

do not invalidate either but suggests that each method should be used for different purposes.

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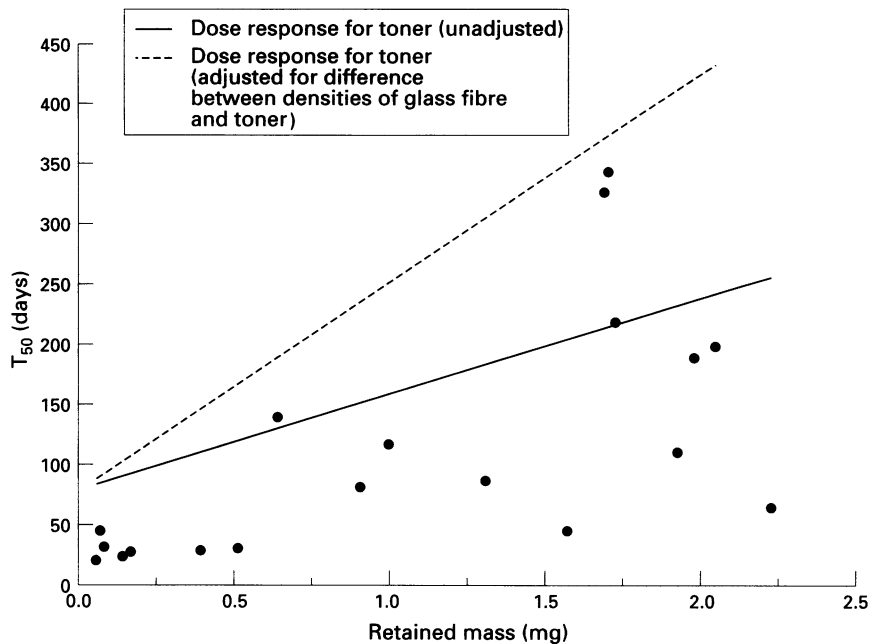
### The influence of retained mass (lung burden) on the results of intratracheal tests

Editor—In a recent paper Yu and Rappaport<sup>1</sup> presented the dose dependency of clearance rate for different materials. We discuss the problem of lung burden in intratracheal tests based on these results.

Intratracheal tests have been used by several investigators to evaluate the clearance of fibres or dust from the lung. Recently this kind of test has been used in the German (BMBF) project "Persistenzuntersuchungen von Mineralfasern in Vivo und in Vitro und Entwicklung von Beurteilungskriterien für die Kanzerogene Potenz". The instilled mass of fibres in the German investigation was four times 0.5 mg (~2 mg), and the first sacrifice day was three days after the last instillation (~100% in the successive clearing of the fibres). The biopersistence of different fibres is represented by the calculated half times ( $T_{1/2}$ ) based on the clearance of the number of World Health Organisation (WHO) fibres, or the number of long fibres (> 20  $\mu\text{m}$ ), or of fibre mass (calculated from the number and size distribution of the fibres in the lung).

The clearance of fibres is a combination of the physical clearance (alveolar macrophage mediated clearance and transport through lymphatic channels), the disintegration of fibres, and the dissolution of fibres.<sup>2</sup> It is influenced by several variables such as diameter, length, and retained mass or number of fibres.<sup>2</sup> Increasing half times with increasing lung burdens have been found by several authors.<sup>3,4</sup>

In the initial period after instillation the fibres are cleared from the upper airways and the lung by several mechanisms, including mucociliary clearance. As the evaluation



Relation between the measured half time ( $T_{1/2}$ ) of WHO fibres and the lung burden. The solid line represents the dose response for toner and the dotted line is the same dose response adjusted for the differences in density between fibre glass and toner

of the biopersistence of the fibres, expressed by the half time, should only represent the clearance from the lung, the clearance of fibres in the initial period is not thought to be relevant. The half time of the fibres is therefore calculated on the basis of the retained number of fibres or fibre mass (lung burden) after an initial period of two to three days after the last instillation.

The table shows that there are substantial differences between instilled dose (mg) and retained mass (mg). When the half time values are stated as the results of the tests, the influence of the different lung burdens is rarely discussed or taken into consideration. This may give misleading results about the relative ranking of the biopersistence of the different fibre types.

