Aerosols in a nutshell: Nobody can escape it and it affects us all the time. Every day we inhale approx. 15 000 liter of air. Depending on the location we live in and the time of the year we are exposed to the effects of civilization in terms of sulfur- or nitric oxides, airborne particle matter and aromatic hydrocarbons. According to the WHO, about 7 million people die every year as a result to air-pollution related diseases. At first pollutants deposit in the deeper lung where they trigger bronchitis and even lung cancer. The smaller-sized pollution fraction even trespasses into the blood circulatory system drastically increasing the risk of heart attacks and strokes. Besides these known adverse effects, more hidden side-effects become evident that are attributable to air-pollution and include cancer pathologies outside the lungs, diabetes and epigenetic factors.

This lab-course material provides background information to aerosol dynamics, effects on climate and health. In addition it provides basic information on selected tools to measure and quantify aerosol inventories and how these data can be implemented into a computer code for lung deposition modeling. The core issue with air pollution: nobody can escape as it affects everyone. With a breathing turnover of 8.6kL a day (sedentary lifestyle at 12 Bpm, tidal volume 0.5L of an adult) and based upon the location we live in, we are exposed to the traces of civilization that include sulfur-, and nitrogen-oxides, ozone, particle matter as well as hydrocarbons.

Image: Particle Deposition in the human respiratory tract. [1]

Pierre MADL
Div. of Material Sciences
Dep. Physics & Biophysics
University of Salzburg
Hellbrunnerstr. 34
A-5020 Salzburg
pierre.madl@sbg.ac.at
http://biophysics.sbg.ac.at/talk/trott-2012.pdf

v2019.01

Part V
Modelling
Lung Model

Modelling particle deposition in the human lung:

i) Random Single Path (Lagrangian) ….
   • Random walk of inhaled and exhaled particles through an asymmetric, stochastic airway model of the human lung
   • Behaviour of inhaled particles is simulated by the action of individual particles inhaled at random times during the inhalation phase

Versus

i) Comp. Fluid Dynamics (Eulerian) ….
   • Behaviour of an inhaled bolus (population of particles is simulated.

Pichelstorfer, 2014

18-10-04  Madl

…. see also: biophysics.sbg.ac.at/talk/IDEAL.pdf

The Human Respiratory tract:

i) Extra-thoracic (ET) region (nose & mouth)

i) Tracheo-Bronchial (TB) region (bronchial tubes)

i) Bronchial region (bronchili tubes)

i) Alveolar region (acinar tubes and alveolar sacs)

Koblinger and Hofmann (1985, 1990): Asymmetric stochastic lung geometry based on morphometric measurements (Raabe et al. 1976)

Weibel (1963): All airways in a given airway generation have identical linear dimensions (symmetric branching) and thus all pathways of an inhaled particle can be represented by a single path. Functional residual capacity (FRC) for an adult male: 3300 cm³

Inserts: **Silicone Rubber Casts**: Silastic is injected into the airways, allowed to cure 24 hrs, then tissue is digested in sodium hydroxide.

As the heart requires some space, the left lung lobe is usually smaller than the right lobe. This results in a asymmetrical bifurcation angle between right and left main bronchi – the angle to the right lobe poses less restriction to the flow of air than the left angle, thereby favouring ventilation of the right lobe. Hence inhaled particles are predominantly deposited in the right pulmonary lobe.

Jeder Segmentbronchus teilt sich in zwei so genannte *Rami subsegmentales*. Bis zum Durchmesser von 1 mm erfolgen weitere Teilungen und nur bis hierher enthält die Bronchialwand Knorpel, um das Offenbleiben der Bronchien und damit die Belüftung der gesamten Lunge zu gewährleisten. Mit fortschreitender Teilung nehmen Becherzellen und Flimmerepithel ab und es bildet sich unter der Schleimhaut ein ringförmiges Muskelsystem. Die Kontraktion desselben kann zum spastischen *Asthma bronchiale* führen.

**Image**: Schematic description of the upper tracheobronchial tree (Raabe et al., 1976). The binary identification number system used for the tracheobronchial airways starts with 1 for the trachea and designates major and minor branches with 1 and 2, respectively.

**Table**: Airway parameters of the typical path model of the human lung proposed by Yeh and Schum (1980).

Geometry of airways is based on data from Lovelace [3]


Morphology (3/5)

The Human Respiratory tract:

i) Geometry - fractal bifurcation pattern

i) Generations & Bifurcations
- Radius,
- Diameter,
- Length,
- Branching (gravity) angle

Source: Winkler-Heil R (person. communication)
Breathing frequency (f): Number of breaths per minute

Tidal volume (TV): Air volume inhaled during a single breath

Respiratory minute volume (RMV) = TV·f

Air volume inhaled per min or hour

NRC, 1991

To estimate the intakes of radon (or thoron) progeny activity by men, women, children, and infants for unit exposure to potential α-energy at various levels of physical exertion, the committee has assumed the breathing rates given in Table 9-5, p.227

Table: Summary of the Respiratory Data Assumed by the Panel to Calculate Exposure-Dose Conversion Coefficients for Various Subjects Exposed to Radon and Thoron Progeny

Source: http://www.nap.edu/openbook.php?record_id=1799&page=R1

Morphology (5/5)

Respiratory parameters:

i) Tidal volume (TV): Air volume inhaled for single breath [cm³]

i) Breathing frequency (f):
Cycle per minute [min⁻¹]

i) Respiratory minute volume (RMV):
RMV = TV · f [m³·min⁻¹]

i) Flow rate (Q): Air volume inhaled during inspiration [cm³·s⁻¹]

i) Corresponding physical quantity for aerosol deposition: particle velocity

The laboratory mouse is often used as a human surrogate in aerosol inhalation studies. Morphometric data on the tracheobronchial geometry of three in-situ lung casts of the Balb/c mouse lung produced by the Air Pollution Health Effects Laboratory were analyzed in terms of probability density functions and correlations among the different airway parameters. The results of this statistical analysis reveal significant differences in diameters and branching angles between major and minor progeny branching off from the same parent airway at a given airway bifurcation. Number of bronchial airways generations along a given path, expressed by the termination probability, branching angles, and daughter-to-parent diameter ratios indicate that the location of an airway with defined linear airway dimensions within the lung is more appropriately identified by its diameter (or its parent diameter) than by an assigned generation number. We therefore recommend classifying the mouse lung airways by their diameters and not by generation numbers, consistent with our previous analysis of the rather monopodial structure of the rat lung (Koblinger et al., 1995; Koblinger and Hofman 1995) … The computed distributions of the geometric airway parameters and their correlations will be used for random pathway selection of inhaled particles in subsequent Monte Carlo deposition calculations.

Though the morphometry data contained measurements on more than 2,000 tracheobronchial airways from three Balb/c mice (additional three mice for the first 6 bronchial generations), much more morphometric information is needed for a more rigorous statistical analysis. Despite these restrictions, however, the distributions and correlations found in our study form a solid basis for development of a stochastic Balb/c mouse lung model that can be used in modeling of inhaled particle deposition. Our stochastic lung model differs from other deterministic, morphometric models (Kliment, 1973; Yeh et al., 1979; Oldham and Robinson (2007) in that (i) it allows for the inherent intrasubject variability of linear airway dimensions, such as diameters, lengths and branching angles, and (ii) airways are characterized by their diameters and not by their generation numbers. While the generation concept represents a reasonable approach for the more symmetric and dichotomous human lung, the diameter concept is certainly more appropriate for the more monopodial structure of the mouse lung and hence very similar to the rat lung.

The independence of the termination probabilities and of the branching angle distributions from generation numbers, as well as the marked differences in the daughter- to-parent diameter ratios leads to the conclusion that the location an airway with defined linear airway dimensions within the bronchial tree is more appropriately identified by its diameter (or its parent diameter) than by an assigned generation number. Thus the structure of the mouse lung is very similar to that of the rat lung, where the common classification by airway generations was already replaced by the classification by airway diameters (Koblinger and Hofmann, 1988). The distributions and correlations of the morphometric data presented highlight the monopodial structure of the mouse lung as opposed to the more symmetric branching structure of the human lung.

Aerosol Deposition Mechanism (ADM)

Source: http://www.esrl.noaa.gov/csd/groups/csd2/instruments/pvci/
Here is a draft what processes are usually considered when talking about aerosol dynamics:

What we see here is an aerosol situated in a containment. There is an inflow and an outflow.

We have interaction of the aerosol with the surface of the containment.

And finally, the typical dynamic processes: phase transition, coagulation nucleation and diffusion.

Note, we also take into account simple chemical reactions represented by numeric solution of chemical kinetics (no equilibrium assumptions).

