A computer model for the simulation of fiber–cell interaction in the alveolar region of the respiratory tract

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ABSTRACT

A mathematical model is presented that describes the health-endangering interaction of fibrous particles deposited in the human alveoli with alveolar fluids, cells, and tissues. As suggested by the theoretical approach, short fibers (diameter: 0.5 µm, length: 2–10 µm) are preferably ingested by alveolar macrophages and removed from the alveolar surface 10–15 days after exposure. Long (diameter: 0.5 µm, length: 10–50 µm) biopersistent fibers are not effectively cleared from the alveoli due to the repeated process of frustrated phagocytosis. Long biosoluble fibers also undergo a frustrated phagocytosis, with processes of extensive lysis leading to their significant shortening. The decrease in length causes the initiation of those clearance mechanisms that are efficient for short fibers.

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1. Introduction

As demonstrated by epidemiological studies [1–10], occupational cohorts exposed to natural or artificial fibers (i.e., particles with an aspect ratio greater than 3) are at increased risk of lung cancer or mesothelioma. As found by Everitt [11], both physical and chemical properties of fibers may be essential concerning the generation of pulmonary carcinomas. Early experimental studies on the harmful effects of asbestos demonstrated that fiber length constitutes a main determinant in the development of pulmonary diseases [12,13]. Thereby long (length: > 5 µm) fibers turned out to be the most dangerous, and highest carcinogenic potency could be related to fibrous particles being greater than 8 µm in length and smaller than 0.25 µm in diameter [14–16]. As further underlined by more recently conducted examinations [5,16,17], fibers with the ability to remain in the pulmonary lung tissue (Figs. 1 and 2a) for a long time are commonly characterized by a greater likelihood to cause a lung disease. This long-term retention of fibrous particles is described in the literature using the terms durability or biopersistence [5,10,16]. Besides the significance of fiber chemistry for biopersistence, its role within carcinogenic processes still remains uncertain and thus will be a topic of future research.

As soon as fibrous material is deposited in the pulmonary region of the human respiratory tract, several interactions between various lung cells and fibers are initiated, which should mainly serve for the evacuation of accumulated particles from the region of gas exchange. Thereby, considerable significance may be related to the clearance of fibers by macrophages, 1 to 2 representatives of which are located in

each lung alveolus of a healthy human [17,18]. Early fiber experiments carried out with rats yielded evidence that short fibrous particles (up to 5 µm in length) are cleared rather efficiently by macrophages (uptake by phagocytosis), whilst fibers of 30 to 60 µm in length are subjected to an ineffective removal by macrophages or on the surfactant layer [19,20]. According to our current knowledge human lung macrophages are able to completely engulf fibrous particles of up to 25 µm in length [16], but with such an enhanced overload with fibers their migration distances, normally being in the range of several lung generations, are strongly limited. On the other hand, short fibers have practically no influence on the migration behavior of the clearance cells [16,19,20]. In the case of very long fibers, that are fibers with an aspect ratio greater than 100, a single macrophage can only engulf part of the fiber length, often resulting in the fusion of several macrophages to form foreign body giant cells with the ability to enclose the whole fibrous particle. Cell aggregates of this kind only exhibit minimal migration and disintegrate again after a while [16,20]. Besides the phagocytosis of fibrous material by pulmonary macrophages, particles deposited on type-I alveolar epithelial cells (pneumocytes) may be also subjected to a transcytosis with subsequent reaching of the alveolar interstitium [21]. Within this region, some of the fibers are taken up by interstitial macrophages and undergo a transport towards the lymph vessels. This process may result in very high fiber burdens of the lung-associated lymph nodes [16,18]. Based upon recent experiments with hamsters [22], for very thin fibers (diameter < 0.1 µm) an alternative clearance route consists in their direct transport towards the blood capillaries and their continuous evacuation via the cardiovascular system. Transfer of fibrous particles into the capillaries is assumed to take place within a time period of several minutes.

The influence of biopersistence or non-solubility of fibrous material deposited in the pulmonary region on lung clearance

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was investigated in numerous studies [5,6,23–27]. The authors came to the unanimous result that highest durability and, as a consequence of that, slowest clearance is given for amphibole
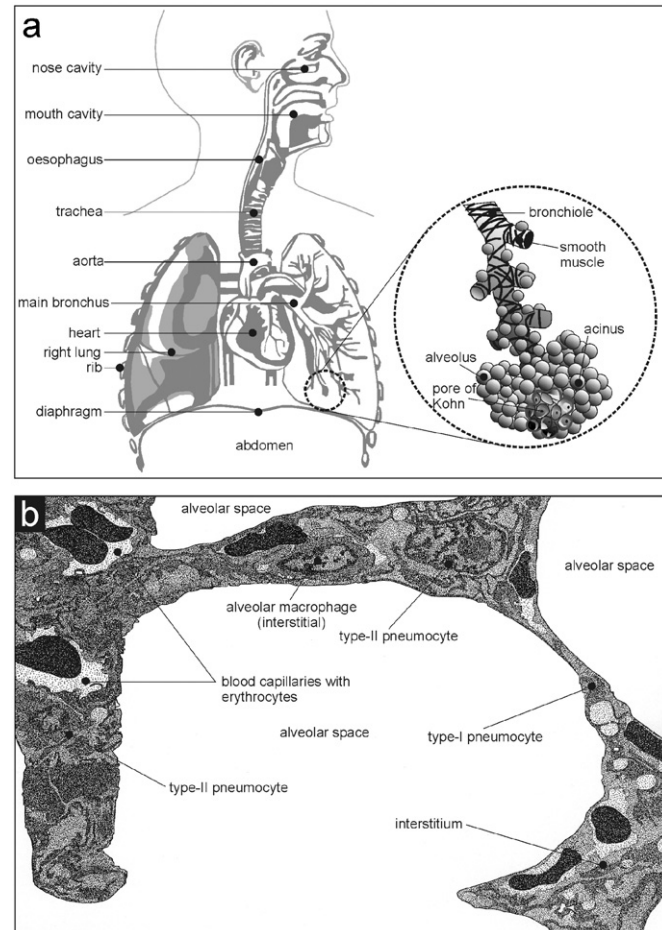

