

RAPID COMMUNICATION

Extrapolation of the Carcinogenic Potency of Fibers from Rats to Humans

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In 1999 Berry published a model for mesothelioma incidence following fiber exposure. He concluded, that the influence of the solubility of fibers on the mesothelioma rate is 17 times higher in humans than in rats. This conclusion may be helpful for evaluating the carcinogenic risk from man-made vitreous fibers, but it had little influence on some recent discussions. It has been demonstrated using this model, that in an injection experiment with rats, fibers with elimination constants of 0.1/year and 1/year—which would approximately correspond to crocidolite and perhaps ceramic fibers—differ in their mesothelioma risk only by a ratio of 3.2:1. In contrast, for humans exposed continuously from age 20 to age 60 a risk ratio of 4,750:1 is obtained. This result may be helpful for the assessment of the human cancer risk e.g., from exposure to refractory ceramic fibers. However, uncertainty is large, since the life-span of rats is too low to measure the elimination rate of bio-persistent fibers sufficiently.

INTRODUCTION

In 2003 I was involved in controversial discussions on the extrapolation of the experimental results on the carcinogenic potency of fibers from rats to humans. On this occasion I came to the conclusion that Berry (1999) makes an important contribution to this item which was not applied successfully during these discussions. Therefore I intend to remind of Berry's paper and to discuss its consequences on the extrapolation from rats to humans.

Assessment of the Human Cancer Risk from Exposure to Refractory Ceramic Fibers

During a colloquium in October 2003 the risk of human cancer resulting from exposure to refractory ceramic fibers was discussed controversially (Roller & Wardenbach, 2003; Turim, 2003). Rat bioassay experiments with crocidolite and various *synthetic vitreous fibers* (SVFs) suggest that *refractory ceramic fiber* (RCF) is at least as potent as crocidolite asbestos. The apparent relative potency of these two fibers in rats is a function of how this is calculated, whether on the basis of exposure concentrations or lung burdens and on which fibers (WHO fibers or those longer than 20 μm). Interpretation of these experiments

is made more difficult by the fact that the period of crocidolite exposure was shorter than that for other SVFs (McConnell et al., 1994), including RCF, and a possible confounding effect of a non-representative ratio of particles to fibers in the RCF experiment (Mast et al., 2000; Maxim et al., 2003). Pott and Roller (1996) and Roller and Wardenbach (2003) estimated the relative potency of RCF and crocidolite in rats was approximately 8:1 measured as the relative proportion of tumors to WHO fiber exposure concentrations. This relation is modified for including chrysotile and for counting asbestos fibers by light microscopy and it is used to estimate the human cancer risk from RCF. Brown (2000) argued, in contrast, that differences in the biopersistence of crocidolite and RCF might have different consequences in rats and humans.

Turim has presented a biologically founded model (Moolgavkar et al., 1999, 2000, 2001) which takes into account the different life spans, the differing pools of susceptible cells and the toxicokinetics of humans and rats. This model, yields the human risk ranges two or three orders of magnitude lower than the estimate obtained by Roller and Wardenbach. Reasons for the differences in risk estimates developed by Roller and Wardenbach (2003) and Turim (2003) were not apparent.

The Interspecies Comparison of the Toxicity of Asbestos and Synthetic Vitreous Fibers of Maxime and McConnel

An evaluation of the carcinogenic risk to humans caused by man as a result of vitreous fibers was made in 2002 by a working group of the IARC (2002). In contrast to the analysis

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of 1988, where experimental evidence for fibers from glass wool had been judged “sufficient” from intraperitoneal injection, experimental evidence was now only regarded as “limited.” Concerning the intraperitoneal injection as one of the routes of administration two points of view were opposed in the general remarks of the monographs: Muhle and Pott (2000) hold the view that positive results from intraperitoneal injection experiments can not be disproven by negative results from inhalation experiments, since the latter are not sensitive enough to predict the carcinogenic potency for humans. In contrast, Maxime and McConnel (2001) reported that well-conducted inhalation studies of carcinogenicity are very sensitive.

