

# ESTIMATING IN-VITRO GLASS FIBER DISSOLUTION RATE FROM COMPOSITION

Walter Eastes, Russell M. Potter, and John G. Hadley

Owens Corning, Science and Technology Center, Granville, Ohio, USA

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## ABSTRACT

A method is presented for calculating the dissolution rate constant of a borosilicate glass fiber in the lung, as measured in vitro, from the oxide composition in weight percent. It is based upon expressing the logarithm of the dissolution rate as a linear function of the composition. It was found that the calculated dissolution rate constant agreed with the measured value within the variation of the measured data in a set of compositions in which the dissolution rate constant ranged over a factor of 100. The method was shown to provide a reasonable estimate of dissolution over a considerably wider range of composition than what was used to determine the parameters, such as a set of data in which the dissolution rate constant varied over a factor of 100,000. The dissolution rate constant may be used to estimate whether disease would ensue following animal inhalation or intraperitoneal studies.

## INTRODUCTION

The dissolution rate constant of a fiber as measured in vitro is an important predictor of the biological effects of the fiber ([Eastes and Hadley, 1996](#)). This paper exhibits a reasonably accurate and efficient method for computing this dissolution rate constant directly from the inorganic borosilicate glass fiber oxide composition.

The dissolution rate constant  $k_{dis}$  expresses the rate at which an extracellular fiber, especially one longer than 10 to 20  $\mu\text{m}$  or too long to be effectively enveloped by alveolar macrophages, dissolves in the mammalian lung and is thereby eliminated. The complete elimination of the long fiber may take place by total dissolution and removal of the dissolution products to the blood stream, by breakage of the partially leached fiber and subsequent macrophage mediated clearance of the fragments, or by a combination of these mechanisms. The exact extent and contribution of each of these mechanisms is not so important as the fact that they both occur because of dissolution, which is captured in the  $k_{dis}$  parameter.

It has been shown that glass fibers decrease in diameter after intratracheal instillation in rats at the rate predicted by  $k_{dis}$  for the same fiber composition measured in vitro ([Eastes et al., 1995](#)). It has also been shown that  $k_{dis}$  predicts the biopersistence, or the disappearance of long fibers from the rats' lungs after short term inhalation ([Bernstein et al., 1996](#); [Eastes and Hadley, 1995](#)). Finally, it was shown that  $k_{dis}$  can predict the incidence of fibrosis and lung tumors after chronic inhalation in rats and tumors following intraperitoneal injection in rats through a mathematical model that also takes into account the dose of long fibers ([Eastes and Hadley, 1994](#); [Eastes and Hadley, 1996](#)). Also, the close relationship between biopersistence and toxicity has been demonstrated experimentally ([Bernstein, 1998](#)). It is clear, therefore, that an accurate estimate of  $k_{dis}$  from composition data alone allows the prediction both of long fiber clearance and of chronic effects associated with the fibers. Such information is of great practical value to manufacturers and to the regulatory community.

The dissolution rate constant  $k_{dis}$  has been measured for a large number of different borosilicate glass fiber compositions ([Förster, 1982](#); [Klingholz and Steinkopf, 1982](#); [Leineweber, 1982](#); [Scholze and Conradt, 1987](#);

[Bauer et al., 1988](#); [Potter and Mattson, 1991](#); [Christensen et al., 1994](#); [De Meringo et al., 1994](#); [Mattson, 1994a](#); [Thélohan and De Meringo, 1994](#)) and a standardized protocol is available for performing these measurements ([Bauer et al., 1997](#)). A number of different protocols were used in the references just mentioned, and they are not always quantitatively comparable, but the results have several features in common. The measured values range over many orders of magnitude: from below 1 ng/cm<sup>2</sup>/hr for most amphibole asbestos fibers, through single digits in these units for some refractory ceramic fibers and thin E glass fibers that have been associated with fibrosis and lung tumors in rats and mesothelioma in hamsters. Double digit values have been measured for a conventional rock wool that was associated with fibrosis but not lung tumors in rats, triple digits (greater than 100 ng/cm<sup>2</sup>/hr) in almost all conventional insulation glass wool, to four or five digits for some new fibers. No fiber with a  $k_{dis}$  above 100 ng/cm<sup>2</sup>/hr has produced fibrosis or tumors in animal inhalation studies.

