

Mathematical model of phagocytosis and inflammation after the inhalation of quartz at different concentrations

by Chi-Lang Tran,¹ Alan D Jones,¹ Ken Donaldson²

Tran CL, Jones AD, Donaldson K. Mathematical model of phagocytosis and inflammation after the inhalation of quartz at different concentrations. *Scand J Work Environ Health* 1995;21 suppl 2:50—4.

A mathematical model was developed with several distinctive features to represent the various processes leading to silicosis. It assures the phagocytosis of quartz by the resident alveolar macrophages. It then models the necrosis of macrophages caused by the ingestion of quartz particles and the subsequent release of these clusters onto alveolar surfaces. The inflammatory recruitment of alveolar macrophages and neutrophils in response to the cell necrosis caused by the ingestion of quartz particles is described in a functional form and is included in the model. The model also describes the pathological and other biological reactions to quartz particles in the interstitium. Specifically, once the quartz particles arrive at the interstitium, they can be phagocytosed by interstitial macrophages. The pathological interaction between quartz and interstitial macrophages may lead to quartz particles being sequestered in silicotic nodules, and also cleared to the efferent lymph nodes.

Key terms alveolar macrophage, interstitial macrophage, neutrophil, silicosis.

The function of the immune system of the alveolar region of the lung is to protect its integrity from damage caused by invading pathogens. The first line of the defense is the resident alveolar macrophage (1), the primary function of which is to take up the pathogens and, incidentally, particles and fibers, and neutralize and remove them from the site of injury. The breakdown of these functions is known to be the cause of lung pathologies.

The purpose of this paper is to describe these functions mathematically and to make available the key concepts of the model so as to provide a framework for the analysis and interpretation of data from animal studies involving the instillation or inhalation of cytotoxic quartz particles.

Phagocytosis, clearance and inflammation

The clearance of silica particles depends primarily on the ability of the alveolar macrophages to detect, phagocytose, and transport particles to the mucociliary escalator, where they are eliminated from the lung. Macrophages can detect particles either by random encounters or by chemotaxis generated by the particles (2). The balance between the rate of macrophage efflux and replacement is maintained in a steady state (3). The ability of macrophages to phagocytose and remove the particles from alveoli becomes impaired as the maximum load capacity ($n_{\max}$) approaches saturation. Impaired phagocytosis and macrophage immobility is known as the "overload" phenomenon (4).

When macrophages are overloaded, they lose their ability to respond to chemotactic gradients and fail to migrate from the

alveoli to the mucociliary escalator (5); they die and release particles into the extracellular environment (6, 7).

The difficulty facing local macrophages in eliminating particles is manifested by the release of acute inflammatory mediators by particle-laden macrophages, especially interleukin-1 and leukotriene (LTB_4). Inflammation can occur in "overload" situations, although small doses of toxic particles may not elicit any reaction (9).

Further recruitment of phagocytes is required if inhaled silica dusts are not eliminated. Chronic deposition of dust leads to the necrosis of the macrophages, and the subsequent release of particles ensures that free quartz remains on the alveolar surface. This cyclic capture and release of particles leads to a continuing recruitment of alveolar macrophages and neutrophils, and over time produces "chronic inflammation." A schematic description of the process of inflammation is presented in figure 1.

Modeling phagocytosis

The basic model. Let AM_i be the population of AM cells containing i quartz particles ($i = 0, 1, \dots, n$), AM_0 being the population of particle-free alveolar macrophages, and AM_n the population of macrophages with the maximum load, containing n particles. The total population of macrophages at any time t is $AM(t)$ and is the total sum of all the macrophages belonging to their respective load class:

$$AM(t) = \sum_{i=0}^n AM_i(t). \quad \text{equation 1}$$

¹ The Institute of Occupational Medicine, Edinburgh, Scotland, United Kingdom.

² The Department of Biological Sciences, Napier University, Edinburgh, Scotland, United Kingdom.

Reprint requests to: CL Tran, The Institute of Occupational Medicine, 8 Roxburgh Place, Edinburgh EH8 9SU, Scotland, UK.