On the basis of an interspecies comparison of the toxicity of asbestos and synthetic vitreous fibers Maxime and McConnel state that “there is no reason to conclude, that humans are more sensitive to fibers than rats with respect to the development of lung cancer.”

By restricting their statement to lung cancer these authors first of all avoid the discussion of mesothelioma. However, this restriction is not justified, especially since they object to the “Rödelsperger—Woitowitz—Pott hypothesis” on the sensitivity of the inhalation experiment. This hypothesis is based among other things on the results of a mesothelioma case control study (Rödelsperger & Woitowitz, 1995; Rödelsperger et al., 1999) which are compared to the results from the rat inhalation experiment with crocidolite (McConnel et al., 1994). As in other studies, the risk of human mesothelioma was clearly associated with the pulmonary burden of amphibole asbestos. A significant increase of the risk was even observed below 200,000 fibers per gram dry lung tissue. The upper limit of this interval lies 6,000 times below the concentration of crocidolite fibers, which was necessary in the lungs of the rats to obtain a positive result from the inhalation experiment.

Further, according to Berry (1999) and Eastes and Hadley (1996) not just for mesothelioma but also even for lung cancer it should be expected that highly biopersistent asbestos fibers are more effective in humans than in rats if they are compared to highly soluble synthetic vitreous fibers. Therefore a statement about the sensitivity of humans compared to rats should not generally refer to “fibers.” Maxim and McConnell (2001), referring to the paper by Berry (1999), note that “A fiber with a biological half time of two years would be resident throughout the rat’s life but only a relatively small portion of the human’s life span. This differential life span of rodents and humans alone has suggested to some investigators that rats are at least 17 times more sensitive than humans for the development of mesothelioma.” While the first part of the statement correctly indicates, that the consequences of biopersistence may be different in humans and rats, the second part has to be handled with caution. Actually, what Berry wrote was “The influence of solubility of fibers on the mesothelioma rate is 17 times higher in humans than in rats.” The next section provides a more accurate and complete explanation of the influence of biopersistence.

THE MODEL OF BERRY

On the basis of the multistage model of tumour induction, Berry adopts the proposal of Doll and Peto (1985), that the relationship between the incidence of mesothelioma and the time since start of exposure increases with a power of 3 to 4. From this model each increment of exposure, which is administered to the lung, contributes to the mesothelioma incidence at the time T as a function of the duration of its residence after deposition. Therefore the total incidence at time T has to be estimated by integration over the duration of exposure.

This model satisfactorily explains the incidence of mesothelioma after exposure to durable fibers of amphibole asbestos, which may persist in the human lung tissue for several decades. Thus Berry estimated the rate of elimination λ for crocidolite fibers at $\lambda = 0.1$ to 0.15 per year in humans, corresponding to a half-life of about 5 to 7 years. To estimate the incidence of mesothelioma, which is caused by fibers of lower persistency, it has to be considered, that the dose of these fibers in the lung decreases with time. Therefore, to estimate mesothelioma incidence for fibers of low bio-persistency, retention of these fibers is considered using a first order elimination model for a constant elimination constant λ .

Application of the Elimination Model

Berry applied his model to humans continuously exposed to fibers from age 20 to age 60 years, a hypothetical working lifetime. He calculated the cumulative incidence of mesothelioma at ages up to 100 years depending upon the kinetic constant for elimination, λ (Table 1 of Berry (1999)). This model considered the mortality from other causes in addition to mesothelioma from the Australian life table for men in 1994. For this group the median lifetime was 78 yr. Berry selected values for the parameters of his model to standardize the cumulative incidence of mesothelioma for a very durable fiber ($\lambda = 0.01/\text{yr}$) at 50% for 75-year old men. He calculated the incidence of mesothelioma for this and other fibers assumed to be identical except for the value of λ for men at ages ranging from 70 to 95 years for values of λ ranging from 0.0001/yr to 1.5/yr.