Source: Pichelstorfer L. (2014). Seminar talk at PLUS, AUT
Flow Dynamics Extrathoracic region

i) Flow characterized by the action of the laryngeal jet \( (Q = 30 \text{L/min}) \) 

Xi & Longest, 2008

The objective of this study is to assess the effects of geometric simplifications on diffusional transport and deposition characteristics of inhaled ultrafine aerosols in models of the extrathoracic oral airway. A realistic model of the oral airway with the nasopharynx (NP) included has been constructed based on computed tomography scans of a healthy adult in conjunction with measurements reported in the literature. Three other geometries with descending degrees of physical realism were then constructed with successive geometric simplifications of the realistic model. A validated low Reynolds number k-ω turbulence model was employed to simulate laminar, transitional, and fully turbulent flow regimes for the transport of 1–200 nm particles. Results of this study indicate that the geometric simplifications considered did not significantly affect the total deposition efficiency or maximum local deposition enhancement of nanoparticles. However, particle transport dynamics and the underlying flow characteristics such as separation, turbulence intensity, and secondary motions did show an observable sensitivity to the geometric complexity ….. The orientation of the upper trachea was shown to be a major factor determining local deposition downstream of the glottis and should be retained in future models of the respiratory tract. In contrast, retaining the NP produced negligible variations in airway dynamics and could be excluded for predominantly oral breathing conditions. [1]

Image: Midplane velocity vectors, contours of velocity magnitude, and in-plane streamlines of secondary motion for the realistic model with the NP under light activity conditions (\( Q_{in} = 30 \text{L/min} \))

Figs. Predicted aerosol DE versus particle diameter in the four models considered with a comparison to experimental data for inspiration flow rates of \( a) ... Q_{in} = 4 \text{ l/min} \) and \( b) ... Q_{in} = 10 \text{ l/min} \)

Deposition efficiency by diffusion [2]: 

\[
\eta D = a_2 D \exp(a_3)
\]

\( a_2 = 2.965, a_3 = 0.568 \)

\( \Delta = D l/(d^3 \nu) \) or \( \Delta = p l D/(4Q) \)

\( D = \text{Diffusion coefficient}, l = \text{airway length}, d = \text{airway diameter}, \nu = \text{velocity in airway}, Q = \text{flow in airway} \)


Flow Dynamics of Inspiration

1) Trachea: flow characterized by the action of the laryngeal jet
2) Upper TB-tree: transition from uniform to parabolic flow
3) Lower TB-airways: regime of laminar flow with a parabolic profile
4) Alveolar: laminar flow fully with fully developed parabolic profile

Flow Dynamics of Expiration

1) prevailing laminar flow across all regions,
2) uniform profile caused by merging flows at airway bifurcations

In large bronchial airways (e.g., from generation G0 to G6), micron-particle depositions mainly occur around the carinal ridges (see figure). However, in medium- to small-sized airways (e.g., from G0 to G15), sedimentation cannot be neglected, and the deposition patterns change somewhat. In this case, many particles essentially settle on the tube wall that is normal to the direction of gravity. At the same time, the presence of gravity and its direction affect the deposition patterns. In general, some particles that may land directly on the carinal ridges when considering impaction only can be diverted. As a result, the maximum DEF values may decrease owing to gravitational sedimentation. Specifically, it was demonstrated that the maximum deposition enhancement factor (DEF) values may reduce one order of magnitude [e.g., from O(103) in generations G0–G3 to O(102) in G12–G15] with a much broader distribution of micron particles due to gravitational settling. Furthermore, the carinal ridges are not the unique deposition hot spots anymore; in fact, the entire airway surfaces that are normal to the direction of gravity may become high-deposition regions. The Comparisons of micron- and nano-particle deposition in an idealized upper airway model.

Image: Comparisons of micron- and nanoparticle deposition in an idealized upper airway model.

Respiratory parameters w/n lung:

1) Sedimentation: dependent on terminal settling velocity of particle

2) Impaction: dependent on stopping distance of particle

3) Diffusion: dependent on Brownian motion (mean displacement)

4) electrostatic attraction: dependent on charge of particle

Balásházy et al., 1999

CFD-simulation of the deposition within the tracheo-bronchial tree
Respiratory parameters w/in lung:

1) Sedimentation: dependent on terminal settling velocity of particle

\[ u_s = \frac{d \cdot g \cdot d_p}{18 \cdot \eta} \]

2) Impaction: dependent on stopping distance of particle

\[ h_i = \frac{(u \cdot \sin \theta) \cdot u_s}{g} \]

3) Diffusion: dependent on Brownian motion (mean displacement)

\[ \Delta = \sqrt{2 \cdot D \cdot t} = \sqrt{\frac{k \cdot T \cdot C}{3 \cdot \pi \cdot \eta \cdot d_p}} \]

4) Electrostatic attraction: dependent on charge of particle

\[ \text{TB} : n_e = q_c \cdot \frac{8 \cdot B \cdot l_0}{\pi \cdot \varepsilon_0 \cdot d_p} \]
\[ \text{AL} : n_e = \frac{1}{d_p} \cdot \frac{S \cdot B \cdot q_c^2}{\varepsilon_0} \]

5) Dose of un-attached fraction

\[ H_d(n) = \sum W_i \cdot D_i \cdot (Gy) \]

18-10-04 Madl

Particle Deposition Mechanisms: The lung can be seen as a selective filter, into which the particle are stripped off the gas stream in different ways[1]. In the upper air ways (nose, throat) the air-speed is high enough to cause particles to deposit by impaction. Airway branching pattern favors non-uniform (focal) areas of deposition, especially when impaction is an important deposition mechanism.

Naso-pharyngeal: impaction, sedimentation, electrostatic (particles >10 μm & <0.1 μm)
Tracheo-bronchial: impaction, sedimentation, diffusion (particles <5 μm)
Pulmonary: sedimentation, diffusion (particles <2.5 μm)

The lung has, like any filter, a certain range in which neither impaction nor diffusion predominates and typically occurs at around 300 nm.

Impaction: The particle’s momentum in air stream prevents it from making turn at a bifurcation (occurs in the following compartments naso-pharyngeal and tracheo-bronchial). Sedimentation: When gravitational forces on a particle are greater than air resistance and buoyancy, the particle will fall out of the air stream. As air moves deeper into the lung, air flow rate decreases. Sedimentation is proportional to:
• particle time in airway
• particle size and density
• respiratory rate, i.e. breaths/minute
(occurs in naso-pharyngeal, tracheo-bronchial, and pulmonary compartment).

Diffusion: Particles have random motion, resulting in random impacts. The diff. coefficient is:
• inversely related to particle size
• independent of particle density
(diffusion occurs in the tracheo-bronchial and pulmonary compartment).

Electrostatic Precipitation: A minor mechanism, but may be more important for freshly generated particles because these particles tend to have greater surface charge. Particle surface charge induces an “image” charge on lung surface.

Particle characteristic that affect deposition: Size will effect location of deposition; sequential removal of particles as go through the lung. Particle hygroscopicity: If a particle is hygroscopic, it can pick up water in the humidified air of the lung. This will increase particle density and alter deposition. Particle surface charge: This will affect electrostatic deposition.

E-static deposition: \( B \) is the mechanical mobility of the particle, \( \varepsilon_0 \) is the electric permittivity of air, and \( t_{\text{m}} \) is the is the mean residence time of particles in airway tube.

Image: Basic process of Rn decay product behavior in air defining “unattached” and “aerosol-attached” activities.[2]

The electrostatic charge carried by aerosol particles greatly enhances their deposition in the airways. Systematic measurements have been performed on volunteers with unipolar charged monodisperse aerosols of both polarities. In the charge concentration used, the increase in deposition is due to image forces between wall and particle. The particle sizes were 0.3, 0.6 and 1.0µm monodisperse within ±10% and charged with a number of elementary units between 12 and 230 with a distribution of charge within ±18%. Since in the size range investigated the deposition takes place only in the alveolar region, we think that also the deposition for electrostatic effects is alveolar, under the experimental conditions described.[1]

The charge on an aerosol particle may affect its behaviour in three ways: (1) it will be deflected by an electric field; (2) coagulation and interaction with other particles is altered; (3) particles are attracted to neutral surfaces by image forces.