Fig. 1. (a) General sketch illustrating the morphology of the human respiratory tract and the pulmonary region with its high number of alveoli, within which the O_2–CO_2 gas exchange takes place. (b) Detailed histology of the alveolar epithelium and the interstitium with its dense network of capillaries containing the red blood cells (diameter: ca. 5 μm).

asbestos, followed by ceramic fibers, p-aramid fibrils, synthetic mineral fibers, and chrysotile asbestos. Based upon these findings, clearance of fibers is generally thought to take place according to the following steps (Fig. 3; [27,40]): (1) immediately after exposure to airborne fibers, short and long particles with variable biopersistences are deposited in the pulmonary region. (2) An early clearance process, taking place within the first days after exposure, leads to the removal of short (biosoluble and biopersistent) fibers by macrophages, whilst long fibers remain in the alveoli. (3) Long biosoluble fibers undergo processes of dissolution and breakage and are evacuated from the alveolar region during a second stage of clearance. (4) Long biopersistent fibers remain in the alveoli for an undefined period of time, thereby acting as possible causes for a significant number of lung diseases [23–27].

Concerning the theoretical approach of fiber–cell interaction in the human respiratory tract, countable modeling efforts describing an idealistic removal of deposited material were chiefly undertaken during the past two decades [18,28–30]. Thereby, most of these models aimed to estimate overall clearance rates of the fibrous material by the definition of linear differential equations. In the approach introduced by Hori et al. [29] constant translocation rates of fibrous particles engulfed by macrophages were assumed. Additionally fiber disintegration was approximated by a dissolution rate increasing proportionally with the surface area of the particles. Bernstein et al. [28] outlined a fiber clearance model consisting of both a fast (short fibers) and a slow clearance phase (long biosoluble fibers). In the multicompartmental approach most currently described by Sturm and Hofmann [30] earlier mechanistic models of bronchial clearance [31–33] were extended by the alveolar part, thereby considering all clearance pathways in the alveoli that are presently known.

The contribution presented here has two main objectives: first, an innovative mathematical approach including all known types of alveolar fiber–cell interaction is subjected to a comprehensive description. As a main progress with respect to other clearance models described in the literature, the approach presented here tries to consider specificities of fibers concerning their physicochemical properties or their extra- and intra-cellular transport and storage. The new model is thought to form an appropriate basis for future simulation attempts of cancer development and cardiovascular diseases caused by extremely thin fibers and
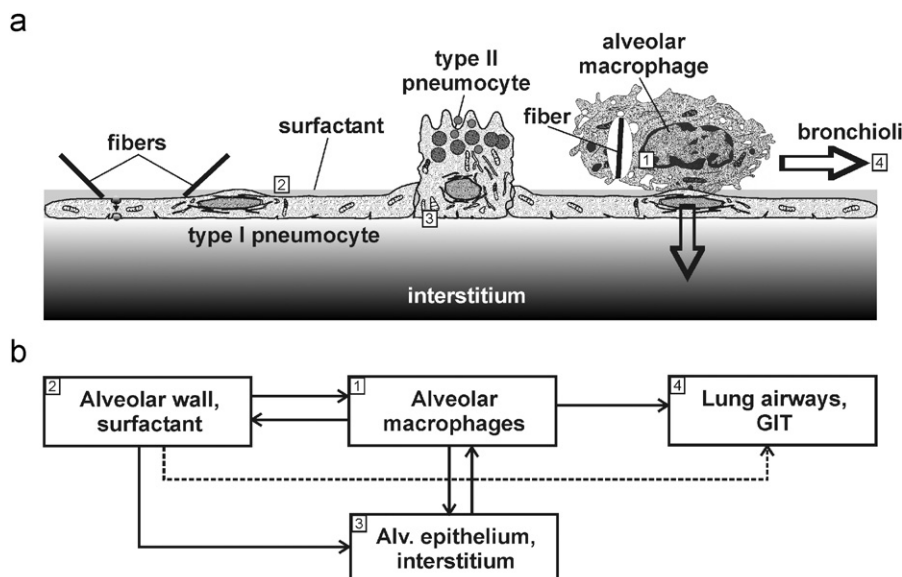

Fig. 2. (a) Sketch illustrating the possible types of fiber–cell interaction in the alveoli; (b) multicompartment model describing the fiber–cell interaction.

ultrafine particles in general. Second, preliminary modeling results are presented and, as far as possible, compared with respective experimental results.

2. Methods—formulation of the multicompartment model for fiber–cell interaction in the alveolar region of the lung

2.1. General description of the multicompartment model

The model introduced here with its single fiber transfer paths (note: most of these paths have been already defined for spherical particles [18], whilst the remaining ones are at least founded on a histological basis [22]) is depicted in Fig. 2. It is assumed that fibrous particles deposited in the alveoli are subject to several interactions with specific cells of the alveolar lung tissue, whereby highest significance is attributed to the clearance of the particulate mass by alveolar macrophages. Those macrophages, which have taken up fibrous material, either migrate towards the bronchioles and bronchi, where further clearance chiefly takes place via the

