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REVIEW ARTICLE

Internal dose of particles in the elderly—modeling based on aerosol measurements

Marina Almeida-Silva[1,2] · Marika Pilou[3] · Christos Housiadas[3] · Susana M. Almeida[1]

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Abstract

The paper presents an integrated methodology that combines experimental and modeling techniques and links exposure to airborne particulate matter (PM) with internal dose in the respiratory system and burden in adjacent tissues over a period of time. The methodology is used to estimate doses in the respiratory systems of elders that reside in 10 elderly care centers (ECCs) in the metropolitan area of Lisbon. Measurements of PM were performed in the ECCs and combined with a time-budget survey for the occupants. This information served as input to the first model that estimated particle doses in the different regions of the respiratory tract of the elderly, and then a second model was used to calculate particle build-up in the alveolar region, the interstitium and the hilar lymph nodes of the elders over a 5-year exposure period. It was found that in 5 years of continuous exposure to the average particle concentration measured over all ECCs, 258 mg of all particles are deposited on the surface of the alveoli of which 79.6% are cleared, 18.8% are retained in the alveolar region, 1.5% translocate to the hilar lymph nodes, and 0.1% are transferred to the interstitium.

Keywords Elders · Particulate matter · Model · Deposition · Human respiratory tract · Clearance

Introduction

Associations between air pollution and cardiovascular and respiratory morbidity and mortality have been thoroughly reviewed by several authors (Almeida et al. 2014; Simoni et al. 2003). These associations, even though scarce (Andersen et al. 2008), are particularly relevant when referred to institutionalized elderly people, not only because they are considered a susceptible group but also because they spend the majority of their time indoors (Almeida-Silva et al. 2014a).

Particulate matter (PM) represents pollutants that have most consistently been associated with health effects (Pope et al. 2002). PM enters the human body mainly through the inhalation route. Health risk assessment for inhaled particles requires information on local deposition patterns within the human respiratory tract (HRT) and such information can be provided by computational modeling (Morawska et al. 2013). A significant amount of particles may translocate from the lungs into the bloodstream and be then transferred to the heart and other tissues, possibly giving rise to adverse human health effects (Simkhovich et al. 2008).

Exposure is defined as "an event that occurs when there is a contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time" (NAS 1991). The effective integrated exposure assessment should be estimated by the time spent by people in different environments and the concentration of the pollutants for the period of interest (WHO 2000; Sexton et al. 1995). The authors

Highlights
- Ten percent of the mass of the inhaled particles per breath ends up in the alveolar-interstitial.
- In the bedroom, 79% of the inhaled particle mass deposits.
- In the living room, 90% of the inhaled particle mass deposits.
- Ninety-seven percent of the daily dose in mass can be attributed to particles sized between 2.5–10 μm.

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✉ Marina Almeida-Silva
marina@ctn.tecnico.ulisboa.pt

[1] Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Estrada Nacional 10, Km 139.7, 2695-066 Bobadela LRS, Portugal

[2] H&TRC - Health & Technology Research Center, ESTeSL - Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Lisbon, Portugal

[3] Thermal Hydraulics & Multiphase Flow Laboratory, INRASTES, NCSR "DEMOKRITOS", 153 10 Agia Paraskevi, Greece

had already calculated the elderly exposure to particles and its components in a previous study (Almeida-Silva et al. 2014a).

There are two different ways to assess the dose, since in one case, it is possible to calculate the inhaled dose and in the other the deposited dose. According to the first approach, to calculate the inhaled dose is crucial to integrate the time spent in each microenvironment, the concentration of the pollutants for the period of interest, the inhalation rate, and the body weight. This approach was performed by the authors to calculate the inhaled dose of the PM components, such as carbonaceous fraction and trace elements (Almeida-Silva et al. 2015). In the second approach, the inhaled dose can be calculated according to a numerical model that needs to input the particles concentration, the time spent by people in each microenvironment, the physicochemical characteristics of the PM, and the physiological parameters of the people exposed. This model was already described and validated in several publications elsewhere (Mitsakou et al., 200%; Mitsakou et al. 2007a, b). The greatest differences between both approaches is the fact that in the first one, it is possible to calculate the estimated inhaled dose not only for PM but also for its components, which cannot be done (yet) in the numerical model. On the other hand, using the second approach, it is possible to study more deeply the inhaled dose of particles in HRT, since the model estimates the PM deposition in three different regions: extrathoracic, tracheobronchial, and alveolar-interstitial.

Modeling of particle dynamics and transport can be particularly beneficial in two specific respects: (a) it can provide useful physical insight and enable the interpretation of systems without the need of experiments; and (b) it can be used for parametric investigation and optimization of already developed systems.

The first mathematical model of particle deposition was developed in 1935 by Findeisen (1935). Even with several limitations, this model was pioneer in establishing the basic norms for the development of other later models (Findeisen 1935). Since then, several mathematical models have been developed and applied in different fields, such as, occupational, pharmaceutical, epidemiological and toxicological studies (Almeida-Silva et al. 2015; Mitsakou et al. 2007a, b; Pilou et al. 2013; Tena and Clarà 2012; Martonen 1993; Yeh and Schum 1980). The use of mathematical models is an advantage on regional dose estimation since, in practice, the regional dose in the respiratory system is very difficult to be addressed experimentally (Hussein et al. 2013).

The human respiratory tract is especially designed, both anatomically and functionally, so that air can reach the most distal areas of the lungs in the cleanest possible conditions. For that, the respiratory tract has natural barriers, such as nasal hair, nasal turbinate, vocal cords, the cilia of the bronchial epithelium, and the sneeze. Even so, over the years, the unintentional and intentional introduction of drugs and/or pollutants in the HRT weakens the protective barriers, allowing the pollutants to reach the alveoli.

The mathematical model that was used in this work provided an empirical estimation for the exposure and dose pattern in the respiratory system. However, the best approach is not always possible due to experimental limitations. Human exposure should be measured in real-time by accompanying portable instruments to the volunteers and recording the air pollutants concentrations near the breathing zone. Nevertheless, to keep and carry on instruments while the volunteers are moving around has become annoying, disturbing and stressful. So, an alternative method has been used to record the exposure levels in different microenvironments and to combine that with the other parameters—e.g., time-activity pattern, physiological parameters, and PM physicochemical parameters—schematic of the methodology.