The ability of  $k_{dis}$  to predict biological effects reliably depends critically on measuring it in a way that is relevant to the dissolution that occurs for long fibers in the lung. Not only is it important that the composition and pH of the simulated lung fluid be the same as in the lung in those components that affect fiber dissolution, but also it is important that the dissolution products be removed as quickly in vitro as they appear to be in the lung. Otherwise the dissolution products may build up in vitro to the point at which they affect the measured dissolution rate in ways that do not happen in the lung. To avoid this problem, the typical in-vitro dissolution measurement apparatus causes the simulated lung fluid to flow through a loose assembly of fibers at a rate high enough to remove the dissolution products so that the pH and measured dissolution rate constant is not affected significantly ([Mattson, 1994b](#)). In this way,  $k_{dis}$  values are obtained that predict reasonably well the dissolution of long fibers in the lung.

The dissolution rate of a fiber is proportional to its surface area and is thus a zero order reaction ([Scholze, 1988](#)). The parameter  $k_{dis}$  in this reaction is a property of the material in the fiber, and does not depend on its size or shape. Thus  $k_{dis}$  depends on the fiber composition, conventionally expressed as the weight percent of oxides. One may expect, therefore, to be able to calculate  $k_{dis}$  to a reasonable approximation directly from the oxide composition. (The  $k_{dis}$  also depends, but to a much lesser extent for most fibers, on the glass structure that is affected by the fiber cooling rate and thus by the method of fiberizing and the fiber diameter ([Potter and Mattson, 1991](#); [Scholze, 1988](#)). These effects are much smaller than the influence of composition on  $k_{dis}$ ; usually they are so small as to be unobservable ([Scholze, 1988](#)); and they may be ignored for the present purposes.)

The next section describes the theory for calculating  $k_{dis}$  from composition, and the following one shows the application to a large set of compositions with measured dissolution rate. In the last section, this method is contrasted with other ways of estimating fiber biodurability.

## THEORY

The dissolution of glass fibers in nearly neutral water solutions occurs by the reaction of a water molecule or some part thereof with a part of the glass structure containing a cation, here called the "dissolving species", replacing it with the water species. Since the dissolution products in the lung appear to be rapidly removed from the vicinity of the fiber, the reaction is most likely not diffusion limited, and the reaction with water is the rate limiting step. Although it does not apply strictly because it models isolated molecules, chemical reaction rate theory ([Eyring et al., 1944](#)) is useful here if it is applied to the species that are dissolving, neglecting the lesser influence of more distant atoms. The reaction rate is given by

$$\ln k_{dis} = \ln A - \Delta G/kT, \quad (1)$$

where  $k_{dis}$  is the reaction rate,  $A$  and  $\Delta G$  are constants for the given reaction,  $k$  is the Boltzmann constant, and  $T$  is the absolute temperature, here fixed at body temperature, and  $\ln$  is the natural logarithm. Equation (1) is the logarithmic form of the familiar Arrhenius equation. The constant  $A$  is related to the frequency of collisions among the reacting species, which would be approximately the same for every dissolving species in the glass fiber. The constant  $\Delta G$  is the free energy required to create the transition state involving both the dissolving

species and the water species, starting from the original glass in water. The  $\Delta G$  thus depends on the dissolving species, with the average  $\Delta G$  given by

$$\Delta G = \sum \Delta G_i X_i, \quad (2)$$

where  $\Delta G_i$  is the  $\Delta G$  for dissolving species  $i$  present at mole fraction  $X_i$ , and the sum is over all the dissolving species in the glass structure.

Thus it is seen that  $\ln k_{dis}$  is linear in the mole fractions  $X_i$  and therefore so is  $\log k_{dis}$ , the logarithm to the base 10. Equations (1) and (2) may be combined and new constants  $P_i$  defined merely for convenience so that

$$\log k_{dis} = \sum_{i=1}^n P_i W_i, \quad (3)$$

where  $W_i$  is the weight percent of oxide  $i$  and the sum is over all  $n$  oxides including  $\text{SiO}_2$ . Equation (3) invokes the approximation that the oxide weight percents  $W_i$  are proportional to the mole fractions of the corresponding dissolving species, which could be justified only over relatively narrow ranges of composition. Indeed, the nature of the dissolving species might well be different for widely different glass compositions. Thus rock wool fiber compositions, for example, require a different set of coefficients  $P_i$  than the ones for borosilicate glass fibers exhibited in this paper.

