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A dynamical model of the transport of asbestos fibres in the human body

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ABSTRACT

We present a model for the transport of a single type of asbestos fibre through the human body. The model captures the transport modes that pertain particularly to the lungs and the mesothelium. Numerical solutions of the system follow observed movement in the body. We compare the accumulation of fibres in the lungs versus the mesothelium, and then we give analysis and results for various cases of exposure level and exposure time. Models, such as the one developed here, can give clues as to how asbestos fibres impact the body, and where to look for major impact.

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Asbestos; exposure; transport; fibres; mesothelium; macrophage




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1. Introduction

Asbestos fibres are common in the modern environment, in industrial settings [2,6,19,35], in outdoor environments [30,33] and indoors as well [34]. Asbestos has excellent insulating properties and has been used in creating fire resistant materials, but use of asbestos is now restricted due to adverse effects on the human body. Asbestos fibres are often hard to detect but exposure can have detrimental effects on human health. Epidemiological evidence indicates a causal relationship between asbestos exposure and diseases like asbestosis, fibrosis, lung and laryngeal carcinoma, and malignant mesothelioma [3,8,16,29,31]. Asbestos minerals are found in the environment and industrial applications [18]. U.S. regulatory agencies recognize six asbestos and asbestiform minerals. They are actinolite, amosite, anthophyllite, chrysotile, crocidolite and tremolite [1]. These fibres have different characteristics, and a single type of asbestos may include both short and long fibres, which are handled somewhat differently in the body but are both harmful [13]. There are also non-regulated fibres probably just as dangerous with properties similar to asbestos. For example, carbon nanotubes may pose the same risks as asbestos, [14,25]. In this paper we will consider a single type of fibre.

A person who has had heavy or lengthy exposure to asbestos will have various amounts of fibres in virtually every organ of the body [9–12]. There are indications that the body has a threshold below which there is very little health risk, [27]. Organs in which asbestos is associated with cancer include the lungs and mesothelium [17].

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Asbestos fibres may be ingested orally but the most concerning route of entry is through the lungs. When dust is inhaled the first response is to cough and some of the load is removed by this primitive action. Some fibres that reach the lung are removed by mucociliary clearance and then are removed by coughing or ingestion [20,32]. Fibres that make it into the alveoli are attacked by the second line of defence in the lungs, alveolar macrophages. Macrophages envelop fibres in a process called phagocytosis and are moved to the airways where the particle-containing macrophages are transported out of the lung by mucociliary clearance [1]. This paper begins with fibres that have entered the lungs. Fibres that are not cleared from the lungs may be translocated to lymphatic fluid and from there to all parts of the body [4,5,7,17,21]. They may enter or leave a region, become lodged in tissue, or embedded in a single cell of tissue [17,21]. The processes by which fibres are translocated, cleared, lodged in tissue, and embedded in cells are the basis for the model presented here.

There is a very large body of material on the transition from healthy cells to cancerous cells caused by asbestos fibres, for example see the papers, [15,23,26]. The lymph system plays an important role in the immune response to asbestos [22,28] since immune cells move through the lymphatics, mature, and become activated there. These two aspects of the body's response will be left to a future paper.

Models, such as the one developed here, give clues as to how the fibres impact the body, what conditions favour accumulation of lodged and embedded fibres, and where to look for major impact. As with all models we make a number of simplifying assumptions but the model developed in this paper captures the transport modes described in the literature that pertain particularly to the lungs and the mesothelium.

In the paper we make the following explicit assumptions.

- All fibres are the same length and diameter. Asbestos fibres come in multiple lengths and diameters but for the purpose of this paper and for the simplicity of the model we will restrict to one fixed length and diameter.
- The exposure to asbestos will be from the air only. In fact there can be exposure through the gastrointestinal tract but in many cases that exposure is perhaps not as impactful.
- Accumulation of asbestos in the kidneys or gastrointestinal tract is not included in the model. Some asbestos is lost by passing from the body and some is gained by oral ingestion. Losses through excretion or the GI tract are included in the model.