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Field charging occurs on the presence of a strong electrical field, field charging is developed by unipolar ions. Ions rapidly impact on the particles at the initial stage because the electrical field lines guide the ions towards the particle. Then charges transfer from ions to the particle. Field charging is more significant for particles larger than 1 µm and the charge magnitude increases with the square of the particle diameter.[3]

Diffusion charging appears when an ion randomly collides with a particle, then the particle acquires charges from ions. Consequently, the charging rate reduces because few ions have sufficient velocity to overcome the repulsive force arising from charges on the particle. For a particle less than 1 µm, diffusion charging is the main charging mechanism.[3]

When the particle size increases, the space charge force is less significant. The space charge force depends significantly on the concentration of particles and arises only when there is a high concentration of particles with sufficient charge.[3]

Thus, the image charge force is the important mechanism for the transport of charged aerosol in small airways and alveolar regions when the particles carry sufficient charge.[3]

The air inside the human lung has a high humidity (typically 99.5% relative humidity). Nguyen & Nieh have suggested that under these conditions particle charges are effectively eliminated. Furthermore their experimental studies showed that the charges are practically neutralised at a level of 78% relative humidity. However this process has a decay time to complete the charge neutralisation. The numerical model assumes no charge elimination as a result of the high humidity in the lung, because of the short residence time in tracheobronchial region (< 50, ms for sedentary breathing).[3]

The study of particle deposition in the respiratory tract generally accounts for only the space and image charge forces. The space charge is due to the mutual repulsion of particles, which is a function of concentration of particles and charge values on the particles. The image charge force is the interaction of charged particles with the lung wall. Triboelectric charging results in bipolar charges, but diffusion and field charging results in unipolar charges. This phenomenon (also sometimes known as contact charging) arises during the separation of dry, non-metallic particle from the surface of device.[3]

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A computer model has been developed for analysing the deposition of inhaled electroaerosols in human airways. The effect of electrostatic charges on the total aerosol deposition efficiency in the human respiratory tract has been investigated. Based on measured data, a computer prediction can be made of the site of deposition in human airways.[1]

Enhanced deposition due to particle electrostatic charge may take place by two deposition processes, i.e., due to (i) space charge effects and (ii) the image charge force. The space charge effect arises if densely charged aerosols are inhaled. The repulsive force among the charge cloud may result in deposition, but this effect is usually insignificant … surface. During image charge attraction, a particle always induces an equal and opposite charge to itself on a surface such as an airway wall, which always results in a net attractive force, regardless of particle polarity. Although human airways are normally electrically neutral, image charges with equal magnitude and opposite polarity to the charged particles may be induced on the surfaces, especially inside small airways in the peripheral lung … for particle concentrations lower than \(1\times10^5\) particles/ cm\(^3\), the electrostatic repulsive force is not important because the particles are relatively far apart. Therefore, increased deposition of charged particles is mainly due to image force.[2]

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The electrostatic charge properties of drug-free metered dose inhaler (MDI) aerosols containing the propellants HFA-134a and 227ea were studied using a modified electrical low pressure impactor (ELPI) with aerodynamic cutoff diameters ranging from 0.028 to 10.07 μm. The MDIs were spiked with various amounts of water and crimped with Hostaform and PBT (polyester) valves. Polypropylene actuators were dried or wetted by storage in a desiccator or a box saturated with water vapour, respectively. The air humidity was controlled at 5%, 50%, and 92% RH to maintain the actuator surface dryness or moisture during the experiments. The droplet size distributions in the ELPI were determined by chemical assays of another set of inhalers containing crystal violet as a marker. The charge profiles measured were highly variable but on average both HFA-134a and 227ea charged negatively, which was ascribed to the electronegative fluorine atoms in the HFA molecules withdrawing anions from the MDI components. The drug-free MDIs produced lower charges than the commercial medicated ones. The charges of both HFAs shifted towards neutrality or positive polarity as the water content increased. The spiked water would increase the electrical conductivity and/or decreased the electronegativity of the liquid propellant surface. The mean number of elementary charges per droplet decreased with decreasing droplet size.

**Image**: Mean charge profiles of HFA-134a (closed symbols) and HFA-227ea (open symbols) MDIs used with dry actuators in dry air. (■ low water content; ○ medium water content; ▲ high water content). Error bars represent standard errors (n = 30 for all except n = 20 for of HFA-227ea, PBT)

**Formula**: \[ n = \frac{q \cdot \rho \cdot V}{e} \]

where \( q \) is the density of the propellant concerned (1.226 and 1.408 kg/dm³ at 20°C for HFA-134a and 227ea, respectively), \( V \) the volume of a particle, and \( e \) the elementary charge (1.60210⁻¹⁹ C).

A novel method for characterizing the electrostatic charge in pharmaceutical aerosols was developed. Electrical low-pressure impaction (ELPI) was modified and optimized to allow the measurement of aerosol particles from metered dose inhalers (MDIs) for anti-asthmatic drugs. Two commonly used MDIs, VentolinTM and FlixotideTM, were investigated for the charging properties of their emitted aerosols. VentolinTM aerosol was found negatively charged, whilst FlixotideTM aerosol was bipolarly charged, containing both positive and negative charged particles. The electrostatic charge measurements for both MDIs were reproducible with %CV ranging from 3.3% to 12.5% for 10 actuations from each of the inhalers. In addition, chemical assay was undertaken to obtain mass distributions of the aerosol collected inside the ELPI. Both MDIs showed that only a small amount of the drug was recovered from the submicron size range where a large amount of charge was present (negative charge for VentolinTM and positive for FlixotideTM). For the FlixotideTM, the majority of drug was recovered from the 1 to 10 m particles which were negatively charged. Hence, different particle size fractions of the aerosol can contribute differently to the charge which can feasibly be studied by the ELPI method.

**Image**: Mean mass and charge distribution for a single actuation of the Ventolin and of Flixotide type MDI.

Triboelectric aerosol charging:

due to a dry powder inhaler (DPI) using

i) Albuterol in milled lactose (ML)
0.5% albuterol in 45-75μm sieve fraction of excipient; set of actuation conditions (40mg).
GMD around 1μm!

Telko, 2009

i) Budesonide in milled lactose (ML)
similar mass & charge distribution
but w/ prevailing neg. charge;
peaks @ -20-25pC.

ADM (8a/9)

Electrostatics and triboelectrification phenomena in dry powder inhalers (DPI) are not well understood, but as shown in this study they may play an important role. Using model formulations of albuterol in lactose, the extent of triboelectrification in the operation of DPI was investigated using an electrical low pressure impactor (ELPI™). An experimental apparatus was developed, the performance of the ELPI™ was evaluated for consistency and reproducibility, and compared to a conventional inertial impactor. Using a statistical experimental design the effects of lactose type, drug load, capsule fill, capsule material, and inhaler were assessed. DPI formulations appear to be subject to strong triboelectric effects. Charge separation can occur between different size fractions, i.e. different fractions can carry charges of different sign. In particular, lactose type, inhaler, and capsule material have a strong effect on the magnitude and polarity of the charge developed during DPI operation. The study suggests that the polarity of the aerosol can be controlled by choice of lactose type, capsule material, and inhaler, which could be exploited for targeting different lung physiologies.[2]

Triboelectric charging results in bipolar charges, but diffusion and field charging results in unipolar charges. This phenomenon (also sometimes known as contact charging) arises during the separation of dry, non-metallic particle from the surface of device.[3]

Image: Formulation (0.5% albuterol in 45-75μm ML80 lactose, 40mg) actuated from SET A (three times) on different days, separated by 5 days of storage. The differences in deposition (actual quantities shown) are minimal. Differences in charge distribution mirror the differences in deposition, and are within a standard deviation from one another.

Not shown: Same formulation (0.5% budesonide in 45-75μm SV425 lactose) actuated from SET A on different days, separated by 36 days of storage. Also shown remade formulation, actuated day after it was made. The remade formulation has FPF similar to the old formulation without storage, while storage results in higher deposition. Charge deposition profiles are similar for all.

Large Image: Charge distribution (average particle charge) for drug deposited in ELPI. Shown are 0.5% budesonide in ML80 lactose (45-75μm) (yellow diamonds), both actuated from SET A. For comparison, the graph shows the charge limit expected for the particles (green triangles) and the Boltzmann charge distribution (red squares). In both cases, over 80% of the deposited particles carry >100 charges per particle.

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**Image**: Formulation (0.5% albuterol in 45-75µm ML80 lactose, 40mg) actuated from SET A (three times) on different days, separated by **5 days of storage**. The differences in deposition (actual quantities shown) are minimal. Differences in charge distribution mirror the differences in deposition, and are within a standard deviation from one another.

Not shown: Same formulation (0.5% budesonide in 45-75µm SV425 lactose) actuated from SET A on different days, separated by **36 days of storage**. Also shown remade formulation, actuated day after it was made. The remade formulation has FPF similar to the old formulation without storage, while storage results in higher deposition. Charge deposition profiles are similar for all.

**Large Image**: Charge distribution (average particle charge) for drug deposed in ELPI. Shown are 0.5% budesonide in ML80 lactose (45-75µm) (blue diamonds), 0.5% albuterol in ML58 lactose (45-75µm) (yellow diamonds), both actuated from SET A. For comparison, the graph shows the charge limit expected for the particles (green triangles) and the Boltzmann charge distribution (red squares). In both cases, over 80% of the deposited particles carry >100 charges per particle.