Similarly, the macrophage burden at any time t is:

$$X_2(t) = \sum_{i=0}^n imAM_i(t), \quad \text{equation 2}$$

where m is the average mass of a single quartz particle and i is the number of quartz particles representing the load class i . Note that during phagocytosis, macrophages enter the next load class when they ingest additional quartz particles.

The process of phagocytosis by alveolar macrophages can be described as

$$\begin{aligned} \frac{dAM_0}{dt} &= R_{AM} - k_{10}X_0AM_0 - (p_0 + q_0)AM_0 \\ \frac{dAM_j}{dt} &= k_{j-1}X_0AM_{j-1} - k_{j+1}X_0AM_j - (p_j + q_j)AM_j, \quad 0 < j < n \\ \frac{dAM_n}{dt} &= k_{n-1}X_0AM_{n-1} - (p_n + q_n)AM_n, \end{aligned} \quad \text{equation 3}$$

where R_{AM} is the inflammatory recruitment rate of alveolar macrophages, p_j and q_j are respectively the transfer rate to the mucociliary escalator and the death rate of macrophages belonging to class j , X_0 is the number of free quartz particles caused in the alveolar region by inhalation plus release via the necrosis of alveolar macrophages and neutrophils, k_{j-1} is the phagocytosis rate coefficient for alveolar macrophages of class $j-1$ (ie, the average probability

that a given macrophage from load class AM_{j-1} will ingest a free quartz particle in time dt). The system of differential equation 3 is also used to model the process of phagocytosis by neutrophils, and the process is shown diagrammatically in figure 2.

Constraints. As the phagocytosis of silica particles progresses, the cytotoxic effect of quartz on alveolar macrophages renders them less mobile and, consequently, their capacity for further phagocytosis is reduced. If s is the number of quartz particles representing the sublethal dose ingested by an alveolar macrophage, then we can assume that the phagocytosis rates (k) for macrophages with fewer than s particles is the same for all; for alveolar macrophages with more particles than s , the rate of phagocytosis diminishes as the load increases:

$$k_{10} = k_{21} = \dots = k_{s-1}; k_{s+1} > \dots > k_{n-1}. \quad \text{equation 4}$$

Similarly, the transfer rates depend on particle load:

$$p_0 = p_1 = \dots = p_s > p_{s+1} > \dots > p_n. \quad \text{equation 5}$$

The death rate of macrophages is also expected to increase with the number of quartz particles ingested once the sublethal number of quartz particles ingested has been reached, and again a similar type of relationship is assumed:

