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Determinants of the pathogenicity of man-made vitreous fibers (MMVF)

Abstract ***Introduction and objectives:*** A number of man-made vitreous fibers (MMVF) have been developed over the years to replace asbestos fibres in its uses as insulating material. Concerns have been raised that these man-made fibers may also pose a significant health hazard when inhaled during their manufacture and application. As will be discussed in this brief overview, dose, dimension and durability of fibrous particles are key parameters with respect to the induction of adverse pulmonary effects, including carcinogenicity as well as non-cancer effects. In particular, fiber biopersistence plays a most important role for pulmonary pathogenicities, and consequently biopersistence receives greatest attention in the search of new fibrous materials. ***Methods and results:*** Tests to evaluate fiber biopersistence include the administration of fibers by a short-term inhalation (5 days) or intratracheal instillation into rats. Advantages of the inhalation methodology include the even distribution throughout the lung administered by a physiological process. A disadvantage of this method is the limited respirability of long fibers in the rat whereas they are well respirable by humans. Such long fibers (>20 μm) have the greatest potential for tumorigenicity and need special consideration in connection with the evaluation of fiber biopersistence. Enrichment of the inhaled aerosol by these long fibers needs to be considered in order to deposit enough of them in the lower respiratory tract of the rat. In contrast, the advantage of the instillation technique is that these long fibers can be delivered to the lung. However, the major disadvantages of intratracheal instillations are the potential of the administered fibers to form clumps and aggregates in the airways and the induction of a major inflammatory response when high-bolus doses are administered. This could influence fiber dissolution in the lungs significantly. ***Conclusions:*** At the same delivered lung dose, a fiber of low biopersistency has the least effect and is, therefore, less likely to induce lung or pleural tumors even under chronic exposure conditions. Respective animal studies with more fibers of different biopersistence have confirmed this general principle. It is very important that, when evaluating and interpreting fiber effects observed in experimental animals, species differences with respect to respirability, lung retention and mechanisms of responses are considered.

Key words Biopersistence · Man-made vitreous fiber · Durability · Dimension · Lung tumor · Inflammation · Fibrosis

Introduction

Asbestos fibers, both amphiboles and serpentines, have been found to be biologically much more active than man-made vitreous fibers (MMVF). However, among the different MMVF, there is also a considerable difference in their pathogenicity, and there is a continuing effort to develop new fibers without significant pathogenic potential. In most cases, there are insufficient human data regarding the pathogenicity of MMVF, either because of their low toxicity, their use in more recent times only, their much lower exposure concentration than historically had been the case for asbestos fibers, or because of a very long latency period. Because of the difficulty to obtain respective human data to evaluate pathogenicity, results of animal studies are being used to determine potential adverse effects of synthetic vitreous fibers after different routes of administration. Routes of administration in animal studies include inhalation as

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well as intratracheal instillation and also intraperitoneal injection, and the assumption is that the mechanisms of inducing adverse effects is the same in animals and in humans with respect to cancer and non-cancer endpoints. The cancer endpoints include lung and pleural tumors, and the non-cancer endpoints pulmonary inflammation, cell proliferative responses, target cell activation and fibrosis. There are a number of host and fiber-related parameters that influence the pathogenicity of inhaled fibers, and the following sections will discuss some of these related to the fiber dose, fiber dimension, and fiber durability (3Ds).

Fiber dose and adverse effects

The dose of a particulate compound delivered to the lung by inhalation is generally expressed as particle mass. Other dosemetrics that have been used in particle toxicology are particle volume (for example, particle overload responses, [Morrow 1988]), particle surface area (correlation of different pulmonary responses with different particle sizes down to ultrafines [Oberdörster et al. 1996]), and particle number. With respect to fibrous particles, it is generally accepted that fiber number is the best dose parameter to characterize responses. Also, occupational exposure standards for fibers are expressed as fiber number/cm^3. It should, however, be remembered that an exposure concentration (number of fibers/cm^3) is not a dose, and the term exposure-dose should be avoided since it is confusing. Figure 1 shows the exposure–dose–response paradigm, demonstrating the correlation between those three parameters. The respirability of an inhaled concentration of fibers determines the dose to the lower respiratory tract which in turn via specific mechanisms eventually may result in a response. The initially deposited dose will be different from the dose retained after a period of time has elapsed, due to the amount cleared in that time period (Fig. 1).

When rodents and humans are exposed to the same exposure concentration, the dose depositing in their respective lower respiratory tracts will be quite different since fiber respirability between these two species is significantly different. Figure 2 shows predicted deposition efficiencies between rats and humans of fibrous and non-fibrous particles with different aspect ratios. Although the general shape of these deposition curves are similar between rats and humans, the aerodynamic diameters of those fibrous and non-fibrous particles which will reach the alveolar structures of the rodent and human lung are very different, with a maximum aerodynamic size of ~5 μm reaching the alveoli in the rat and ~10 μm in the human lung (Dai and Yu 1998).