In Section 2 we describe the model that will be used in this paper. The model is a simple linear model for the most part but a non-linearity enters due to certain rates being bounded. It could be argued that the model is too simple but it cannot be argued that it fails to capture the essence of the movement of asbestos fibres in the human body. In Section 3 we give the results and discussion. In Section 3.1 we describe how fibres are lodged in the mesothelium and lungs. In Section 3.2 a very important case is considered. What happens if after exposure the body is removed from exposure permanently? In addition to short-term clearance of fibres by macrophages, a slower clearance occurs through the lymphatic system [12]. The model captures that aspect of exposure, with free fibres being cleared from the body while fibres embedded in cells or lodged in tissue remain. In Section 3.3 we consider the question of what happens after long high level exposure. As would be expected, the load of asbestos increases in all of the organs. In Section 3.4 a closed subsystem is studied. We look

at the behaviour of free particles in the lungs and the macrophages. We are able to give a complete analysis of the behaviour of the model in this case and it follows observations of what happens in the body. In Section 3.5 we look at the differences in the consequences of short-term exposure versus long-term exposure for different levels of exposure. Section 4 concludes the paper.

2. A model of asbestos translocation in the body

An input function I describes asbestos particles that have entered the lung. From here, particles may be removed by macrophage ingestion, may become lodged in lung tissue or embedded in lung cells. They may also be translocated to the lymphatic system and from there pass to the pleural cavity, the mesothelium, the blood or soft tissue. Fibres may be cleared from the blood, through macrophage ingestion and subsequent elimination via the GI tract. The compartment model pictured in Figure 1 gives an overview of the processes modelled.

We note that there is a limit to the number of fibres removed by macrophages. Some particles are highly reactive and toxic to macrophage cells. Also, ‘overload’ conditions can occur where the number of inhaled particles overwhelms the ability of alveolar macrophages to clear them from the alveoli. Finally, macrophages may not be able to engulf larger particles in the alveoli and this results in ‘frustrated phagocytosis’ [24].

We note that Miserocchi *et al.* [21] present a block diagram that separates the translocation of fibres to pleural spaces and lymphatics. It also includes translocation from lungs to pulmonary capillaries or lymphatics; both leading to the blood. To simplify our system, we

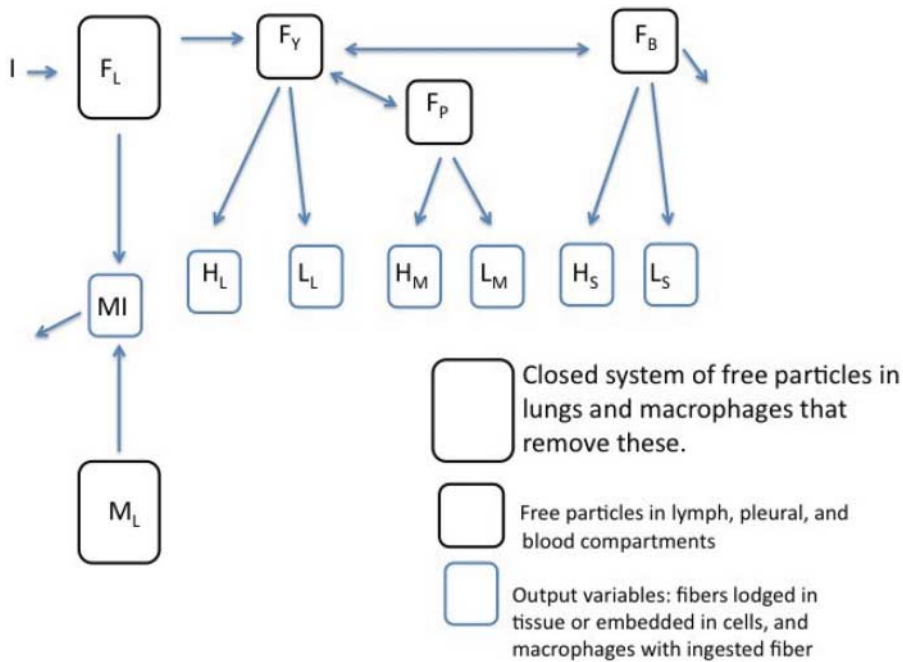


Figure 1. Compartment model.

do not include pulmonary capillaries directly and we model the movement of fibres from the lungs to the pleural cavity via the lymphatic system.