$$q_0 = q_1 = \dots = q_s < q_{s+1} < \dots < q_n. \quad \text{equation 6}$$

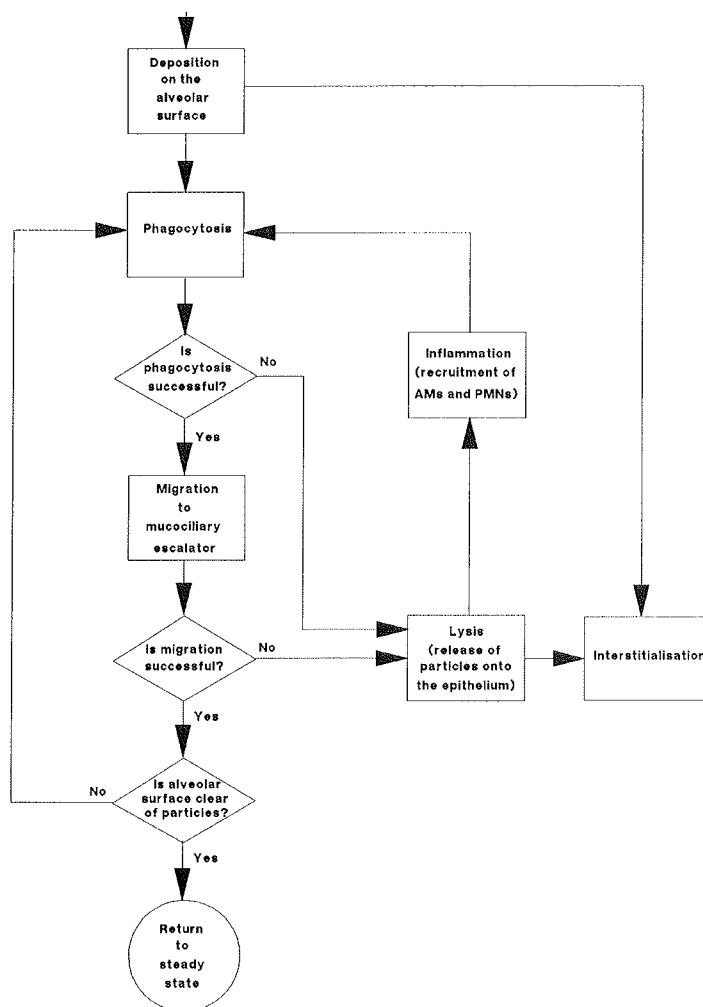


Figure 1. Phagocytosis, migration to the mucociliary escalator, interstitialization, and inflammation. (AM = alveolar macrophages, PMN = neutrophils)

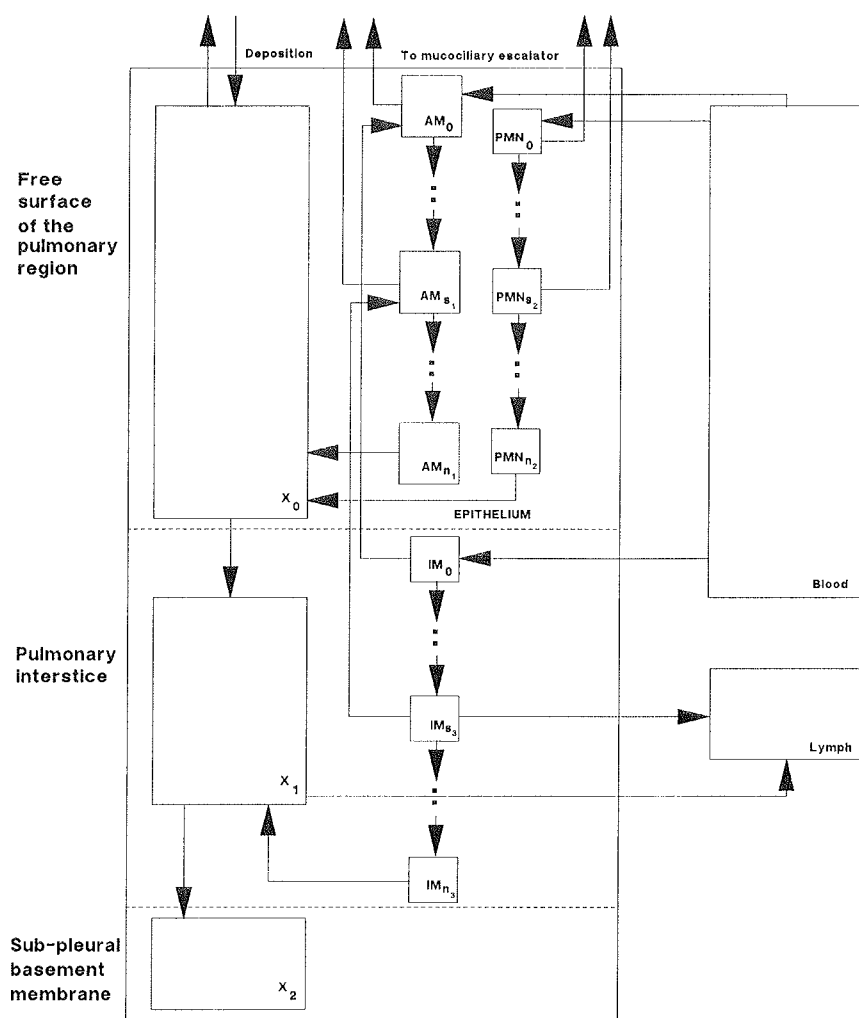


Figure 2. Mathematical model for phagocytosis and inflammation after the inhalation of quartz particles. (X_0 = free quartz particles on the alveolar surface, AM_j = alveolar macrophages of load-class j , $0 \leq j \leq n_1$, n_1 = maximum number of quartz particles ingested per alveolar macrophage, s_1 = critical number of quartz particles ingested per alveolar macrophage, Blood = blood compartment, PMN_j = neutrophils of load-class j , $0 \leq j \leq n_2$, n_2 = maximum number of quartz particles ingested per neutrophil, s_2 = critical number of quartz particles ingested per neutrophil, X_1 = free quartz particles in the interstitium, IM_j = interstitial macrophages of load-class j , $0 \leq j \leq n_3$, n_3 = maximum number of quartz particles ingested per interstitial macrophage, s_3 = critical number of quartz particles ingested per interstitial macrophage, lymph = lymph node compartment, X_2 = free quartz particles in the subpleural basement membrane)