In order to facilitate the comparison of the influence of elimination between humans and rats, Berry developed a corresponding table for rats assuming a single injection of fibers at age 6 weeks. He chose the parameters of the rat model to standardize the incidence of mesothelioma at 50% 110 weeks after injection (i.e., an age of 116 weeks) for a very durable fiber ($\lambda = 0.01$). The natural mortality of standard Wistar rats (Berry & Wagner, 1969) was used as the life table; the median lifetime following the injection was 120 weeks. Berry then calculated the mesothelioma incidence for rats at various times post-injection ranging from 100 to 150 weeks for an otherwise identical fiber with various values of λ ranging from 0.0001/yr to 35/yr (included in Table 2 of his paper).

Figure 1 compares the cumulative incidence for men (age 85 years) and rats (age 130 + 6 = 136 weeks) as a function

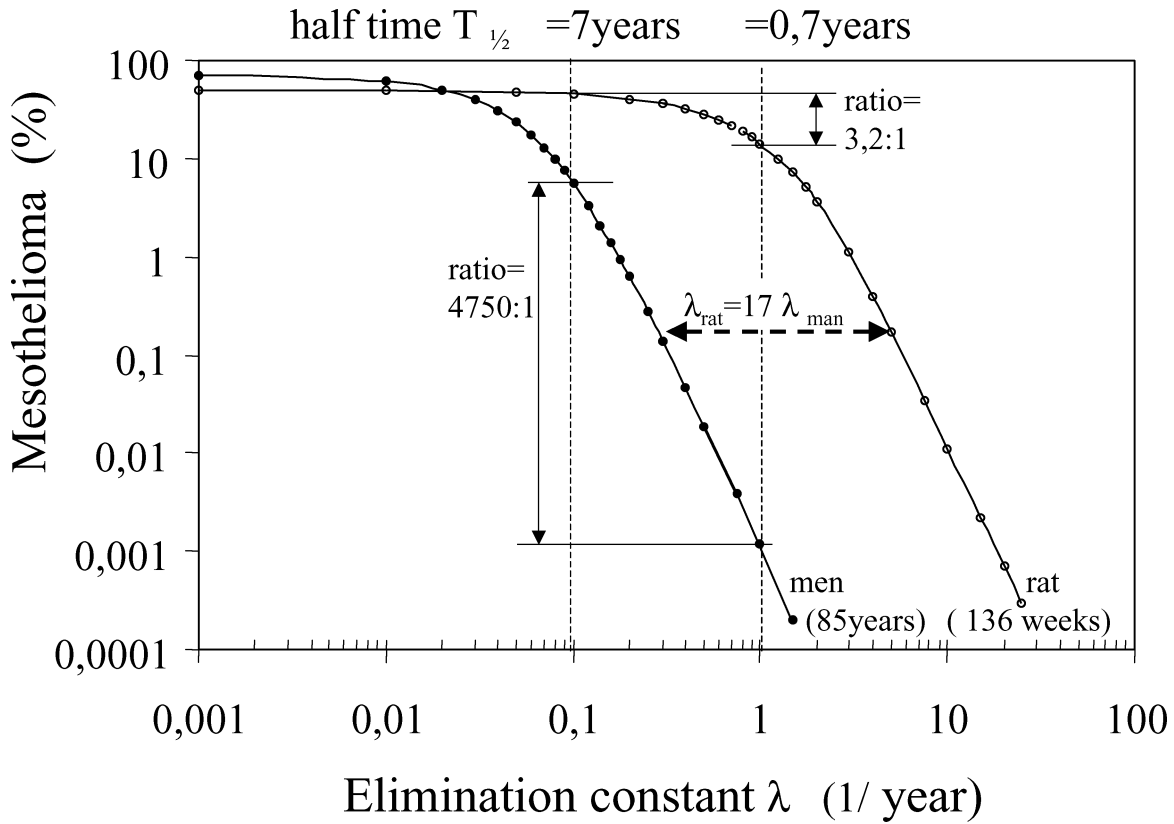


FIG. 1. Cumulative incidence of mesothelioma for man and rats after exposure to fibers. Dependence on the elimination constant of these fibers (modified from Berry, 1999).

