MODELS FOR MESOTHELIOMA INCIDENCE FOLLOWING EXPOSURE TO FIBERS IN TERMS OF TIMING AND DURATION OF EXPOSURE AND THE BIOPERSISTENCE OF THE FIBERS

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The health effects of inhaled fibers are related to the intensity and duration of exposure and occur many years after the exposure. In particular, the incidence of mesothelioma after exposure to asbestos is proportional to the intensity of exposure (fibers per milliliter of air) and the duration of exposure, and to the time that has elapsed since the exposure. The incidence increases with time since exposure to a power of between 3 and 4. The disease process resulting from exposure to fibers in the air is presumably related to the dose of fibers in the lungs, which depends on the exposure level and duration, and also on the size characteristics of the fibers influencing their inhalation and retention in the lungs. Models incorporating these characteristics have been found to be satisfactory in explaining the incidence of mesothelioma over time after exposure to asbestos. Most of the epidemiological modeling has been for occupational exposure to one of the amphibole asbestos types (crocidolite or amosite), for which heavy exposure produces a high incidence of mesothelioma. Occupational exposure to chrysotile asbestos has resulted in a much lower incidence of mesothelioma. Crocidolite asbestos is much more biopersistent than chrysotile asbestos in the sense that after retention in the lungs it is eliminated only slowly (half-time of several years). If fibers are eliminated then the dose in the lungs declines following exposure, and this may influence the disease process. This concept is more important for synthetic mineral fibers, such as glass wool, which are used as a substitute for asbestos. These fibers are much less biopersistent than asbestos, with half-times of weeks or even days. Biopersistence is related to the dissolution of fibers. This is a physical-chemical process that may be expected to proceed at about the same rate in rats and humans. The predicted effect of biopersistence of fibers has been explored using the basic mesothelioma incidence model generalized to include a term representing exponential elimination over time. The influence of solubility of fibers on the mesothelioma rate is 17 times higher in humans than in rats. This is because rats are aging and developing cancer at a much quicker rate than humans, and hence the influence of dissolution is less. Thus, the predicted mesothelioma incidence in humans is highly dependent on the rate of elimination across the range covering asbestos and the more durable synthetic fibers, but in rats a similar dependence occurs at a 17 times higher rate of elimination corresponding to the less durable synthetic fibers. The possible carcinogenic effects of fibers are often determined from animal experiments, but these results suggest that the extrapolation from rats to humans is

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highly dependent on the biopersistence of fibers, in the situation where the elimination is through dissolution of fibers at a rate independent of species and the speed of the cancer process is species dependent. This implies that relatively soluble fibers that do not produce disease in rat experiments are even less likely to produce disease in humans.

The adverse health effects of occupational exposure to asbestos are well established. Such exposure leads to the development of asbestosis, a fibrotic disease of the lungs, and to an excess of lung cancer and the malignant tumor, mesothelioma, arising in the pleura or peritoneum. The excesses of lung cancer and mesotheliomas do not occur until at least 10 yr after exposure, and the majority of cases occur more than 20 yr after exposure. There are three types of asbestos that have been used commercially: chrysotile, crocidolite, and amosite. Crocidolite and amosite are in the amphibole series and chrysotile is in the serpentine series of naturally occurring mineral silicate fibers. After occupational exposure, crocidolite has been found to give the highest incidence rates of mesothelioma and amosite asbestos also produces mesotheliomas. The mesothelioma rate following occupational exposure to uncontaminated chrysotile is much lower than with the amphiboles, but chrysotile contaminated with tremolite, a noncommercial amphibole asbestos, produces mesotheliomas (McDonald et al., 1997).

It has been recognized for over 25 yr that a feature of asbestos that is important for its carcinogenic properties is its fibrous nature, with long thin fibers that can be inhaled and retained (Timbrell et al., 1971) and are not readily cleared by macrophage action responsible for the effect. The durability of fibers has also been recognized as important for a long time. Stanton and Wrench (1972) concluded that the “simplest incriminating feature for both carcinogenesis and fibrogenesis seems to be a durable fibrous shape,” and Pott and Friedrichs (1972) also pointed out the importance of durability. The effect of durability has only been considered in detail in recent years, as the influence of durability on biological effect was recognized as important because of the use of synthetic mineral fibers, which are less durable than asbestos, as substitutes for asbestos. McDonald (1994) suggested that variability in durability between fibers types is an important factor in etiology, especially in considering the safety of synthetic mineral fibers (McDonald et al., 1997).