Modeling the inflammatory recruitment of alveolar macrophages and neutrophils. Macrophages and neutrophils with more than their respective sublethal dose of quartz particles will be in distress. The chemotactic signal released by these phagocytes is

$$G = l_1 \sum_{i=s_1+1}^{n_1} AM_i + l_2 \sum_{i=s_2+1}^{n_2} PMN_i, \quad \text{equation 7}$$

where l_1 and l_2 are the chemotactic signals released by each alveolar macrophage and neutrophil, s_1 and s_2 are the sublethal numbers of quartz particles for alveolar macrophages and neutrophils, and n_1 and n_2 are the maximum numbers of quartz particles ingested by alveolar macrophages and neutrophils, respectively.

The inflammatory recruitment for alveolar macrophages can be described in a functional form as:

$$R_{AM} = \frac{(R_{1max} - R_{min})}{\left[\frac{k_1}{G} + 1\right]} + R_{min}, \quad \text{equation 8}$$

and similarly, for neutrophils:

$$R_{PMN} = \frac{(R_{2max})}{\left[\frac{k_2}{G} + 1\right]}, \quad \text{equation 9}$$

R_{1max} and R_{2max} are the maximum recruitment rate for alveolar macrophages and neutrophils (10). R_{min} is the minimum recruitment rate for alveolar macrophages required when the AM population is in a steady state. The k 's are constants determining how fast the recruitment rate approaches its maximum value. A differential equation for the kinetics of the total alveolar macrophage (AM) population can be derived by adding all the individual equations of the system 3:

$$\frac{dAM}{dt} = \sum_{i=0}^n \frac{dAM_i}{dt} = R_{AM} - \sum_{i=0}^n (p_i + q_i) AM_i, \quad \text{equation 10}$$

The solution to equation 10 can be compared with data of alveolar macrophage kinetics available from instillation and inhalation studies (11).

Interstitial model

The continuing presence of quartz particles on the epithelium will increase their likelihood of being transferred to the interstitium. As quartz particles are transported, they are confronted by interstitial macrophages. Equation 3 is also used to describe the phagocytosis of quartz particles by interstitial macrophages. Fibroblast

cells (N_f) proliferate while they are activated by the chemotactic signals produced by distressed interstitial macrophages:

$$\frac{dN_f}{dt} = k_3 \sum_{i=s_3+1}^{n_3} IM_i, \quad \text{equation 11}$$

where s_3 and n_3 are the sublethal doses of quartz and the maximum number of silica particles ingested by an interstitial macrophage and k_3 is the chemotactic signal released per interstitial macrophage cell. These fibroblast cells are also activated to produce collagen leading to interstitial fibrosis.

Results

Experimental rat studies on deposition and clearance were carried out at the Institute of Occupational Medicine (5, 12). The purpose of these studies was to determine the retention and clearance of cytotoxic and inert dusts such as quartz and titanium dioxide and the cellular response from the alveolar region of the lung following the inhalation of these dusts.

The quartz burdens on lungs and lymph nodes (12), together with the alveolar macrophage and neutrophil numbers in the bronchoalveolar lavage (BAL) fluid, were used to test the current model. The strategy for simulation is (i) to obtain as many estimated parameters from the literature as possible (10, 13, 14, 15); (ii) to use one data set of the aforementioned experiments — the exposure of rats to quartz at $50 \text{ mg} \cdot \text{m}^{-3}$ — to estimate the remaining parameters of the model; (iii) to develop a complete estimated parameter set to be used in simulations of other exposure situations; and (iv) and to compare the results with the experimental data (ie, exposure to 1, 10 and $30 \text{ mg} \cdot \text{m}^{-3}$). The aim of this strategy was to reduce the number of parameters to be estimated from the data set to a minimum. Figures 3 and 4 show the inflammatory recruitment of alveolar macrophages and neutrophils after the inhalation of quartz at 10 and $50 \text{ mg} \cdot \text{m}^{-3}$ and the simulation of this recruitment by the model. Similarly, the results from the

simulations and the experimental data for the lung burdens and lymph node burdens are shown in figures 5 and 6. Additional details can be obtained from our earlier work (16).