In this work, a computational model uses PM exposure data obtained in elderly care centers (ECCs) and calculates particle transport and deposition in the HRT of the elders. Subsequently, a second mathematical model predicts particle clearance and translocation from the HRT over time. This way, it is possible to link the PM exposure to the average daily dose and the 5-year burden due to PM for the elders.

Materials and methods

Experimental data

The PM measurements were performed in 10 elderly care centers (ECCs) located in Lisbon, Portugal, in collaboration with 384 elders. The volunteers were on average 85 years old and were institutionalized in the ECCs. The number of occupants in the ECCs ranged from 7 to 95. An exhaustive questionnaire has been applied, in order to acquire information about the number of the elders in each ECC, the type of building, the location (urban, rural or suburban area), the ventilation systems, etc. Extensive analysis regarding the findings of this questionnaire can be found in Almeida-Silva et al. (2014a).

In addition, a time-budget survey (TBS) was built in collaboration with the volunteers, in the form of a close-ended questionnaire. The TBS included information about (a) different activities performed during the day, (b) mealtimes, (c) sleep times, and (d) microenvironments where they spend their time. The questionnaire differentiated between time allocation on weekdays and weekends, and was applied with the help of collaborators (e.g., socio-cultural technicians). The results of the TBS indicated that the following five microenvironments could be taken into account: (a) bedroom, (b) living room, (c) canteen, (d) outdoor, and (e) other indoor microenvironments.

The number size distributions were measured in bedrooms and living rooms during the occupied period that is all night and all day, respectively. The sampling campaign occurred between October and November of 2012, avoiding extreme temperature and humidity.

Measurements of particulate matter were performed using a portable direct-reading equipment (Handheld 3016-IAQ – Lighthouse) that gives information regarding the mass size distribution, namely, 0.3–0.5, 0.5–1, 1–2.5, 2.5–5, and 5–10 μm. The available equipment did not allow for the measurement of ultrafine particles, i.e., particles < 0.1 μm. The equipment was placed at breathing height (± 1.5 m) in the middle of the indoor microenvironments. In the indoor of ECCs, the measuring time ranged from 7 to 16 h. Data reduction and analysis of the recorded size distribution was performed by arithmetic means of the total sampling period, for each studied indoor microenvironment. The detailed information about the elders and ECCs characterization, air pollutants measurements, methods validation and results, has been published previously and can be found in literature (Almeida-Silva et al. 2014a, b, 2014c, 2015; Viegas et al. 2014).

Numerical models

Deposition of inhaled airborne particles in the respiratory tract is related to both the physical properties of the particles and the anatomical and physiological characteristics of respiration. The particles that deposit in the HRT over time may stay at the deposition site, be cleared by biological processes, or translocate to adjacent tissues. Herein, a modeling approach was adopted in order to combine these pieces of information (Fig. 1) (Pilou et al. 2015). The models used in this study have been developed, validated, and published earlier. Thus, only a brief description is included herein.

Transport and deposition in the HRT

Particle transport and deposition within the regions of the HRT are determined using a computational model based on an Eulerian approach describing the air flow and aerosol dynamics in the respiratory tract. The model predicts the temporal variation of the number concentration and the regional deposition of the inhaled particles during a breathing cycle by solving the aerosol general dynamic equation (GDE):

$$\overbrace{\frac{\partial}{\partial t}(A_t\, n_i)}^{\text{temporal variation}} = \overbrace{-\frac{\partial}{\partial x}(A_A\, u\, n_i)}^{\text{convection}} + \overbrace{\frac{\partial}{\partial x}\left(A_t\, D_i\, \frac{\partial n_i}{\partial x}\right)}^{\text{diffusion}} - \overbrace{U_{d_i}\,\Gamma\, n_i}^{\text{deposition}} + \overbrace{\left(\frac{\partial}{\partial t}(A_t\, n_i)\right)_{\text{growth}}}^{\text{condensation}} + \overbrace{\left(\frac{\partial}{\partial t}(A_t\, n_i)\right)_{\text{coagulation}}}^{\text{coagulation}} \quad (1)$$

where t the time, n_i the particle mass concentration in section $i$of the size distribution, u the fluid velocity, D_i the diffusion coefficient of particles with size i, A_t and A_A the time-dependent and constant cross-section of all air ducts, respectively, at distance x from the respiratory system entrance, Γ the circumference of air ducts, and U_{d_i} the particle deposition velocity. The GDE is considered in a one-dimensional form along the flow direction and describes the different processes (convection, axial diffusion, deposition, condensational growth, coagulation) acting simultaneously on the inhaled particulate matter. The description of the above deposition mechanisms is based on standard theory for the respective aerosol processes, avoiding the use of empirical correlations. The respiratory tract consists of the thoracic (lung) and the extrathoracic regions. The thoracic region of the respiratory tract is described with the help of the classical morphometric model "A" by Weibel (1963). The volume of the alveolated section of the lung is left to vary with time to accommodate effects due to breathing dynamics. The flow path in the lungs is described through the "trumpet" model (Fig. 2), where the cross-section of the airways increases rapidly with the distance from the trachea, because it is equal to the sum of the cross-sections of all airways of the same generation. A simplified morphological scheme that consists of sequential cylindrical

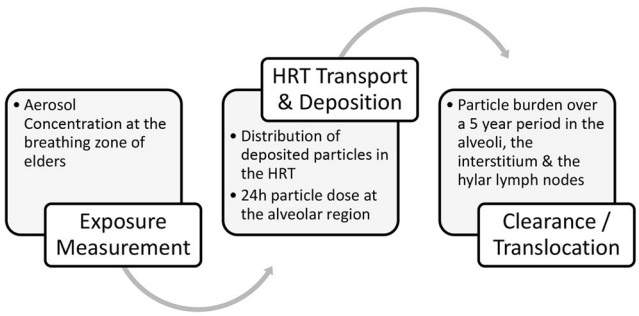

Fig. 1 Flow of information from exposure measurement to particle burden calculation—link between the measurements and the models