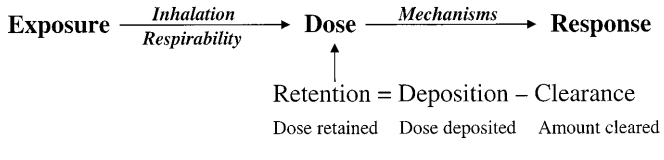

Fig. 1 Exposure–dose–response paradigm

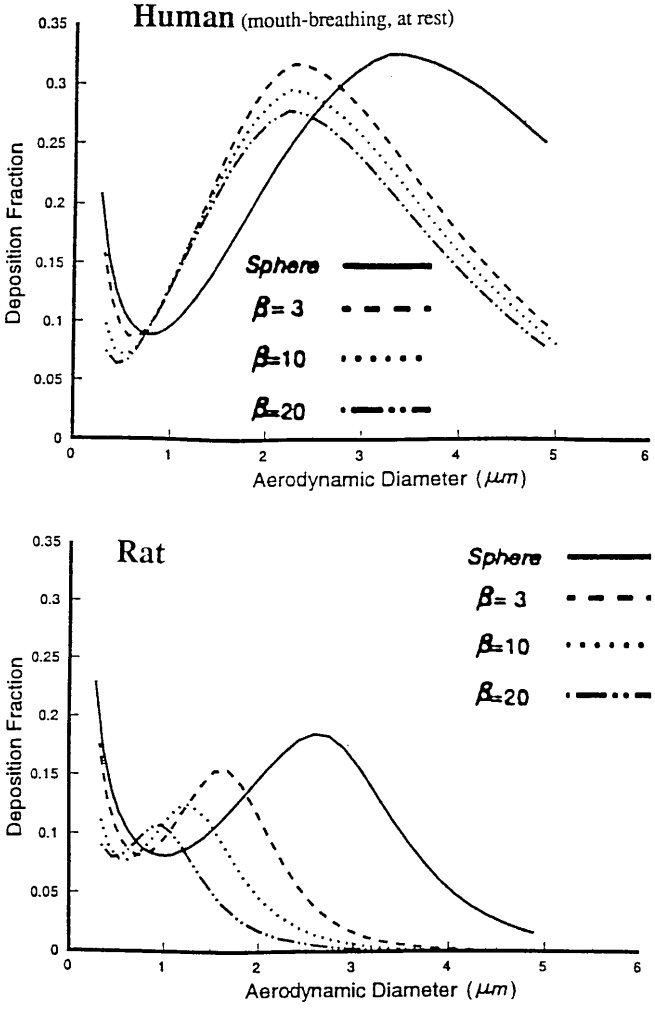

Fig. 2 Respirability (deposition efficiency in alveolar region) of spherical and fibrous particles in humans and rats. (From Dai and Yu 1998)

Figure 3 is an example of the complexity of a dose–response curve obtained in a chronic 2-year inhalation study with refractory ceramic fibers in rats (Mast et al. 1995a, b). Shown is the tumor response in a multi-dose 2-year inhalation study in rats correlated here with both the exposure concentration and the retained dose, which range from 36 to 234 fibers/cm^3 and from 0.71×10^4 to 4.81×10^4 fibers/lung. It turned out that only the highest exposure concentration resulted in a significant tumor response, whereas the lower concentrations were not significantly different from control levels. Although this result is consistent with a non-linear response similar to what has been observed in high-concentration particle overload studies in rats, a non-linear response cannot be excluded given the large scatter of the observed tumor incidences. For risk assessment purposes the shape of the dose–response curves has to be considered since a linear extrapolation to very low concentrations

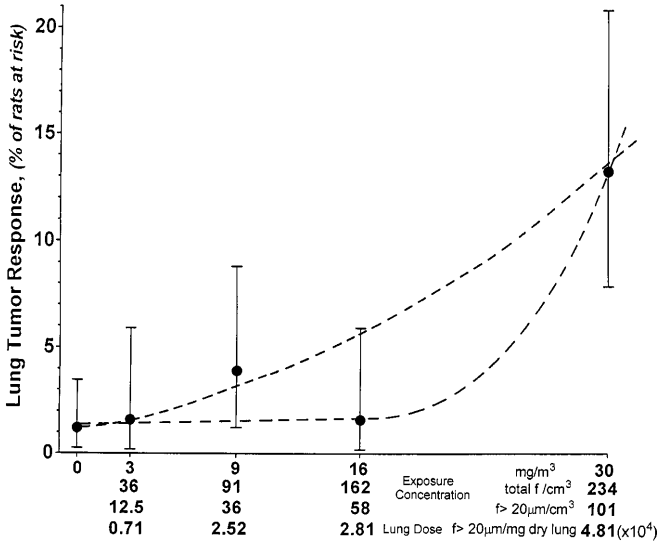

Fig. 3 Rat lung tumor response after 2-year RCF exposure correlated with inhaled fiber concentration and retained lung burden of fibers longer than 20 μm (percent of rats and 95% CI)