The simulations of the alveolar macrophage and neutrophil response to the deposition of quartz, as well as the time course of lung and lymph node burden of this dust under different exposure levels, have compared well with the data from experimental studies carried out at the Institute of Occupational Medicine. However, the current model is one of a very complex system; thus the problem of over-parameterization is hard to avoid. Nonetheless the main aims of the model are (i) to offer a mathematical description of the hypotheses regarding the mechanisms of this system (eg, the phagocytosis rate or the inflammatory recruitment rate) which can be refuted, verified, and measured by further experimental investigations and (ii) to identify important areas in the system for which further investigations are needed. Thus it is hoped that this exercise will stimulate further experimental studies aimed at identifying the complete model.

Concluding remarks

The process of phagocytosis of quartz particles by alveolar macrophages and neutrophils is described as a system of differential equations. A Michealis-Menten type of equation is used to model the inflammatory recruitment of alveolar macrophages and neutrophils. The same types of differential equations are also used to describe the movement of free quartz particles to the interstitium and their subsequent phagocytosis by interstitial macrophages. These equations, together with the parameter values found in the literature or estimated from experimental data (10, 13, 14, 15) provide a framework for the simulation of data for the retention and clearance of quartz particles in the alveolar region. This mechanistic model elucidates the effects of impaired phagocytosis and chronic inflammation leading to the development of interstitial fibrosis. The consequences of phagocytosis such as the release of

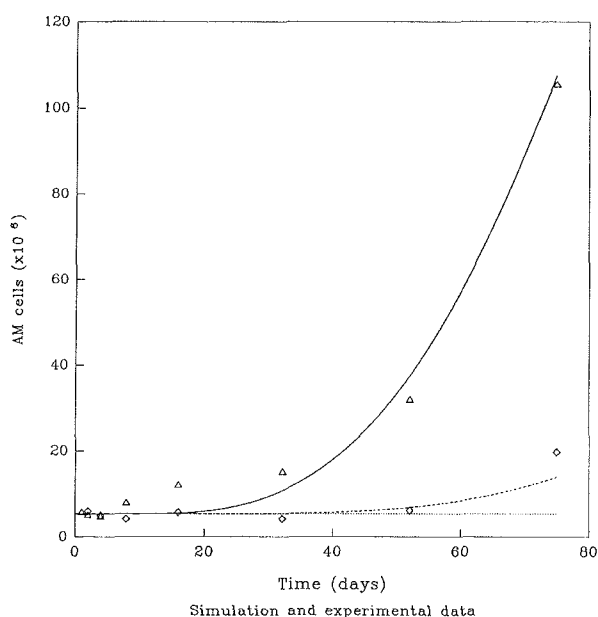


Figure 3. Alveolar macrophage (AM) population following the inhalation of quartz at 50 and $10 \text{ mg} \cdot \text{m}^{-3}$. (Δ = concentration $50 \text{ mg} \cdot \text{m}^{-3}$, $\diamond$ = concentration $10 \text{ mg} \cdot \text{m}^{-3}$, — = simulation at $50 \text{ mg} \cdot \text{m}^{-3}$, --- = simulation at $10 \text{ mg} \cdot \text{m}^{-3}$, ... = steady state population)