In order to compute  $k_{dis}$  for a glass fiber composition given by the oxide weight percent  $W_i$ , for  $i = 1, 2, \dots, n$ , the coefficients  $P_i$  in Eq. (3) are all that are needed. These may be determined most easily by fitting measured  $k_{dis}$  values to the  $W_i$  for a range of compositions. The best fit  $P_i$  in the sense of minimum chi squared is desired, but estimates of their precision and the quality of the fit are also important.

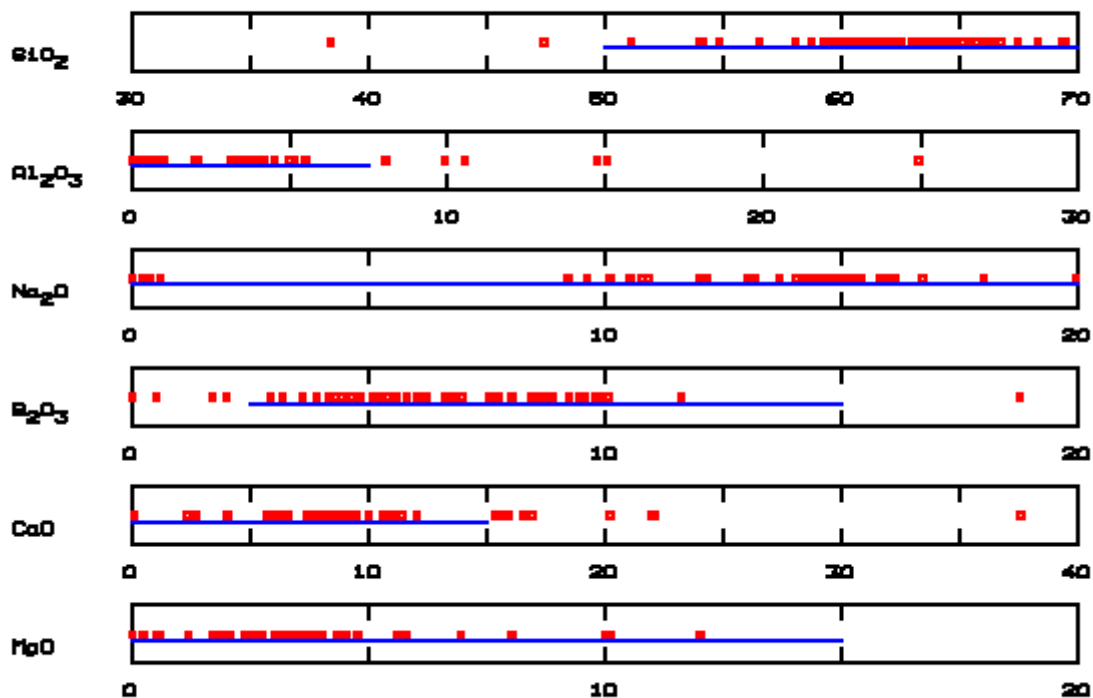
An important practical consideration in applying (3) to a variety of glass fiber compositions is to deal with extra oxides, those present in small quantities for which corresponding coefficients  $P_i$  are not available. It is a poor approximation to simply ignore these extra oxides, because the weight percents  $W_i$  for which coefficients are available may sum to significantly less than 100% and the predicted  $k_{dis}$  will be biased low. A better method, and the one used here, is to normalize each composition to 100% in those oxides for which coefficients are available. This method is equivalent to treating the extra oxides as a weighted average of the oxides for which coefficients are known.