For all modelled quantities a standard notation is used. X_Y gives two pieces of information. X describes the local condition of particle: Free (F), Inside a macrophage (MI), embedded inside a Human tissue cell (H), Lodged or adsorbed in tissue (L). Y describes the location of particle in body: Lungs (L), Lymphatic (Y), Pleural cavity (P), Mesothelium (M), Blood (B), Soft tissue (S). For example, H_M refers to a fibre embedded in a mesothelial cell, whereas L_L is a fibre lodged in lung tissue. One quantity, M_L does not describe any asbestos fibres, rather it tracks the macrophages in the lungs that have not yet ingested a fibre.

2.1. Model equations

Free particles in the lungs (F_L) enter at some rate I and from there either pass into the lymphatic system or are removed by macrophages at a nonlinear rate G_{LM} .

$$F'_L = I - p_{LY}F_L - G_{LM}. \quad (1)$$

Macrophages arrive at the lungs at a constant rate c_1 and either ingest a fibre at nonlinear rate G_{LM} or are cleared naturally.

$$M'_L = c_1 - G_{LM} + G_I - c_2M_L. \quad (2)$$

Equations (1) and (2) do not depend on subsequent processes. Those free particles that are translocated to the lymphatic system will not return to the lungs but will circulate throughout the body as pictured in Figure 1. In particular, free particles in the lymphatic system, F_Y , arrive from the lungs, the blood, and the pleural cavity. These are lost by being lodged or embedded in lung tissue, or passed to the blood or pleural cavity, as described in Equation (3).

$$F'_Y = p_{LY}F_L + p_{BY}F_B + p_{PY}F_P - r_{YL}F_Y - u_{YL}F_Y - p_{YB}F_Y - p_{YP}F_Y. \quad (3)$$

Free particles in the pleural cavity, F_P , enter from the lymphatic system and may be returned to it or else lodged or embedded in mesothelial tissue, as described in Equation (4).

$$F'_P = p_{YP}F_Y - p_{PY}F_P - r_{PM}F_P - u_{PM}F_P. \quad (4)$$

Free particles in the blood, F_B , enter from the lymphatic system and may be returned to it or may become lodged or embedded in soft tissues which are lumped together as a single compartment. Fibres may also be cleared via the kidneys at nonlinear rate K_B .

$$F'_B = p_{YB}F_Y - p_{BY}F_B - r_{BS}F_B - u_{BS}F_B - K_B. \quad (5)$$

Macrophages that have ingested fibres, MI_L , are counted in a different compartment from which they are cleared via the nose or GI tract.

$$MI'_L = G_{LM} - a_MMI_L. \quad (6)$$

Equations (1)–(6) describe translocation of fibres in the body. In the lungs, mesothelium or soft tissue fibres may become lodged (L_L, L_M, L_S) or embedded (H_L, H_M, H_S) where they

remain. Accumulation in these compartments is described in Equations(7)–(12). These quantities are output variables that do not affect the above system.

$$H'_L = r_{YL}F_Y, \tag{7}$$

$$L'_L = u_{YL}F_Y, \tag{8}$$

$$H'_M = r_{PM}F_P, \tag{9}$$

$$L'_M = u_{PM}F_P, \tag{10}$$

$$H'_S = r_{BS}F_B, \tag{11}$$

$$L'_S = u_{BS}F_B. \tag{12}$$

Most of the transitions between compartments are linear. However some rates are bounded. The rate at which macrophages can ingest fibres in the lungs, G_{LM} is bounded. When exposure is high, macrophages will not be able to remove fibres beyond a certain rate, g_1 . This phenomenon is captured in Equation (13) .

$$G_{LM} = g_1 M_L F_L (g_2 + F_L)^{-1}. \tag{13}$$

Similarly, the rate at which kidneys can remove fibres from the blood, K_B , and the rate at which macrophages are recruited in the presence of irritation from fibres, G_I , are also bounded, as in Equations (14) and (15) .