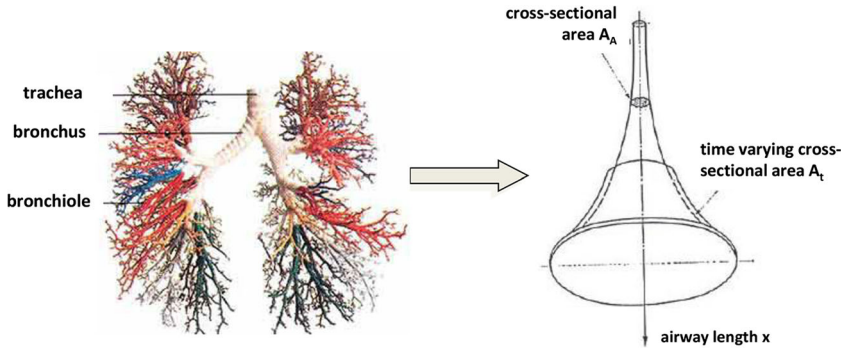

Fig. 2 Lung model and the "trumpet" model

airways describes the extrathoracic region through the mouth pathway. The air velocity along the airways of the respiratory tract is determined by solving the equation of continuity.

Solution of Eq. (1) allows for the determination of the mass concentration of each section n_i as a function of time along the whole respiratory tract. The mass of deposited particles of size i, DM_i, in an area of length L (e.g., a generation) over a breathing period T is given by:

$$DM_i = \int_0^T \int_0^L n_i N U_{d_i} \Gamma dx dt,$$

where N the total number of airways in the respective generation.

The model has been extensively validated against a large body of experimental and numerical respiratory data, for both inert and hygroscopic aerosols, and the predictions of the empirical model that is used by the International Commission on Radiological Protection (ICRP). A detailed description of the model, its validation, and application potential can be found in literature (Mitsakou et al. 2005, 2007a, b).

Particle retention and clearance from lungs

The mathematical model of particle clearance/retention describes the progress over time of the retention of particles and the alveolar macrophage (AM)-mediated clearance process in the pulmonary region, together with the particle redistribution and the overload phenomena (Fig. 3).

The model is described as a series of nine conceptual compartments and is defined by a set of differential equations. The location of inhaled particles, plus the main translocation routes between these compartments is described in Fig. 3, where M_i represents the quantity (in mass) of free particles on the alveolar surface.

Inhaled particles reach and deposit on to the alveolar region of the lung as free particles (compartment M_1). Some of these particles migrate out of the lung and are transferred into the interstitium (compartment M_5) while others are phagocytosed and removed by active AMs to the mucociliary escalator (compartment M_2). As AMs eventually decay and become inactive macrophages (compartment M_3), their particle load is released and particles become available for re-phagocytosis. As a result, these free particles may be phagocytosed by active AMs. However, released particles cause overload of AMs that makes the redistribution of free particles to effective AMs increasingly difficult. Indeed, an amount of free particles becomes trapped by overloaded AMs which form an alveolar sequestration of compartment, M_4.

In the same manner, free particles that are migrated to the interstitium, are correspondingly phagocytosed by mobile IMs (compartment M_6) that as they go through a life cycle, become inactive and particles become available for phagocytosis by mobile IMs (compartment M_7). If particulate loading is excessive, IMs become overloaded with released particles and form an interstitial granuloma (compartment M_8). Finally, some particles (free or inside IMs) are transported to the mediastinal lymph nodes (compartment M_9).

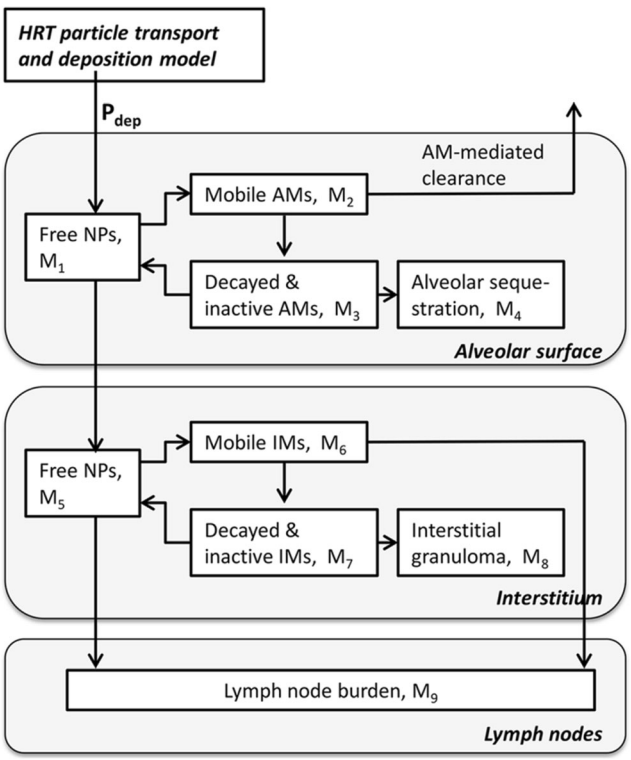

Fig. 3 Compartments of the particles clearance/retention model

In general, changes in the particle burden in compartment i, dM_i/dt, is described by equations in the form

$$\frac{dM_i}{dt} = E_i + \sum_{j=1}^{m} R_{in}^{j\to i} - \sum_{k=1}^{n} R_{out}^{i\to k}, \quad i = 1, \ldots, l \tag{2}$$

where E_i is the (mass) rate of particles entering compartment i from outside the system, $R_{in}^{j\to i}$ the rate of particles entering compartment i from compartment j, and $R_{out}^{i\to k}$ the rate of particles exiting from compartment i to compartment k. In Eq. (2), m is the number of compartments from which compartment i receives input, n is the number of compartments to which compartment i outputs, and l is the total number of compartments which make up the system. The rates of particle transfer from one compartment to another, i.e., $R_{in}^{j\to i}$ or $R_{out}^{i\to k}$, are assumed directly proportional to the mass of particles (or burden) of the compartment, e.g., $R_{in}^{j\to i} = r_{ji}M_i$, where r_{ji} is the transfer rate from compartment j to i per unit time. It should be noted that the clearance/retention model takes into account the effect of overload, i.e., the gradual impairment of the macrophage mediated clearance at high lung burdens. In this case, some of the transfer rates (r_{ji}) are no longer constant, but rather change as a function of the particle surface area.