It is interesting and useful that the theory developed here, although tacitly assuming that all components of the glass fiber dissolve at the same rate, works well in practice even in many cases in which some components leach out of the fibers much more rapidly than others and leached layers form on the fibers. This behavior has been observed both in vitro and in vivo. The fact that a single dissolution rate constant can fit the observed dissolution data reasonably well even in these cases suggests that these leached layers are not dense enough to hinder significantly the movement of the dissolving species away from the fiber or significantly change the environment in which the fibers dissolve.

## RESULTS

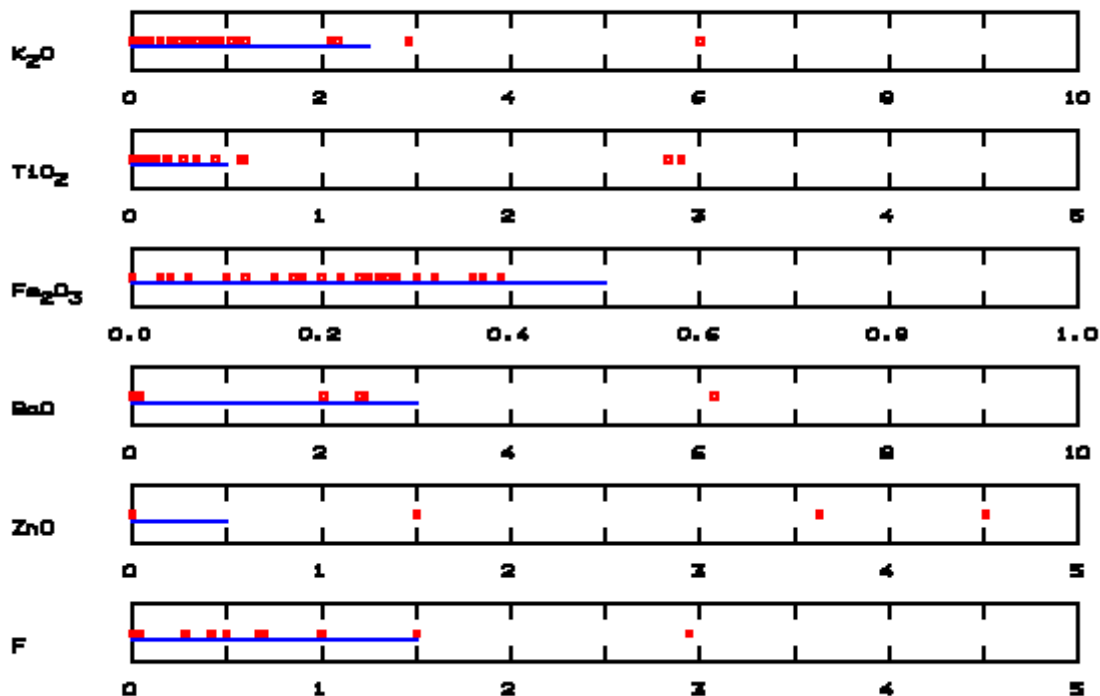
An excellent data set of measured  $k_{dis}$  with the composition of each fiber is available ([Potter and Mattson, 1991; Mattson, 1994a](#)) for over 90 fiber compositions obtained by the same protocol. A tab delimited text file containing these data are available by [clicking here](#). The range of composition covered by these data is shown for the six major oxides in Figure 1 and for six minor oxides in Figure 2. In these diagrams, there is one panel for each oxide, and it has a small red square marking the weight percent of that oxide in each fiber. It is seen in Figures 1 and 2 that the oxides are distributed somewhat unevenly. For some oxides like ZnO the data are so sparse that it would not be possible to obtain a reliable coefficient for it. Other oxides, like  $\text{TiO}_2$  and  $\text{Fe}_2\text{O}_3$  vary over such a small range in weight percent that the measured  $k_{dis}$  would not be expected to be sensitive to these

variations. The data for  $K_2O$  have both of these problems, and a coefficient was not determined for it, either. For the remaining eight oxides, it is possible to choose a range in each oxide that the available data cover reasonably well. The other oxides, for which the data are not sufficient to determine reliable coefficients, are limited to a small enough weight percent that the oxide is not expected to impact the dissolution rate significantly. These ranges are indicated by horizontal lines in the middle of each panel. There are 62 fiber compositions in the data set that fall within the ranges indicated by the horizontal lines in Figures 1 and 2, and these are fit to Eq. (3) to determine the coefficients  $P_j$ .