The influence of retained mass ( $m_r$ ) of a nearly inert material (toner) was investigated by Muhle *et al.*<sup>5</sup> (The same material with low solubility has later been used together with fibres to lower the macrophage mediated clearance.<sup>11</sup> Muhle *et al.* found that the retardation of clearance is detectable at lung burdens > 0.5 mg.<sup>3</sup>) Based on the investigation of Muhle *et al.*<sup>5</sup> Yu and Rappaport<sup>1</sup>

found that the correlation between half time and the retained mass for this inert material can be expressed as:

$$T_{1/2} = 77.8 + 80.3 \cdot m_r$$

There is experimental evidence that the particle volume is the critical variable for the clearance function.<sup>6</sup> The density of toner is 1.2 g/cm<sup>3</sup> and of fibres about 2.6 g/cm<sup>3</sup>. Taking into account the differences in density the equation for inert non-soluble fibre material should be expressed as:

$$T_{1/2} = 77.8 + 174.0 \cdot m_r$$

In the figure the half time of WHO fibres for a large range of different man made vitreous fibres are plotted against the retained mass. The solid line represents the macrophage mediated clearance of the inert toner material already mentioned and the dotted line could represent inert non-soluble fibre material. It seems reasonable to evaluate the clearance of fibres from the lung relative to the clearance of an inert material at a similar lung burden, to answer the question: How much faster is a given fibre type cleared from the lung compared with a material with only macrophage mediated clearance? The table shows the instilled

Compilation of results from different intra-tracheal tests and the calculated  $T_{1/2}$  value relative to toner and relative to an inert non-soluble fibre material

Fibre name	Reference	Instilled dose mg	Lung burden mg	Retained/instilled %	Half time WHO (days)	Half time relative to toner*	Half time relative to non-soluble fibre material
RCF 1	9	1 × 2.00	1.700	85	343	1.60	0.92
RCF 1	11	2 × 0.25	0.643	129	138	1.07	0.73
MMVF 21	12	1 × 2.00	1.689	84	326	1.53	0.88
M-E	9	1 × 2.00	1.731	87	218	1.01	0.58
MMVF 11	9	1 × 2.00	2.051	103	199	0.82	0.46
TL	9	1 × 2.00	1.981	99	188	0.79	0.45
M-Stein	9	1 × 1.00	1.036	104	116	0.73	0.46
M-Schlacke	9	1 × 1.00	0.908	91	81	0.54	0.34
M-753	9	1 × 0.10	0.078	78	45	0.54	0.49
HT-3	12	1 × 2.00	1.929	96	110	0.47	0.27
Z-wolle	10	4 × 0.50	1.311	66	82	0.45	0.27
O (K40)	10	4 × 0.50	0.173	9	28	0.31	0.26
B-01	9	1 × 0.35	0.088	25	32	0.38	0.34
B-01	11	1 × 0.25	0.059	12	20	0.24	0.23
M (K40)	10	4 × 0.50	0.147	7	24	0.27	0.23
EXP 3	12	1 × 2.00	0.522	26	32	0.27	0.19
C	10	4 × 0.50	0.400	20	29	0.26	0.20
HT-7	10	4 × 0.50	2.227	111	64	0.25	0.14
X-607	9	1 × 2.00	1.581	79	46	0.22	0.13

\*The half time relative to toner is calculated as:  $T_{1/2}$  (WHO fibres) over  $T_{1/2}$  (toner).

mass, the lung burden (retained mass at first sacrifice point), the half time of WHO fibres, and the relative relation between these and the half time of inert material and inert non-soluble fibre material.

There is no correlation between the instilled mass and the retained mass. The retained mass is therefore used in the further evaluation.

All the measured half time values except two are placed on or below the solid line representing the inert toner material. Fibres that are known to have a low dissolution rate in vitro at both pH 7.5 and pH 4.5<sup>7,8</sup> are placed close to the line for the inert material. Two measurements give higher half times than for inert toner material at a similar dose. One of these, RCF 1, was also tested at lower lung burdens, which bring the measured half time on line with the expected values for the toner material. Most of the fibres have a half time lower than expected for the toner material. In these cases macrophage mediated clearance is only one of the acting mechanisms for clearances.

If the half times are evaluated against the volume based relation no results fall above the line representing an inert non-soluble fibre material (dotted line in figure).

Two examples of measurements of the same fibre type at different instilled and retained masses are given in the table. At least for the RCF 1 there seems to exist a significant dose dependency, which exceed the dose dependency for toner. In both examples a lower retained mass gives a lower relative half time.

In conclusion, it seems that differences in the retained mass cannot be ignored in the evaluation of intratracheal data. A constant instilled mass does not ensure constant retained mass. As the clearance in the first days of the test is out of control, it is not possible to take into account the different clearance mechanisms in this period. As it is a practical problem to ensure a constant retained mass for tests of different fibre types it seems necessary to find a way to make an appropriate mass correction. This should be based on tests which are designed to elucidate the problem. Until results of such tests are available, it might be appropriate to use the half times for the tested fibre type relative to the half time for an inert material at a similar dose to characterise the biopersistence of the fibre. Other reference materials than toner may be considered, as a dose dependency of the calculated relative values for the two fibres tested twice still remains.