mucociliary escalator, enter the alveolar interstitium, with the lymphatic vessels acting as their main targets for particle release, or remain in the alveoli. In the case of insoluble fibers exceeding the loading capacity (i.e., the highest possible cellular volume made available for phagocytosis) of the macrophages, particles are engulfed by a group of phagocytotic cells and again released to the alveolar surface after a while (see above). This process, termed 'frustrated phagocytosis' [27,28], is repeated as long as the particles have not changed their sizes due to breakage induced by the extensive activity of macrophages. A possible evacuation path of the fibrous material, which is also considered by the model, but does not involve any cellular compartments, is represented by the transport of single particles on the surfactant, a very thin liquid layer facilitating alveolar gas exchange. As found by Sosnowski et al. [34] the surfactant is subjected to microscopic turbulences and displacements, which are directed towards the bronchioles. Very small fibers, being not able to overcome the surface tension of the liquid and being not detected by alveolar macrophages, may be evacuated to the tracheobronchial tree in this way. A significant cell–fiber interaction, which is restricted to
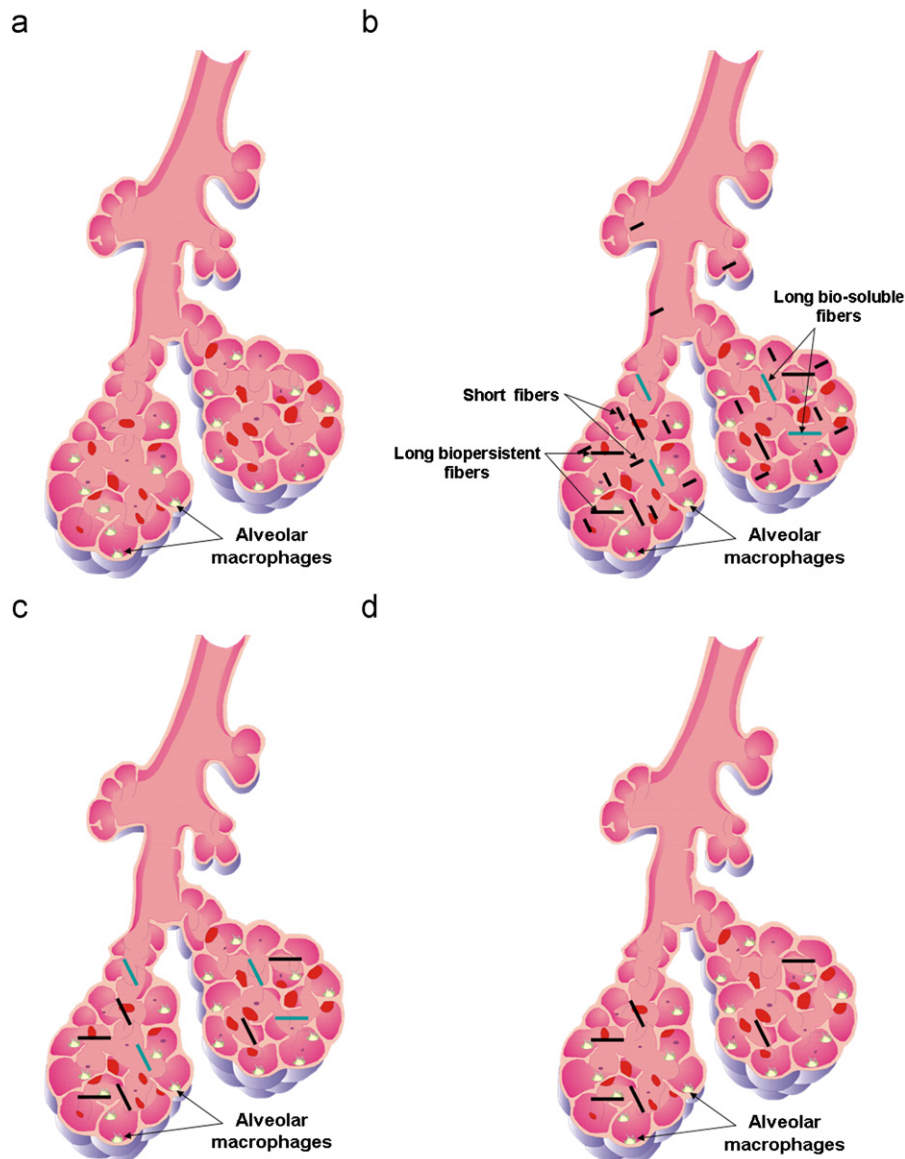

Fig. 3. General scenarios standing behind the clearance and storage of short and long fibers in the alveoli of the human respiratory tract: (a) initial state with unaffected alveoli; (b) alveoli after deposition of short fibers as well as long biopersistent and biosoluble fibers; (c) the first clearance phase exclusively concerns the short fibers, which are evacuated rather rapidly; (d) the second clearance phase is associated with the long biosoluble fibers, whilst the long biopersistent fibers remain in the alveoli [40].

short or very thin fibrous particles, concerns the direct transport of deposited material through the epithelium (type-I pneumocytes) into the alveolar interstitium. Within this subepithelial region the fibers may be transferred to capillaries and, as a consequence of that, channeled into the cardiovascular system. Alternatively, particles may be taken up by interstitial macrophages and evacuated towards the lymph. As a third possibility, interstitial fibers are subjected to a local storage for an undefined period of time. For the simulation of mesothelioma this particle group plays an essential role.

2.2. Mathematical formulation of single fiber transfer routes and fiber–cell interactions

As depicted in Fig. 2b, fiber clearance as well as the interaction between different alveolar cells and the fibrous material may be expressed appropriately by application of a multicompartment model. The theoretical approach includes four compartments (alveolar macrophages, alveolar surface with surfactant, alveolar epithelium/interstitium, and lung airway system/gastrointestinal tract) that are partly connected by transfer paths. The selection of single transfer paths took place according to the most current knowledge of fiber–cell interaction noted in the previous section. From a mathematical point of view any temporary change of fiber concentration in a 1-compartment system may be described by the general equation:

$$\frac{dC}{dt} = k_{in}A - k_{out}C, \tag{1}$$

where k_{in} denotes the mass transfer into the compartment C, A the fiber concentration outside the compartment C, and k_{out} the mass transfer out of the compartment C. In the case of the 4-compartment system presented here the following set of linear differential equations is obtained:

$$\begin{pmatrix} dC_1/dt \\ dC_2/dt \\ dC_3/dt \\ dC_4/dt \end{pmatrix} = \begin{pmatrix} -(k_{12}+k_{13}+k_{14}) & k_{21} & k_{31} & 0 \\ k_{12} & -(k_{21}+k_{23}+k_{24}) & 0 & 0 \\ k_{13} & k_{23} & -k_{31} & 0 \\ k_{14} & k_{24} & 0 & 0 \end{pmatrix} \begin{pmatrix} C_1 \\ C_2 \\ C_3 \\ C_4 \end{pmatrix}. \tag{2}$$

In Eq. (2), C_1–C_4 represent the fiber mass concentrations in the compartments 1–4, whilst k_{xy} describes the mass transfer into and out of single compartments. Thereby, the subscript x always marks the source compartments, whereas the subscript y labels that compartment serving as target of particle mass transfer.