$$K_B = k_1 F_B (k_2 + F_B)^{-1}, \tag{14}$$

$$G_I = g_{I1} F_L (F_L + g_{I2})^{-1}. \tag{15}$$

To obtain quantitatively accurate results good estimates of all of the parameters in the above equations are necessary. However qualitative results might be possible knowing only relative sizes of parameters. As default we set all parameters describing transitions between free particle compartments equal, while those that describe embedding of particles within a cell as small, while lodging of particles between cells or in tissue occurs at even smaller (tiny) rates. This relative size describes shorter, thinner fibres that more easily pass between cells but also more easily penetrate individual cells. For longer, thicker fibres these relative sizes would be reversed. In the event of inflammation, the pressure gradient from the lymphatic system to surrounding tissues will reverse, causing some transfer rates to rise and others to fall. In a situation of fibrosis, fibres have difficulty passing through tissue and some transition rates will fall. Table 1 describes how the model might be modified to address different conditions. Parameters that might vary from normal conditions are capitalized.

Table 1. Model parameters for short fibre asbestos.

Parameters	Relative size			
	Normal conditions	Inflammation	Fibrosis of lung	Fibrosis of mesothelium
p_{LY}	big (1)	big	SMALL	big
p_{YB}	big (1)	BIGGER	big	big
p_{BY}	big (1)	big	big	big
p_{YP}	big (1)	BIGGER	big	big
p_{PY}	big (1)	big	big	SMALL
r_{YL}	small (0.25)	big	small	small
r_{PM}	small (0.25)	small	small	small
r_{BS}	small (0.25)	small	small	small
u_{YL}	tiny (0.125)	SMALL	tiny	tiny
u_{PM}	tiny (0.125)	tiny	tiny	tiny
u_{BS}	tiny (0.125)	tiny	tiny	tiny
a_M	big (1)	big	big	big
g_1	big (2)	big	big	big
g_2	tiny (0.01)	tiny	tiny	tiny
k_1	big (1)	big	big	big
k_2	tiny (0.01)	tiny	tiny	tiny
g_{I1}	big (1)	big	big	big
g_{I2}	tiny (0.01)	tiny	tiny	tiny
c_1	medium (0.5)	medium	medium	medium
c_2	medium (0.5)	medium	medium	medium
I	varying (1)	varying	varying	varying

3. Results and discussion

3.1. Relative deposition of fibres in the lung and mesothelium

The model was implemented in MATLAB using constant input $I = 1$ and the initial number of macrophages in the lungs $M_L(0) = 3$. All other initial conditions were set to zero. At rates described in Table 1 as ‘normal’ the model predicts more fibres embedded and lodged in the lungs than in the mesothelium. The parameter values used in implementation are in parentheses after the relative size terms for normal conditions in the first column of Table 1. Figures 2 and 3 illustrate this result.

3.2. The effect of halting exposure

At negligible asbestos inputs, we can assume the nonlinear rates are zero, and also the input $I = 0$. Thus, in Equation (2) we have

$$M'_L = c_1 - c_2 M_L, \quad (16)$$

and at equilibrium, $M_L = c_1/c_2$. Similarly, macrophages that have ingested particles, MI_L , start at zero and obey

$$MI'_L = -a_M MI_L, \quad (17)$$

thus remaining at zero. This leads to a simplified form of Equations (1)–(4), yielding:

$$F'_L = -p_{LY} F_L, \quad (18)$$

$$F'_Y = p_{LY} F_L - (r_{YL} + u_{YL} + p_{YB} + p_{YP}) F_Y + p_{BY} F_B + p_{PY} F_P, \quad (19)$$