In this article attention is restricted to mesothelioma, and a model for mesothelioma incidence that takes account of the elimination of fibers from the lungs (Berry, 1991, 1995) is explored in relation to occupational exposure of humans and the testing of fibers by animal experiments. The general approach of modeling the effect in terms of durability has been followed by Eastes and Hadley (1996) for animal experiments. Although the details of their approach differ from those considered in this article, the general conclusions are similar.
MESOTHELIOMA AND TIME SINCE EXPOSURE

The relationship between mesothelioma rate and time since a period of exposure to asbestos may be modeled on the assumption that each increment of exposure results in an incidence rate at time $t$ since exposure of

$$i(t) = aft^p$$

(1)

where $a$ and $p$ are constants, and $f$ is the concentration of fiber in the air. This model, the third asymptotic extreme value distribution, may arise if a large number of cells each had a small risk of malignancy and a cancer cell was formed when the first such cell succumbed, or if a cancer cell was the end result of a multistage sequence of cellular changes, provided each such change occurred with low probability (Nordling, 1953; Armitage & Doll, 1954). The model was formulated for the situation where there is continuous exposure. This has been considered to apply in animal experiments in which asbestos has been injected into the pleural cavity on the grounds that the asbestos fibers remain and hence constitute continuous exposure to the target organ.

This experimental method of administering the dose to the target organ is unrealistic in relation to the exposure experienced by those working with asbestos. The route of exposure is then inhalation, and the dose consists of the asbestos fibers in the air that is breathed, and that have the appropriate dimensions to reach the peripheral airways and are retained there. Occupational exposure is effectively continuous over a period of years, and each short period of exposure makes a continuing contribution to the dose at the target organ. For exposure by inhalation of duration $d$ and at a constant intensity the incidence at time $T$ after the start of exposure is given by integrating Eq. (1), for $t = T - d$ to $T$ with the lower limit set as zero if $T$ is less than $d$, to give

$$I(T) = a'fT^{p+1}$$

(2a)

$$I(T) = a'f[T^{p+1} - (T - d)^{p+1}]$$

(2b)

for $T > d$

where $a' = a/(p + 1)$. These may be written in a uniform form as

$$I(T) = a'f[T^{p+1} - u^{p+1}]$$

(2c)

where $u = 0$ for $T \leq d$ and $u = T - d$ for $T > d$.

When the duration of exposure is short relative to the period of observation, the incidence can be approximated by

$$I(T) = cT^k$$

(3)
where \( k \) is between \( p \) and \( p + 1 \), and \( c \) is proportional to the product of exposure level and duration of exposure, the cumulative exposure; for example, Doll and Peto (1985) showed this was a good approximation for an exposure duration of up to 10 yr where the majority of mesotheliomas occur more than 10 yr after the end of exposure.

This model gives a nonzero incidence for all \( T > 0 \). This is unrealistic since it does not allow time for a tumor to develop to the stage where it causes symptoms or death. An extension (Pike, 1966) includes a lag period, \( w \), so that, for example, Eq. (3) becomes

\[
l(T) = c(T - w)^k
\]

for \( T > w \) (for \( T \leq w, I = 0 \)). This modified model, Eq. (4), gave a good fit to the times of occurrence of mesotheliomas in rats after intrapleural inoculation of asbestos (Berry & Wagner, 1969; Wagner et al., 1973).

The basic model, Eq. (3), has been shown to fit data from a number of epidemiological follow-up studies: workers in a factory in London involved in manufacture of products containing asbestos (Newhouse & Berry, 1976; Newhouse et al., 1985); North American insulation workers (Peto et al., 1982); workers at an amosite asbestos factory in New Jersey (Seidman et al., 1986); workers at HM naval bases in England (Sullivan et al., 1988); and miners and millers at the crocidolite asbestos mine in Western Australia (de Klerk et al., 1989). The value of \( k \) has been found to be between 3 and 4. Although mesotheliomas have not been observed to occur earlier than 10 yr from the onset of exposure, the simpler model, Eq. (3), has been found to be adequate because the estimated parameters ensure that the fitted probability of mesothelioma in the first 10 yr is very small.