Mathematical solution of the linear differential equations noted above is carried out according to well-defined techniques, including the solutions of the related homogeneous differential equations and the determination of one particular solution of the inhomogeneous expressions, respectively. Concerning compartment C_1 representing the alveolar macrophages, solution of the related differential equation yields

$$C_1(t) = \left(C_1^{ini} - \frac{k_{21}C_2 + k_{31}C_3}{k_{12}+k_{13}+k_{14}} \right) \exp\left[-(k_{12}+k_{13}+k_{14})t \right] + \frac{k_{21}C_2 + k_{31}C_3}{k_{12}+k_{13}+k_{14}}. \tag{3}$$

As a major simplification of the approach to fiber uptake by macrophages, the number of these cells in the alveoli is supposed to be constant over the whole clearance process. Hence, if a macrophage dies due to its age or particle load, particles released from this cell are immediately taken up by another fresh macrophage. In future models, life and production of macrophages will be considered using non-linear transfer rates associated with this compartment.

For compartment C_2 being associated with the alveolar surface and surfactant layer, the following solution of the differential

equation may be obtained:

$$C_2(t) = \left(C_2^{ini} - \frac{k_{12}C_1}{k_{21}+k_{23}+k_{24}} \right) \exp\left[-(k_{21}+k_{23}+k_{24})t \right] + \frac{k_{12}C_1}{k_{21}+k_{23}+k_{24}}. \tag{4}$$

Regarding the fiber accumulating compartments C_3 and C_4 respective solutions adopt the following forms:

$$C_3(t) = \left(C_3^{ini} - \frac{k_{13}C_1 + k_{23}C_2}{k_{31}} \right) \exp\left[-(k_{31})t \right] + \frac{k_{13}C_1 + k_{23}C_{21}}{k_{31}}, \tag{5}$$

$$C_4(t) = (k_{14}C_1 + k_{24}C_2)\Delta t. \tag{6}$$

In Eqs. (3)–(5) C_1^{ini}, C_2^{ini}, and C_3^{ini} denote the fiber mass concentrations in the compartments C_1, C_2, and C_3 immediately after exposure to the airborne particles and their deposition in the alveolar region of the human respiratory tract. Since the probability of inhaled fibers for directly hitting alveolar macrophages is only given for high amounts of deposited particulate mass, C_1^{ini} and C_3^{ini} are assumed to take the value 0. On the other hand, C_2^{ini} corresponds to the complete particulate fraction deposited on the alveolar wall.

Fiber deposition calculations, representing a necessary requirement for the theoretical simulation of fiber–cell interactions, were conducted using an extensively validated stochastic particle transport and deposition model (IDEAL; [35]). Thereby, deposition of fibrous particles was assumed to take place in a standard lung (FRC=3300 ml) under normalized breathing conditions (light-work breathing: tidal volume=1250 ml, breathing frequency= 20 min^{-1} [18]). Particle properties included a density of 2.7 g cm^{-3}, corresponding with the average density of most mineral fibers, a fiber diameter ranging from 0.05 to 3 µm and an aspect ratio, that is the ratio between fiber length and fiber diameter, ranging from 3 to 100.

As comprehensively noted in the introduction, fiber–cell interaction and related clearance of fibrous particles out of the alveolar lung region mainly depends upon fiber size (diameter and length) as well as durability of the fiber material. Both parameters are very essential regarding the definition of the transfer rates or rate constants k_{xy} defined in Eq. (2). The effect of fiber geometry on k_{xy} is expressed insofar, as both increasing length and growing diameter cause a rapid (exponential) drop of a specific transfer rate. This important phenomenon can be exhibited by the following formula:

$$k_{xy}^f = k_{xy}^{ves} \left[0.5\exp\left(\frac{d_f}{a_1 d_{ves}} - 1 \right) + 0.5\exp\left(\frac{d_{ves}}{a_2 l_f} - 1 \right) \right]. \tag{7}$$

In Eq. (7) k_{xy}^f and k_{xy}^{ves} denote the transfer rates of fibers with diameter d_f and spheres with diameter d_{ve}, corresponding with the so-called volume-equivalent diameter, i.e., the diameter of a sphere with exactly the same volume as the fibrous particle. Whilst l_f represents the length of the fibers deposited in the alveoli and corresponds to d_f via the aspect ratio, a_1 and a_2 are specific correction factors influencing the shape of the exponential functions. In the present study these factors were commonly set to 1, since experimental investigation of fiber-specific transfer rates is still under progress. Values of k_{xy}^{ves} are among others provided by the ICRP [18] and by Sturm and Hofmann [33] as well as Sturm [36]. Concerning the interaction of fibers with macrophages, transfer rates for comparable spheres commonly take values between 0.02 and 0.04 d^{-1}. Particle transfer towards the epithelium involves rate constants being at least one order of magnitude smaller (0.0001–0.002 d^{-1}). Similar slowness is assumed for a possible movement of fibers on the surfactant layer and subsequent evacuation to the bronchial airways ($k_{24} \approx$ 0.001 d^{-1}).

Biopersistence of inhaled fibers is described by the change of fiber volume with time, which may be expressed by the formula [29]

$$-\frac{d(\pi d_f^2 l_f/4)}{dt} = m\left(\pi d_f l_f + \frac{2\pi d_f^2}{4}\right),\tag{8}$$

where m denotes the so-called dissolution constant (μm month^{-1}). For long fibers $d_f^2/2$ may be assumed as much smaller than $d_f l_f$, so that Eq. (8) is simplified in the following way:

$$-\frac{dd_f^2}{dt} = 4md_f.\tag{9}$$

Solution of this linear differential equation yields

$$d_f = d_f^{ini} - 2mt,\tag{10}$$

with d_f^{ini} representing the initial diameter of the fiber. In the case of biopersistent fibrous material m commonly amounts to 0, and Eqs. (8)–(10) do not show any effect. For biosoluble fibers time-dependent changes of d_f have a significant effect on Eq. (7) and thus on the definition of k_{xy}.