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**Figure 1.** Composition range of the available measured dissolution rate data in six major oxides in weight percent. Each small red square shows the weight percent of the corresponding oxide in one measured glass composition. The data displayed here and used throughout this paper, including the composition in all oxides and the measured dissolution rate, are available as a tab delimited text file by [clicking here](#).



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**Figure 2.** Composition range of the available measured dissolution rate data in six minor oxides in weight percent. Each small red square shows the weight percent of the corresponding oxide in one measured glass composition. The data displayed here and used throughout this paper, including the composition in all oxides and the measured dissolution rate, are available as a tab delimited text file by [clicking here](#).

Not only the measured dissolution rate for the compositions but also an estimate of the standard error of the measured  $\log k_{dis}$  is needed in order to minimize chi squared. Since 13 of the compositions in the data set were measured more than once, the pooled standard deviation of these replicate measurements was used as an estimate of the standard error of every datum. The pooled standard deviation of  $\log k_{dis}$  was 0.1158.

The coefficients  $P_i$  determined by minimizing chi squared using the method of singular value decomposition ([Press et al., 1992](#)) along with the standard error of each coefficient and various statistics are shown in Table 1. It may be seen that the coefficients for CaO, MgO, Na<sub>2</sub>O, B<sub>2</sub>O<sub>3</sub>, and BaO are similar in magnitude to one another, taking into account the standard error of each, and the coefficient of Al<sub>2</sub>O<sub>3</sub> is approximately twice as large and negative. These results mean that Al<sub>2</sub>O<sub>3</sub> "strongly decreases dissolution rate by a factor approximately two times greater than those of the [former] group" ([Potter and Mattson, 1991](#)), which was noted when these measurements were published originally.

**Table 1.** Coefficients for the calculation of the dissolution rate constants and statistics of the fit.

Oxide	Coefficient	Standard Error
SiO <sub>2</sub>	-0.01198	0.00285
Al <sub>2</sub> O <sub>3</sub>	-0.21410	0.01102
CaO	0.10806	0.01119

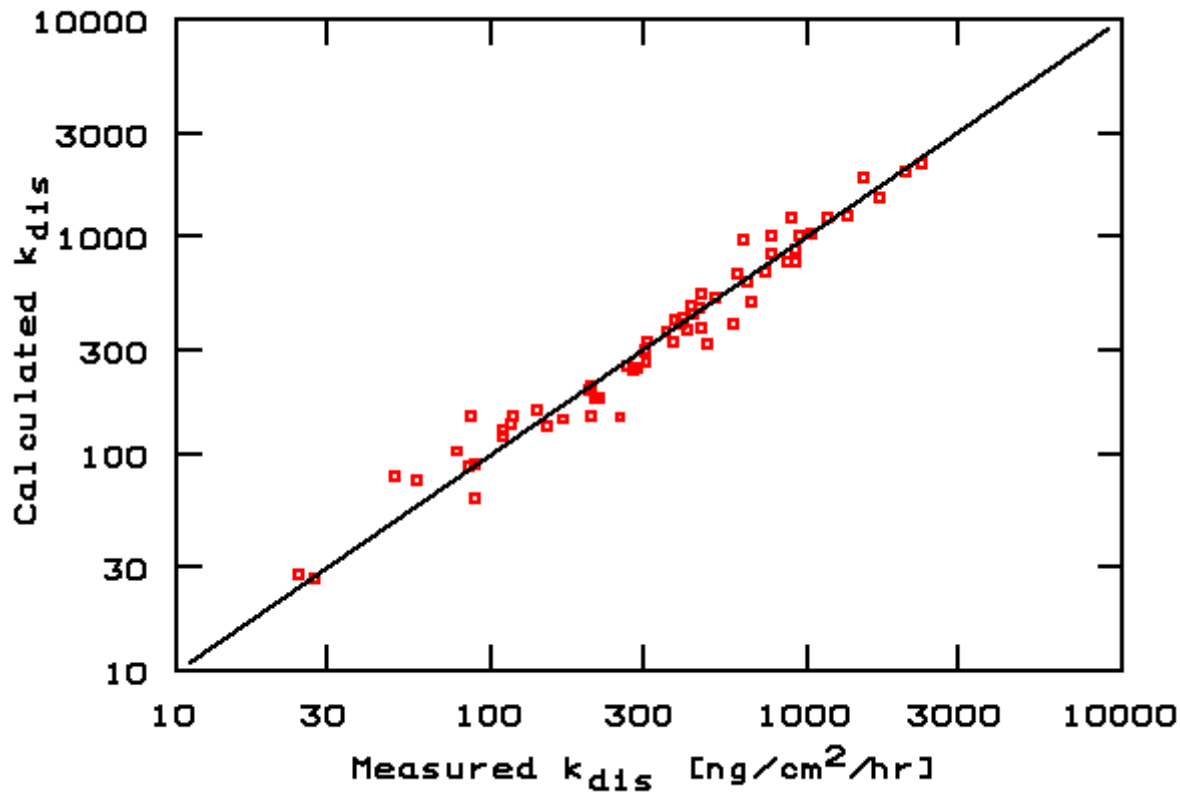
MgO	0.13761	0.01262
Na <sub>2</sub> O	0.09386	0.00867
B <sub>2</sub> O <sub>3</sub>	0.14669	0.00908
BaO	0.06921	0.03095
F	0.11867	0.06134
$R^2$	0.96	
Significance	0.97	
Degrees of Freedom	54	

