Computational toxicology:
an *in silico* dosimetry model
for risk assessment of air pollutants

T. Martonen\(^1,2\) \& K. K. Isaacs\(^1,3\)
\(^1\)Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, USA
\(^2\)Department of Medicine, University of North Carolina, USA
\(^3\)Department of Environmental Sciences and Engineering, University of North Carolina, USA

Abstract

To accurately assess the threat to human health presented by airborne contaminants, it is necessary to know the deposition patterns of particulate matter (PM) within the respiratory system. To provide a foundation for computational toxicology, we have developed an *in silico* model which describes the behavior and fate of inhaled PM. It is intended to be employed in a complementary manner with human subject experiments. The key components of the model are algorithms defining the morphology of the respiratory system, breathing conditions, and PM characteristics. The model gives spatial deposition patterns within human lungs, moreover local doses delivered to airways are calculated per unit surface area. This is of special importance because natural PM removal (i.e., clearance) processes vary with locations within lungs. For example, in tracheobronchial (TB) airways PM is cleared within about 24 hours by the mucociliary mechanism but PM deposited in pulmonary (P) airways may not be removed by macrophage action for several days. The salient point to be made is that the toxicity of air pollutants can be directly related to sites of initial deposition and local doses within human lungs. The PM *in silico* dosimetry model defined herein will permit air pollution risk assessment protocols to be put on a scientific basis, and will provide a foundation for the determination of ambient air quality standards.

*Keywords*: risk assessment, PM dosimetry, *in silico* model, human health.
1 Introduction

To evaluate the threat to human health presented by the inhalation of ambient air pollutants, the protocol most widely accepted by regulatory institutions throughout the world is to conduct experiments with volunteers. The tests are performed in well defined laboratory environments where factors affecting the deposition of inhaled particulate matter (PM) including PM size and subject ventilation are studied. Such tests have proven to be laborious and expensive, and are very strictly regulated. Hence, data are limited. It must be emphasized that a key factor limiting the usefulness of the human subject experiments is that it is difficult to extrapolate the data to real air pollution episodes. To aid in the regulatory process, we have developed an in silico dosimetry model to complement the laboratory protocols. We suggest that modeling be considered as a prudent and cost effective alternative to human subject experimentation.

2 Methods

Our laboratory has devoted considerable time and effort to the development of a biologically realistic in silico model capable of describing the behavior and fate of inhaled PM. The model was designed to be applicable to inhalation toxicology (i.e., the risk assessment of airborne contaminants) and aerosol therapy (i.e., the targeted delivery of inhaled pharmacologic drugs). The modeling has revealed a synergistic interface between science and medicine; for example, risk assessment research has produced a methodology to aid in the treatment of respiratory diseases caused or exacerbated by air pollutants.

The in silico model consists of a mathematical template and associated computer code [1]. To demonstrate versatility, the template/code has been used to describe the behavior and fate of inhaled pharmaceuticals used in treatment of asthma, a disease which has reached the status of an epidemic on a global scale [2]. Components of the model shall be addressed, albeit briefly, below.

2.1 Ventilation

To be useful in risk assessment protocols, a range of breathing conditions typical of a general population and occupational level must be addressed. We shall consider three sets of ventilatory parameters, defined in Table 1.

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Occupational Status</th>
<th>Tidal Volume (mL)</th>
<th>Frequency (Breaths/Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>Office</td>
<td>750</td>
<td>12</td>
</tr>
<tr>
<td>Moderate</td>
<td>Industry</td>
<td>1500</td>
<td>15</td>
</tr>
<tr>
<td>Exertion</td>
<td>Construction</td>
<td>2250</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 1: Respiratory intensities with corresponding levels of activity.
2.2 Particulate matter

Airborne pollutants have been separated into size fractions as a basis on which to ascertain the threat presented to human health [3]. The three most recognized size regimes of inhaled PM are coarse mode aerosols [4], fine mode aerosols [5], and ultrafine mode aerosols [6]. In nature these coarse, fine and ultrafine mode aerosols are polydisperse and composed of characteristic ranges of individual particle sizes. In our work we shall consider representative PM sizes for these respective modes to be 5 µm, 1 µm and 0.05 µm so as to be consistent with the work of Oberdorster et al. [7].

Figure 1: Description of human lungs. [A] The outer bounding surface of the right lung as determined by magnetic resonance imaging (MRI) is shown. [B] The branching network of tracheobronchial airways within the left lung is displayed (i.e., for clarity the P airways have been omitted).

2.3 Morphology

The anatomical structure of the respiratory system must be described properly if an associated computational toxicology program is to be acceptable [8]. Indeed, morphology has arguably the seminal role in the definition of a PM dosimetry model [9]. The reason is straightforward: the trajectories of entrained particles are influenced by the motion of the fluid transporting them, which, in turn, is affected by the geometry of the branching network of individual tubes within which it is flowing. In our laboratory, we have made attempts to be evermore biologically realistic by relating our models with single photon emission computed tomography (SPECT) data [10]. The morphology depicted in Figure 1 will be employed in this work. Figure 1 is a composite, separately illustrating the lung and its complex internal branching system of airways.
Human lungs have complex structures, functions and processes. We refer the audience to a set of classic handbooks for a comprehensive introduction to the subject matter [11, 12]. Herein, to keep matters focused, lungs may be visualized as being composed of two compartments, tracheobronchial (TB) and pulmonary (P), having distinctive physiological features. The TB airways (generations 0 # I # 16) are lined with smooth muscle and provide physical support for the peripheral P airways wherein gas exchange takes place. The P airways (generations 17 # I # 23) contain alveoli which are lined with surfactant. Regarding health effects, the important point is that PM deposited within the TB compartment will be removed by the natural mucociliary clearance process within about 24 hours [13]. In contrast, PM deposited in the P compartment will not be removed by natural macrophage action for a much longer period, perhaps weeks [14]. The relative efficiencies of these two processes will affect air pollution exposures of airway cells and will have, therefore, obvious implications to PM toxicity and health effects issues.