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*Author's reply*—Thank you for the opportunity to respond to the letter of Jensen and Guldborg regarding application of our proposed linear relation<sup>1</sup> between the elimination half time ( $T_{1/2}$ ) and lung burden ( $m$ ) to fibrous particles. The form of this linear relation derives from an underlying kinetic model analogous to Michaelis-Menton kinetics for enzymatic reactions. Jensen and Guldborg empirically compared the linear relation which we had reported for photocopy test toner (PTT, derived from inhalation data of Muhle *et al.*<sup>2</sup>) with values of half time and lung burden for a variety of mineral fibres instilled intratracheally into rat lungs. With minor exceptions, values of half time for the fibres were considerably smaller than those predicted by our model for PTT at a given lung burden. They concluded that inert particles such as PTT are more biopersistent than the mineral fibres, possibly due to the effects of disintegration and dissolution of the fibres in the lung.

Jensen and Guldborg did not evaluate the linear relation between half time and lung burden for the data which they presented in the table of their letter. As such an evaluation would allow more direct comparisons to be made between fibrous and non-fibrous aerosols, we performed the necessary calculations, and briefly summarise the results.

After regressing half time upon lung burden for the pooled data presented by Jensen and Guldborg in the table, we found the following relation:

$$T_{1/2} \text{ (days)} = 25.1 + 81.2 m, \quad (1)$$

with intercept  $\alpha = 25.1$  days and slope  $\beta = 81.2$  days/mg. Although the linear relation was highly significant ( $P = 0.004$ ), the regression coefficient of  $r = 0.63$  was considerably smaller than that which we found previously for non-fibrous insoluble particles ( $r = 0.99$ ).<sup>1</sup> Furthermore, the residuals under the linear model indicated some heteroscedasticity, suggesting that the variability of half time was somewhat dose dependent. This less than optimal fit of the linear model to the pooled data could be due to differences in the various experimental protocols or the different types of fibrous

particles which were included in the table. We recommend that future applications of our model to fibrous dusts be evaluated with data covering a range of burdens for single fibre types so that differences between fibres can be evaluated.

Assuming that the estimates of  $\alpha = 25.1$  days and  $\beta = 81.2$  days/mg, from the pooled data, provide overall measures of fibre clearance, it is interesting to compare them with the corresponding estimates for non-fibrous aerosols. Firstly,  $\alpha$  represents the intrinsic clearance half time for a particular dust when the burden approaches zero and the lungs are functioning normally.<sup>1</sup> As the intrinsic clearance half time for fibrous particles (25.1 days) was much smaller than that for non-fibrous insoluble particles (77.8 days),<sup>1</sup> we agree with Jensen and Guldborg that mechanisms other than physical clearance—for example, disintegration and dissolution, must have played some part in clearing fibres from the lungs. Secondly, we regard the parameter  $\beta$  as a measure of the potency of a particular particle for inhibiting clearance mediated by alveolar macrophages.<sup>1</sup> It is reasonable to expect that particles with different potentials for impairing clearance (for example, due to the cytotoxicity) would have different  $\beta$ s and our work provided some evidence of this behaviour for non-fibrous dusts. Comparison of the estimated  $\beta$  for the pooled fibrous particles (81.2 days/mg) with that for PTT (80.3 days/mg)<sup>1</sup> suggests that mineral fibres were about as potent as PTT in impairing clearance mediated by macrophages. Again, it would be important to estimate  $\beta$  for each type of fibrous particle to evaluate possible fibre-specific differences in potency.

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#### Electromagnetic fields and cancer: incorrect citations

Editor—Several articles that have appeared in the *British Journal of Industrial Medicine* (forerunner to *Occupational and Environmental Medicine*) in recent years have either been cited incorrectly or used in contexts that are misleading in other publications. As Feinstein and Spitzer<sup>1</sup> have mentioned, "The error is grievous if the source statement is either unresponsive or contradictory to what has been claimed for it." My letter considers misleading citations relating to alleged hazards of electromagnetic fields (EMFs).

Some incorrect citations have been summarised previously.<sup>2,3</sup> Specifically, several studies<sup>4-9</sup> were reported to support a positive association between exposure to EMFs and cancer. In these studies, however, no unique exposure to EMFs in electrical or telecommunication workers was mentioned by any of the authors. In most of these studies, there were not even any attempts to assess exposure, and, in fact, the studies were not