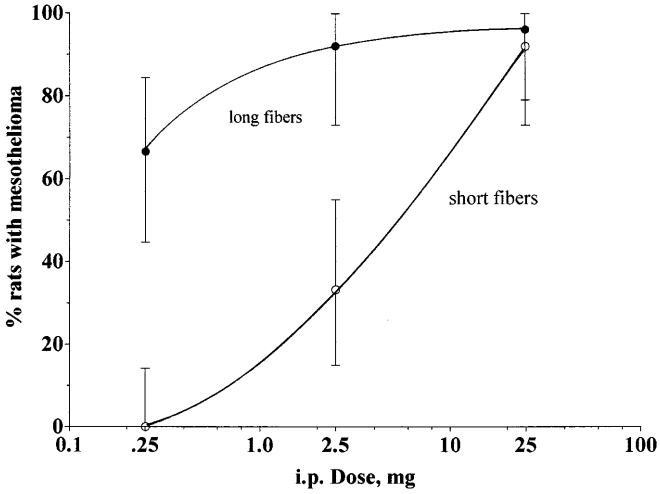

Fig. 4 Peritoneal mesothelioma after i.p. injection of long and short chrysotile (percent of rats and 95% CI) (Davis and Jones 1988)

experienced by humans may not always be appropriate. Furthermore, issues related to chronic carcinogenicity studies in a rodent bioassay such as the highest dose exceeding the Maximum Tolerated Dose in the exposure design have to be considered as well (Oberdörster 1997). Because of the differences in respirability between species mentioned above, it is important to always consider the actual doses retained in the lung rather than exposure concentrations when extrapolating results from rats to humans.

Fiber dimension

Since the early pioneering work of Stanton and Wrench (1972) and Pott et al. (1974) on the induction of pleural and peritoneal mesothelioma after direct injection of fibers into the respective cavities, it has become increasingly obvious that fiber dimension, in particular fiber length of fibers below ~1–2 μm in diameter, is a most important determinant of fiber pathogenicity. These investigators suggested, based on their work, that fibers longer than 8 μm are more potent than shorter fibers to induce mesotheliomas. Since then a number of investigators using preparations of short and long fibers in both in vitro and in vivo studies have demonstrated that, indeed, the long fibers consistently show greater pathogenicity than short fiber preparations of the same fibrous material. For example, using two asbestos fiber preparations, one preferentially shorter than ~5 μm and the other longer than ~5 μm, Dogra and Donaldson (1995) showed increased in vitro tumor necrosis factor (TNF) production by alveolar macrophages with long fibers. Similarly, Mossman (1990) and Goodglick and Kane (1990) demonstrated increased oxidative stress with long asbestos fibers compared to short ones. In vivo studies by Davis and Jones (1988) and Davis et al. (1996) with short and long preparations of chrysotile and amosite asbestos, using inhalation and intraperitoneal injection, showed increased pulmonary fibrosis, lung tumor and mesothelioma induction by the long fiber preparation. Goodglick and Kane (1990) also found increased inflammatory and oxidative stress responses in the peritoneal cavity after injection of long crocidolite preparations in contrast to short ones.

These are only a few of a number of studies confirming the greater potency of long fiber preparations and, although in most of these studies the short fiber preparations also included long fibers and vice versa, it appears that the presence of fibers longer than ~15–20 μm is the most critical predictor of tumorigenicity, given other parameters being equal. This conclusion was also reached most recently from an evaluation of results of a number of in vivo and in vitro studies which affirmed that long thin fibers (longer than 20 μm, thinner than 1 μm) are most pathogenic (Miller et al. 1999).

Figure 4 demonstrates the results of an intraperitoneal injection study with long and short type chrysotile fibers (Davis and Jones 1988), showing the significantly increased tumor incidence in the peritoneal cavity after a relatively low dose of long fibers. This low dose did not induce any response with the short fiber preparation. In contrast, at the 100-fold higher injected dose of both preparations, the tumor-inducing potency of both fiber preparations was the same, i.e., a near maximal tumor response. This is most likely due to the fact that at this very high i.p. dose, the number of longer fibers present in the short fiber preparation was sufficient to also induce this maximum response. A short fiber preparation which contains nothing but short fibers presumably would have resulted in a lower or no tumor response.

With respect to defining a threshold of fiber length below which fibers are less pathogenic, the hypothesis was formed that phagocytosis by alveolar macrophages is a decisive factor. Fibers deposited in the lung that are

too long to be phagocytized by alveolar macrophages will be less likely to be cleared out of the alveolar compartment. Thus, they can interact with epithelial cells and become interstitialized and are more likely to be transported to pleural sites than short fibers which are readily phagocytized by alveolar macrophages. A limiting factor for alveolar macrophage phagocytosis is the diameter of the macrophages in the alveolar space, and respective values have been reported to range between 10.5 and 13 μm for the rat and between 14 and 21 μm for humans (Crapo et al. 1983; Lum et al. 1983; Stone et al. 1992; Sebring and Lehnert 1992; Krombach et al. 1997). Although these numbers should not imply that fibers longer than a given diameter cannot be phagocytized – alveolar macrophages certainly can phagocytize fibers longer than their diameter by adapting their shape – they indicate those fiber length categories that may be most pathogenic. This concept of long fiber pathogenicity has more recently been emphasized by regulatory agencies (e.g., EC Directive on Classification of Synthetic Vitreous Silicate Fibers) and at scientific meetings (Vu et al. 1996), i.e., that fibers longer than 20 μm in length should primarily be considered with respect to a tumorigenic potential, and special attention should be given to their determination in respective animal studies evaluating biopersistence of newly developed fibers (see next section). It appears, however, that for non-cancer endpoints the number of all fibers should be considered; even phagocytized fibers result in activation of alveolar macrophages and will contribute to increasing the degree of an inflammatory response.