$$F'_P = p_{YP} F_Y - (p_{PY} + r_{PM} + u_{PM}) F_P, \quad (20)$$

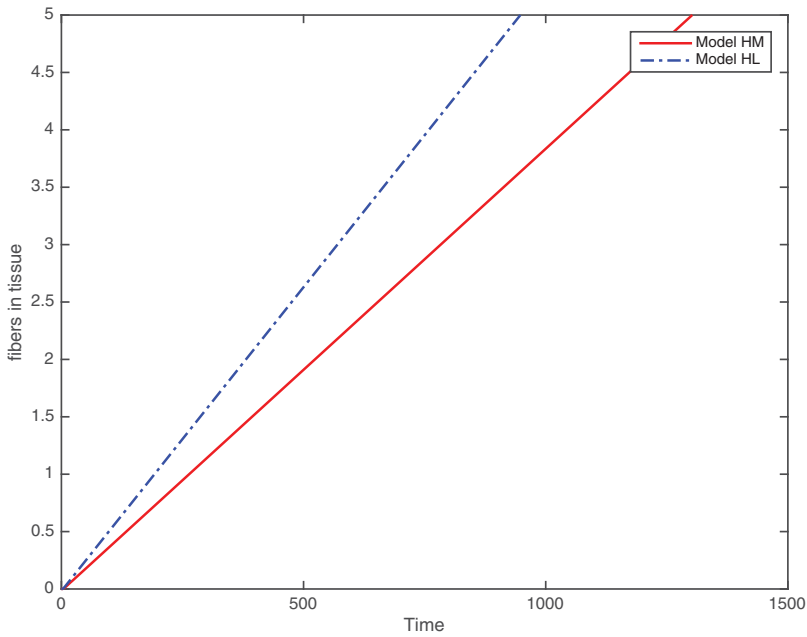


Figure 2. Accumulation of fibres in human tissue for lungs vs. mesothelium. HM represents the number of fibres embedded inside a human tissue cell in the mesothelium at time t , and HL represents the number of fibres embedded inside a human tissue cell in the lungs at time t . The graph shows that both quantities grow linearly with $HL > HM$ over time.

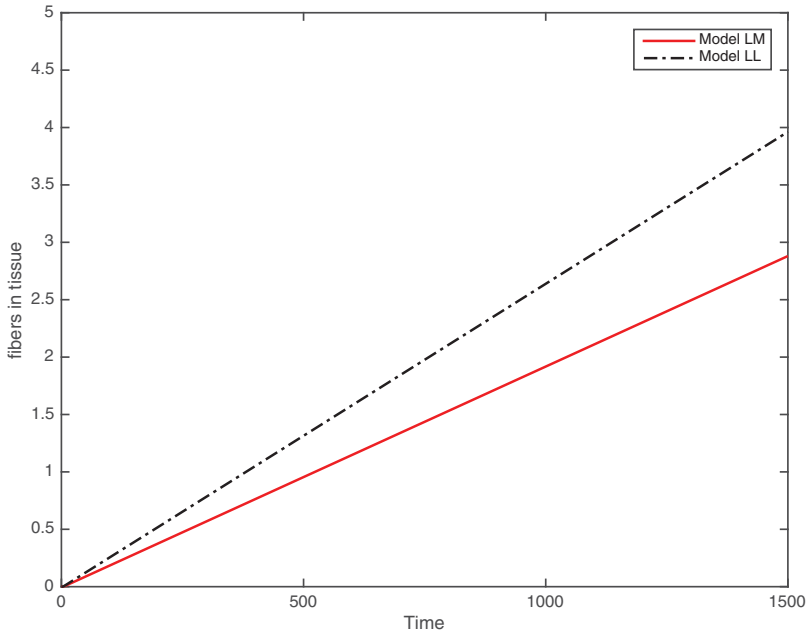


Figure 3. Accumulation of lodged fibres over time for lungs vs. mesothelium. LM represents the number of fibres lodged between cells or in tissue in the mesothelium at time t , and LL represents the number of fibres lodged between cells or in tissue in the lungs at time t . The graph shows that both quantities grow linearly with $LL > LM$ over time.

$$F'_B = p_{YB}F_Y - (p_{BY} + r_{BS} + u_{BS})F_B, \quad (21)$$

or equivalently, a linear system given by:

$$\begin{array}{cccc} -p_{LY} & 0 & 0 & 0 \\ p_{LY} & -\alpha & p_{PY} & p_{BY} \\ 0 & p_{YP} & -\beta & 0 \\ 0 & p_{YB} & 0 & -\gamma \end{array}$$

where $\alpha = r_{YL} + u_{YL} + p_{YB} + p_{YP}$, $\beta = p_{PY} + r_{PM} + u_{PM}$, $\gamma = p_{BY} + r_{BS} + u_{BS}$.