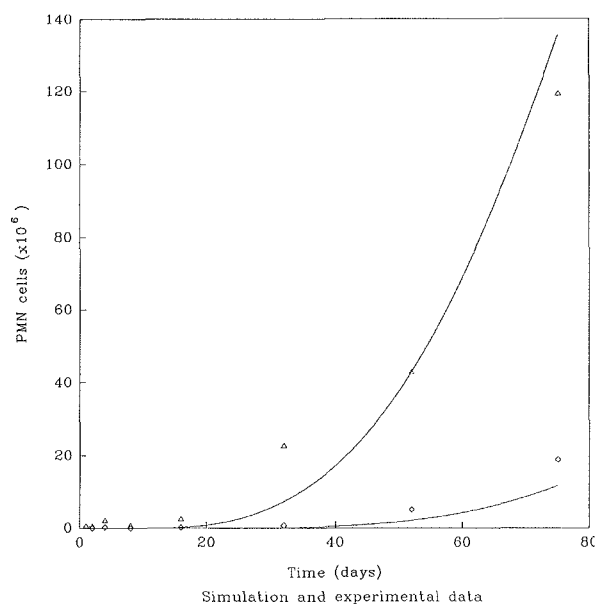


Figure 4. Neutrophil population following the inhalation of quartz at 50 and $10 \text{ mg} \cdot \text{m}^{-3}$. (Δ = concentration $50 \text{ mg} \cdot \text{m}^{-3}$, $\diamond$ = concentration $10 \text{ mg} \cdot \text{m}^{-3}$, — = simulation at $50 \text{ mg} \cdot \text{m}^{-3}$, --- = simulation at $10 \text{ mg} \cdot \text{m}^{-3}$)

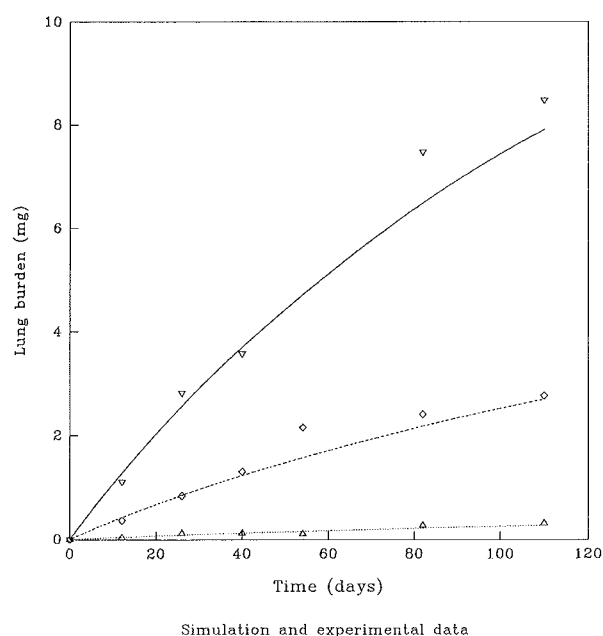


Figure 5. Lung burden following the inhalation of quartz at 1, 10 and 30 $\text{mg} \cdot \text{m}^{-3}$. ($\circ$ = concentration 30 $\text{mg} \cdot \text{m}^{-3}$, $\diamond$ = concentration 10 $\text{mg} \cdot \text{m}^{-3}$, $\triangle$ = concentration 1 $\text{mg} \cdot \text{m}^{-3}$, — = simulation at 30 $\text{mg} \cdot \text{m}^{-3}$, --- = simulation at 10 $\text{mg} \cdot \text{m}^{-3}$, ... = simulation at 1 $\text{mg} \cdot \text{m}^{-3}$)

oxidant radicals and proteases can be quantified readily. The damage to type I epithelial cells by oxidant stress and the replacement of these cells by type II cells can also be modeled. Such modeling will form the basis for a mechanistic model of the development of silica-related carcinomas.

References

- Brain JD. Lung macrophages: how many kinds are there? What do they do? *Am Rev Respir Dis* 1988;137:507—9.
- Warheit DB, Overby LH, George G, Brody AR. Pulmonary macrophages are attracted to inhaled particles through complement activation. *Exp Lung Res* 1988;14:51—66.
- Blusse van Oud Alblas A, Mattie H, van Furth R. A quantitative evaluation of pulmonary macrophage kinetics. *Cell Tissue Kinet* 1983;16:211—9.
- Morrow PE. Possible mechanisms to explain dust overloading of the lungs. *Fundam Appl Toxicol* 1988;10:369—84.
- Donaldson K, Bolton RE, Jones AD, Brown GM, Robertson MD, Slight J, et al. Kinetics of the bronchoalveolar leukocyte response in rats during exposure to equal airborne mass concentration of quartz, chrysotile asbestos or titanium dioxide. *Thorax* 1988;43:159—62.
- Allison AC, Harington JS, Birbeck M. An examination of the cytotoxic effects of silica on macrophages. *J Exp Med* 1966;124:211—9.
- Katsnelson BA, Priladova LI. Recruitment of phagocytosing cells in the respiratory tract as a response to cytotoxic action of deposited particles. *Environ Health Perspect* 1984;55:313—25.
- Adamson IYR, Friedlitis H, Bowden DH. Instillation of chemotactic factor