TABLE 1
Comparison of the half-life of crocidolite and ceramic fibers estimated for different types of application

Experiment	T ¹ / ₂ 95% CI				Type	Reference
	Crocidolite fibers		Ceramic fibers			
Inhalation 5 days						
Weighted, L > 20 μm	817	246-∞	55	44-66	RCF1a	Hesterberg et al., 1998
Weighted, L > 20 μm			41		RCF1	Jones et al., 1997 cited by Bernstein, 2001
Inhalation 3 weeks						
WHO-fibers*			61	49-74	RCF1a	Bellmann et al., 2001
			103	94-112	RCF1	
L > 20 μm*			61	56-66	RCF1a	
			77	72-83	RCF1	
Intratracheal instillation						
WHO-fibers	976	214-∞	304	38-∞	**	Muhle et al., 1994
WHO-fibers			343	291-416	RCF1	Muhle et al., 1998
L > 20 μm			300	256-363	RCF1	
Intraperitoneal injection						
WHO-fibers			371	193-4743	RCF1	Muhle et al., 1998
L > 20 μm			410	200-7953	RCF1	

*Nonlinear regression according to the protocol of the European commission 1998.

**Recalculated from Bellmann et al., 1987.

of the elimination constant λ . It is plotted from data contained in Tables 1 and 2 of the Berry paper and corresponds to his Figure 3. It is important to note that Figure 1 does not purport to represent the absolute incidence of mesothelioma in rats and men. Rather, this figure shows how the relative incidence of mesothelioma in each species varies with λ .

When discussing these results, it is useful to address the following question: What is the difference in the cumulative incidence of mesothelioma in humans compared to rats, if a fiber with the elimination constant $\lambda = 0.1/\text{year}$ ($T^{1/2} = 7$ years) is compared to a fiber with the elimination constant $\lambda = 1/\text{year}$ ($T^{1/2} = 0.7$ years)? According to Berry an elimination constant of 0.1/year approximately describes the bio-persistence of a crocidolite fiber (Berry suggests a range from 0.1 to 0.15). In contrast, an elimination constant of 1/year is characteristic of a less bio-persistent fiber e.g., to an ordinary rock or glass wool fiber or a ceramic fiber of the WHO-definition, if the bio-persistence—according to the experimental conditions assumed by Berry—is measured after intratracheal instillation or intraperitoneal injection, while it would be distinctly lower from short-term inhalation, c.f. Table 1.

In Figure 1, λ values for crocidolite and a less biopersistent fiber (e.g., RCF) are represented by two vertical lines ($\lambda = 0.1/\text{year}$ and $\lambda = 1.0/\text{year}$, respectively). Consider first the curve for men. For 85-year old men the estimated mesothelioma incidence corresponding to crocidolite exposure is 5.7%; for the less biopersistent fiber it is (from Berry Table 1) 0.0012%. Thus, the relative ratio of mesothelioma incidence in men following lifetime occupational exposure to the durable compared to the less durable fiber is $5.7/0.0012 = 4,750:1$. The effect of biopersistence on relative mesothelioma incidence in men is dramatic for this difference in λ . In comparison, for rats aged 136 weeks (130 weeks post-exposure) the estimated mesothelioma incidence decreases from 56.9% for crocidolite to 17.8% for the less biopersistent fiber, a ratio of approximately 3.2:1. Although substantial, this ratio is very much less than that for humans. Indeed, the ratio of relative mesothelioma values comparing humans with rats is $4,750/3.2 = 1,500:1$ (approximately).

This numerical example provides a more complete depiction of the relative sensitivity of rats and humans. While it is true that the *horizontal* displacement in the curves shown in Figure 1 differs by a factor of 17, the relative incidence of mesothelioma depends upon the ratio of the *vertical* differences.

DISCUSSION

According to Berry these results are plausible in principle, since “the physical chemical process of dissolution is expected at about the same rate in rats and in humans” and since “rats are aging and developing cancer at a much quicker rate than humans and hence the influence of dissolution is less.” The average lung burden during the first year of the life time is most relevant for tumour induction in rats. Hence, related to this time period the administration of ceramic fibers with a half-life of 1 year yields at least half of the lung burden, which is obtained

with crocidolite fibers. In contrast, in humans one half of the mesothelioma cases occur more than 30 years after the start of exposure and more than 99% of the ceramic fibers have been eliminated during the first 7 years of this time period, while about half of the crocidolite fibers are still present.