In addition to the particle burden of the different compartments, the model estimates the recruitment of polymorphonuclear leukocyte (PMN) cells into the affected region, which is an important indicator of inflammation. The rate of PMN cells recruitment is described by

$$\frac{dPMN}{dt} = Rec\, r_{interst} M_1 - Rem\, PMN \tag{3}$$

where PMN is the number of recruited cells, Rec is the number of cells recruited per unit particle surface area burden, and Rem the PMN cells removal rate.

The particle retention and clearance mathematical model describes the distribution of the internalized dose in different target systems (interstitium and lymph nodes) beyond the portal of entry organ, which is in this case the lung, as well as the recruitment of PMN cells into the affected region. Additionally, the model describes the time course of the buildup of the dose after exposure. The model has been calibrated with data from various experimental studies. An extensive description of the model and its validation can be found in Tran et al. (1999), Tran and Kuempel (2007), and MacCalman et al. (2009).

Results and discussion

Time-occupancy data

Several studies have already evaluated the daily time pattern of people from different countries (Hussein et al. 2013; Almeida-Silva et al. 2014b, c; Viegas et al. 2014; Fisher and Robinson 2011; Eurostat 2003, 2006). However, these studies either excluded the old people or studied simultaneously all age groups, from young children to elderly.

Table 1 shows the time spent by the elders in each microenvironment for all ECCs. Due to the lack of differences between weekdays and weekends, the results are presented for typical 24 h. The microenvironment referred as "Others" is defined as other indoor microenvironments inside and/or outside the elderly care centers, such as family houses, restaurants, or café.

Old people in ECCs spent the majority of their time inside bedrooms (57%) and living rooms (30%). Due to this fact, these two microenvironments were chosen to perform a detailed IAQ characterization. In ECC 3, people spent more time in bedrooms due to the high number of bedridden (13%) in this institution. On the other hand, in ECC 1 and ECC 7, all the elders are daily lifted and placed in the living rooms, which can explain the less percentage of time spent inside the bedrooms. In all ECCs, the same pattern was observed: from 8:00 to 20:00 the majority of the elders were in living room, moving to the canteen at the meal times and to the bedrooms at 21:00.

A study developed in Italy showed that elderly spend 70 to 83% of their time inside the buildings (Simoni et al. 2003). The National Human Activity Pattern Survey (NHAPS) developed in the USA refers that the American elders spend 87% of their time indoors (Klepeis et al. 2001). These values are lower than the ones obtained in this work, which could be explained by the fact that the present study only considers elders living in ECCs.

Particles measured in ECC

Measured particle mass concentrations per PM size for each ECC and the average across all ECCs for bedroom and living room microenvironments are given inTable 2. In average, there were no statistical differences between each ECC (p value >

Table 1 Time-budget data for all 384 voluntaries in 24 h per studied site (values in percentage)

	Bedroom	Living room	Canteen	Outdoor	Others
ECC 1	52	22	19	3	4
ECC 2	62	22	13	2	1
ECC 3	76	15	5	0	3
ECC 4	64	20	9	1	7
ECC 5	57	22	14	7	0
ECC 6	50	42	0	8	0
ECC 7	46	48	0	4	3
ECC 8	55	30	7	8	0
ECC 9	54	46	0	0	0
ECC 10	56	32	11	1	0
Average	57	30	8	3	2

Table 2 Measured particle mass concentration per ECC. Results are presented in μg m^{-3} (*AVG* average and *STD* standard deviation)

Particle Mass Concentration (μg.m-3)												
	ECC1	ECC2	ECC3	ECC4	ECC5	ECC6	ECC7	ECC8	ECC9	ECC10	AVG	STD
$PM_{0.5}$	2.2	1.4	1.3	2.0	3.3	1.1	7.9	1.1	1.8	19.3	4.1	5.7
PM_1	3.1	2.5	2.2	3.1	4.7	1.7	14	2.7	2.7	28	6.5	8.4
$PM_{2.5}$	4.6	4.8	4.2	5.9	9.2	2.8	21	8.9	4.7	34	10	10
PM_5	8.1	11	11	16	15	3.9	29	12	7.0	40	15	11
PM_{10}	10	16	17	24	29	6.2	41	16	11	47	22	13
Living room												
	ECC1	ECC2	ECC3	ECC4	ECC5	ECC6	ECC7	ECC8	ECC9	ECC10	AVG	STD
$PM_{0.5}$	0.22	2.5	4.7	2.6	2.6	4.9	2.7	0.72	1.9	2.5	2.5	1.5
PM_1	1.0	4.2	6.9	4.3	4.6	7.5	5.1	2.3	2.7	4.5	4.3	2.0
$PM_{2.5}$	4.2	8.2	10	10	11	11	16	9.4	4.2	12	9.6	3.5
PM_5	14	23	21	28	19	15	25	14	6.2	19	18	6.5
PM_{10}	19	34	29	43	43	27	35	19	11	31	29	10

0.05) for all particle sizes. Results showed that in average, PM concentrations in living rooms were significantly higher than in bedrooms, except for ECC 7 ($p = 0.79$). Living rooms of ECC 4, ECC 5, ECC 7, and ECC 10 presented the highest PM_{10} average concentration (44, 43, 41, and 47 μg m^{-3}, respectively). For ECC 4 and ECC 5, PM_{10} maximum values were 860 and 347 μg m^{-3}, respectively. These concentrations exceeded the limit value of 50 μg m^{-3} defined by the Portuguese legislation (Portaria 353-A/2013). ECC 7 and ECC 10 did not exceed the limit value. The high PM_{10} concentration measured in ECC 7 can be explained by the high outdoor PM_{10} concentration (71 μg m^{-3}). The bedrooms of ECC 7 and ECC 10 presented a $PM_{2.5}$ average concentration of 21 and 34 μg m^{-3}, respectively.