Energy deposition and cellular radiation effects arising from the interaction of single $^{218}$Po and $^{214}$Po alpha particles with basal and secretory cell nuclei were simulated for different target cell depths in the bronchial epithelium of human airway generations 2, 4, 6, and 10. To relate the random chord lengths of alpha particle tracks through spherical cell nuclei to the resulting biological endpoints, probabilities per unit track length for different cellular radiation effects as functions of LET were derived from in vitro experiments. The radiobiological data employed in the present study were inactivation and mutation (mutant frequency at the HPRT gene) in V79 Chinese hamster cells and inactivation and transformation in C3H 10T1/2 cells. Based on computed LET spectra and relative frequencies of target cells, probabilities for transformation, mutation, and cell killing in basal and secretory cells were computed for a lifetime exposure of 20 WLM. While predicted transformation probabilities were about two orders of magnitude higher than mutation probabilities, they were still about two orders of magnitude lower than inactivation probabilities. Furthermore transformation probabilities for basal cells are generally higher than those for secretory cells, and $^{214}$Po alpha particles are primarily responsible for transformations in bronchial target cells.

Image: Effect probabilities for transformation of C3H 10T1/2 cells by Po-alpha particles as functions of depth in bronchial epithelium for airway generations 2, 4, 6, and 10. Probabilities are normalized to a source density of 1 Bq/cm$^2$ (top). Effect probabilities for cell killing (V79 and C3H 10T1/2), mutation (V79) and transformation (C3H 10T1/2) by $^{214}$Po-alpha particles as functions of depth in airway generation 4. Probabilities are normalized to a source density of 1 Bq cm$^2$.

Clearance Mechanisms (CM)
The human bronchial tree. The tracheobronchial region (includes larynx, trachea, bronchi, bronchioles and terminal bronchioles) and the pulmonary region (respiratory bronchioles, alveolar ducts, alveoli). Not shown is the nasopharyngeal region (anterior nares to larynx). [1]

Epithelial cells: Respiratory epithelium is a type of epithelium found lining the upper and lower respiratory tracts, where it serves to moisten and protect the airways. It also functions as a barrier to potential pathogens and foreign objects, preventing infection by action of the ciliary escalator. The cilia of the respiratory epithelium beat in a concerted effort to move secreted mucus containing trapped foreign particles towards the oropharynx for either expectoration or swallowing to the stomach where the acidic pH helps to neutralize foreign material and micro-organisms. This system is collectively known as the ciliary escalator and serves two functions: to keep the lower respiratory tract sterile, and to prevent mucus accumulation in the lungs from drowning the organism.

Clara cells: are non-mucous and non-ciliated secretory cells found in the primary bronchioles of the lungs. Clara cells are dome-shaped and have short microvilli. One of the main functions of Clara cells is to protect the bronchial epithelium. They do this by secreting a small variety of products, including Clara cell secretory protein (CCSP) and a component of the lung surfactant. They are also responsible for detoxifying harmful substances inhaled into the lungs. Clara cells also multiply and differentiate into ciliated cells to regenerate the bronchiolar epithelium. Clara cells play an important defensive role, and they also contribute to the degradation of the mucus produced by the upper airways. The heterogeneous nature of the dense granules within the Clara cell's cytoplasm suggests that they may not all have a secretory function. Some of them may contain lysosomal enzymes, which carry out a digestive role, either in defense. Clara cells engulf airborne toxins and break them down via their cytochrome P-450 enzymes present in their smooth endoplasmic reticulum; or in the recycling of secretory products. Clara cells are mitotically active cells. They divide and differentiate to form both ciliated and non-ciliated epithelial cells.

Pneumocytes: The lungs contain about 300 million alveoli, representing a total surface area of 70-90 (?) m², each wrapped in a fine mesh of capillaries. The alveoli have radii of about 0.1 mm and wall thickness of about 0.2 µm. The alveoli consist of an epithelial layer and extracellular matrix surrounded by capillaries. In some alveolar walls there are pores between alveoli. There are three major alveolar cell types in the alveolar wall (pneumocytes):

- **Type I cells** that form the structure of an alveolar wall. They are very large, thin cell stretched over a very large area. This cell cannot replicate and is susceptible to a large number of toxic insults. Type I pneumocytes are responsible for gas exchange occurring in the alveoli.
- **Type II granular pneumocyte** is a roughly cuboidal cell that is usually found at the alveolar septal junctions. Type II cells cover about 5% of the surface area of the alveoli, whereas type I pneumocytes (because of their squamous shape) cover 95% of the total area. Even though they cover less surface area, type II cells greatly outnumber type I cells. Type II cells are responsible for the production and secretion of surfactant, which lowers the surface tension of water thereby to increase the capability to exchange gases. The Type II pneumocyte can replicate in the alveoli and will replicate to replace damaged Type I pneumocytes.
- **Type III cells** that destroy foreign material, such as bacteria.

The alveolus have an innate tendency to collapse (atelectasis) because of their spherical shape, small size, and surface tension due to water vapor. Phospholipids, which are called surfactants, and pores help to equalize pressures and prevent collapse.

Clearance mechanisms:

i) Mass balance for a given bronchial airway depo-rate: \[ \frac{dm}{dt} + \frac{dm_{dt}}{dt} + \frac{dm_{dt2}}{dt} = \frac{dm_{out}}{dt} \]

- Mass rate leaving the airway: \[ \frac{dm_{out}}{dt} = \frac{m}{Tr} \]
- \( Tr \): residence in airway
- Mucus velocity \( v = \frac{L}{Tr} \)
- \( L \): airway length
- Mass rate entering the airway from the 2 daughter airways
- Actual deposition rate

**Intrasubject variability**: Mucus velocity and mucus transit time in a given airway are related to the diameter and length of that airway (variability of airway diameters and lengths).

Yeates et al. (1975, 1982):
- Tracheal mucus velocity: Median = 4.2 mm min\(^{-1}\) (normalized to 5.5 mm min\(^{-1}\)), GSD = 1.8
- Mucus velocities are rescaled in relation to the randomly selected tracheal mucus velocity.

Background: A mathematical model describing mucociliary clearance in cystic fibrosis (CF) patients and its development with progressing course of the disease was developed. The approach should support the prediction of the disease state on the basis of measured bronchial clearance efficiencies.

Methods: The approach is based on the assumption of a steady-state steady-flow mucus transport through the tracheobronchial tree which enables the determination of airway generation-specific mucus velocities by using a measured tracheal mucus velocity and a realistic morphometric dataset of the human lung. Architecture of the tracheobronchial tree was approximated by a stochastic model, reflecting the intra-subject variability of geometric parameters within a given lung generation.

Results: As predicted by the appropriately validated mathematical approach, mucociliary clearance efficiency in CF patients is partly significantly decreased with respect to healthy controls. 24-h retention of patients with mild CF (FEV1 > 70% of predicted) is reduced by 10% compared to healthy subjects, whilst 24-h retention of patients with moderate to severe CF (FEV1 < 70% of predicted) differs by 25% from that of the healthy controls. These discrepancies are further enhanced with continuation of the clearance process.

Conclusions: The theoretical results lead to the conclusion that CF patients have a higher risk of inhaled particle accumulation and related particle overload in specific lung compartments than healthy subjects.

A mathematical model of retention of insoluble aerosol particles penetrating the lungs during inhalation has been described. Based on data of the streams of deposited particles and their residence times in the subsequent generations of the respiratory system - due to different mechanisms of clearance - the retention dynamics of particles has been determined. The influence of particle concentration and particle toxicity on retention is considered.


the IDEAL code

Inhalation & Deposition of Aerosols in the Lung
Modelling particle deposition:

i) Comparison of models …
- semi-empirical
- trumpet
- single path (IDEAL)
- Multiple path (CFD)
- Stochastic (IDEAL)

Hofmann, 2011
Taulbee & Yu, 1975

Conceptual models:
- semi-empirical regional models
- one-dimensional cross-section (“trumpet”) models
- deterministic symmetric generation (“single-path”) models
- deterministic asymmetric generation (“multiple-path”) models
- stochastic asymmetric generation (“multiple-path”) models

Eulerian model: A population of particles is tracked through the human airway system and deposition in a given airway generation is given by the difference between the incoming and the outgoing number (or mass) concentrations.

Lagrangian model: Trajectories of single particles are followed through the whole lung; simulations have to be repeated many times to obtain statistically significant average deposition fractions.

Image: Comparison of model predictions of total deposition for unit density particles ranging from 1 nm to 10 mm under nasal sitting breathing conditions (ICRP, 1994), applying 5 different deposition models: semi-empirical (ICRP, 1994), trumpet (Choi & Kim, 2007), single path (Hofmann, 1982a), multiple path (Asgharian et al., 2001), and stochastic (Koblinger & Hofmann, 1990).

Insert: Human airway system is approximated by a one-dimensional, variable cross-section channel, mass balance equation with different loss terms for the various deposition mechanisms (1-dimensional Eulerian model).

Modelling particle deposition:
i) Comparison of models ….

Semi-empirical ….
• for regional deposition efficiencies
• function of particle size & flow rate
• obtained from mathematical fits through the available experimental data (Eulerian model).