As can be seen from Figure 1 the predicted incidence of human mesothelioma is a sensitive function of the elimination constant over the range from amphibole asbestos ($\lambda = 0.1/\text{year}$) to the less durable fibers, like rock wool or ceramic fibers ($\lambda = 1/\text{year}$). In contrast, the incidence of mesothelioma in rats is only influenced to a minor degree over this range. In terms of the life span, the rate of dissolution is effectively 17 times higher in humans than in rats. Hence, a decline of the incidence of similar extent may be expected amongst rats if the two fiber species are both 17 times less durable, e.g., if conventional glass wool fibers are compared to newly developed bio-soluble glass fibers.

Comparison of Amphibole Asbestos and Chrysotile

In humans amphibole asbestos causes a much higher rate of mesothelioma than chrysotile (Doll & Peto, 1985; HEI.AR, 1992). This is clearly predicted for humans by the elimination model since the bio-persistence of chrysotile is generally much lower than that of amphibole asbestos (Churg & Wright, 1994). In addition, it is a consequence of the model, that in accordance with the results from animal experiments, these differences are less distinct for rats.

Intraperitoneal Tests in Rats

Intraperitoneal injection experiments revealed that the dose response relationships decreased in their steepness up to 1000-fold, on crocidolite fibers comparing ceramic, glass wool, stone wool and slag wool fibers (Pott & Roller, 1996). This decrease can be predicted from Figure 1. The rate of mesothelioma in rats decreases by 3 orders of magnitude as the elimination constant increases—corresponding to the transition from crocidolite to slag wool—from $\lambda = 0.1$ ($T^{1/2} = 7$ years) to $\lambda = 5.8/\text{year}$ ($T^{1/2} = 40$ days).

Variation of the Age and Standardization of Mesothelioma Incidence

The curves shown in Figure 1 and the specific ratios calculated based upon these curves depend upon several numerical assumptions. For example, the cumulative incidence was standardized at 50% for 75-year old men and for rats of an age of 116 weeks. However, the ratio of the incidence for two fiber species is not influenced by this procedure since it affects both values equally by the same factor.

Further the curves for men and rats are shown for specific ages, 85 years and 130 weeks post-exposure, respectively. Berry calculated normalized mesothelioma incidence for other ages. Likewise, assuming that an appropriate value of λ for crocidolite is 0.1/year, the relative mesothelioma incidence associated with

exposure to a less biopersistent fiber (1/year) depends upon the value of λ for that fiber. The relative ratio (approximately 1,500 in the original example) as calculated by considering men and rats of various ages only varies between 1030 and 1600. While the lower ratio results from a comparison between men aged 70 and rats with 120 weeks post exposure, the higher one obtains for men aged 95 compared to rats 100 weeks post exposure. The slight irregularity that the lowest ratio is not observed for the oldest rats probably results from round-off errors in the Berry tables. The mesothelioma incidence in older men or rats is arguably a more valid basis for comparison and this ratio does not vary greatly.

The Uncertainty of the Half-Life Measurement

The data available for fiber retention suggest, that the estimate of the half-life of a particular fiber depends on fiber definition (WHO-fibers or fibers longer than 20 μm) the route of administration (intratracheal, intraperitoneal or inhalation) and the statistical model of evaluation (e.g., single or two compartment). Which of these half-lives should be used if the influence of the solubility of fibers on their carcinogenicity is to be compared between rats and humans?

According to the example in Figure 1 it is assumed that human exposure is by inhalation whilst a single intratracheal or intraperitoneal injection has been assumed for rats. However, if these types of application are compared, results are fairly similar for crocidolite but very different for ceramic fibers, Table 1.