To show that the eigenvalues have negative real part it suffices to show this for the 3 by 3 sub matrix

$$\begin{array}{ccc} -\alpha & p_{PY} & p_{BY} \\ p_{YP} & -\beta & 0 \\ p_{YB} & 0 & -\gamma \end{array}$$

Gerschgorin's circle theorem guarantees negative real parts when

$$\alpha = r_{YL} + u_{YL} + p_{YB} + p_{YP} > p_{PY} + p_{BY}, \quad (22)$$

$$\beta = p_{PY} + r_{PM} + u_{PM} > p_{YP}, \quad (23)$$

$$\gamma = p_{BY} + r_{BS} + u_{BS} > p_{YB}. \quad (24)$$

As long as transfer rates for free particles are of comparable size among compartments, these criteria will be satisfied and the free particles will eventually be removed from the system of free particles. However the output variables describing fibres embedded in cells or lodged in tissue will reach a nonzero equilibrium that depends on initial conditions.

3.3. The effect of high asbestos inputs over a long period

At high asbestos inputs, we can assume that these rates are close to maximal, so that $G_{LM} = g_1$, $K_B = k_1$ and $G_I = g_{I1}$.

$$F'_L = I - p_{LY}F_L - g_1, \quad (25)$$

$$F'_Y = p_{LY}F_L - r_{YL}F_Y - u_{YL}F_Y - p_{YB}F_Y - p_{YP}F_Y + p_{BY}F_B + p_{PY}F_P, \tag{26}$$

$$F'_P = p_{YP}F_Y - p_{PY}F_P - r_{PM}F_P - u_{PM}F_P, \tag{27}$$

$$F'_B = p_{YB}F_Y - p_{BY}F_B - r_{BS}F_B - u_{BS}F_B - k_1, \tag{28}$$

$$MI'_L = g_1 - a_M MI_L, \tag{29}$$

$$M'_L = c_1 - g_1 + g_{I1} - c_2 M_L. \tag{30}$$

The last equation at equilibrium gives

$$M_L = c_2^{-1}(c_1 - g_1 + g_{I1}) = m_1 \tag{31}$$

and

$$MI_L = g_1 a_M^{-1} = m_2 \tag{32}$$

The four remaining differential equations then reduce to the same linear system as in the last section but with input vector $(I - g_1, 0, 0, -k_1)$. Under the same assumptions as above (that all transfer rates of free particles are about the same magnitude) the system will reach a unique stable equilibrium. Under such conditions the output variables describing lodged and embedded particles grow linearly over time, as seen in Figures 2 and 3.

3.4. The subsystem of free particles in the lung and macrophages

In the full nonlinear system, the subsystem below is independent of the other four differential equations:

$$F'_L = I - p_{LY}F_L - G_{LM}, \tag{33}$$

$$M'_L = c_1 - G_{LM} + G_I - c_2 M_L, \tag{34}$$

$$G_{LM} = g_1 M_L F_L (g_2 + F_L)^{-1}, \tag{35}$$

$$G_I = g_{I1}(F_L)(F_L + g_{I2})^{-1}. \tag{36}$$

Simplifying the calculation by setting $g_2 = g_{I2}$, eliminating the input of asbestos ($I = 0$) and setting both of the resulting differential equations to zero yields:

$$0 = p_{LY}F_L - G_{LM}, \tag{37}$$

Which gives two nullclines of

$$F_L = 0 \tag{38}$$

and

$$p_{LY}F_L + g_1 M_L = -p_{LY}g_2, \tag{39}$$

and the second equation gives

$$0 = -(g_1 + c_2)M_L F_L + (c_1 + g_{I1})F_L - c_2 g_2 M_L + c_1 g_2. \tag{40}$$

Substituting yields a quadratic in F_L all of whose coefficients are positive. By DesCartes' rule of signs, there is no positive real root. Thus the only equilibrium of this pair of equations is when $F_L = 0$ and $M_L = c_1 c_2^{-1}$. Thus, with only minimal assumptions on the size of parameters, the lungs in this model eventually clear of free fibres.