The average particle concentrations measured in this work were similar to those found in a study developed with elders living in Amsterdam and Helsinki that presented $PM_{2.5}$ average concentrations of 16 and 11 μg.m^{-3}, respectively (Lanki et al. 2007). In UK houses PM_{10}, $PM_{2.5}$ and PM1 concentrations (13, 6 and 3 μg m^{-3}, respectively) were lower comparing with current work (Nasir and Colbeck 2013). In an Italy study, the average $PM_{2.5}$, PM_5, and PM_{10} concentrations presented lower results comparing with the current work. Nevertheless, the same study showed higher concentrations in lower particle sizes 17.5 and 9.2 μg.m^{-3} ($PM_{0.5}$ and PM_1, respectively). This fact could be due to the strong association between indoor $PM_{0.5}$ and the number of cigarettes smoked (Urso et al. 2015), since previously, studies had already demonstrated that environmental tobacco smoke is the most significant source of indoor-generated fine particles (Chen and Zhao 2011). $PM_{2.5}$ and PM_{10} average concentrations measured in several houses demonstrated a similarity of results: 7.9 and 16.5 μg.m^{-3} (Jones et al. 2000); 9.1 and 22.5 μg.m^{-3} (Lawson et al. 2011); 7.3 and 22.3 μg.m^{-3} (Molloy et al. 2012). However, it is possible to find studies with higher particle concentrations, such as the one developed by Chao and Wong (2002), where $PM_{2.5}$ and PM_{10} average concentrations of 45 and 63 μg m^{-3} were measured in Hong Kong' houses, respectively. Those values could be explained by the existence of different sources: smoking, cooking, and burning incense (Chao and Wong 2002; Urso et al. 2015).

Table 3 Reference respiratory values at different levels of activity (ICRP 1994). *FRC* functional residual capacity, V_T: tidal volume, f_R respiration frequency

Male			
Activity	FRC [10^{-3} m^3]	V_T [10^{-3} m^3]	f_R [min^{-1}]
Resting (sleeping)	3.3	0.625	12
Sitting awake		0.750	12
Female			
Activity	FRC [10^{-3} m^3]	V_T [10^{-3} m^3]	f_R [min^{-1}]
Resting (sleeping)	2.68	0.444	12
Sitting awake		0.464	14

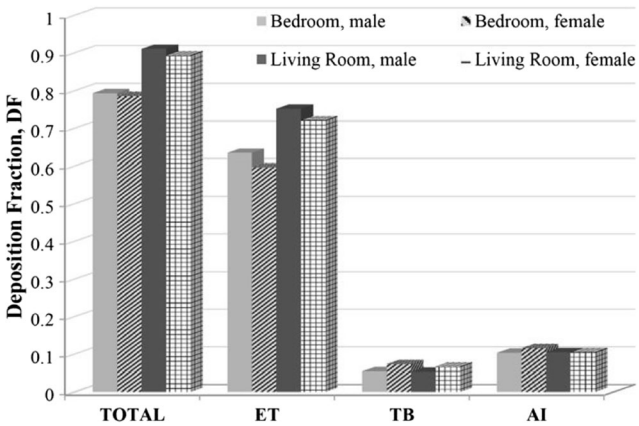

Fig. 4 Fraction of the inhaled particle mass deposited in the HRT (total) and its regions extrathoracic (ET), tracheobronchial (TB), and alveolar-interstitial (AI)

Table 4 Daily dose of particulate matter in the human respiratory tract (total) and how it is distributed in its regions (ET, TB, and AI). The daily dose is averaged over all ECCs and both genders

	Daily dose [μg/day]			
d_p [μm]	TOTAL	ET	TB	AI
0.3	3.3	0.3	0.4	2.6
0.5	6.1	1.0	0.7	4.4
1	24.1	8.3	2.5	13.3
2.5	261	144	26.5	91.0
5	175	137	15.6	22.7
10	742	701	34.1	7.5
Total	1212	992	79.9	141

Comparing the living room with the bedroom, it is possible to observe that the coarse fraction was dominant in the living room whereas fine fraction was dominant in the bedroom. This fact indicates the importance of particle re-suspension in the living room.

Particle deposition in the HRT

The combination of the lung transport and deposition model and the lung clearance/retention model, was used in the present study, in order to estimate the average daily dose of particles in the respiratory tract of the elders and the retention/clearance of these particles over the course of time. The developed integrated approach and the corresponding software in FORTRAN programming language, consists of two consecutive steps. Initially, the averaged exposure concentrations obtained by experimental monitoring of airborne exposure levels are introduced to the lung transport and deposition model and the average daily dose of particles in the respiratory system of the elders is calculated. The average daily dose in the alveolar region is the input to the second step, the mathematical clearance/retention model, where the effective internal dose in the lungs and adjacent tissues is estimated over time.

Average daily dose

The HRT particle transport and deposition model is used in order to calculate the daily burden of PM in the respiratory tract of the ECC occupants. It should be noted that in the present study, hygroscopic growth is not considered in the calculations due to a lack of information regarding the nature of the particulate matter. In addition, coagulation is neglected because it was thought irrelevant for the particle population under study; coagulation is one mechanism that affects mostly the ultrafine particles (UFPs), and in fact, its effect is stronger for the smaller UFPs.

The physiological parameters of the respiratory tract used in the model were obtained by ICRP (1994) and are shown in Table 3. For the bedroom, the resting (sleeping) parameters were used, whereas for the living room and other environments, the sitting awake activity level was assumed. In all cases, the values correspond to a healthy, adult, Caucasian male or female subject.

The fraction of the particles that deposit into the HRT to the particles that were inhaled, i.e., the deposition fraction DF, and how this was distributed in the different regions of the HRT are shown in Fig. 4 for both genders in the bedroom and the living room. The presented DFs were calculated using the average measured particle mass concentrations overall ECCs. In both microenvironments, the DF for males are slightly higher than the one for females, but their differences are not high; in the bedroom, around 79% of the inhaled particles deposit in the HRT of the elders, whereas the DF rises to around 90% in the living room. In both rooms and for both genders, 10% of the mass of the inhaled particles per breath