Lagrangian vs. Eulerian
• trajectories of single particles
• population of particles

Approach (3a/10)

Modelling particle deposition @ PLUS:

i) Comparison of models ....

i) IDEAL & ADiC

IDEAL (developed by HOFMANN & KOBLINGER) .... currently used
This aerosol dynamics model has been implemented into an extended version of the IDEAL (Inhalation, Deposition and Exhalation of Aerosols in the Lungs) code to compute particle deposition in the airway generations of the human lung.

ADiC (currently under development by Pichelstorfer) .... future extension model
The dynamic changes of the droplets during puffing, mouth-hold and within the lungs during inspiration and expiration are described by the aerosol dynamics model ADiC (Aerosol Dynamics In Containments), which considers coagulation, conductive heat transport, diffusive vapor transport, phase transition and particle deposition.
A new aerosol dynamics model, ADiC (Aerosol Dynamics in Containments), was developed, which considers the effects of coagulation, heat and vapor transfer, phase transition and deposition of particles. The particle size distribution is represented by individual uniform distributions situated in a fixed size grid. That way numerical diffusion is avoided and quasi simultaneous simulation of coagulation and growth processes is possible. Due to the complexity of the computer model, partial model validation was performed by testing the individual sub-models against the existing experimental evidence. The ADiC model was used to simulate the aerosol dynamics of freshly generated cigarette smoke in acid-covered denuder tubes. Modeling results were compared to data from several studies that report nicotine deposition rates. Simulations revealed that several parameters with large uncertainties potentially can have great effects on the nicotine deposition rate. A nicotine protonation interval from 75% to 90% of the nicotine mass initially on the particle fits the experimental data well in the posterior tube sections. For the anterior tube sections, however, a steady increase of nicotine protonation by roughly 15% is required. Loss of water in denuder tubes has not been documented in the experimental studies found in the literature. Increased deposition rates by a factor up to 7 have been simulated in case of the denuder tube being a perfect sink for water. A simplified sub-model describing diffusion limited phase transition showed a considerable effect on total nicotine deposition in the order of 10% and more for experimentally determined viscosity values. Temperature differences between the tube wall and the aerosol have a considerable, however timely very limited, effect on deposition rate. Several poorly quantified processes and parameters have been discussed and simulated with respect to their potential to affect nicotine deposition rate in a denuder tube. While some of them are difficult to measure (e.g. nicotine protonation, diffusion limited transport within particles), others (e.g. water deposition within the denuder tube) can easily be determined. Thus, the ADiC model can be used, apart from evaluating experimental data, as a tool to plan and design experimental setups.

Modelling particle deposition:
i) Comparison of models ….
i) IDEAL & ADiC
i) Breathing (oral vs. nasal)

Modelling particle deposition:

i) Comparison of models …

i) IDEAL & ADiC

i) Breathing (oral vs. nasal) & humidification

Inhalation:
• dry NaCl aerosol

Exhalation:
• humidified NaCl aerosol

Anselm et al., 1989
Modelling particle deposition:
i) Comparison of models ....
i) IDEAL & ADiC
i) Breathing (oral vs. nasal) & humidification

Hygroscopic Growth:
• prevailing rH ~99.5%
• hydrophilic particle growth

Vitamin-C enriched sodium-chloride (15% NaCl solution) from the Dead Sea and organically grown and extracted olive-oil samples with traces of supplemented Vitamin-D (totaling 5mL each) were separately nebulized by ultrasound atomizers in a therapeutic aerosol chamber constructed by Selsonics GmbH. Particle growth dynamics from aerosol processing reactions were measured with a Scanning Mobility Particle Sizer (SMPS) immediately after a 3 minutes long sample injection sequence. Scanning times with the SMPS covered a potential exposure window of at least 9 minutes in the size range of 0.01 to 1.1 µm. Based on the data obtained from the SMPS measurements, the stochastic lung particle deposition model IDEAL-2 (Koblinger & Hofmann, 1990; Hofmann & Koblinger, 1990) was applied and the associated particle deposition analyzed.

The air inside the human lung has a high humidity (typically 99.5% relative humidity). Nguyen & Nieh have suggested that under these conditions particle charges are effectively eliminated. Furthermore their experimental studies showed that the charges are practically neutralised at a level of 78% relative humidity. However this process has a decay time to complete the charge neutralisation. In drug delivery application, the particles reach the alveolar region very quickly due to the small residence time in tracheobronchial region. The charge elimination process should be highly effective when particles are suspend in the alveolar region .... The numerical model assumed no charge elimination as a result of the high humidity in the lung, because of the short residence time in tracheobronchial region (< 50 ms for sedentary breathing).[3]

Image: Selsonics’s nebulization chamber. The nebulizer on the top left (1) is used to emit the NaCl aerosol, whereas the one on the top right (2) is used for olive-oil vaporization. The drawers for the vials (3) house the monosable NaCl- and oil vials respectively (image: Selsonics, 2007).

Insert: Hygroscopic growth. Particles absorb moisture as they traverse the humid environment of the airways resulting in increased particle size.

Modelling particle deposition:
i) Comparison of models …. 
i) IDEAL & ADiC 
i) Breathing (oral vs. nasal) 
i) Tracheo-Bronchial Section 
  grouped into sections
  • Extra-thoracic Region (ET) mouse, nose
  • Bronchial (BB) / bronchiole Region (bb)
  • Alveolar Region ( AL)

Calculation of 
• deposition probability
• particle progresses till exhaled, fully deposited or breathing time has elapsed

• Inhalation of particle (ET: mouth/nose)
• Statistical weight  \( w=1 \)
• Deposition probability \( p \) in ET
• Statistical weight reduced (\( w=w-wp \))
• Deposition probability in laryngeal yet
• Stat. weight \( w \) reduced
• Deposition probability in bifurcation 1
• Stat. weight reduced
• Deposition probability in bifurcation 2, etc.
• Continued till particle is
• Exhaled
  • Fully deposite
  • Time of breathing is over
• Path selection and calculation of deposition is repeated many times (\( N=10000 \))

Source: Winkler-Heil R (person. communication)
**Modelling particle deposition:**

- i) Comparison of models …
- i) IDEAL & ADiC
- i) Breathing (oral vs. nasal)
- i) Tracheo-Bronchial Section
- i) Respiratory Tract

**ET-region:**
- **TB-region:**
- **Alveolar region:**

Hofmann, 2009

**Extra-thoracical:** Mouth/nose: $f(\text{dae}, \text{flow}, \text{diffusion \ coefficient})$; e.g. Cheng 2003, Stahlhofen 1989, Swift 1982, etc.

**Tracheo-bronchial tree:** Brownian diffusion: $f(t, dp, R)$
- Sedimentation: $f(dp, \rho, t, R)$
- Impaction: $f(v, \text{branching angle, } dp, \rho, R)$

Modelling particle deposition:

i) Comparison of models ….
ii) IDEAL & ADiC
iii) Breathing (oral vs. nasal)
iv) Tracheo-Bronchial Section
v) Respiratory Tract
   Rule of thumb:
   • Nano P’s found in alveolar regime
   • Midsize P’s found in TB regime
   • Coarse P’s found in ET

Modelling particle deposition:
- Comparison of models
- IDEAL & ADiC
- Breathing (oral vs. nasal)
- Tracheo-Bronchial Section
- Respiratory Tract

Parameters to take into account:
- Properties of particles (size, density, shape)
- Inhalation pattern (tidal volume/inhalation time) for different activities
- Subject (male, female, FRC-scaling) scaling is possible as not only the bifurcation pattern of the lung is structured according to the fractal principles, but moreover the entire organism relates to these fractal properties;
- Mono- & polydispers particle distributions
- Deposition equations (ET, for sedimentation, brownian, impaction)
- Hygroscopicity of particle (Y/N)

Modelling particle deposition:
  i) Comparison of models ....
  i) IDEAL & ADiC
  i) Breathing (oral vs. nasal)
  i) Tracheo-Bronchial Section
  i) Respiratory Tract
  i) Parameters to take i/o account:
    i) Output as Deposition fractions

- \( f(\text{bifurcation}) \) dependent on the overall lung generation
- \( f(\text{region}) \), according to the main regions (extra-thoracic, bronchial, bronchiole, alveolar and intermixed regions)
- \( f(\text{diameter class}) \), of the corresponding lung morphometry (tube & ducts)
- \( f(\text{lobe}) \), according to the five lobes of the lung

Modelling particle deposition:
i) Comparison of models …
ii) IDEAL & ADiC
ii) Breathing (oral vs. nasal)
ii) Tracheo-Bronchial Section
ii) Respiratory Tract
ii) Parameters to take i/o account:
ii) Output as Deposition fractions
ii) Radioactive particles


• based on its **radioactive decay** properties
• based on the **clearance** mechanism
  - fast mucociliary clearance
  - slow bronchial clearance
  - blood-absorption: Half time $T_{1/2}$
    - 2 h (Vezzu)
    - 10 h (Hofmann,1982)
    - 1 h (unattached) and 10 h (attached)
    - 10 min (unattached) and
    - 10 h (attached) (assumption)
    - 15 min (10%) and
    - 90% with $T_{1/2}=10$ h (Marsh&Bailey, 2013)
Approach (10/10)