**THE ELIMINATION MODEL**

The preceding models were formulated for the situation where each increment of exposure constitutes continuous effective exposure to the agent responsible for causing the cancer. This assumption has been considered reasonable for amphibole asbestos fibers inhaled during occupational exposure since the fibers are retained in the lungs for long periods of time after exposure. However, if it is assumed that asbestos is gradually eliminated from the lungs, or rendered inactive by some protective process within the body, then the mesothelioma rate would be moderated by a factor representing a decline in risk corresponding to the reduction in retained asbestos fiber, leading to modified models (Berry, 1991, 1995). If elimination were at a constant rate of \( \lambda \), then, corresponding to Eq. (1), each increment of exposure results in an incidence rate at time \( t \) since exposure of

\[
\tilde{i}(t) = aft^p e^{-\lambda t}
\]
Corresponding to Eq. (2) for exposure by inhalation of duration $d$ and at a constant intensity, the incidence at time $T$ after the start of exposure is given by integrating Eq. (5). For an integer value of $p$ there is an analytical integral solution, and in particular for $p = 3$,

$$I(T) = af\lambda^{-4}[e^{-\lambda u}(6 + 6\lambda u + 3\lambda^2 u^2 + \lambda^3 u^3) - e^{-\lambda T}(6 + 6\lambda T + 3\lambda^2 T^2 + \lambda^3 T^3)]$$  \hspace{1cm} (6)

For a short period of exposure, Eq. (6) takes the limiting form

$$I(T) = ce^{-\lambda T}T^3$$  \hspace{1cm} (7)

where $c = afd$, equivalent to Eq. (5). As $\lambda \to 0$, Eq. (6) takes the limiting form of Eq. (2c).

The elimination model may include a lag period, $w$, and then Eqs. (5) to (7) would be rewritten by subtracting $w$ from all the times on the right-hand sides. That is, Eq. (7) becomes

$$I(T) = ce^{-\lambda(T-w)}(T-w)^3 \quad \text{for } T > w$$  \hspace{1cm} (8)

The rate of elimination $\lambda$ implies that half of the fiber load in the lungs is eliminated after a time of $\ln(2)/\lambda$ ($0.693/\lambda$) and this time is referred to as the half-time.

**APPLICATION TO WITTENOOM**

This model was proposed and applied to a group of men formerly employed at the crocidolite asbestos mine at Wittenoom in Western Australia (Berry, 1991), and these results are reviewed briefly. The health consequences of their exposure have been studied extensively (e.g., Armstrong et al., 1988; de Klerk et al., 1989, 1991). There were 6501 men employed in the production of crocidolite asbestos at Wittenoom at some time between 1943 and 1966. Exposure was generally brief, with about 45% of the men staying for less than 3 mo and less than 3% for more than 5 yr. Fiber concentrations in the mill were high but, because of the short exposures, more than half of the men accumulated less than 10 fiber-yr/ml and less than 4% more than 100 fiber-yr/ml. In 6258 men followed for more than 10 yr and up to age 65 there had been 719 recorded deaths, of which 72 were due to mesothelioma. The mortality from mesothelioma increased with cumulative exposure and rapidly with time since first exposure, from 7 per 100,000 person-yr between 10 and 15 yr after first exposure to 360 per 100,000 person-yr between 30 and 35 years after first exposure. Although the rate after 35 or more years since first exposure was only 220 per 100,000 person-yr, little significance can be attached to this apparent decline as it was based on only 2 mesotheliomas and about 1% of the person-years of follow-up.
The fits of Eqs. (4) and (8) were not statistically significantly better than using the simplest model (3); that is, there was no evidence from these data to reject the hypothesis that both \( w \) and \( \lambda \) are zero. The three models give similar mesothelioma incidence rates up to 35 yr from first exposure and, as most of the observations were within that period, this explains why the three models fit equally well. For many analyses the model with zero lag period and zero elimination would be favored on the grounds of parsimony. When extrapolated beyond 35 yr follow-up the fitted rates diverge markedly. With elimination of asbestos the incidence rate increases only slightly compared with a trebling or quadrupling of the rates without elimination.