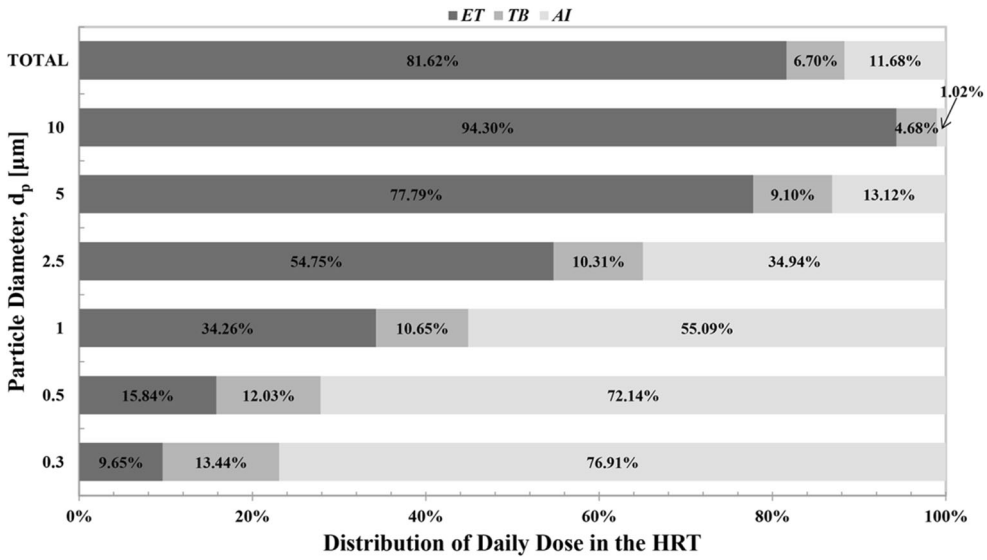

Fig. 5 Distribution of the daily dose of the differently sized particles and the whole particle population in the extrathoracic (ET), tracheobronchial (TB), and alveolar-interstitial (AI) regions of the HRT

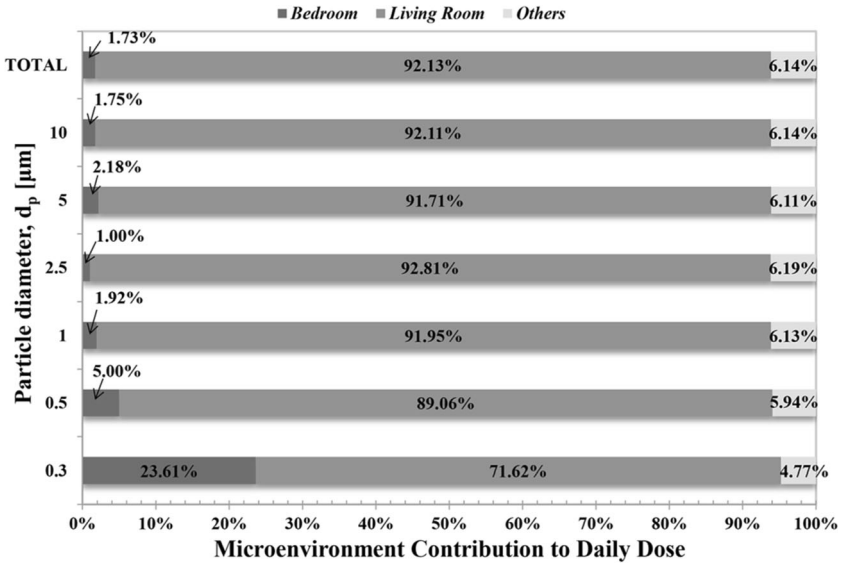

Fig. 6 Contribution of each microenvironment to the daily dose per particle size and for the whole particle population

ends up in the alveolar-interstitial (AI) region and 5–7% in the tracheobronchial (TB) regions of the lung, whereas the rest are filtered in the extrathoracic (ET) region of the HRT. The increased total DF in the living room in comparison to the one in the bedroom is attributed to the increased activity level, which results in more frequent breathing and the larger volumes of air consumed for both genders. Moreover, it is observed that this increase in the total DF translates almost solely in increased deposition in the ET region.

The average, over both gender and ECCs, daily dose of deposited particles in the whole HRT and its different regions, i.e., in the extrathoracic (ET), the tracheobronchial (TB), and the alveolar-interstitial (AI), is given in Table 4. It is shown that more than 97% of the daily dose can be attributed to particles sized between 2.5–10 μm, thus only 3% of the daily dose comes from particles of 1 μm or smaller. In addition, in Fig. 5, the distribution of the daily dose in the different regions of the HRT is given per particle diameter and for the total particle population. Almost 82% of the deposited particles are filtered in the ET region, whereas around 12% end up in the deeper parts of the lungs, the AI region. Based on their size, the ET region holds more than 94% of the 10-μm, 78%

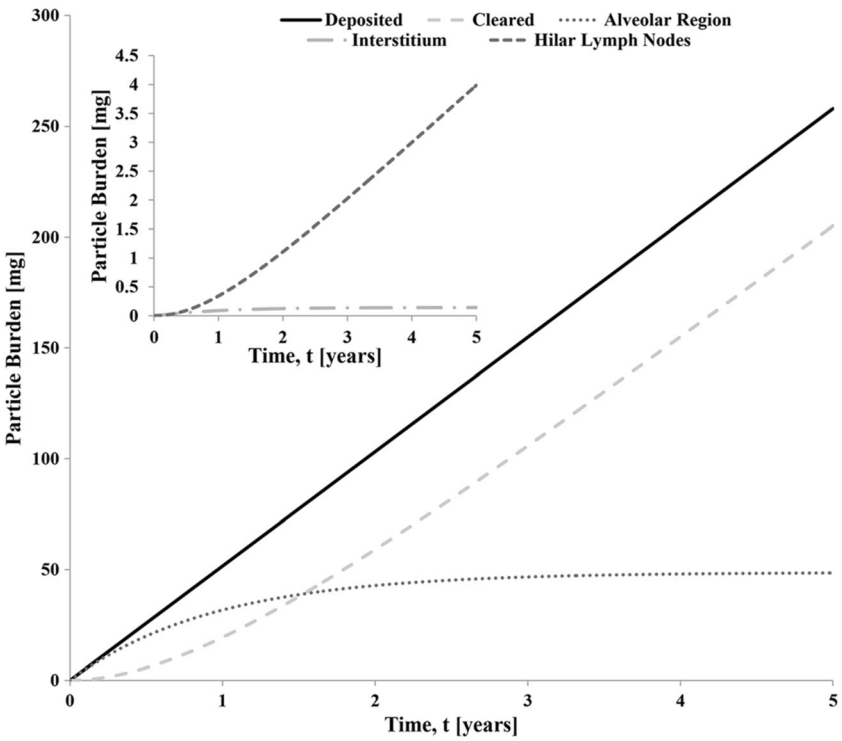

Fig. 7 Particle clearance/translocation from the alveolar-interstitial region of the HRT over a 5-year exposure period based on the whole particle population