In Figure 2 airway surface area is presented as a function of depth within human lungs. Its marked increase with distal location has immense implications to risk assessment, as noted below.

2.4 Dosimetry

A dosimetry model has been developed which describes the behavior and fate of inhaled PM [1, 2]. The model has continually evolved to become increasingly biologically realistic as anatomical data detailing human airway morphology become available in the medical literature, and computer hardware and software...
increase in computational power and versatility. Unfortunately, a detailed technical discussion of the model per se is beyond the scope of this text simply because of the imposed page limitations. We refer an interested reader to the aforementioned peer-reviewed manuscripts.

3 Results

The results of our systematic series of simulations are presented in Figures 3-5. For ease of comparing data, the abscissas are identical in the series of panels for a given figure. The findings are self-explanatory, but a few observations will be made to orient a reader not familiar with integrating the subjects of dosimetry and risk assessment. First of all, we note that PM deposition will be presented as a function of spatial distributions within lungs. This is very important because sites of initial PM deposition will be related to residence times (i.e., the TB and P compartments have clearance processes that differ in effectiveness), and, therefore, the subsequent exposures of underlying airway cells to toxic substances. Secondly, PM deposition will be presented in two formats: (i) per airway generation; and, (ii) per unit airway surface area. The former format (i.e., (i)) is most commonly used in risk assessment protocols throughout the world. However, we consider that methodology to be outdated in view of the fact that a new methodology (i.e., (ii)) is available. We believe local doses delivered to airway surfaces to be the critical factor to be addressed in inhalation toxicology.

In Figure 3 PM deposition patterns within human lungs are shown for sedentary subjects. This would be applicable to clerical personnel in an office and people at rest. The salient point to be observed is that PM deposition is a very sensitive function of inhaled PM size. As noted previously, sites of initial PM deposition will determine the durations of exposures experienced by cells lining TB and P airway walls. Clearly, accounting for surface areas has pronounced effects on the computation of doses delivered to airways. For example, when the data from Panel A are viewed from a per-generation perspective, PM deposition is greatest in the P compartment; but, when normalized to airway surface area the peak of the deposition curve is shifted to the upper TB compartment. The meaning is straightforward and of paramount importance: whereas the dose delivered to the P compartment per se in terms of PM mass (e.g., gm) is pronounced, the concentration of PM (e.g. gm/cm²) is actually much greater in the TB compartment, indicating greater doses of toxic substances being delivered to those airway cells.

In Figure 4 a moderate level of respiratory intensity is addressed. This would correspond, for instance, to industry exposures and individuals of the general population engaged in outdoor activities. In Figure 5, a more intense level of activity is considered. This condition would correspond to construction workers and individuals exercising (e.g., jogging along road sides and inhaling automobile exhaust). Clearly, the results given in Figures 4 and 5 demonstrate that deposition patterns are highly dependent on PM size, and again, that airway surface areas must be addressed in computational toxicology.
Figure 3: Deposition pattern of inhaled PM as a function of airway generation, I, for resting (see Table 1) conditions.
Figure 4: Deposition pattern of inhaled PM as a function of airway generation, I, for moderate activity (see Table 1) conditions.
Figure 5: Deposition pattern of inhaled PM as a function of airway generation, I, for exertion (see Table 1) conditions.
4 Summary

The data from our systematic computations are presented in a manner to facilitate their use in PM risk assessment analyses. A few key results are listed below.

- The findings show that the deposition of air pollutants is a sensitive function of inhaled PM size.
- A prescribed data set represents a designated level of respiratory intensity (or, physical activity). For instance, Figure 3 addresses a resting state and would be related to administrative staff exposed to indoor air pollution. The sequence of panels [A, B, C] indicates exposures to identified PM sizes [5, 1 and 0.05 µm].
- The findings indicate that PM deposition is markedly affected by human subject breathing parameters.
- A given PM size, as indicated by a prescribed panel, can be tracked as a function of physical activity by comparing different Figures. For instance, the deposition patterns of secondary cigarette smoke (i.e., panel [B] for 1 µm) can be examined as a function of increasing respiratory intensity in Figures 3-5, respectively.
- Perhaps the most important finding is that the current PM risk assessment protocols may be inappropriate. This is so simply because PM doses delivered to human lungs are not presently normalized to airway surface areas. Our work provides a new scientific foundation for inhalation toxicology.

In conclusion, the results of this study clearly demonstrate the relevance of in silico modeling in estimating the threat to human health presented by ambient PM. We propose, therefore, that such bioengineering analyses be employed by air pollution regulatory institutions in their attempts to provide quantitative bases for PM health effects.

Disclaimer

The information in this document has been funded wholly (or in part) by the U.S. Environmental Protection Agency. It has been subjected to review by the National Health and Environmental Effects Research Laboratory and approved for publication. Approval does not signify that the contents necessarily reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Acknowledgement

K. K. Isaacs was supported by NHEERL-UNC DESE Cooperative Training in Environmental Sciences Research, EPA CT826513.

References


