion of transport, evolution and deposition mechanisms.
- What level of respiratory tract complexity is needed to improve predictions of aerosol dosimetry from a PBPK modeling perspective?
- Which computational dosimetry approaches (whole-lung or CFD-coupled) are recommended for development and coupling while simultaneously accounting for accuracy vs feasibility and practical use?
- **Is there an optimal (required or sufficient) number of lung segments to be used for dosimetry prediction and subsequent linking to PBPK compartments?**

ADME and PBPK modeling

- Methodologies to predict the rates and amounts of selected compounds cleared by mucus based on physiochemical properties of aerosols are not published. A detailed inclusion of mechanistic biology (e.g., inclusion of expression of cytochrome P450

enzymes, transporters etc.) of the respiratory tract would be beneficial.

Quantitative in vitro to in vivo Extrapolation (QIVIVE) and Risk Assessment

- Improvement of dose-response extrapolations of in vitro concentrations to in vivo outcomes is needed. Quantitative translation strategies need to be adapted for determining such doses.
- There is a need to develop strategies for employing in vitro tools and preclinical in vivo studies to further support the quantitative extrapolation of inhaled aerosol dose-exposure-response paradigm.
- **What might be the best validation experiments in preclinical species that are pertinent to humans for evolving and non-evolving aerosols especially considering anatomical and physiological differences?**
- How to appropriately apply QIVIVE in scaling of the lung geometry and aerosol particle size distributions to facilitate such extrapolations?

Computational Platform

- Comparing and benchmarking various models to predict transport, deposition and transfer of aerosol mixtures to identify their applicability in PBPK modeling is required.
- **Would there be an interest in an open source platform development for inhaled aerosol deposition and exposure modeling, which would allow for exchange of knowledge (physics, chemistry and toxicology) and mathematical models to further advance this field of multidisciplinary science?**

In the subsequent sections we further reflect on challenges in development of aerosol inhalation PBPK models specifying more detailed view on them. Better understanding of the key drivers of local and systemic exposure such as the rate of aerosol deposition, and an improved ability to characterize and model these processes should be considered for the risk assessment approaches. Most models assume a fixed deposited dose or homogeneous exposure in the respiratory tract when determining the dose deposited in the respiratory region and in the GI tract [14]. These assumptions may hold true for occupational or environmental exposures, yet are too simple to be

applied to the deposition of self-administered aerosols. Inhalation parameters such as the rate of air inflow and breath-hold, can alter deposition patterns and thus influence exposure.

Quantitative exploration of an inhaled dose from preclinical species to human is challenging due to anatomical and breathing respiratory differences. For example, a higher ratio of aerosol particle size distribution to rodent respiratory tract size/dimensions will cause increased particle deposition in the upper respiratory tract whereas, the same aerosol particle size distribution could be deposited in deeper generations of the human respiratory tract (as the ratio of same aerosol particle size distribution to human respiratory tract sizes is smaller). These differences raise the need to address the anatomical or aerosol particle scaling challenges as well as to identify the best validation preclinical experiments pertinent for human dose-exposure translation.

Mathematical modeling has advanced in recent years and numerous PBPK models are being developed to address several scientific questions. The question that still remains “is the level of detail necessary for PBPK modeling of inhaled aerosol available?” Are the answers to such questions as the number of lung regions/generations modelled and the refinement of region specific physiological parameters e.g., permeability, tissue metabolism or solubility in lung fluid available? In addition, coupling and developing a CFD-PBPK models may enable accurate prediction of tissue exposures, and CFD may serve to improve and validate whole-lung model approaches predicting aerosol dosimetry for PBPK use. Development and validation of these advanced models head-to-head will facilitate deeper understanding of the key dependencies that are required for reliable predictions. Moreover, scientific communities from various disciplines may contribute greatly to the advancement of the field by collaborative model development on a publicly available computational platform.

C. Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.

PBPK modeling methods are driven by problem formulation and the specific scientific question to be answered. A PBPK model for oral dosing differs from a PBPK model for topical exposures. As described earlier, an aerosol inhalation PBPK model with solid or liquid particle aerosol exposure will require detailed respiratory tract anatomical descriptions. An understanding of

aerosol physiochemical properties and their influence on evolution and deposition in the respiratory tract is important. Upon accounting for these factors, the model may become sufficiently general to be used directly and/or extrapolated for use with other chemicals, aerosols and bioactive substances.

D. Discuss the overall strengths and limitations of the methodology.

The preliminary methodology is applicable for estimating deposited doses and exposures based on pharmacokinetic profiles. The approach will need to be further refined and validated to address transport, evolution and absorption/deposition for novel liquid aerosol compositions. This proposal is geared towards identifying the essential requirements and possible limitations for developing such a methodology.

E. Outline the minimum data requirements and describe the types of data needed.

The reliability of predictions can be increased by developing a data-driven model. Some of the data requirements could be;

- Initial aerosol properties including particle size distributions, chemical composition and phase partitioning
- Inhalation pattern during exposures and its influence on regional deposition
- Plasma and tissue exposures concentrations of aerosol compounds over time
- Physiochemical properties of aerosol constituent (bioactive compound) diffusivity (or active transporter) across respiratory tract barriers and mucociliary clearance rate of compound
- Physiological changes relating to aging and diseased patients

3. DOES THE CASE STUDY:

A. Describe the dose-response relationship in the dose range relevant to human exposure ?

The clinical data used here compromises doses that are relevant to human exposure. However, looking beyond the confined clinical setting, the consumption and exposures can vary. Hence, we could explore the outcomes of scenarios with increased and varying inhalation aerosol uptakes.

B. Address human variability and sensitive populations?

Currently, the method does not explicitly or quantitatively address human variability or sensitive populations. The model has been fitted using data based on a randomized cross over study. Human variability for product consumption and sensitivity to metabolism can be incorporated at a population-based level modeling.

C. Address background exposures and responses?

A certain level of background exposure may occur and will require a whole body-PBPK model. The current method (PBPK modeling of inhaled aerosol) is primarily focused on determining the dose-exposures of voluntarily inhaled aerosols for short durations.

D. Address incorporation of existing biological understanding of the likely mode of action (MOA)?

The pharmacokinetics of a number of aerosol mixtures have been studied and as described here can be used to understand the likely MOA of nicotine and other similarly-acting chemicals. Incorporating existing biological understanding of the pharmacodynamics (PD) effects could be beneficial. However, assessment of the PD effects are out-of-scope of the current proposal and further discussion on the inclusion of any transport mechanisms that can influence dose-exposure is needed.

E. Address other extrapolations, if relevant – insufficient data, including duration of extrapolations and interspecies?

In vivo data for the deposition of aerosols are difficult to obtain. Extrapolation of aerosol exposures from animals to humans (or any interspecies extrapolation) is challenging (due to different breathing patterns and anatomy) as outlined in this document.

F. Address uncertainty.

Uncertainty in dose-exposures can be estimated using traditional uncertainty factors, or chemical-specific adjustment factors (CSAFs) [15, 16]. Further, uncertainty due to human variability can be accounted based on the biological understanding of species-specific or population level data.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

A fully validated method would allow calculation of the delivered dose. The delivered dose and exposures can then be used to determine risk for the human population.

H. Work practically? If the method still requires development, how close is it to practical implementation?

The proposed method remains under development and the implementation can be done at various levels of sophistication/resolution that is the subject of discussion for the proposed session.

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CONFLICTS OF INTEREST:

Aditya Reddy Kolli, Florian Martin, Arkadiusz K. Kuczaj, Manuel C. Peitsch and Julia Hoeng are employees of Philip Morris Products, S.A.

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