Fiber biopersistence

The longer a fiber persists in the lower respiratory tract the greater is the likelihood that it will cause adverse effects, especially if this fiber is longer than 20 μm. Thus, the aim of developing new fibers is a low persistence after deposition in the respiratory tract. Several methodologies have been proposed and are being used to determine biopersistence. Both in vitro techniques to determine fiber durability at different pHs and in vivo tests to directly determine the overall biopersistence in the lung have been developed. Short fibers that are ingested by alveolar macrophages encounter an acidic pH of 4.5–5 inside the phagolysosomes (Lundborg et al. 1995), whereas longer fibers not phagocytizable by alveolar macrophages are subjected to the extracellular fluid pH of around 7.4. Thus, in vitro tests to determine fiber durability measured by leaching of specific fiber constituents into the dissolution medium are generally performed both at an acidic pH of 4.5 and a pH of 7.4 simulating the intracellular and extracellular milieu (Potter and Mattson 1991). Whereas acellular in vitro techniques measure only dissolution rates of the fibers, in vivo methods measure the overall retention behavior of fibers in the lung, which includes dissolution rates in vivo and mechanical clearance.

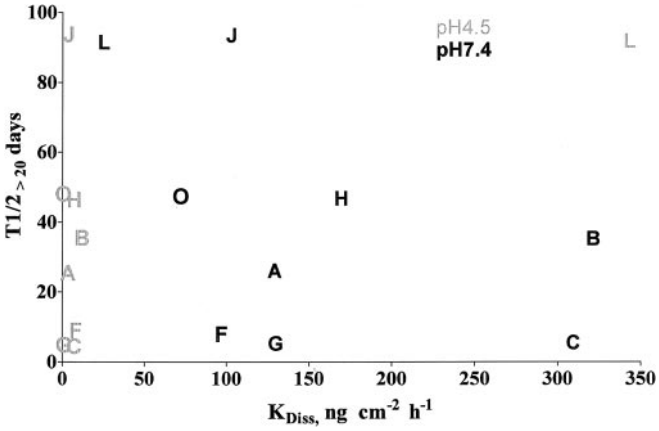

Fig. 5 Correlation between in vitro dissolution rates, K_{Diss}, and pulmonary retention halftimes of fibers longer than 20 μm ($T_{1/2} > 20$) after inhalation exposure of rats of different synthetic vitreous fibers. (After data from Bernstein et al. 1996)

A comparison of results from both techniques is shown in Fig. 5, where the in vitro dissolution rates for different vitreous fibers ranging from very durable to least durable fibers are plotted against the retention halftimes in the lung observed after inhalation of these fibers, with a focus on fibers longer than 20 μm. As can be seen from this figure a correlation between the in vitro dissolution rates at pH 7.4 and the measured in vivo retention halftimes for the long fibers is present but it is not very strong.

The correlation for dissolution rates determined at the pH of 4.5 and in vivo biopersistence is even less satisfactory. It appears that present methods to measure in vitro dissolution rates are not always a good predictor for the in vivo behavior of fibers longer than 20 μm, i.e., fibers not phagocytized by alveolar macrophages; more research is needed to optimize and standardize in vitro dissolution methodologies. The following paragraphs will, therefore, focus on in vivo methods to determine biopersistence of fibers, and not consider in vitro results.

Figure 6 outlines the relationship between fiber biopersistence and different physiological and physicochemical processes contributing to it. In general, biopersistence can be viewed as the sum of the effects of biodurability (dissolution, leaching) and the result of physiological clearance mechanisms. The clearance rates based on the latter are different between species, whereas it is assumed that biodurability of a fiber is similar between different species.

The goal of the determination of biopersistence in vivo is to measure biodurability of a fiber in the lung. This means that biopersistence tests performed in rats should attempt to minimize the rat-specific fast alveolar macrophage-mediated clearance of fibers. Also, the induction of inflammatory processes should be avoided, since it may affect fiber dissolution due to a different environment in the inflamed lung. Several methods have been proposed to determine biopersistence of synthetic