For clearance computations only a distinction between long biopersistent fibers (diameter: 0.5 μm, length: 10–50 μm, dissolution constant: 0 μm month^{-1}), long biosoluble fibers (diameter: 0.5 μm, length: 10–50 μm, dissolution constant: 1 μm month^{-1}), short biopersistent fibers (diameter: 0.5 μm, length: 2–10 μm, dissolution constant: 0 μm month^{-1}), and short biosoluble fibers (diameter: 0.5 μm, length: 2–10 μm, dissolution constant: 1 μm month^{-1}) was carried out. Independent of their size, fibers were assumed to be exclusively deposited on the epithelial surface of single alveoli, resulting in $C_1^{ini}=1$, $C_2^{ini}=0$, and $C_3^{ini}=0$ as initial modeling conditions (see above).

3. Modeling results

3.1. Deposition of variably sized fibers in the human respiratory tract

Bronchial and alveolar depositions were computed as functions of fiber diameter and fiber aspect ratio (Fig. 4). Concerning the deposition of fibrous material in the bronchial part of the human respiratory tract peak deposition may be recognized for fibers with a diameter of 3 μm (ca. 35%), whilst minimal deposition commonly occurs for fibers with about 0.5 μm in diameter (ca. 7%). For very thin fibers bronchial deposition is again characterized by a noticeable increase (ca. 14%), thereby certainly not reaching the deposition maximum caused by large fibers. With increasing aspect ratio fibrous particles with diameters greater than 0.5 μm exhibit an additional enhancement in bronchial deposition, whereas deposition of fibrous particles with diameters smaller than 0.5 μm is slightly decreased.

Under the assumed breathing conditions alveolar fiber deposition is less than half as high as bronchial deposition, whereby most remarkable deposition fractions are observed for particles with a diameter of 2 μm (14%). Larger particles (diameter greater than 0.5 μm) are marked by a continuously declining deposition, whilst very small fibers (diameter smaller than 0.5 μm) again perform an enhanced deposition (ca. 8%). Contrary to bronchial deposition the effect of fiber length is given insofar, as both large and small particles are accumulated in the alveoli with slightly smaller amounts.

3.2. Fiber–cell interaction in the alveolar region

Fiber–cell interaction was simulated for both biopersistent (Fig. 5) and biosoluble fibers (Fig. 6), thereby distinguishing

between short fibrous material (diameter: 0.5 μm; length: 2–10 μm), which is subjected to a preferential clearance by alveolar macrophages, and long particles (diameter: 0.5 μm; length: 10–50 μm) that may persist on the alveolar epithelium for an undefined period of time. Concerning short biopersistent fibers deposited in the alveoli, theoretical uptake and removal by alveolar macrophages have to be evaluated as highly effective, with the maximal concentration of phagocytosed particles being reached 15–20 days after exposure (Fig. 5a). Since macrophages have a lifetime of several months, most of them release their insoluble burden on their way through the airway system of the human respiratory tract, so that the concentration of fibrous particles on the airway walls is exponentially increased with time. Some macrophages also penetrate the alveolar epithelium in order to reach the interstitium, where the particle load is either transferred to the lymphatic system or set free in the subepithelial tissue layers. According to the modeling results the ratio between fibers cleared through the airway system and fibers being subject to a transepithelial transport amounts to 3:1. Due to the high efficiency of short fiber clearance, particles originally stored on the alveolar wall are rapidly decreased in their concentration, leading to their complete evacuation from the epithelial surface after 30 days. For long insoluble fibers interaction with alveolar cells is completely different from that theoretically determined for short fibrous particles. As illustrated in Fig. 5b, long and insoluble fibers are exclusively transferred between the macrophage and the alveolar wall compartment (Fig. 3b). According to the applied model parameters, about 30 days after exposure all deposited particles have been subjected to a phagocytosis by macrophages, whereby groups consisting of several macrophages cover one single fiber, respectively. This condition of 'frustrated phagocytosis' is only preserved over a limited period of time, so that particles are successively released to the alveolar surface, again. After 150 days the theoretical ratio between long fibers residing on the alveolar wall and fibers taken up by macrophages amounts to 4:1.

Regarding short fibers characterized by a measurable biosolubility the model computes enhanced clearance efficiency of alveolar macrophages insofar, as 80% of the particulate mass deposited in the alveoli are phagocytosed 10–15 days after exposure. 150 days after exposure 90% of the particulate fraction have been transferred to the airway system, whilst the remaining particles are stored in the interstitium or in the macrophages (Fig. 6a). A very interesting model scenario concerns the long soluble fibers (Fig. 6b), which in the first instance undergo a complete interaction with alveolar macrophages, again. Due to this process the fibrous particles are thought to break into smaller pieces, so that they behave as short fibers from this moment on. The short fiber clearance, being initiated about 50 days after exposure, causes an increase in particulate mass in the airway system. 150 days after exposure equal particle fractions (ca. 40%) reside on the alveolar wall and in the tracheobronchial tree, whereas the remaining fibers are still stored in macrophages or within the interstitium.