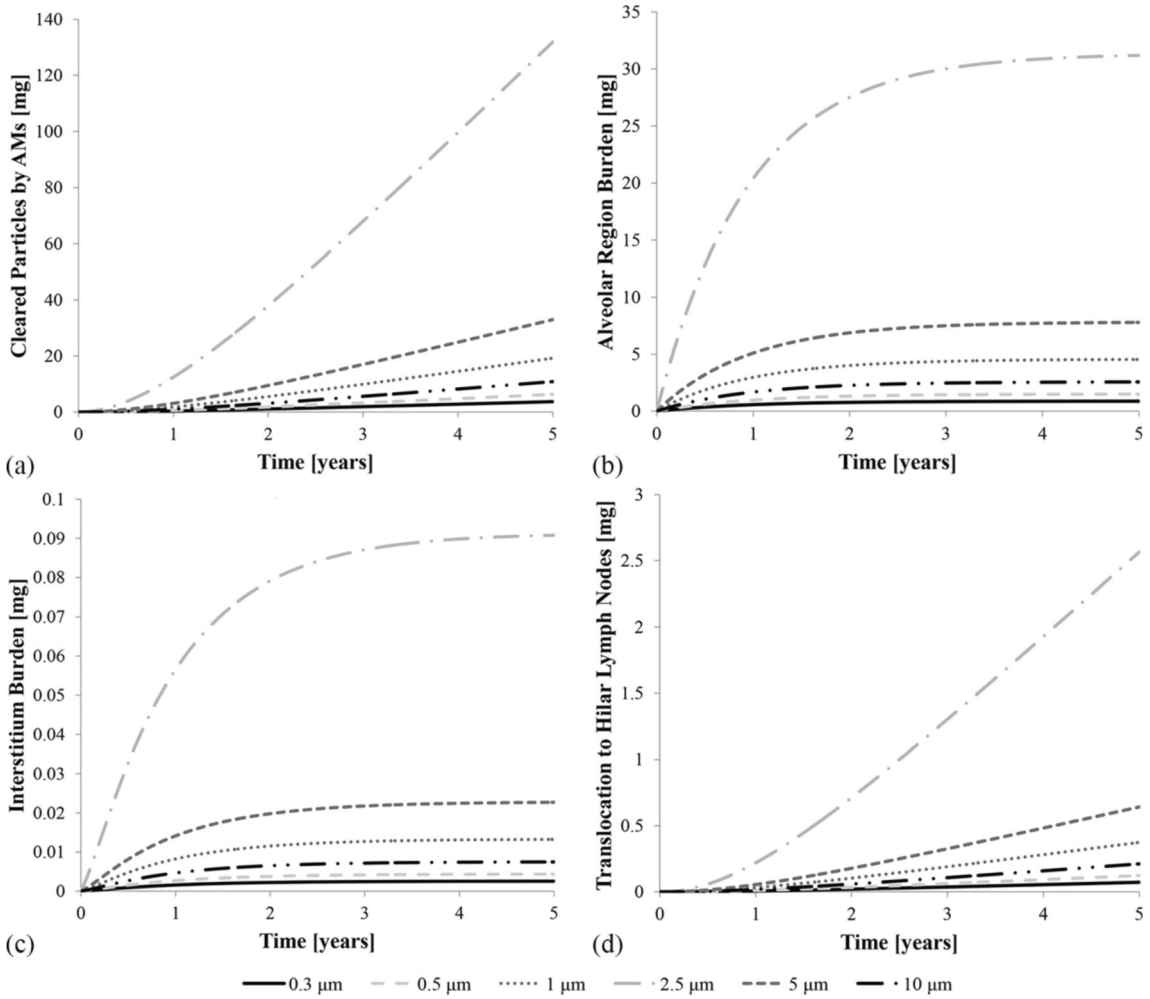

Fig. 8 Particle clearance/translocation from the alveolar-interstitial region of the HRT over a 5-year exposure period per particle diameter. **a** Clearance of particles by alveolar macrophages (AMs). **b** Particle burden on the surface of the alveoli. **c** Particle burden in the interstitium. **d** Particle translocation to the hilar lymph nodes

of the 5-μm, and 55% of the 2.5-μm particles, whereas 55% of the 1-μm, 72% of the 0.5-μm and 77% of the 0.3-μm particles end up in the AI region.

It is found that the living room is by far the microenvironment that contributes more in the daily dose in all ECCs (Fig. 6), regardless of the considerably less time spent in there, compared with the bedroom in most ECCs (Table 1). In average over all ECCs and both genders, the dose from the living room was related to all particle sizes under study (Fig. 6). The microenvironment in the bedroom contributes significantly only for the daily dose of the 300-nm-sized particles (~24%).

Particle clearance/translocation

The average daily dose in the alveolar region of the HRT (AI column of Table 4) is used next as input to particle retention and clearance/translocation model in order to estimate the particle buildup in the alveolar region, the interstitium, and the adjacent hilar lymph nodes over time. The mass of particles

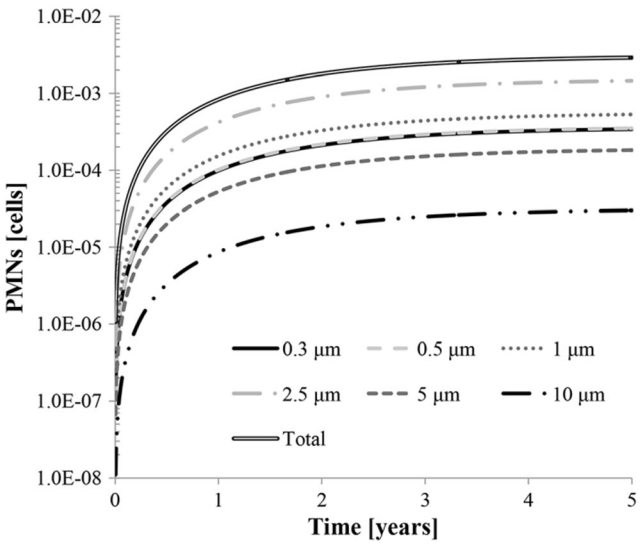

Fig. 9 Recruitment of polymorphonuclear leukocyte (PMN) cells into the alveolar region over time per particle diameter and as a total for the whole particle population

that are cleared from the alveoli to the tracheobronchi over time is also calculated. A 5-year continuous exposure period to the average particle population overall ECCs is assumed in the calculations and results are obtained for the total particle population as well as per particle diameter.