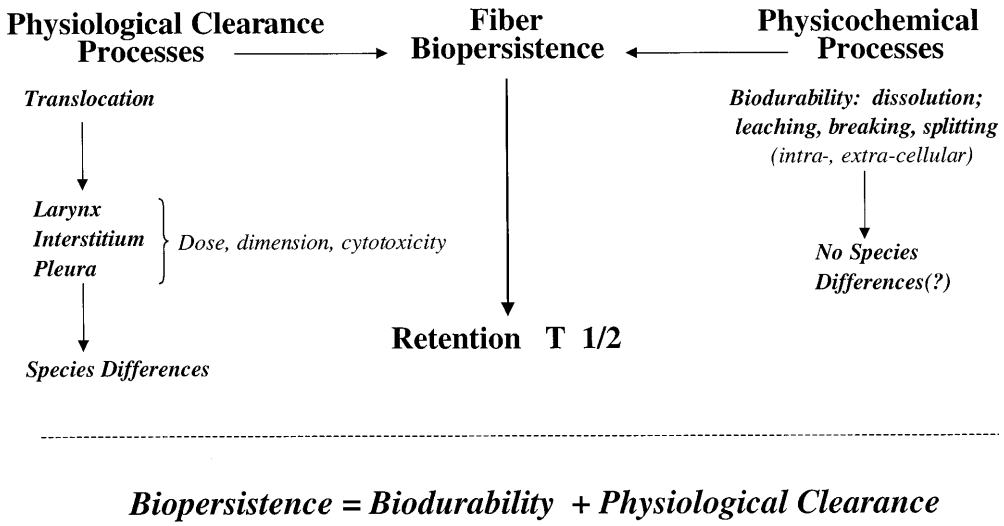

Fig. 6 Factors involved in biopersistence of fibers

vitreous fibers, including a 5-day inhalation test in rats, intratracheal instillation of fibers in rats, or intraperitoneal injection of fibers in rats, each followed by serial sacrifices to determine a retention halftime for different fiber length categories. The focus, however, as will be discussed later, should be on the retention halftime of fibers longer than 20 μm since these are the most pathogenic fibers. Although intraperitoneal injection studies to determine biopersistence of fibers may give useful results, it is suggested to focus on the lung for these assays, i.e., using inhalation preferentially or, possibly, intratracheal instillation.

In order to achieve the goal of determining biodurability with minimizing alveolar macrophage-mediated clearance, the emphasis should be on long fibers which are to be deposited in the alveolar region. These long fibers will not be phagocytized by alveolar macrophages and thus not be subjected to mechanical clearance. The problem when using the inhalation assay is that respirability of long fibers in rats is limited due to effective nasal filtration, as pointed out before (Fig. 2). This problem could be overcome by instilling fibers intratracheally, which would assure that long fibers reach the pulmonary region. However, intratracheal instillation assays generally administer high doses of 2 mg, which are intended to retard alveolar macrophage-mediated clearance by overloading this clearance pathway. However, at the same time a significant pulmonary inflammatory response is induced, and the high dose also can result in significant fiber agglomeration, both of which are likely to influence subsequent fiber dissolution rates. The use of high intratracheal doses is therefore the reason for the different retention halftimes that are observed after intratracheal instillation vs short-term inhalation, because the high-instilled doses result in significant prolongation of the overall biopersistence of fibers compared to the inhalation assay. Possible solutions to these problems associated with intratracheal instillation would be the administration of low doses of long fibers, i.e., 50 μg or less; with respect to inhalation, the aerosol should be enriched with fibers longer than 20 μm to assure that enough of these long fibers are deposited in the lung. Deposition of lung fibers in the rat lung has to be verified. Alternatively, intratracheal inhalation could be used. However, the latter requires additional expertise and equipment which makes it less convenient for routine applications.

The significant species differences which were briefly addressed above and which influence fiber biopersistence between rats and humans are summarized in Table 1. The significantly slower alveolar macrophage-mediated clearance rate and the respective longer retention halftime in humans compared to rats have a greater impact on overall biopersistence of short fibers (phagocytizable by macrophages) in humans than in rats. The total removal rate of short fibers is composed of the sum of the alveolar macrophage-mediated clearance rate plus the intracellular solubilization rate. Assuming that the intracellular dissolution rate is the same between the two species, and assuming a value of 0.01 for it, the total short fiber removal rate for the rat would be $r_{total} = 0.01 + 0.01 = 0.02$, and for humans it would be $r_{total} = 0.0015 + 0.01 = 0.115$. This translates into a retention halftime in the rat of 35 days and for humans of 60 days, which is only a factor of 2 different compared to

Table 1 Species differences influencing fiber biopersistence (rat vs. human)

	Rat	Human
Deposition		
Respirability, D_{ae}, μm	~5	~10
Elimination		
AM size, μm	~12	~17
Clearance rate r_{AM} per day	~0.01	~0.0015
Retention $T_{1/2}$, days	~70	~460
Biodurability		
Intracellular solubility rate (r_{si})	Same between species } assumption	
Extracellular solubility rate (r_{se})	Same between species }	

Table 2 Biopersistence of vitreous fibers in rats

	Advantage	Disadvantage	Solution
Intratracheal instillation	Deposition of long fibers	High doses; clumping, inflammation; uneven distribution	Low doses (~50 μg) enriched with long fibers
Short-term inhalation	Even distribution; low doses	Poor alveolar deposition of long fibers	Enriched for long fibers; intratracheal inhalation

the difference of 6- to 10-fold between the normal alveolar macrophage-mediated retention halftimes in rats vs humans (Table 1). On the other hand, for long fibers that cannot be phagocytized by alveolar macrophages, the resulting biopersistence (retention halftime) should be similar between species, which is the basis for focusing on fibers longer than 20 μm in a biopersistence assay in rats regardless of whether inhalation or instillation is used. However, the shorter life-span in rats compared to humans may be a disadvantage because of the faster target cell turnover in rats, i.e., a fiber retention halftime of 1 year is long for rats, whereas it is short for humans.

Table 2 summarizes advantages and disadvantages of the intratracheal instillation and short-term inhalation assays for measuring biopersistence of synthetic vitreous fibers in rats. Again, the main points are that the focus should be on long fibers in these assays, that high doses should be avoided in order to obtain consistent results between the two techniques and that they should mimic the situation in human lungs.