The statistic  $R^2$  is the fraction of the variance of the data that is accounted for by the prediction. The fact that  $R^2$  is large here, over 95%, indicates that the simple Eq. (3) captures nearly all of the important effects on  $k_{dis}$  for this range of fiber compositions. The degrees of freedom is the number of data used for the fit minus the number of coefficients determined by the fit, here 8.

The significance of the chi squared statistic is the probability that the extent to which the measured data deviate from Eq. (3) could be the result of random variations with the estimated standard error. The fact that the significance is over 95% here indicates that Eq. (3) explains the measured data to well within the variations in the measured data themselves.

In addition to the statistical measures, another way to assess the quality of the prediction is to plot the calculated value against the measured value of  $k_{dis}$  as in Figure 3. It is seen here that the calculated value agrees with the measured one reasonably well over the entire factor of 100 in dissolution rate spanned by the data. Furthermore, Figure 3 does not show any tendency for the predicted  $k_{dis}$  to deviate more at the extremes of  $k_{dis}$  represented in

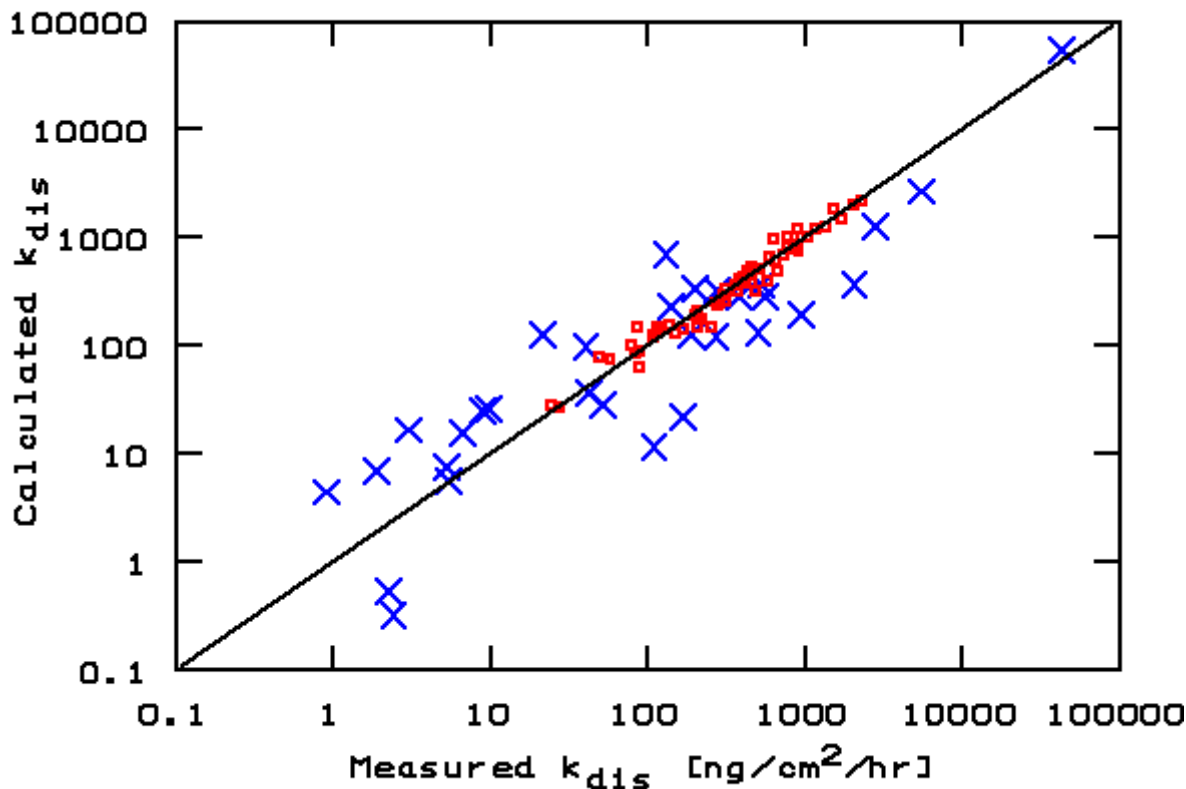
the data.