Although the available data on mesothelioma incidence and time since exposure at Wittenoom do not allow discrimination between the three models of Eqs. (3), (4), and (8), there is sufficient biological rationale to suggest that the three-parameter model is plausible even though the data are currently insufficient to validate it. This implies that when it is required to predict future mortality involving extrapolation to lengths of follow-up not yet observed, the elimination model should be included to provide a range of possible future scenarios. Predictions of the number of mesotheliomas that might be expected to occur in former workers at the Wittenoom asbestos mine, between 1987 to 2020, ranged from 654 using Eq. (3), to 573 using Eq. (4) with a lag of 5 yr, and to 383 using Eq. (8) with a lag of 5 yr and an elimination rate of 0.068/yr (corresponding to a half-life of 10 yr). These predictions took account of competing causes of death including an excess of lung cancer. These values provide a range indicating the uncertainty of prediction. This uncertainty arises from the uncertainty on which is the most appropriate model, not from the statistical uncertainty in estimating parameters in an assumed model.

**OTHER EVIDENCE ON ELIMINATION**

Direct evidence that elimination of asbestos does occur after exposure by inhalation came from animal experiments (Wagner & Skidmore, 1965; Wagner et al., 1974). For rats exposed to amphibole asbestos for 6 mo there was elimination between 6 and 24 mo; for crocidolite, 73% was eliminated in 18 mo following the cessation of exposure by inhalation. For chrysotile, the amount of dust in the lungs did not increase with continued exposure, and it was suggested that this was due to a high elimination rate and an equilibrium for which the rate of elimination was equal to the rate of retention (Wagner et al., 1974). Rendall and du Toit (1994) found in baboons that the half-life for crocidolite fiber was 50 mo and estimated a half-life of 72 mo for deceased crocidolite miners. These half-life times correspond to rates of elimination of 17% and 12% per year, respectively.

Other indirect evidence comes from determinations of the amount of asbestos in the lungs at postmortem (lung burden) for those formerly
exposed to asbestos and from the general population. These determinations have been made using transmission electron microscopy and energy-dispersive x-ray analysis (Pooley & Clarke, 1979). Series have been obtained from mesotheliomas and controls in the United Kingdom (Jones et al., 1980a; Wagner et al., 1982), from the United States and Canada (McDonald et al., 1982), and from Australia (Rogers, 1984). The results from some of these studies were summarized in Berry et al. (1989). It was found that there was more amphibole in the lungs of those who had died of mesothelioma than for controls who had died of other causes. In view of the known association between mesothelioma and exposure to amphibole asbestos this was not an unexpected finding. However, there was overlap between the distributions for mesotheliomas and controls to an extent that implied a higher rate of mesothelioma in those not exposed to asbestos than had been observed. This aspect was explored further by considering lung burden data from a group of women who had been exposed to crocidolite during the manufacture of military gas masks during the period 1940 to 1945 (Jones et al., 1980b). These women were known to have been exposed to high levels of crocidolite but for a relatively short time. Mesotheliomas were observed in this group of women, with the first case occurring in 1965. The mesothelioma incidence in the exposed group was 1500 times higher than the background rate in those with no known occupational exposure. The corresponding ratio of amphibole burden was 150. The lung burdens in those without occupational exposure were assumed to be a result of a low-level environmental exposure. It was further assumed that the mesotheliomas in this group were due to low-level environmental exposure; that is, a background incidence without any exposure was ignored. With these assumptions, it was shown that the ratio of the exposure levels was 100,000 using Eqs. (2) and (3). This is about 650 times the ratio of lung burdens, and taking into account that the average length of exposure was 1 yr for the gas-mask workers and 55 yr for the environmental exposure the ratios are not reconcilable without some other concept. If this is elimination, then \( \lambda \) was estimated as 0.15. In this approach the concept of the elimination also reducing the mesothelioma risk was not incorporated. The calculations have been repeated using Eq. (6), instead of Eqs. (2) and (3). The ratio of the exposure levels in the occupationally exposed women compared with those not so exposed was then estimated as 50,000 and \( \lambda \) was estimated as 0.13. 

There seems to be good evidence that there is elimination of crocidolite fiber from the lung and that the rate of elimination in humans is of the order of 0.1 to 0.15 per year.