Figure 7 shows the pulmonary retention of fibers longer than 20 μm for different MMVF and amosite (Hesterberg et al. 1998). This figure demonstrates the clearance phases of different fibers longer than 20 μm from the rat lung after a 5-day inhalation period. For example, amosite and MMVF-21 do not show any significant differences up to day 90 after exposure, whereas beyond that timepoint there is clearly a difference in the slope of the retention curve between the two fiber types. Two retention phases are apparent, and it becomes important when interpreting retention curves after a short-term biopersistence assay to focus on the slow phase of the retention of the long fibers. The use of weighted halftimes – which takes into account also a proportional part of the fast phase – could be misleading since the difference in weighted halftimes between differently biopersistent fibers can be small. This could make it more difficult to separate fibers of significantly different biopersistencies which would be contrary to the goal of a biopersistence assay. For example, in the case of amosite exposure (Fig. 7), 65% of the deposited fiber dose was cleared with a fast retention halftime such that the weighted retention halftime was only 418 days, whereas the slow phase of the retention halftime was 1160 days, i.e., long amosite fibers exhibit a biexponential retention behavior.

On the other hand, if ≥95% would be cleared with a fast phase, such fibers can be considered as being cleared by a monoexponential clearance. However, if the

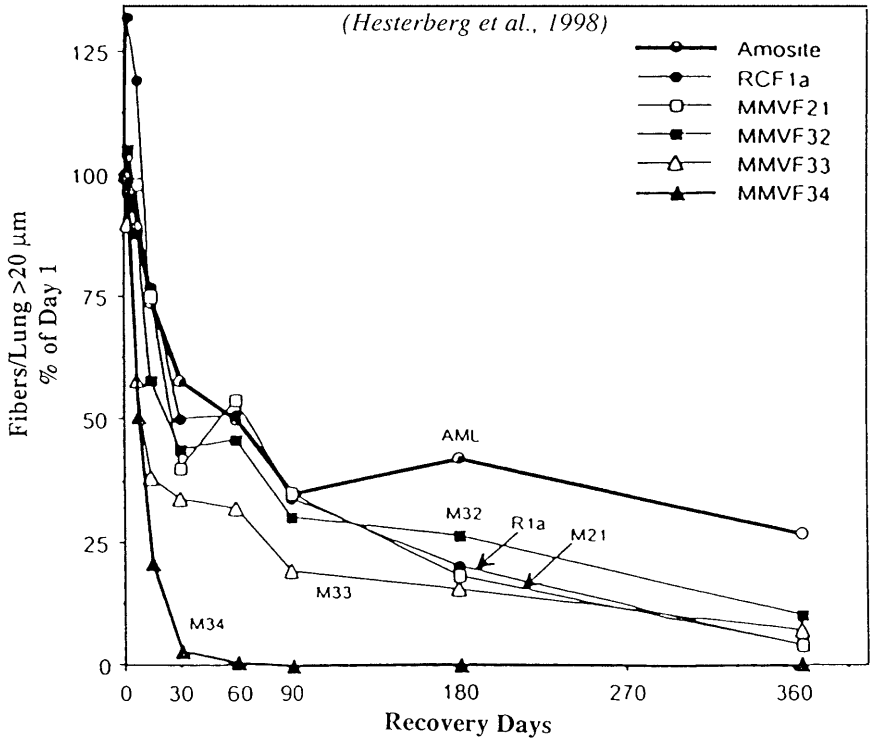

Fig. 7 Pulmonary retention of fibers longer than 20 μm after 5-day inhalation exposure of rats. (From Hesterberg et al. 1998)

Table 3 Pulmonary retention $T_{1/2}$ (days) of fibers >20 μm in rats (excerpted from Pott and Roller 1998)

Fiber type	Inhalation exposure (biexponential) ($T_{1/2}$)			Intratracheal instillation (mono exponential)
	Fast	Slow	Weighted	$T_{1/2}$
Amphiboles (amosite, crocidolite)	17	1300	466	346
Ceramic fiber	5	87	41	233
B-01-0.9	2	36	2	5
MMVF-0	6	–	–	12
Ratio				
Amphibole:MMVF-0		217	78	29
Ceramic F:MMVF-0		15	7	19

amount being cleared by the slow phase is more than ~15% one has to be concerned that this may be a significant amount that is being retained with a potentially very long retention halftime in the lung, and one would need to consider the slow clearance phase of fibers longer than 20 μm. Thus, although in European regulations the use of the weighted retention halftimes for long fibers has been accepted, this may in certain cases be misleading and is scientifically not justifiable. Results of intratracheal instillation studies can more often be described by a monoexponential expression.