3.3. Comparison of experimental and theoretical data

Data of alveolar fiber–cell interaction derived from experiments with laboratory rats were published by Bernstein et al. [27,28] and served as an appropriate basis for model validation. In this context it has to be noted that comparable data of fiber deposition and clearance in human lungs do not exist for ethic reasons, but clearance processes in rat alveoli may be more or less put on a level with those in human alveoli. Preceding deposition calculations using a rat lung anatomy showed that fibrous particle fractions reaching the alveoli of the rodents are much higher than
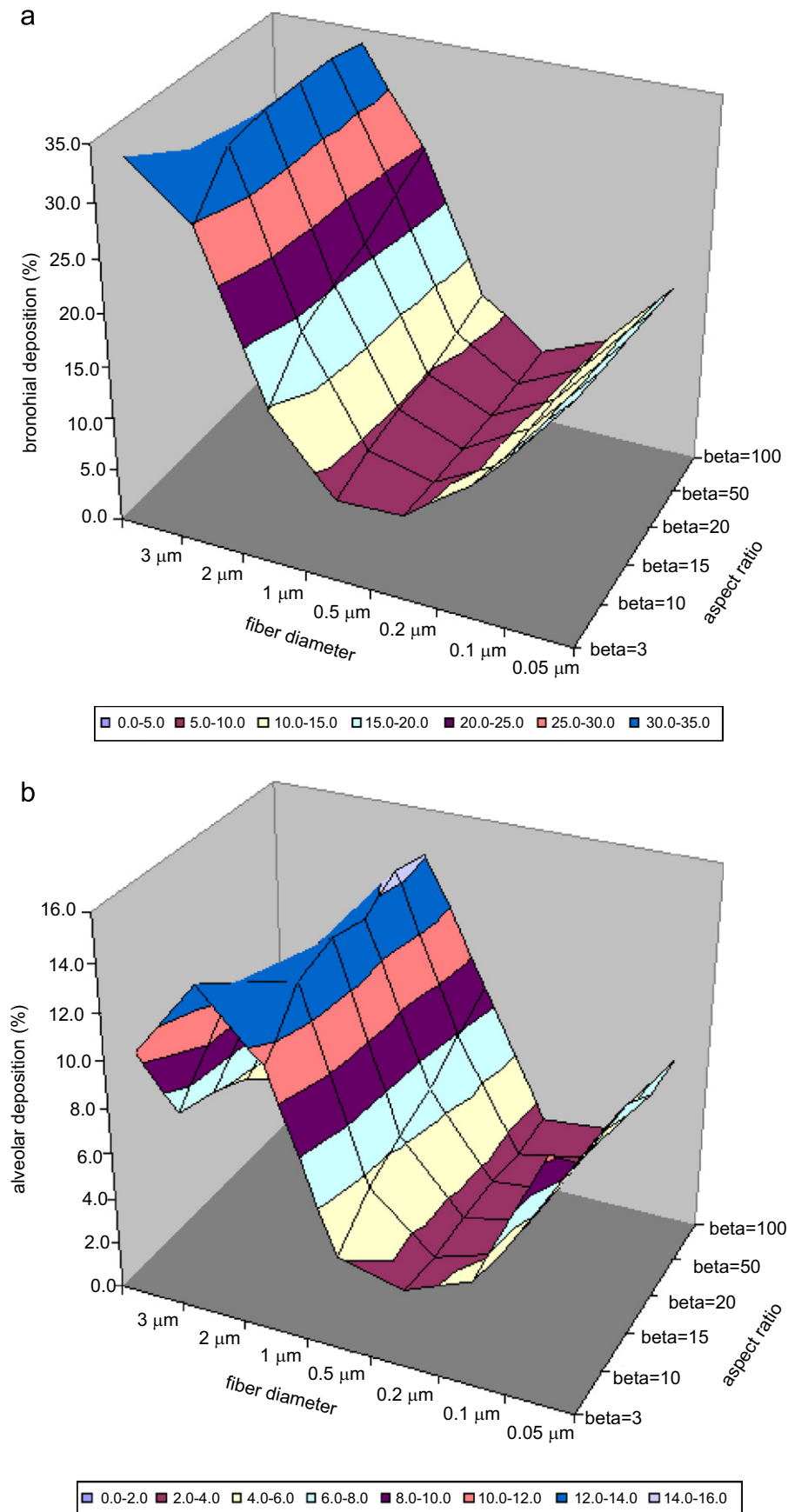
Fig. 4. Results of fiber deposition calculations assuming light-work breathing conditions (tidal volume: 1250 ml, breathing frequency: 20 min^{-1} [18]) and a mean particle density of 2.7 g cm^{-3}. (a) Bronchial deposition as function of particle diameter and aspect ratio; (b) alveolar deposition as function of particle diameter and aspect ratio.
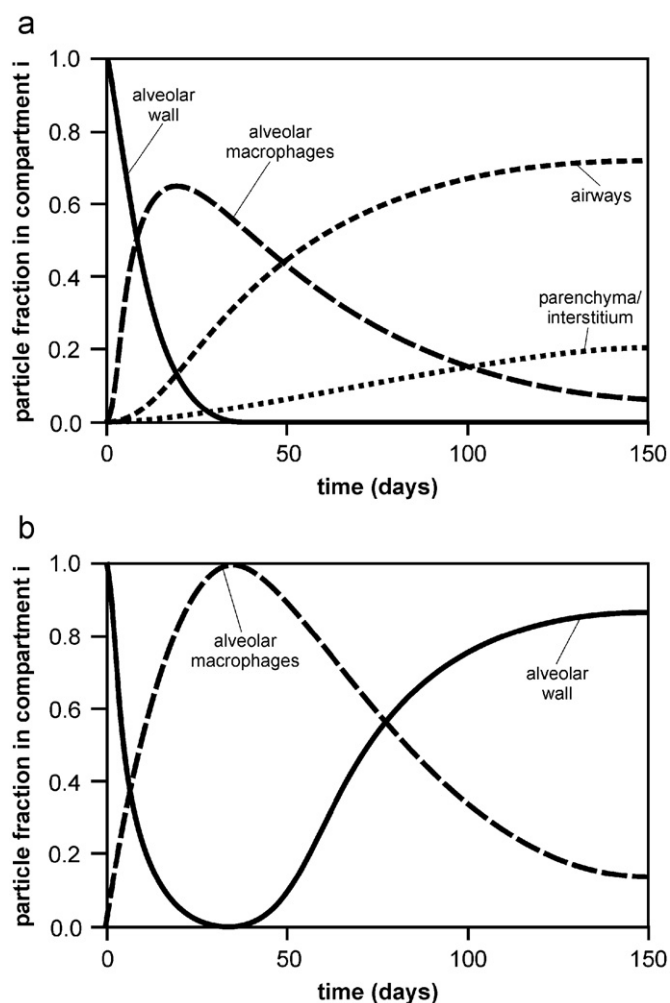
Fig. 5. Preliminary results derived from the multicompartment model introduced in Fig. 2b: (a) time-dependent particle fractions in single compartments computed for short biopersistent fibers (diameter: 0.5 μm, length: 2–10 μm, dissolution constant: 0 μm month^{-1}); (b) time-dependent particle fractions in single compartments computed for long biopersistent fibers (diameter: 0.5 μm, length: 10–50 μm, dissolution constant: 0 μm month^{-1}).