It should be remembered that because of their small size, crocidolite fibers will reach the alveolar space much more readily than ceramic fibers and in addition, they heavily impair mechanical clearance on account of their cytotoxicity. On the other hand, after an inhalation for three weeks with RCF1 the alveolar clearance of tracer particles was delayed much more ($T^{1/2} = 1200$ vs. 66 days in controls) than with RCF1a ($T^{1/2} = 80$ vs. 60 days in controls) (Bellmann et al., 2001). The main difference between the two samples was the higher content of non-fibrous particles. In spite of this, the clearance of the RCF1-fibers themselves is only slightly impaired, Table 1.

While short-term inhalation test has been adopted for classification of MMVF by the European Union according to directive 97/69/EC of 5. December 1997, German regulations are solely based on WHO-Fibers which are measured after intratracheal instillation. It has been argued (Roller & Pott, 1998; Wardenbach, Pott, & Woitowitz, 2000) that

- the half-life of only 41 days obtained by inhalation for ceramic fibers is not plausible,
- the inhalation test yielding a much higher content is confounded by bronchial clearance of undissolved fibers,
- the physiological clearance rate is much faster in rats and therefore cannot be extrapolated to humans and
- inhaled fibers with diameters $>1 \mu\text{m}$ only are deposited in the noses of the rats.

Altogether it remains doubtful which of the data sets of Table 1 are adequate for use. Naturally the ratio of the incidences in Figure 1 is heavily influenced by this uncertainty. So for a half-life of ceramic fibers of 371 days—which according to Table 1 corresponds to intraperitoneal testing of fibers of the WHO-definition—compared to the half-life of 2530 days ($\lambda = 0.1/\text{year}$) for crocidolite—the ratio between humans and rats decreases to 560:1. Instead of this it would increase to about 8,100:1, if—according to human exposure—one of the half-lives from inhalation testing were used. In contrast, Moolgavkar et al. (1999) used (in their Figure 3) a longer half-life of about 3 years from which only a ratio of about 15:1 would be obtained. This half-life results from a dosimetry model for humans (Yu et al., 1997) which was developed from a dosimetry model for rats (Yu et al., 1996). The latter is based on estimates of dissolution, breakage and mechanical clearance obtained from the lung burden data of the inhalation experiment of Mast et al. (1995) with RCF. The dissolution rate roughly was estimated to $k = 0.065 \text{ nm/day}$ from the decrease of the average diameter of the fibers. Yu et al. (1997) give the following characterisation of this result: “For RCF, the value of k is very small and fiber removal is insignificant over the lifetime of the rat.” They examine their model with lung burden data from three workers who spent 13 to 17 years in a RCF production facility with unknown exposure concentration. The criticism has been made that RCF1 fiber elimination was heavily retarded by an unusual amount of non-fibrous particles during this experiment (Hesterberg et al., 1998; Bellmann et al., 2001; Mast et al., 2000; IARC, 2002), but Maxim et al. (2003) state, “that there is no known reason why the dosimetry model would either under or over-predict lung burdens.” However, the dissolution rate k is very low and the decrease of the average diameter of all fibers, may be attenuated by the breakage of long and thick fibers. This breakage should be expected since after the end of exposure the percentage of fibers longer than 20 μm decreased rapidly (Mast et al., 1995).

Altogether, it is difficult to establish a clear difference between the bio-persistence of crocidolite and ceramic fibers from animal experiments. However, the life-span of rodents obviously is too short to measure the half-life of amphibole asbestos with any precision. So the confidence intervals of the half-lives of amphibole asbestos fibers obtained from intratracheal instillation for rats (Bellmann et al., 1987, 1994; Muhle et al., 1994, 1998) as well as for sheep (Dufresne et al., 1999) overlap with the corresponding confidence intervals quoted for ceramic fibers. However, the upper limit values of the confidence intervals for amphibole fibers are always infinite. Furthermore, it should be considered, that the deposition and mechanical clearance of bio-persistent particles (including short fibers) is different for rats and humans (Yu et al., 1997, 1998; IARC, 2002). In contrast, the *in vivo* dissolution of the fibers is expected to be similar for different species. However, since mechanical clearance is much faster in rats than in humans a given dissolution rate has a greater influence on the half-life in humans than it does in rodents (IARC, 2002).