Modelling particle deposition:
  i) Comparison of models ….
  i) IDEAL & ADiC
  i) Breathing (oral vs. nasal)
  i) Tracheo-Bronchial Section
  i) Respiratory Tract
  i) Parameters to take i/o account:
  i) Output as Deposition fractions
  i) Radioactive particles
  i) Dosimetry (see Hofmann lecture)

- Depth dose conversion factors
- Depth of basal and secretory cells
- Surface activity
- Time of exposure

Winkler-Heil, 2012

Parameters for Dose calculation: Clearance rates (10 min – 10 h)
  Depth of target cells and Volumetric fractions of target cells

Output of dose calculation: effective dose

WLM (working level month) is a historical unit of potential alpha energy exposure: 1 WLM = 3.534 mJ·h/m³.

the code
i) Practical demo
   • main program,
   • subroutines / functions
   • common blocks (arrays)
   • data specification / definition

Winkler-Heil, 2012

The laboratory mouse is often used as a human surrogate in aerosol inhalation studies. Morphometric data on the tracheobronchial geometry of three in situ lung casts of the Balb/c mouse lung produced by the Air Pollution Health Effects Laboratory were analyzed in terms of probability density functions and correlations among the different airway parameters. The results of this statistical analysis reveal significant differences in diameters and branching angles between major and minor progeny branching off from the same parent airway at a given airway bifurcation. Number of bronchial airways generations along a given path, expressed by the termination probability, branching angles, and daughter-to-parent diameter ratios indicate that the location of an airway with defined linear airway dimensions within the lung is more appropriately identified by its diameter (or its parent diameter) than by an assigned generation number. We, therefore, recommend classifying the mouse lung airways by their diameters and not by generation numbers, consistent with our previous analysis of the rather monopodial structure of the rat lung (Koblinger et al., J Aerosol Med 1995;8:7–19; Koblinger and Hofmann, J Aerosol Med 1995;8:21–32). Because of lack of corresponding information on respiratory airways, a partly stochastic symmetric acinar airway model was attached to the tracheobronchial model, in which the number of acinar airways along a given path was randomly selected from a measured acinar volume distribution. The computed distributions of the geometric airway parameters and their correlations will be used for random pathway selection of inhaled particles in subsequent Monte Carlo deposition calculations.[1]

Image: First steps to implement the obtained morphometric model into the IEAL code.

The code

i) Practical demo

i) PRGM-structures

main program:

Function Name/ Subroutine Name (variable)

Commands

- If (number1.eq.number2) ....
  elseif (number1.eq.number3) ....
  endif [eq..ne..gt.lt.]
- goto format-number (e.g. goto 200....200 continue]
- Do k=1,10 ....enddo (Do index-name=start index,end index ....enddo)
- do 200 k=1,10....200 continue (do format-number index-name=start index,end index...format-number continue)

Winkler-Heil, 2012

Image: First steps to implement the obtained morphometric model into the IEAL code.

the code

i) Practical demo

i) PRGM-structures

main program:
Function Name/ Subroutine Name (variable)
Commands
In- and Outputs (screen & files)
  • read(“,“) [* = screen; number = file number]
  • write(“,“) [* = screen; number = file number]

Winkler-Heil, 2012

Image: First steps to implement the obtained morphometric model into the IEAL code.

Image: Basic process of Rn decay product behavior in air defining “unattached” and “aerosol-attached” activities.[2]


the code
i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
tidal volume inh, FRC
scaling factor for length and diameters: \((FRC/5563.88)\exp(1/3)\)

breathing cycle (sleep, sit, light & heavy exercise)

inhalation, -, tidal volume exh

1: nose, 2: mouth, 3: no ET-depos
0/1 mono/polydisperse, density, dp, dae

hygroscopic growth 0: N 1: Y

no of simulation per run

2, etc. for further runs

Image:
aerosol size distribution

unattached Rn fraction (i.e. 0.8 nm)

attached Rn fraction (i.e. 0.5 mm)
(aerosol + Radon progenies)
How to convert from Gray [Gy] to Sievert [S]?

Q …. quality factor (20 for α-particles)
wT …. tissue weighting factor

resporatory tract - table below

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Assigned fractions (A) of wT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-thoracic region</td>
<td></td>
</tr>
<tr>
<td>ET, (anterior nose)</td>
<td>0.001</td>
</tr>
<tr>
<td>ET, (posterior nasal passages, larynx, pharynx, and mouth)</td>
<td>1</td>
</tr>
<tr>
<td>LN1 (lymphatics)</td>
<td>0.001</td>
</tr>
<tr>
<td>Thoracic region</td>
<td></td>
</tr>
<tr>
<td>BB (bronchus)</td>
<td>0.333</td>
</tr>
<tr>
<td>bb (bronchial)</td>
<td>0.333</td>
</tr>
<tr>
<td>AL (alveolar-interstitial)</td>
<td>0.333</td>
</tr>
<tr>
<td>LNTH (lymphatics)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The apportionment of detriment, the assigned fractions of the ICRP tissue weighting factors (wT) that are to be applied to extra-thoracic and thoracic respiratory tract tissues, is given in the table. Because of rounding, the total for the extra-thoracic region is not exactly 1. which is not significant for this purpose. The doses so weighted by these factors are summed to obtain a detriment-weighted equivalent dose for the extra-thoracic region and another for the thoracic region. as follows:

\[ H_{ET} = H_{ET1} A_{ET1} + H_{ET2} A_{ET2} + H_{LNET} A_{LNET} \]
\[ H_{TH} = H_{BB} A_{BB} + H_{bb} A_{bb} + H_{AL} A_{AL} + H_{LNTH} A_{LNTH} \]

where \( H_{ET} \) and \( H_{TH} \) are detriment-weighted equivalent doses for the extra-thoracic and thoracic regions. respectively; \( H_{ET1}, H_{ET2}, H_{LNET}, \) and \( H_{BB}, H_{bb}, H_{AL}, \) and \( H_{LNTH} \) are equivalent doses for tissues in the extra-thoracic region and in the thoracic region, respectively; and \( A_{ET1}, A_{ET2}, A_{LNET}, \) and \( A_{BB}, A_{bb}, A_{AL}, \) and \( A_{LNTH} \) are factors for apportionment of radiation detriment from the table for the extra-thoracic region and for the thoracic region, respectively.

Gy-Gray: The name for the SI-unit of the absorbed dose. I Gy = 1 J/kg.
Sv-Sievert: The name for the SI-unit of the tissue specific equivalent dose. I Sv = 1 J/kg.

the code

i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
i) Output File

5656 18-10-04 Madl
the code
i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
i) Output File

Simulation results of
- 73 kg male,
- Sitting,
- nasal breathing
- @ 12 Bpm

IDEAL output file of all parameters bronchial, duct (tubes + acinar) tubes (bronchioles), alveolar, acinar (alveolar + tubes w/ alvoli) and sum

i) Aerosol fraction only
i) unattached Rn fraction only
i) attached (aerosol+Rn) fraction

Image:
the code
i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
i) Output File

Simulation results of
• 73 kg male,
• Sitting,
• nasal breathing
• @ 12 Bpm

IDEAL (12c/12)

Parameters (bronchial & sum only)
i) aerosol fraction only
i) unattached Rn fraction
i) attached (aerosol+Rn) fraction

IDEAL output file of all parameters bronchial, duct (tubes + acinar) tubes (bronchioles), alveolar, acinar (alveolar + tubes w/ alvoli) and sum

i) Aerosol fraction only
i) unattached Rn fraction only
i) attached (aerosol+Rn) fraction

Image:
the code
i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
i) Output File

Simulation results of
- 73 kg male,
- Heavy exercise,
- mouth breathing
- @ 26 Bpm

Change parameters (input file) from sitting to heavy
Work-load, mouth breather and higher ventilation:

- Breathing Rate
  was $BR_{sitting} = \frac{60 \text{ sec}}{5 \text{ sec \ breath}} = 12 \text{ breaths/min}$

  to  $BR_{heavy \ work} = \frac{60 \text{ sec}}{2.3 \text{ sec/ breath}} = 26 \text{ breaths/min}$

  • implies that $t_{inha} \text{ needs to be halved (breath ex)}$
  • mouth breathing (extra-thoracic 1: nose, 2: mouth)
  • modify these parameters in the \text{IDEAL4.dat} file

IDEAL output file of all parameters bronchial, duct (tubes + acinar) tubes (bronchioles), alveolar,
acinar (alveolar + tubes w/ alvoli) and sum

i) Aerosol fraction only
i) unattached Rn fraction only
i) attached (aerosol+Rn) fraction

Image:
the code
i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
i) Output File

Simulation results of
• 73 kg male,
• Heavy exercise,
• mouth breathing
• @ 26 Bpm

IDEAL output file of all parameters bronchial, duct (tubes + acinar) tubes (bronchioles), alveolar, acinar (alveolar + tubes w/ alvoli) and sum

i) Aerosol fraction only
i) unattached Rn fraction only
i) attached (aerosol+Rn) fraction

Image:
Aerosol Climate Health Tools Model

IDEAL (12f/12)

the code
i) Practical demo
i) PRGM-structures
i) Aerosol Parameters
i) Input File
i) Output File

Simulation results of
• 73 kg male,
• Heavy exercise,
• mouth breathing
• @ 26 Bpm

IDEAL output file of all parameters bronchial, duct (tubes + acinar) tubes (bronchioles), alveolar, acinar (alveolar + tubes w/ alvoli) and sum

i) Aerosol fraction only
i) unattached Rn fraction
i) attached (aerosol+Rn) fraction

Image:
Background: Occupational (nano)safety assessment requires the link of real-life data from aerosol generation with an estimation of particle deposition in human lung (exposure) and the determination of cellular/biological effects (hazard). For acute effects, the safety margin of materials with potential to be inhaled lies between effective concentrations causing biological responses in in vitro assays and the amount of material deposited in the human lung within a given time.