Fig. 6. Further preliminary results derived from the multicompartment model: (a) time-dependent particle fractions in single compartments computed for short biosoluble fibers (diameter: 0.5 μm, length: 2–10 μm; dissolution constant: 1 μm month^{-1}); (b) time-dependent particle fractions in single compartments computed for long biosoluble fibers (diameter: 0.5 μm, length: 10–50 μm, dissolution constant: 1 μm month^{-1}).

respective fractions reaching the human alveolar regions (Fig. 4b). Although total clearance (bronchial and alveolar) is much faster in rat lungs than in human lungs, alveolar compartments and transfer rates describing the interactions between the fibrous material and tissues, cells, and liquids were assumed to be nearly identical between rats and humans, which, in the worst case, resulted in an overestimation of alveolar clearance times. Concerning the clearance of amosite fibers with lengths greater than 20 μm (Fig. 7a) experiments showed that about 65% of the deposited mass are removed within the first 100 days after exposure, whereas the remaining particles seem to be characterized by long-term retention. Model predictions suggest a very similar shape of the clearance curve, whereby differences with respect to the experimental results are on the order of 5–10%. The clearance of long (length: > 20 μm) chrysotile fibers illustrated in Fig. 7b takes place with significantly higher efficiency, i.e., 200 days after exposure the complete fibrous particle mass deposited in the alveoli has been evacuated. By considering a higher biosolubility of chrysotile fibers with respect to amosite fibers, model predictions provide very similar results, with discrepancies between experimental and theoretical curve ranging from 0% to about 5%.
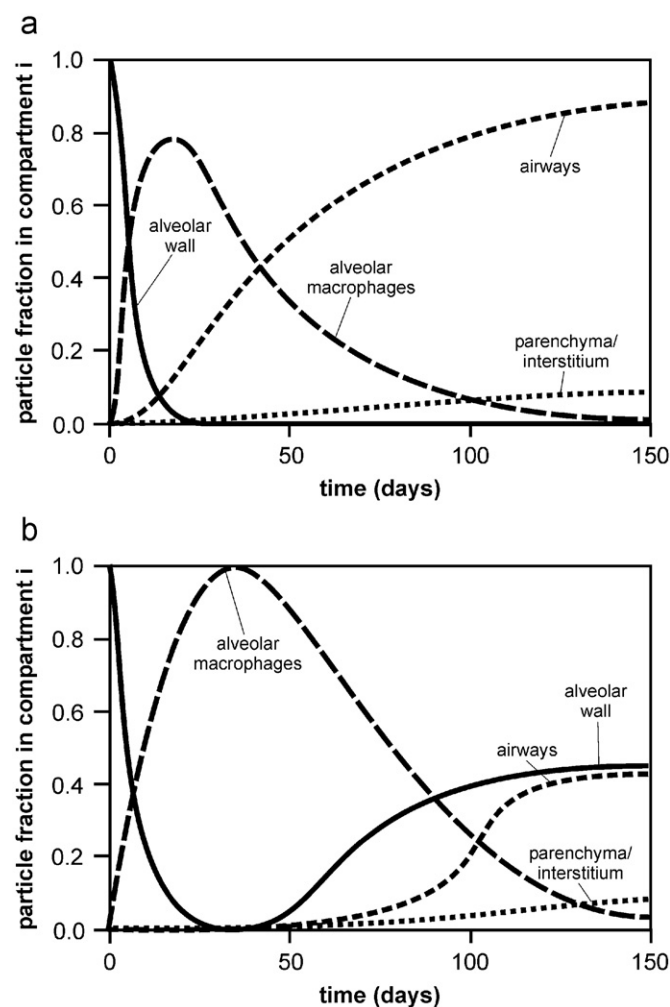
4. Discussion and conclusions

Airborne fibers deposited in the alveolar region of the human respiratory tract are subject to various interactions with cells and tissues, which have a common aim, i.e., the rapid and efficient removal of the particulate mass from this sensitive part of the lung. Numerous studies could provide sufficient evidence for the fact that this fiber–cell interaction is chiefly affected by (1) the length of the inhaled fibrous material, with long fibers being retained much longer in the alveoli than short ones, and (2) the biopersistence or durability of the particles [10,16]. The latter phenomenon describes the possibility of lytic cells such as alveolar macrophages to induce a dissolution of the fibrous material. Where this process fails, fibers only undergo very limited mechanisms of alveolar clearance (Fig. 5). This hazardous behavior of fibers, underling their role as a serious cause of a high number of lung diseases, may be among others led back to the fact that thin fibrous particles, no matter how long they are, can rather easily penetrate to the alveoli. As found in previous studies [27,30,33,37], deposition of respirable fibers in animal and human lungs is mainly controlled by the fiber diameter, whereas fiber length has crystallized out as a less significant parameter. Therefore, fibrous particles with a diameter of less than 0.5 μm and an
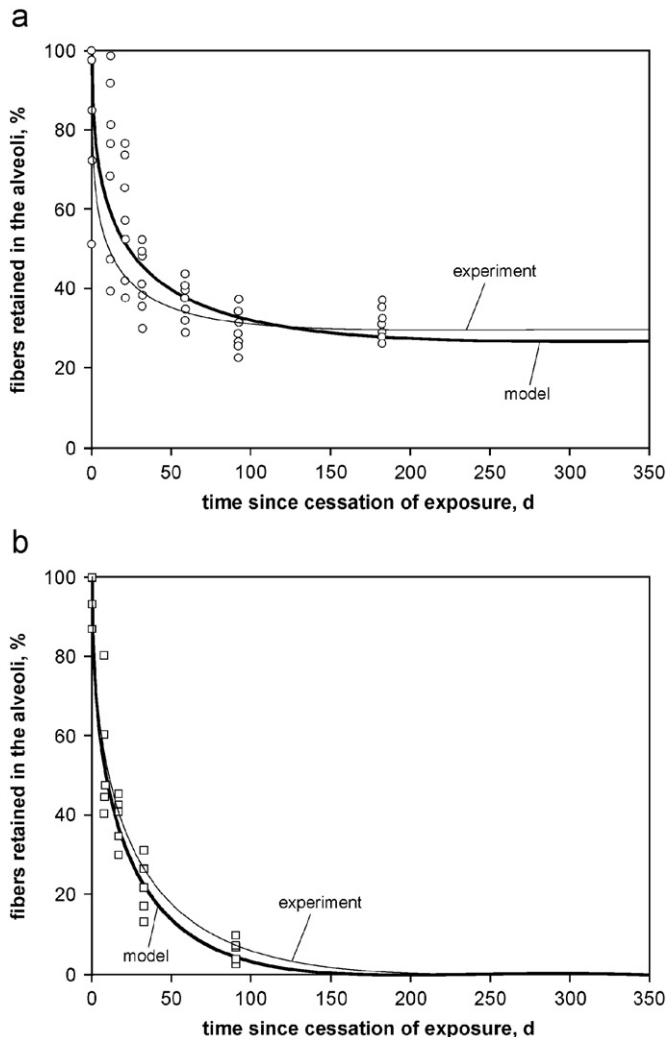
Fig. 7. Comparison between experimental clearance data of amosite (a) and chrysotile asbestos (b; [27,28]) and related theoretical data.