**SYNTHETIC MINERAL FIBERS**

As the dangers of asbestos became known there was a move to the use of substitutes. One group of substitutes is the synthetic mineral fibers, which include glass wool, rock wool, slag wool, and refractory ceramic
fiber. The hypothesis that asbestos was carcinogenic because of its fibrous nature led to concern that synthetic fibers could also be carcinogenic, particularly if produced in the size ranges that seemed to be most associated with a carcinogenic effect, long thin fibers. Early animal experiments involving implantation or injection of fibers showed that glass fibers and other mineral fibers produce tumors in rats and that the results were compatible with the hypothesis that the long thin fibers are the most carcinogenic (Stanton & Wrench, 1972; Wagner et al., 1976; Pott et al., 1976; Stanton et al., 1977).

The experimental findings led to the initiation of large epidemiological studies in Europe (Saracci et al., 1984; Simonato et al., 1987; Boffetta et al., 1997) and in the United States (Enterline et al., 1987; Marsh et al., 1990, 1996). The European study was a historical cohort study of 22,000 production workers in 13 man-made mineral fiber (MMMIF) plants in 7 countries, followed up to 1990–1992. There had been 4521 deaths in total, and 344 due to lung cancer. There was no excess lung cancer among glass wool workers but there was an excess for rock/slag wool workers, although the authors were unable to conclude that the excess was due to exposure to rock/slag wool. There were five mesotheliomas, but two of the people had been exposed to asbestos and the authors considered it doubtful whether there was an excess. The U.S. study was a historical cohort study of 16,700 MMMIF workers in 17 fibrous glass and mineral wool plants, employed for a year or more during the period 1945–1963. At follow-up to 1985 there had been 5806 deaths including 497 due to respiratory cancer. There was a small excess of respiratory cancer, which showed no consistent relationship with indicators of exposure to the synthetic fibers. There were four mesotheliomas recorded on death certificates. One of these was rejected on pathological review, and a second person had been exposed earlier to asbestos in a naval shipyard, leaving two possibly related to exposure, but neither was confirmed pathologically.

The increasing use of synthetic mineral fibers also led to more experimental work with exposure by the inhalation route. The RCC series of animal experiments with exposure by inhalation was also carried out. Results have been reported by Hesterberg et al. (1993) and McConnell et al. (1994) and were summarized by McConnell et al. (1996), who concluded that there were mesotheliomas and an increased incidence of lung tumors after exposure to refractory ceramic fibers but no evidence of an increase in tumor rates in rats after exposure to glass wool, slag wool, or rock wool. These conclusions are not free of controversy (see Infante et al., 1994; Rossiter & Chase, 1995; and Pott & Roller, 1996).

It is clear that in humans the risk of excess lung cancer from exposure to synthetic mineral fibers is less than that following exposure to asbestos, and the risk of mesothelioma is considerably less than that following exposure to amphibole asbestos. Contributory reasons are that the synthetic man-made fibers are mostly of a larger median fiber diameter than
amphibole asbestos and that the levels of fine fibers in the air are much less than occurred with amphibole asbestos, so the dose at the target organs is presumably less. Another factor is the lower durability of the man-made fibers in the lungs, so that those that reach the target organ remain there for a shorter period before dissolution; a fuller discussion of these points is given by Eastes and Hadley (1996).

Bernstein et al. (1995, 1996) investigated the biopersistence of a number of synthetic mineral fibers by exposing rats to an aerosol for 5 days and sacrificing subgroups at intervals up to 1 yr following exposure. The half-times of fibers in the lung ranged from 8 to 54 days, corresponding to elimination rates ($\lambda$) of 4.7 to 31.6/yr. Hesterberg et al. (1996) carried out a similar experiment comparing four types of synthetic mineral fibers with crocidolite asbestos. For long fibers (>20 µm) more than 95% of the synthetic fibers had been eliminated from the lung after a year compared with only 17% of crocidolite fibers, corresponding to values of $\lambda$ of >3.7 for synthetic fiber and 0.23 for crocidolite. In both of these studies it was found that the longer fibers were eliminated more rapidly than the shorter fibers. Bernstein et al. (1995) found that long fibers (>15 µm) were cleared about twice as rapidly as shorter fibers and also that the three fibers (MMVF11, Fiber B, Fiber J) cleared considerably faster than reported for crocidolite by Musselman et al. (1994). The clearance rate after inhalation was four to five times more rapid than after intratracheal (IT) instillation, which they suggested was related to the IT method rather than the dose. Bernstein et al. (1996) extended this work using MMVF11, three relatively soluble glass fiber samples, and five stone wool samples. They found that a single exponential function did not fit the data adequately because there was an initial fast clearance phase followed by a slower rate of clearance. This was modeled as a linear combination of two exponential functions, and a weighted half-time was defined with weights proportional to the coefficients in the fitted model. For WHO fibers ($l \geq 5$ µm, $d \leq 3$ µm) the half-time was between 11 and 54 days. The investigators also did in vitro dissolution tests using the same fibers at pH of 4.5 and 7.4. There was an inverse association between the half-time of clearance for long fibers ($l \geq 20$ µm) after inhalation and the rate of dissolution at pH 7.4, which was in the range of 23 to 320 ng cm$^{-2}$ h$^{-1}$. As noted by the authors, this association was influenced by one of the fibers, which had a solubility of less than a third of the other fibers, and results for intermediate solubility fibers are needed to give more confidence in this finding. The results were compared with Musselman (1994), who had reported experiments with a similar protocol for four synthetic glass or stone wools, including MMVF11, and crocidolite. For long fibers the weighted half-time for crocidolite was 536 days, compared with 8 to 85 days for the synthetic fibers.