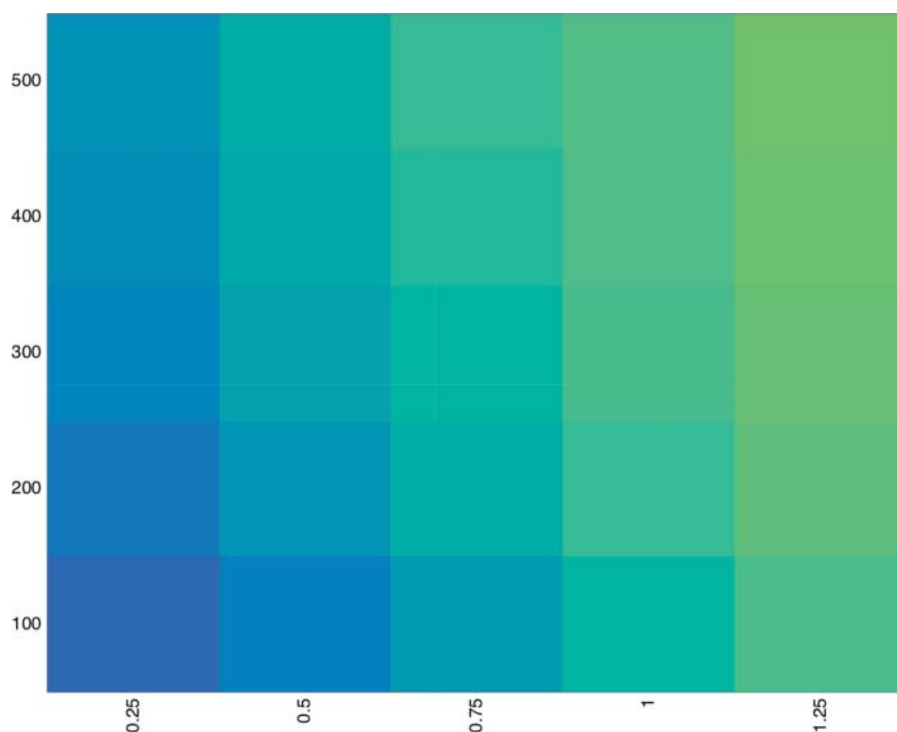


Figure 4. Heat map for accumulation of fibres in the mesothelium. The horizontal axis denotes exposure level, I and the vertical axis denotes duration of exposure in (unspecified) time units. After exposure ends, the model was run to equilibrium. The colour scale goes from low levels of fibre in the mesothelium (blue) to high levels (green). The values range from 0.0196 to 6.9821. Note that at low levels of exposure, the eventual amount of fibre in the mesothelium remained low. At the highest level of exposure, even a short exposure time leads to high levels of fibres in the mesothelium.

3.5. The effect of high exposure levels versus long exposure time

A numerical experiment was conducted under the ‘normal’ conditions parameterized in Table 1 to see the qualitative effects of varying exposure times and exposure levels. The exposure level, I was varied from 0.25 to 1.25, while the duration of exposure was varied from 100 to 500 time units. After exposure ceased the model was run to equilibrium. The amount of fibres embedded in mesothelial cells is shown in Figure 4 on a colour scale from blue (few) to green (many). Figure 4 suggests that, under conditions described as ‘normal’ in Table 1, low exposure for a long time is less detrimental than high exposure for a relatively short amount of time.

4. Conclusion

The model developed here illustrates some qualitative aspects of asbestos translocation in the body. Under conditions corresponding loosely to normal (undiseased) physiology, the model predicts that for short, thin fibres:

- When exposure ends the system will clear of free asbestos fibres, leaving only those that are embedded in cells or lodged in tissue.

- Under conditions of prolonged constant high exposure, the subsystem of free asbestos fibres will arrive at equilibrium but the fibres that are embedded in cells or lodged in tissue will continue to rise linearly.
- Long, low level exposure results in fewer fibres embedded in mesothelial cells than relatively short, high exposure levels.

The results of this study suggest that the model will have some value in understanding qualitative differences in outcomes for different types of fibre and under changes in health condition. In addition, better information about model parameters may allow for more precise, quantitative predictions about the amount of fibre likely to be found embedded in cells after a certain amount of exposure for a given length of time. This type of prediction is needed to settle outstanding questions about safe exposure levels.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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