Methods: A number of biological effects were investigated in vitro in human lung alveolar A549 cells using a set of particulate materials collected in a paint factory. Particle deposition in the human lung was assessed based on experimental data on the generated aerosol at the production site.

Conclusions: This study links data from in vitro cellular responses and particle aerosol generation with modelling of particle deposition in the lung relevant for occupational nanosafety assessment. It shows, furthermore, the applicability of a panel of fluorescent stable reporter cell lines for a mechanistic screening procedure on real-life materials collected from a paint factory.

Image: Layout of mixing room in paint production factory (map). NF respirable mass concentration time series for sampling during a routine working day. Gravimetrical personal and NF samplers show the mean mass concentration level defined for specific sampling time intervals (unloading of bags w/ corresponding exposure). The particle size distribution of selected substance can be seen b/w 6 nm and 30 μm.

Cabin Air (1/2)

Car Ventilation:
SMPS-measurements & Modeling Lung Deposition (IDEAL code)

While it is clear that the reduction in particle concentration in the VA and RCA setting is a result of fewer aerosols entering the passenger cabin of the car, the RCA/AC setting does influence the particle concentration in some other way. It is likely that condensation and coagulation processes take place, as changes in temperature and humidity result from the air-conditioning system (Ashgarian, 2004). The apparent drop in the particle burden starting at around 300 nm is caused by the fact, that fresh vehicle exhaust contain relatively few particles in this size range (Imhof et al., 2005).

Applying the data to the lung deposition model reveals a deposition peak past the 15th generation (alveolar region of the lung) for all ventilation settings. This alveolar deposition is common for predominantly hydrophobic particles such as urban traffic exhausts. It has been proposed that alveolar deposition is associated with increased cardio-circulatory problems, as the immune system is the primary organ to remove entrapped particles (Donaldson et al., 1988).

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This campaign investigated the size distribution of aerosols in the range below 1 μm, comparing its influence on lung deposition. Sampling sites were located in the downtown area of Salzburg, Austria, measuring New Years fireworks particle load and burden of traffic exhaust during a typical work day under winter weather conditions.

The sampled nano-particle inventory shows a difference in its distribution. We found that the main burden in ultrafine particles originated from traffic exhaust. Although both fireworks and traffic show a similar total particle concentration of 78,790 [N/cm³] (fireworks) and 75,518 [N/cm³] (traffic) respectively, traffic creates significantly more particles below 100 nm with a broadened distribution within that range. Fireworks particles fingerprint past the 100 nm range. This difference in distribution is of great influence for the deposition in the human lungs.

Image: SMPS-scans of the aerosol size distribution of the firework-related combustion aerosol.

Although elevated short-term and localized aerosol concentrations readily deposit within the human lung, firework-related increase in aerosols or brief exposure to accumulated traffic-related aerosols are much better tolerated than elevated background aerosol-concentrations as can be found during periods of inverse temperature conditions. The lasting effect of prolonged exposure due to inversion events pose a serious challenge to susceptible individuals with a history of respiratory difficulties.

Image: Lung-deposition modeling for the inhalable fraction of the firework-related combustion aerosol.

Fireworks (3/3)

Firework: ChangSha (HuNan Province, CHN)

- 20 min choreography w/ background music;
- due to stagnant atmospheric conditions, combustion aerosols prevail over the site for more than an hour (probably even longer);

Latern festival (元宵节, Yuan Xiao Jie) in ChangSha marking the official end of the spring festival (11th February 2017, Hunan, CHN).
The explosion of fireworks causes intense air pollution due to the release of particulate matter (PM) consisting of toxic substances. Toxins include trace metals such as chromium, titanium, iron, copper, aluminium and nickel, as well as lead, manganese, manganese dioxide, barium, strontium, magnesium, calcium, zinc, sodium, vanadium, lithium, bismuth, arsenic and cobalt. In addition, sulphur dioxide and nitrogen dioxide, dioxins, fluorine, sulphate, chlorobenzenes and chlorophenols have been detected in air polluted by fireworks alongside extractable organic compounds such as alkanes, hopanes and polycyclic aromatic hydrocarbons. The size of the PM is generally in the micrometer range, but novel fireworks also use nano-powders, resulting in PM in the nanometer range. This can increase the toxicity of PM further due to the ability of nanoparticles to reach the deepest alveolar area of the lungs, penetrate cellular membranes and bypass detoxification mechanisms of the human body.

Image: Figure 1: (a)-(c): Maps of the air pollution by particulate matter (PM$_{10}$) in Germany from 31st Dec. 2016 to 2nd Jan. 2017. The green circle and the black arrow indicate the location of Stuttgart. (e): Development of the PM$_{10}$ concentration around New Year in Stuttgart (at two locations: Neckartor and Bad Cannstatt). The blue horizontal line indicates the current EU safety limit …. (h) Daily PM10 average values for Stuttgart (measurement location: Bad Cannstatt). (i) Daily PM10 average values for Zurich (location: Kaserne). (f): Lead 214 concentration in the air of Stuttgart around New Year (measurement location: Stuttgart TV tower). The symptom strengths of dyspnea, chest pain and cough are shown in (g), (j) and (k), respectively.

Aerosol Formation: Depending on the flow conditions, coarse fly ash particles are partly precipitated in the furnace and the boiler. The particles remaining in the flue gas leave the boiler as coarse fly ash emissions and range from a few μm up to 200 μm in diameter. Yet, from an inhalation point of view, the coarse fraction is insignificant in numerical numbers when compared to the finest fraction in the nanometer size range. This second type of aerosol emissions formed during biomass combustion can be divided into inorganic and organic aerosols. The figure shows a simplified scheme of the most relevant processes involved. At the boiler outlet, the aerosol fraction usually shows a quasi mono-disperse, log-normal particle size distribution. Due to the huge temperature gradient between the site of combustion and at the tailpipe end of the stack, nano-aerosols grow by coagulation processes.

Image: SMPS-scans of the aerosol size distribution of the wood-logs combustion aerosol.

Although combustion of renewable energy sources such as wood has the potential to drastically reduce dependence and consumption of unsustainable energy sources, the aerosol load generated in such furnaces is still considerably high. Since it is known that alveolar deposition is associated with increased cardio-circulatory problems, treating the exhaust aerosols with an additional water nebulizer could significantly reduce the nano-aerosol fraction. In addition, such an auxiliary treatment unit could further increase the energy efficiency of the entire unit by extracting remnant thermal energy from the exhaust gas stream. Electrostatic particle-precipitation should be another option in order to achieve even better cleansing result.

Image: Lung-deposition modeling for the inhalable fraction of the wood-logs combustion aerosol (when directly exposed w/o dilution).

Inhalation Therapy:

Determining the biophysical effects of a Gradierwerk-Aerosol in Bad Reichenhall – Germany with an SMPS & meteo-data; Lung deposition modeled with IDEAL code;

This study has shown that there is a filtering effect in the ultrafine particle size regime. This unexpected finding of our investigation can be seen on days when the “Gradierwerk” (GW) was in operation. This may be linked to the “waterfall effect”, i.e. the formation of nanometer-sized charged aerosols and their growth in the lower atmosphere are important processes involved in climate changes and health effects.

The ultrafine range from 5 to 500 nm is primarily affected by diffusion and particle coagulation. Thus deposition in the deeper lungs is associated with particles smaller than 500 nm. Airway generations beyond 15 belong to the pulmonary or alveolar region. We can conclude that the alveolar deposition, especially from hydrophobic particles, such as urban traffic exhaust, tends to increasingly deposit in the higher generation airways (alveolar region), and to a lesser extent in the bronchial region, where ciliary motion can translocate deposited particles towards the trachea (mucociliary clearance). It has been proposed that alveolar deposition is associated with increased cardio-circulatory problems, as the immune system is the primary organ to remove entrapped particles therein.