Unfortunately, the half-life of ceramic fibers is not available from human data (IARC, 2002), whereas the half-life for crocidolite has been estimated to be about 6 to 20 years (Berry, 1999; Churg & Wright, 1994). The lower limit of this estimate may even be tested from our mesothelioma case control study (Rödelsperger et al., 1999). First of all it should be considered, that mesothelioma risk depends, on the one hand, on the burden of amphibole fibers, still present in the lung tissue after the outbreak of the disease and, on the other hand, on the time elapsed since the start of exposure about 30 years earlier. In addition, 1.5×10^6 crocidolite fibers larger than $5 \mu\text{m}$ per gram dry lung tissue were observed for one of the mesothelioma patients from this study. This patient was a clerk whose only asbestos exposure resulted from a residence as a child in Wittenoom for 4 years, when his father had worked in the crocidolite mine (Rödelsperger, 1996). If the time elapsed since the end of exposure, which was more than 30 years, is combined with a half-life of 3 years, the minimum original concentration would have been $2^{10} = 1024$ times 1.5×10^6 fibers/g dry, while it would have been $2^5 = 32$ times this value ($= 48 \times 10^6$ fibers/g dry) for a half-life of 6 years. However, the maximum lung burden among the 132 patients of our case control study only was 12.4×10^6 amphibole fibers/g dry weight. In contrast, heavy exposure of craftsmen to rock or glass wool resulted in only very few fibers assignable to these produces being detected in the lung tissue, even if exposure had only ended recently (Rödelsperger et al., 1998).

CONCLUSIONS

The carcinogenic potency of crocidolite and ceramic fibers from inhalation and intraperitoneal injection in rats is similar. However, it cannot be predicted, that this similarity likewise exists for humans, despite of differences in fiber size and bio-persistence. Rather the consequences of the dissolution rates may be quite different for humans and rats. If fibers with elimination constants of 0.1/year (representing crocidolite) and 1/year (which might represent ceramic fibers) are compared under the conditions proposed by Berry, then induction of mesothelioma differs only by a ratio of 3.2:1 for rats compared to 4,750 for humans. Though Berry restricted his calculation to mesothelioma and though the clearance from the peritoneum is different from the clearance from the lung, similar relationships may also be expected for lung cancer. According to human experience a definite exposure to asbestos fibers causes a definite increase in the relative risk of lung cancer which remains constant after the end of exposure (Nicholson et al., 1981; Doll & Peto, 1985; HEI.IARC, 1992). Therefore, the incidence of lung cancer is expected to increase with the time since end of exposure, in accordance with the the normal age dependency of lung cancer. According to Berry (1999) and Eastes and Hadley (1996) the residence time of the fiber should modify this process in different ways for rats and humans.

Based on the foregoing it is likely that the human cancer risk from ceramic fibers is substantially lower than that for amphibole

asbestos. The estimated difference in risk depends upon the half-lives for ceramic fibers and for amphibole asbestos. Precise estimates of this difference depend upon the interpretation of the available data on biopersistence and on statistical uncertainty of the half time estimate. Since the life-span of rodents is too short to measure the half-life of these fibers sufficiently, data from human lung tissue urgently are needed.

Additionally, it would be interesting to use the Moolgavkar et al. model to estimate the cancer risk from exposure to crocidolite asbestos based upon the rat inhalation experiments as has been done for ceramic fiber. Unfortunately this latter exercise is adversely affected by the uncertainty of the fiber dose estimate for humans, especially since human exposure mainly results from a mixture of chrysotile with unknown amounts of amphibole asbestos.

Finally, the material presented in this paper provides a more accurate summary of Berry's work than that offered by Maxim and McConnell (2001). Specifically, this paper shows that the relative difference in mesothelioma rates in humans compared to rats derived from an animal experiment where two fibers of different biopersistence are compared depends upon the values of the elimination constants for each of the two fibers. However, it does not intend to represent the difference in the incidence of mesothelioma in rats and men for one specific fiber.

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