Eastes et al. (1996) gave data on dissolution rate at neutral pH. The dissolution rate had a range from 3 to 600 ng/cm$^2$/h for a number of syn-
thetic mineral fibers tested, corresponding to 8 to 1700 days to dissolve a 1-µm fiber. For amphibole asbestos the dissolution rate was about 0.2 ng/cm$^2$/h. Eastes and Hadley (1996) and Eastes et al. (1996) noted that dissolution is a physical chemical process determined by the interaction between the fiber and its environment. For fibers in fluids an important feature of the fluid is the pH, and within the lung the pH is similar for both rats and humans. Thus dissolution should proceed at about the same rate in rats and humans. This is the basis for the comparisons presented in the next section and of the discussion of the implications of these results.

APPLICATION OF THE ELIMINATION MODEL FOR MESOTHELIOMA INCIDENCE

The elimination models have been used to assess and compare the cumulative incidence of mesothelioma over a range of values of $\lambda$ for humans and rats. This has been done by applying the incidences given by Eq. (6) or (7) over the lifetimes of groups whose mortality from other causes was obtained from reference sources.

For humans the mortality from other causes was taken from the Australian life table for men in 1994 (Australian Bureau of Statistics, 1995); in this life table the median lifetime was 78 yr. For rats the natural mortality of standard Wistar rats given by Berry and Wagner (1969) was used for mortality after the age of 6 wk; the death rate was an exponential in time and the median lifetime after 6 wk was 120 wk.

For men exposure was taken as continuous from age 20 to age 60 yr, or until death if earlier, corresponding to a lifetime of occupational exposure. The cumulative incidence at ages up to 100 yr was calculated by combining the mortality from other causes with that from mesotheliomas from Eq. (6) using spreadsheet calculations with an interval of 1 yr. For rats exposure was taken as a single intense exposure at age 6 wk, corresponding to an injection of fibers. The cumulative incidence of mesotheliomas was calculated up to 160 wk after injection with an interval of 2 wk in the spreadsheet calculations.

In order to facilitate the comparison of the influence of elimination between humans and rats, the parameters were chosen to standardize the cumulative incidence for a durable fiber ($\lambda = 0.01/yr$) at 50% for men at age 75 yr and for rats at 110 wk after injection. This was achieved by setting the parameter product $af$ in Eq. (6) for men as exp(-16.7336), and for rats the parameter $c$ in Eq. (7) as exp(-1.6741). A lifetime incidence of mesotheliomas of 50% is much higher than has been observed in humans, but such an incidence has been observed in groups of rats following injection with asbestos. The results given next apply only to the relationship between cumulative incidence and elimination rate, and how this relationship differs between humans and rats. They do not imply that the absolute incidence of mesotheliomas in humans can be determined from
experimental studies in rats, since there is no known way of converting the dose from one species to the other.

The cumulative incidences of mesotheliomas for men are given in Table 1 for ages 70 to 95 yr for $\lambda$ up to 1.5/yr. The results at age 85 yr are plotted in Figure 1 with a logarithmic scale for mesothelioma incidence to cover the wide range. Although age 85 yr was chosen for illustration, the corresponding plots for ages 75 and 95 yr are very similar and would have been almost coincident on the plot. Corresponding results for rats are shown in Table 2 for 100 to 150 wk after injection for $\lambda$ up 25/yr, and are plotted for 130 wk in Figure 2.