In Fig. 7, the buildup of particles in the alveolar region, the interstitium, and the hilar lymph nodes is presented over time along with the total number of particles deposited on the surface of the alveoli and the particles that are cleared from the alveoli towards the tracheobronchi ("cleared" curve). In total, after 5 years of continuous exposure to the average particle population, 258 mg of particles are deposited on the surface of the alveoli, the 79.6% (~ 205 mg) of which are cleared, 18.8% (~ 48 mg) are retained in the alveolar region, 1.5% (~4 mg) are translocated to the hilar lymph nodes, and only 0.1% (~ 0.3 mg) are transferred to the interstitium. It is also noticed that rates of clearance and translocation, i.e., the slopes of the respective curves, are not constant the whole period of interest; the rate of clearance increases over the first one and half year, slowly the first months and faster afterwards, until it assumes a more constant value, which is also reflected on the alveolar region retention curve, too. The same holds for the fraction of the deposited particles that eventually translocate to the hilar lymph nodes.

The particle mass over time in the different regions of interest over time is given also in Fig. 8 per particle diameter. In all cases, the 2.5-μm particles are the dominant contributors. As the kinetic rates used in the model (Eq.(2)) are independent of the particle size, this reflects the fact that the 2.5-μm particles are also the dominant contributor in the average daily dose in the alveolar region. However, the fractions of particle mass that either translocate are retained in the AI or is cleared to the mass of deposited particles are constant for all particle sizes and equal to the aforementioned ones for the whole population.

Finally, the calculations showed that for the specific exposure population and duration, there is no overload of either the alveolar or the interstitial macrophages. This is reflected also on the estimation of the recruitment of polymorphonuclear leukocyte cells in the alveolar region; the PMNs level stays well under the population of alveolar macrophage cells (~ 7×10^9 cells) for the whole period of interest (Fig. 9).

Conclusions

In this study, measurements of exposure to particulate matter in elderly care centers were combined with mathematical models in order to estimate the average daily dose to particulate matter in the different regions of the respiratory tract of the elders resident in these centers, as well as the particle buildup in the alveolar region, the interstitium, and the hilar lymph nodes of the elders over a 5-year exposure period.

The PM measurements, in the size range of 0.3–10 μm, showed that the mass concentration in the living room were significantly higher than in the bedroom for all particle sizes. However, the particle population in the living room is dominated by coarser particles (> 2.5 μm), whereas in the bedroom, there is also a significant contribution of the 0.3-μm particles.

Regarding the particle dose in the respiratory tract of the elders, it was found that in both rooms and for both genders, 10% of the mass of the inhaled particles per breath ends up in the alveolar-interstitial and 5–7% in the tracheobronchial regions of the lungs, whereas the rest are filtered in the extrathoracic region of the HRT. In total, the deposition fraction in the bedroom was around 79% of the inhaled particle mass and rose to around 90% in the living room due to the increased activity level.

The average over all ECCs' and both genders' daily dose of particular matter in the HRT of the elders was found equal to 1.21 mg. More than 97% of the daily dose can be attributed to particles sized between 2.5–10 μm; thus, only 3% of the daily dose comes from particles of 1 μm or smaller. In addition, it was found that 82% of the deposited particles are filtered in the ET region, whereas around 12% end up in the AI region.

The living room was by far the microenvironment that contributes more in the daily dose in all ECCs, regardless of the considerably less time spent in there compared with the bedroom in most ECCs; the time-budget survey applied to the residents of the ECCs revealed that on average, elders spend 57 and 30% of their time in the bedroom and living room, respectively.

The use of the particle retention and clearance/translocation model showed that after 5 years of continuous exposure to the average particle population, 258 mg of particles are deposited on the surface of the alveoli of which 79.6% are cleared, 18.8% are retained in the alveolar region, 1.5% are translocated to the hilar lymph nodes, and 0.1% are transferred to the interstitium. It was observed that the fraction of the cleared to the deposited particles increases over the first one and half year, slowly the first months and faster afterwards, until it assumes a more constant value, which is also true for the fraction of the deposited particles that eventually translocate to the hilar lymph nodes. Moreover, the calculations showed that for the specific exposure population and duration, there is no overload of either the alveolar or the interstitial macrophages, and thus, the recruitment of the PMN cells is close to zero.

There are a few of points that need to be emphasized regarding the findings of this study. Primarily, the presented results are based on particle mass concentrations; therefore, it is expected for the fractions/percentages related to particle size to be shifted to the bigger and thus heavier particles. If the metrics were to be based on particle number concentrations, the effect of particle size on the different quantities most probably would be different and in favor of the smaller particles. Secondly, it should be noted that the calculations were

performed assuming healthy adults, which may not be the case for the residents of the ECCs. The presence of disease in the respiratory system could affect many of the assumed parameters related to the physiology of the respiratory system, such as the frequency and the tidal volume of breath as well as the kinetic rates of clearance/translocation of particles from the alveolar region of the lungs. The changes in lung anatomy and breathing physiology in the presence of disease will also affect qualitative and quantitative the deposition of particles in the HRT. However, each lung disease or even the manifestations of the same disease may affect differently particle deposition; in chronic obstructive pulmonary disease, for example, there is higher deposition of bigger particles at bifurcations due to narrower airways, but if emphysema is also present, there is lower particle deposition in the small airways and alveoli due to their increased sizes. In addition, clearance capacity of the HRT is also affected by acute and chronic diseases that may cause mucus hypersecretion or change its viscus properties. As a result, mucus transport may be slower or stopped altogether leading to increased burden of particles in the various regions of the HRT (Kreyling et al. 2007). In our knowledge, there are currently no descriptions of the lung geometry or kinetic rates for the clearance/retention model in the literature, which take into account such changes in the presence of disease. Finally, the kinetic rates used in the particle retention and clearance/translocation model are independent of the particle size, which may not be the case in reality. All the aforementioned issues could be the subject of future study.

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