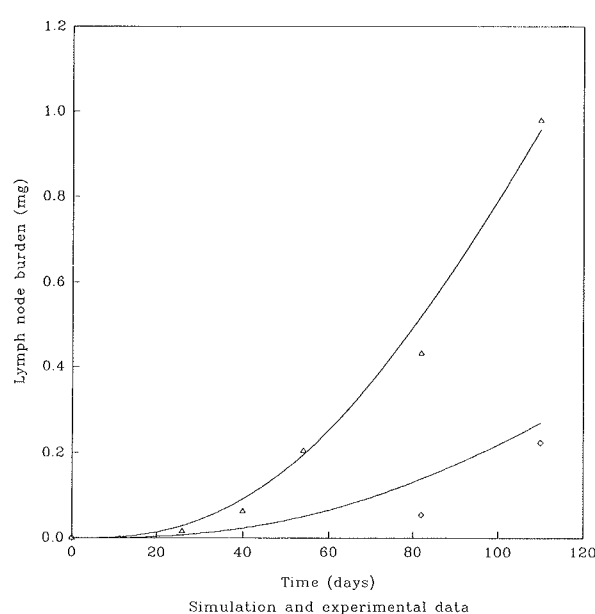


Figure 6. Lymph node burden following the inhalation of quartz at 10 and 30 $\text{mg} \cdot \text{m}^{-3}$. ($\triangle$ = concentration 30 $\text{mg} \cdot \text{m}^{-3}$, $\diamond$ = concentration 10 $\text{mg} \cdot \text{m}^{-3}$, — = simulation at 30 $\text{mg} \cdot \text{m}^{-3}$, --- = simulation at 10 $\text{mg} \cdot \text{m}^{-3}$)

to silica-injected lungs lowers interstitial particle content and reduces pulmonary fibrosis. *Am J Pathol* 1992;141:319—26.

- Brody AR, Roe MW. Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. *Am Rev Respir Dis* 1983;128:724—9.
- Stöber W, Morrow PE, Hoover MD. Compartmental modelling of the long-term retention of insoluble particles deposited in the alveolar region of the lung. *Fundam Appl Toxicol* 1989;13:823—42.
- Driscoll KE, Lindenschmidt RC, Maurer JK, Higgins JM, Ridder G. Pulmonary response to silica and titanium dioxide: inflammatory cells, alveolar macrophage-derived cytokines, and histopathology. *Am J Respir Cell Mol Biol* 1990;2:381—90.
- Jones AD, McMillan C, Johnston AM, McIntosh C, Cowie H, Parker I, et al. Animal studies to investigate the deposition and clearance of inhaled mineral dusts: final report on CEC Contract 7248/33/026. Edinburgh: Institute of Occupational Medicine (IOM), 1988. IOM report TM/88/05.
- Stöber W, Morrow PE, Morawietz G. Alveolar retention and clearance of insoluble particles in rats simulated by a new physiology-oriented compartmental kinetics model. *Fundam Appl Toxicol* 1990;15:329—49.
- Stöber W, Koch W. Steady-state load distribution of insoluble particles in alveolar macrophages. *Inhalation Toxicol* 1991;3:181—93.
- Katsnelson BA, Konyshova LK, Privalova LI, Morosova KI. Development of a multicompartamental model of the kinetics of quartz dust in the pulmonary region of the lung during chronic inhalation exposure of rats. *Br J Ind Med* 1992;49:172—81.
- Tran CL, Jones AD, Donaldson K. Development of a dosimetric model for assessing the health risks associated with coalmine dusts: final report on CEC Contract 7248/07/015. Edinburgh: Institute of Occupational Medicine (IOM), 1994. IOM report TM/94/01.