Table 3 summarizes results of pulmonary retention halftimes of fibers >20 μm obtained by either short-term inhalation or by intratracheal instillation of 2-mg doses. Two more durable fibers (amphibole and ceramic fiber) and two rather soluble fibers (B-01-0.9; MMVF-0) are contrasted in this table in terms of their retention halftimes, either expressed as both the fast phase and the slow phase or as the weighted retention halftime for inhalation, whereas results of a monoexponential model is shown for intratracheal instillation. This table demonstrates that: (1) halftimes after instillations are generally greater than those found after inhalation; (2) results after inhalation exposure can generally be expressed by a biexponential model vs intratracheal instillation, which could best be described by a monoexponential model; (3) the exception for inhalation is a very soluble fiber which also displayed monoexponential clearance characteristics after inhalation; (4) the extremely long retention halftime (slow phase) observed after amphibole inhalation clearly reflects the long biopersistence of these fibers, but may also be due to the more peripheral penetration by inhalation of the finer fibrils of the amphibole asbestos which may not be achieved by intratracheal instillation. Furthermore, the ratios of retention halftimes in Table 3 between durable and soluble fibers, i.e., between the amphiboles and MMVF-0 and between the ceramic fiber and MMVF-0 show that, indeed, the slow phase of the retention halftime better demonstrates the extremes between a low and high biopersistence fiber. In particular, it demonstrates that the weighted retention halftime ratios are lower than the respective ratios for the slow phase of the retention halftimes. This translates into less power to differentiate between different biopersistencies using the weighted retention halftimes as discussed above. This table also shows that the amphiboles are not clearly separated from the ceramic fibers by the instillation technique, possibly indicating – as mentioned above – that inhaled finer amphiboles reach the peripheral alveoli to a greater degree than is possible by instillation.

Table 4 Correlation between fiber biopersistence and lung pathology (in part based on Hesterberg 1998)

Fiber type	Fibrosis	Tumors	$T_{1/2\text{slow}>20}$
MMVF 34	–	–	6
MMVF 21	+	–	53
RCF-1	+	+	88
Crocidolite	+	+	~1000
Amosite	+	+	>1000
Chrysotile	+	+	>100(?)

Table 4 summarizes results of studies correlating biopersistencies of different fibers and lung pathology. It shows that MMVF-induced pathology is well-correlated with increasing retention halftimes of the slow phase of the fibers longer than 20 μm and that amphiboles have extremely long retention halftimes and respective greater lung pathology which is more severe than that observed with the vitreous fibers. With respect to chrysotile, the picture is not as clear-cut since reported retention halftimes for long fibers appear to be rather short (Coin et al. 1992), and yet chrysotile pathogenicity is not different from that of the amphiboles. The difficulty in measuring the very fine or even ultrafine fibrils of chrysotile may be part of the problem of determining more precisely the retention halftimes of this serpentine.

The determinants for fiber pathogenicity for MMVF discussed in this short overview may not be applicable to all man-made fibers. For example, biopersistence may not have the same importance for certain organic fibers as recent results of inhaled thin carbon fibers in rats seem to indicate. In this short-term 5-day inhalation study fibers of long amosite, MMVF-10 and carbon were inhaled at a concentration which resulted in very similar lung burdens of total fibers of $6–8 \times 10^6$ fibers/lung at the end of the 5-day period. Lung burdens of fibers longer than 20 μm ranged from 0.5×10^6 (MMVF-10) to 1×10^6 (carbon fibers) per lung. Lung lavages on days 1, 10 and 30 after the exposures were performed and a number of cellular

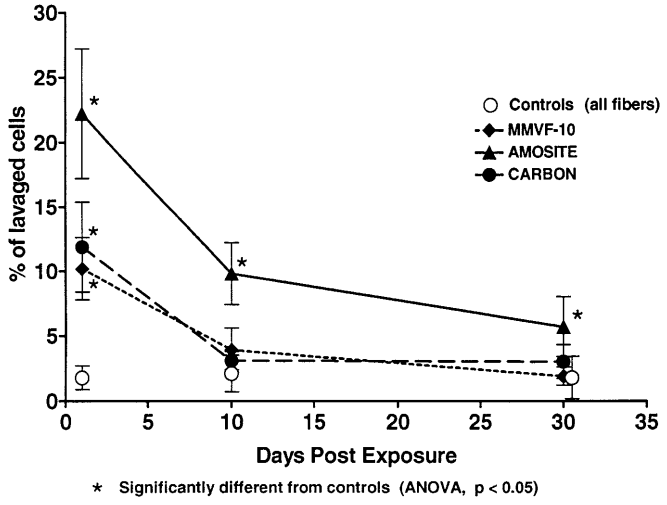

Fig. 8 Pulmonary inflammatory response (% neutrophils in lung lavage) induced in rats by similar lung burdens of total fibers after short-term inhalation of carbon fibers, MMVF-10 and amosite (mean ± SD)

and biochemical lavage parameters determined. It can be assumed that carbon fibers are not soluble in the lung and apparently have a very long biopersistence which probably is mainly reduced by breakage of the long fibers. As Fig. 8 shows, despite this long biopersistence and a greater number of carbon fibers > 20 μm long in the lung, the inflammatory response induced by carbon fibers was not different from that of MMVF-10 and was significantly less than that induced by amosite fibers throughout the post-exposure period. Thus, the importance of biopersistence for fibers other than vitreous fibers for the induction of adverse effects may be different and needs to be evaluated in further studies.

Summary

Dose, dimension and durability of MMVF are key parameters with respect to the induction of adverse effects. In particular, fiber biopersistence plays a most important role for pulmonary pathogenicities, and, consequently, biopersistence receives greatest attention in the generation of new fibrous materials. Long fibers (> 20 μm) have the greatest potential for tumorigenicity and need special consideration in connection with the evaluation of fiber biopersistence. At the same delivered lung dose a fiber of low biopersistency has the least effect. It has become obvious that when evaluating and interpreting fiber effects in experimental animals, species differences with respect to respirability, lung retention, and mechanisms of responses have to be considered.