aspect ratio of 100 (length: 50 μm) have the ability to reach the alveoli in high numbers (Fig. 4). In extreme cases of exposure to airborne fibers fine mineral needles may occupy the whole alveolar space, leading to a successive modification of the distal lung architecture.

As demonstrated by the theoretical approach of alveolar fiber–cell interaction introduced here, short fibers are subjected to a rather rapid removal by airway macrophages. These cells, which can be detected in both the alveolar space and the alveolar interstitium [18,27], represent the protagonists of particle clearance in the pulmonary region, whereby their efficiency is highly affected by the volume and size of the phagocytosed particulate mass. Gradón and Podgórski [38] could theoretically proof that the motility of macrophages exponentially declines with the volume of loaded particles, finally coming to a stand-still for particles that are nearly as large as the clearance cells themselves. According to more current experimental studies performed by Castranova et al. [39] alveolar macrophages of hamsters have the ability to engulf fibers with a maximal length of 7 μm, whilst human macrophages seem to have the capability to phagocytose much longer fibrous particles (up to 20 μm in length). Despite this particulate burden, the cells are still able to move towards the airway system, where any further clearance is mainly accomplished by the mucociliary escalator as well as fresh macrophages originating from the submucosa [18,31,33].

Another question in combination with macrophage clearance of fibers deposited in the alveoli concerns the decision of the phagocytotic cell to evacuate a particle either towards the bronchial airways or towards the lymphatic system. Experimental studies could show that the path of clearance selected by the macrophage among others depends upon the chemical composition of the engulfed material. Hence, quartz dust has a higher probability to be removed via the lymphatic system than other dust particles [16]. The reasons for this selective behavior of macrophages are largely undetected hitherto, but, however, transepithelial removal of particulate mass participates with decreased amounts in total alveolar clearance [18].

Two essential processes considered by the multicompartment model, i.e., the direct transfer of fibers through the alveolar epithelium into the interstitium and the transport of (small) fibrous particles on the surfactant layer, are recently subjected to an increased scientific attention. As demonstrated by Geiser et al. [22], long and very thin fibers deposited in the alveoli of a hamster lung may penetrate the epithelial cell layer within very short periods of time and may even occupy the blood capillaries. The molecular mechanisms standing behind that phenomenon are completely unknown. Nevertheless, this experimental study is a remarkable evidence for the fact that transcytosis has to be increasingly regarded as significant clearance mechanism [31,33]. The role of the surfactant in alveolar clearance has been noted very marginally hitherto, but physical examinations have shown that this layer is subject to a continuous movement. Small particles captured on the surfactant are affected by this movement insofar, as they are evacuated towards the airways.

From the results of the multicompartment model presented here it can be concluded that fiber–cell interaction in the human alveoli is mainly restricted to a few processes, whose efficiency depends upon the physical and chemical properties of the deposited particulate mass. If specific particle characteristics cause a failure of this interaction, particles may act as serious biohazards, inducing various lung diseases with different degrees of exacerbation. Highest uncertainties concern the transfer rates used by the approach, which more and more crystallize out as multivariate parameters. Future research should further facilitate the application of these essential factors.

5. Summary

In the contribution presented here a multicompartment computer model has been developed, which allows the simulation of all possible interactions between deposited fibrous particles and local cellular fluids, cells, and tissues in the alveoli of the human respiratory tract. Considering the alveolar histology and morphology, three compartments, i.e., the alveolar macrophages, the alveolar surface with its cover by the surfactant, and the epithelium/interstitium have been included into the mathematical approach. Additionally, the bronchioles have been defined as a target compartment of fiber clearance by macrophages and, much less significant, by surfactant movement. Transfer rates connecting the single compartments have been extracted from the results of previously published theoretical and experimental studies. As suggested by the model, three different scenarios of fibers interacting with alveolar liquids, cells, and tissues are conceivable: (1) short fibers (diameter: 0.5 μm, length: 2–10 μm), no matter if biosoluble or biopersistent, are preferentially taken up by alveolar macrophages, two or more of which are present in each alveolus. After their ingestion the fibrous particles are removed from the alveoli towards the tracheobronchial tree or, with lower probability, towards the alveolar interstitium. (2) Long biopersistent fibers (diameter: 0.5 μm, length 10–50 μm) undergo a so-called

frustrated phagocytosis involving several macrophages, but due to the ineffectiveness of lytic processes they are released to the alveolar surface, again. This fiber–macrophage interaction may be repeated over an undefined period of time, resulting in the non-clearance of the deposited mass and the possible provocation of malignant transformations. (3) Long biosoluble fibers are also subject to an uptake by adjacent macrophages, but, contrary to long biopersistent fibers, intracellular processes of extensive lysis lead to their continuous decomposition and shortening. The decrease in length causes the initiation of those clearance mechanisms that are efficient for short fibers. Model validation has been carried out by simulation of clearance of amosite and chrysotile fibers from rat lungs, whose histology is well comparable to that of the human respiratory tract. Differences between experimental and related theoretical results are on the order of 0–10%.

Based upon the theoretical results it can be concluded that alveolar clearance of fibers is affected by a high number of factors, whose successive deciphering will be a main goal of future research.

Conflict of interest statement

None declared.

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