The results for men and rats are similar except in one important respect. For men the highest value of $\lambda$ shown is 1.5, giving a cumulative incidence of mesotheliomas of 2.5 in a million. For rats the same incidence does not occur until $\lambda$ is as high as 26. The comparative results for men and rats for $\lambda$ up to 25 on a logarithmic scale are shown in Figure 3. The much larger influence of elimination rate in men than in rats is clear. The relationships appear to differ only in a horizontal displacement corre-

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**TABLE 1.** Cumulative Incidence of Mesotheliomas (%) in Men Exposed from Age 20 yr to 60 yr for Fibers with Different Elimination Rates ($\lambda$).
sponding to a factor difference in the effect of $\lambda$ between men and rats of just less than 20. This is confirmed by the plot in Figure 4 where different scales for $\lambda$ have been used for men and rats. The relationships are then almost identical, showing equivalence when

$$\lambda_{\text{rats}} = 17\lambda_{\text{men}}$$

or equivalently when

$$\text{Half-time (men)} = 17 \times \text{half-time (rats)}$$

These equivalences are relative to a highly durable fiber ($\lambda = 0.01/\text{yr}, \text{half-time} = 69 \text{ yr}$) and show that the influence of solubility of fibers on the mesothelioma rate is 17 times higher in humans than in rats, for the timing of exposure considered. This is a consequence of the difference in aging and cancer incidence in rats and humans. Rats are aging and developing cancer at a much quicker rate than humans and hence the influence of dissolution is less.

**DISCUSSION**

The preceding development is without doubt a simplification of a more complex process. As indicated earlier, there is evidence that the
elimination rate is higher for long than for short fibers, and Bernstein et al. (1996) suggested that the elimination consisted of a combination of two exponential functions. It is not established that the risk of mesothelioma is related only to the amount of fiber remaining in the lung, but the possibility that the products of dissolution pose some risk through transport of chemical properties of the fibers to other parts of the lungs, particularly the pleura, does not accord with observations that the more soluble fibers produce less disease than more durable fibers. A reduction in mesothelioma incidence below that given by the model of Eq. (3) has not been observed, although Newhouse et al. (1985) found a lower number of mesotheliomas over an 8-yr period than they had predicted from an earlier follow-up using an incidence model based on Eq. (4) (Newhouse & Berry, 1976). Walker (1984) observed a declining ratio of observed to expected lung cancer deaths after more than 35 yr following initial exposure and noted that this was consistent with the clearance or encapsulation of asbestos fibers in the lung.

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FIGURE 2. Cumulative incidence of mesotheliomas in rats 130 wk after exposure by injection at age 6 wk for fibers with different elimination rates ($\lambda$).

FIGURE 3. Cumulative incidence of mesotheliomas for men and rats for fibers with elimination rates to 25/yr.
Tran et al. (1997) considered the clearance of particles and fibers in terms of a nine-compartment model. They concluded that short fibers ($l < 15 \mu m$) behaved similarly to particles in that overloading of the lungs by fibers or particles retarded the rate of clearance. The influence of overload declined with increasing length of fibers, and for fibers longer than 25 $\mu m$ they concluded that the rate of disappearance was independent of lung burden, implying that the disappearance was probably due to dissolution. These results are in accord with those given by Eastes and Hadley (1995), who demonstrated that the elimination of fibers from rats’ lungs after exposure by inhalation was in agreement with predictions based on the dissolution rate measured in vitro.

Davis et al. (1996) and Jones et al. (1997) gave some preliminary results from the Colt Fibre Research Programme, which examined the effects of fiber characteristics, including durability, on toxicity. They found an association between in vitro durability at pH 7 and the retention of long (>15 $\mu m$) fibers 12 mo after installation into rat lungs. After intraperitoneal injection there were mesotheliomas produced in a high proportion of animals, although detailed data were not presented except for overall survival. The
authors regarded median survival time as a good indicator of the effect of mesotheliomas on survival and reported much shorter median survival for the durable fibers than for the fibers with low durability, after allowing for the number of fibers >15 µm in length injected. They found a similar association between the percentage of rats developing a malignant lung cancer after exposure by inhalation.