References

Bernstein DM, Morscheidt C, Grimm H-G, Thévenaz P, Teichert U (1996) Evaluation of soluble fibers using the inhalation biopersistence model, a nine-fiber comparison. Inhal Tox 8: 345–385

Coin PG, Roggli VL, Brody AR (1992) Deposition, clearance, and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. Environ Res 58: 97–116

Crapo JD, Young SL, Fram EK, Pinkerton KE, Barry BE, Crapo RO (1983) Morphometric characteristics of cells in the alveolar region of mammalian lungs. Am Rev Resp Dis 128: S42–S46

Dai YT, Yu CP (1998) Alveolar deposition of fibers in rodents and humans. J Aerosol Med 11(4): 247–258

Davis JMG, Jones AD (1988) Comparisons of the pathogenicity of long and short fibers of chrysotile asbestos in rats. Br J Exp Pathol 69: 717–737

Davis JMG, Brown DM, Cullen RT, Donaldson K, Jones AD, Miller BG, McIntosh C, Searl A (1996) A comparison of methods of determining and predicting the pathogenicity of mineral fibers. Inhal Toxicol 8: 747–770

Dogra S, Donaldson K (1995) Effect of long and short fibre amosite asbestos on in vitro TNF production by rat alveolar macrophages: the modifying effect of lipopolysaccharide

Goodglick LA, Kane AB (1990) Cytotoxicity of long and short crocidolite asbestos fibers in vitro and in vivo. Cancer Res 50: 5153–5163

Hesterberg TW, Chase G, Axten C, Miller WC, Musselman RP, Kamstrup O, Hadley J, Morscheidt C, Bernstein DM, Thévenaz P (1998) Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Tox & Appl Pharmacol 151: 262–275

Hsieh TH, Yu CP, Oberdörster G (1999) Modeling of deposition and clearance of inhaled Ni compounds in the human lung. Regulatory Pharmacol and Toxicology 30: 18–28

Krombach F, Münzing S, Allmeling A-M, Gerlach JT, Behr J, Dörger M (1997) Cell size of alveolar macrophages: An interspecies comparison. Environ Health Perspect 105 (Suppl 5): 1261–1263

Lundborg M, Johard U, Johansson A, Eklund A, Falk R, Kreyling W, Camner P (1995) Phagolysosomal morphology and dissolution of cobalt oxide particles by human and rabbit alveolar macrophages. Exp Lung Res 21: 51–66

Lum H, Tyler WS, Hyde DM, Plopper CG (1983) Morphometry of in situ and lavaged pulmonary alveolar macrophages from control and ozone-exposed rats. Exp Lung Res 5: 61–78

Mast RW, McConnell EE, Anderson EE, Chevalier J, Kotin P, Bernstein DM, Glass LR, Miller WC, Hesterberg TW (1995a) Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7: 425–467

Mast RW, McConnell EE, Anderson R, Chevalier J, Kotin P, Bernstein DM, Thévenaz P, Glass LR, Miiller WC, Hesterberg TW (1995b) Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7: 469–502

Miller BG, Jones AD, Searl A, Buchanan D, Cullen RT, Soutar CA, Davis JMG, Donaldson K (1999) Influence of characteristics of inhaled fibres on development of tumours in the rat lung. Annals Occup Hyg 43(3): 167–179

Morrow PE (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam Appl Toxicol 10: 369–384

Mossman BT (1990) In vitro studies on the biologic effects of fibers: Correlation with in vivo bioassays. Env Health Perspect 88: 319–322

Oberdörster G (1996) Significance of particle parameters in the evaluation of exposure–dose–response relationships of inhaled particles. Inhal Tox 8 (Suppl.): 73–89

Oberdörster G (1997) Pulmonary carcinogenicity of inhaled particles and the Maximum Tolerated Dose (MTD). Environmental Health Perspectives 105 (Suppl. 5): 1347–1356

Pott F, Huth F, Friedrich KH (1974) Tumorigenic effects of fibrous dusts in experimental animals Environ Health Perspect 9: 313–315

Pott F, Roller M (1998) How far can carcinogenicity studies of fiber types be substituted by data on their biopersistence? Air Quality Control 58: 85–91

Potter RM, Mattson SM (1991) Glass fiber dissolution in a physiological saline solution. Glastech Ber 64: 16–28

Sebring RJ, Lehnert BE (1992) Morphometric comparison of rat alveolar macrophages, pulmonary interstitial macrophages, and blood monocytes. Exp Lung Res 18: 479–496

Stanton MF, Wrench C (1972) Mechanisms of mesothelioma induction with asbestos and fibrous glass. J Nat Cancer Inst 48: 797–821

Stone KC, Mercer RR, Gehr P, Stockstill B, Crapo JD (1992) Allometric relationships of cell numbers and size in the mammalian lung. Am J Respir Cell Mol Biol 6: 235–243

Vu V, Barrett JC, Roycroft J, Schuman L, Dankovic D, Baron P, Martonen T, Pepelko W, Lai D (1996) Workshop report: Chronic inhalation toxicity and carcinogenicity testing of respirable fibrous particles. Reg Toxicol & Pharmacol 24: 202–212