Image: SMPS-scans of the aerosol size distribution when the GW was in operation and when it was switched off for maintenance.

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Particle deposition calculations for the measured size distributions were carried out with and without HGF. This is of particular importance as exhaust aerosols, especially from urban traffic, are largely hydrophobic. However, this does not imply that oxidized exhaust particles do not show hygroscopic growth to a certain extent. Applying the scanned particle spectrum when the GW was turned off revealed a significantly higher pulmonary deposition originating from urban traffic in all airway generations when compared with those sets of data where HGF was larger than 1. Re-running the model with the spectral data when the GW was in operation, the total pulmonary deposition decreased by almost a third. The results of the lung model show clearly the benefit of inhaling the salty air by reducing the particle deposition as well as increased mucociliary clearance induced by the inhalation of the salt-aerosols. Besides the therapeutic effects of salty aerosols, the air next to the GW contains a smaller particle burden in the ultrafine spectrum. Due to its specific construction, the GW appears to act as an artificial waterfall.

Image: Lung-deposition modeling for the inhalable fraction of NaCl aerosols modeled with various hygroscopic growth factors.

Inhalation Therapy:

Determining the biophysical effects of a pristine salt aerosol from the Dead-Sea & Olive Oil aerosol enriched with Vitamin C

SMPS-measurements & Modeling Lung Deposition (IDEAL code) Madl et al., 2009

Using nano-sized particles greatly enhances the penetration efficiency to evoke various responses of the human body. As observable above, the size range of the inhaled particles easily reaches the alveolar region well beyond the 15th lung generation. Alveolar congestion by the inhaled particle load can largely be excluded, as the detected nano-particles are some $1 \times 10^3$ to $10^3$ times smaller than the tiniest alveolar duct-diameters. As shown in Fig. 2, the potentially huge bolus concentration of the olive oil spectrum, amounting to approx. $103 \times 10^3$ particles·cm$^{-3}$ is spread over 27 lung generations further dividing the overall concentration by an approximated factor of $2^{27}$. Considering particle kinetics after aerosol injection within the chamber along with the volume of air to be inhaled, one can expect a slightly elevated inhaled particle load as the SMPS sampled the chamber by a continuous flow of 0.3 L/min only. That is, a relaxed person inside the chamber would have a tidal respiratory volume of about 0.5 L along with roughly 12 in-/exhalations per minute, which yields a total of 6 L of inhaled respiratory air. In relation to the 0.3 L/min of the sampling device, this corresponds to a 20-fold increase of the inhaled particle load. Since total scanning windows of the SMPS lasted 9 minutes for each nebulized sample and the fact that a person would just be exposed to 5 minutes per sample each – with flushing cycles in-between – the actual proportionality factor would just be $5/9$th of 20 – or roughly 11-times the detected SMPS-concentrations.

Image: SMPS-scans of the aerosol size distribution of both NaCl and Oil samples.

Inhalation Therapy:

Determining the biophysical effects of a pristine salt aerosol from the Dead-Sea & Olive Oil aerosol enriched with Vitamin C

SMPS-measurements & Modeling Lung Deposition (IDEAL code) Madl et al., 2009

The fig’s clearly highlight the partial deposition efficiency modeled with the measured data. In the case of olive oil inhalation about 26% and in the case of sodium chloride between about 16% are deposited within the entire respiratory tract – which includes the extrathoracic deposition.

Nebulization of hydrophilic and hydrophobic substances is not only limited to inhalation per se, whole body dermal exposure is another issue to consider. Dermal and inhalatory absorption of nano-sized aerosols can be considered as being ideal size classes for rapid phagocytic and selective uptake by the exposed cells.

It has been demonstrated that sniffing nano-sized aerosols not only easily pass the blood-brain barrier via humoral transport, but they are also readily absorbed via skin and mucous membranes. Both percutane absorption and inhalation of nano-sized aerosols get rid of the so-called first-pass effect (FPE) – that is the biological transformation and, in some cases, elimination of a substance in the liver after absorption from the intestine and before it reaches systemic circulation. Elimination of the FPE would enable exposure to considerably lower dosage of the substances involved and as a result could significantly reduce potential side effects.

Image: Lung-deposition modeling for both inhalable fraction of NaCl and oil aerosols.

The 500-year-old phrase “the dose makes the poison” can also be paraphrased as the dose makes the mechanism. The mechanistic pathways that operate at low realistic doses are likely to be different from those operating at very high doses when the cell’s or organism’s defenses are overwhelmed. [3]

Image: Some basic shapes of exposure-response or dose-response relationships.

Abbreviations: H, hormetic (biphasic); L, linear (no threshold); S, supralinear; T, threshold, H1, hyper-hormetic (hyper-biphasic).

Prerequisites for establishing these relationships for nanoparticles from in-vitro or in-vivo studies include a sufficient number of data points, that is, over a wide range of exposure concentrations or doses; knowledge about exposure levels; and information about correlation of exposure with doses at the organismal or cellular level (an exposure is not a dose). Dose-response curves of different shapes can be extrapolated when only response data at high dose levels (indicated by dashed oval) are available. Lack of data in the low - oftentimes the most relevant - dose range can result in severe misinterpretation if a threshold or even a hormetic response is present. Consideration also needs to be given to the likelihood that the shape or slope of exposure-dose-response relationships change for susceptible parts of the population.

ad (?) - Low-dose Hypothesis: exposure to extremely low doses of certain substances could cause adverse health effects in humans, whereas no effects are seen at higher doses of the same substance. Bisphenol-A is often named as an example of this hypothesis. (Low-Dose hypothesis: tiny amounts of a substance do have a more toxic effect than a higher dose of the same substance) – An indication of the Weber-Fechner-Law. [2,1]

Threshold Levels (2/4)

Threshold & Risks:

- Threshold limits
- No-effect level

However:
- The smaller the more toxic (Donaldson et al. 2000)

| WHO | 25/40 | 25/50 |
| US Environmental Protection Agency | 15/25 | 35/50 |

Table: Existing recommended guidelines for PM$_{10}$ and PM$_{2.5}$ exposure limits (Langris & Mills, 2013).

In some fine powders, including ultrafine titanium dioxide, carbon blacks, and fumed silicas, specific surface areas in excess of 2·E$^5$m$^2$/kg [200m$^2$/g] are achieved among particles with aerodynamic diameters less than 4 mm. In comparison, an aerosol of spherical particles 4mm in diameter and with unit density would have a specific surface area of 1.5 x 103m$^2$/kg [1.5m$^2$/g]. There is evidence that for some low-solubility materials toxic response may be associated with surface area or even particle number (Oberdorster et al., 1994; Lison et al., 1997; Donaldson et al., 1998).

Donaldson et al. (2000) documented that nano-particles have profound effects upon the recipient tissues. They found that nano-particles are more inflammogenic than their coarser siblings made of the same material. The cut-off size for this increased toxicity was found among a gradient that showed the greatest effect at particles smaller 65 nm and gradually decreased and levelled off towards larger diameters around 200 nm. The properties that drive this toxicity are still largely unknown. Nonetheless, it was possible to relate oxidative stress responses of the target cells to particle number concentration and their associated surface area. In addition, while one kind of nano-particle exerted a moderate inflammogenic response, the effects increased or even became synergistic when otherwise harmless nano-aerosols were added to the mono-specific class of particles.

Legally binding threshold values and the corresponding alarm levels for authorities.

General risk assessment chart, assigned to an exposed public (dots represent the individual members)


Threshold Levels (3/4)

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Aerosol  Climate  Health  Tools  Model

Threshold Levels (4/4)

Threshold & Risks:

NZZ, 09. 2009

Untragbare Luftverschmutzung in São Paulo
Poliäker verleihen den Gesetzen keinen Nachdruck

R.H., São Paulo, im September

Dr. de Paula Santos engagiert sich weiterhin in der Klinikenarbeit und die Forschung auf die permanente Luftverschmutzung. In São Paulo trägt zu etwa 200 verschiedenen Krankheiten bei, darunter Infektionskrankheiten, Schädelhirn- und Lungenkrebs, Lungenkrebs, durchschlagende Infektionskrankheiten bei Kindern unter 5 Jahren und 10.000 Fälle werden auf der Website der Stadtbewegung in der Altersgruppe - nie in São Paulo tritt dazu auch der entscheidende Lauter bei.

Dort: 18-10-04  Madl  78

Conclusion (2v2)
Conclusion (2/2)

In a nutshell:

i) Human respiratory tract reveals a high particle filtering effect

i) Particle deposition due impaction, sedimentation, diffusion, e-static attraction

i) Particle clearance via MC-escalator (till gen. 14-17), macrophages later on

i) Particle deposition modelling to determine potential fate & associated RISKs

i) Upgrading code (IDEAL) to include chemical parameters

Thank You for your attention!

18-10-04 Madl