Pott and Roller (1996) summarized results from intraperitoneal injection experiments in rats for a range of glass and other fibers. There was a range of 1000-fold in the dose, measured as estimated number of fibers ($l > 5 \mu m$, $d < 2 \mu m$) injected, required to produce tumors in 25% of rats. The less durable fibers required the higher doses, although there were no direct determinations of solubility. The range of 1000-fold in dose corresponds to a range in $\lambda$ from 0.1 to 5.8 (see Figure 2), and this range is in accord with the ranges in dissolution rates noted earlier, although it is possible that clearance of fibers after intraperitoneal injection may be different from dissolution in the lungs (see Eastes & Hadley, 1996, for a discussion of this point).

Eastes and Hadley (1996) put forward the hypothesis that a rapidly dissolving fiber is equivalent in effect to a smaller dose of a durable fiber, where a durable fiber was defined as not dissolving during the lifetime of the species, about 2 yr for rats. They considered that a dose of fibers that dissolved in 1 yr acts like half the dose of a fiber that takes at least 2 yr to dissolve. Since the time for a fiber of a given initial diameter to dissolve is inversely proportional to the rate of dissolution, then a fiber’s effect is proportional to the dose divided by the dissolution rate. They demonstrated that data from rats on fibrosis and lung tumors after exposure by inhalation in the RCC experiments, and from mesothelioma incidence after intraperitoneal injection in experiments by Pott and colleagues, were consistent with the hypothesis. The models put forward in this article imply a greater reduction in effect as the dissolution rate increases, because of the hypothesized exponential decline in effect, but in qualitative terms the patterns are similar. From Figure 4 the influence of the dissolution rate in rats is most marked for $\lambda$ greater than about 0.35, corresponding to a half-time of 2 yr or less. In man the same influence occurs for $\lambda$ greater than about 0.02, a half-time of 35 yr or less. Eastes and Hadley (1996) and Eastes et al. (1996) noted that since dissolution is a physical chemical process it is likely to proceed at the same rate in rats and humans, so that the effect of the dissolution leads to a much greater reduction in mesothelioma incidence in humans than in rats. The results in this article (Figure 3) are in accord with this.

The elimination model given by Eqs. (5) to (8) may be modified to incorporate other forms of elimination processes in addition to the exponential process considered in this paper. Thus the process considered by Eastes and Hadley (1996) of a distribution of fiber diameters with fibers of different diameters eliminated by complete dissolution after calcu-
lated times could be explored by appropriate modification to the methodology.

The difference between humans and rats in the range of dissolution rate that is most influential in reducing the carcinogenic effect is important in the way that results from animal experiments may be used to predict the possible effects of occupational exposure of humans. For humans there is a rapid reduction in predicted carcinogenic effect over the range of dissolution rates that links asbestos and the more durable synthetic mineral fibers, while in rats the reduction only occurs with the least durable fibers. This difference has occurred because the development of cancer occurs in a shorter chronological time in rats than in humans, while the dissolution of fibers from the lungs occurs at a similar rate. In terms of the life span of each species the dissolution is effectively 17 times faster in humans than in rats, and this means that fibers covering a range of dissolution rates are active in rats but not in humans. In effect, although durability can be expressed as an absolute measure in units of time, its effect can only be considered in association with species lifetime. A fiber that is dissolved in 2 yr is durable for a rat, since it is present for most of the rat’s life, but nondurable for a human since it dissolves years before any tumor that it might otherwise cause can develop. Thus in relative terms animal experiments give quite different results than predicted to occur in humans. It is possible that this difference explains the apparent contradiction that chrysotile asbestos gives similar mesothelioma incidences to the amphiboles in rats while the amphiboles give much higher rates after occupational exposure in humans.

The approach is given as a possible model of the biological mechanism leading to the development of mesotheliomas after exposure to asbestos or other inorganic fibers. Synthetic mineral fibers may be classified for their carcinogenic effect based on their dissolution rate, or a proxy for that rate, and the dissolution rate may be determined by short-term in vitro studies (Potter & Mattson, 1991; Mattson, 1994). Therefore, it is important to develop information and models pertinent to the relationship between dissolution and cancer rate in humans. The reduction in tumor rate with increasing rate of dissolution appears much greater in humans than in animals.

REFERENCES