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**Figure 3.** Dissolution rate constant  $k_{dis}$  calculated by Eq. (3) compared to the measured value for the data used to determine the coefficients  $P_i$ .

The fact that the deviation of the predicted from the measured  $k_{dis}$  is fairly uniform over a wide range of  $k_{dis}$  and composition and the fact the Eq. (3) is based on the chemistry of the dissolution process, suggests that this equation with the coefficients just determined might provide a reasonable approximation somewhat outside the range over which the coefficients were fit. That this is so is seen in Figure 4 in which the calculated  $k_{dis}$  is plotted against the measured values for all of the compositions in the original data. In Figure 4, the compositions that were used in the fit to determine the  $P_i$  are shown as small squares just as in Figure 3, whereas the other measurements, not used in the fit, are shown as X. It may be seen in Figure 4 that the coefficients of Table 1 provide a reasonable estimate of  $k_{dis}$  over a factor of 100,000, much wider than that of the data used to determine the coefficients. This fact does not necessarily imply that one could develop coefficients that cover a wider range of composition equally well by using all of the data. When that is done, the accuracy of the prediction over the restricted data (the small squares in Figures 3 and 4) becomes worse.



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**Figure 4.** Dissolution rate constant  $k_{dis}$  calculated by Eq. (3) compared to the measured value for the complete set of measured values. The data used to determine the coefficients are denoted by small red squares, whereas the other data, covering a wider range of composition and  $k_{dis}$ , are denoted by a blue X. The agreement is not unreasonable in most cases, even over the wider range.

## DISCUSSION

The method of calculating glass properties by expressing them as linear functions of weight or mole fraction with coefficients determined by fitting to measurements has been used in glass technology for over a century (Huggins and Sun, 1943). The theory outlined here suggests that, for fiber dissolution, the logarithm of  $k_{dis}$  is the appropriate quantity to approximate as a linear function of composition over a fairly wide range of composition, and this possibility was verified in practice.

Another approximation related to  $k_{dis}$  has appeared in European regulatory affairs. The "Carcinogenicity Index"  $K_I$ , proposed in the German TRGS 905 (BMA, 1995), is given as

$$K_I = \sum C_i W_i, \quad (5)$$

with  $C_i = 1$  for  $\text{Na}_2\text{O}$ ,  $\text{K}_2\text{O}$ ,  $\text{CaO}$ ,  $\text{MgO}$ ,  $\text{B}_2\text{O}_3$ , and  $\text{BaO}$ , and  $C_i = -2$  for  $\text{Al}_2\text{O}_3$ . It may be seen that these coefficients  $C_i$  are approximately proportional to those in Table 1, although they are not the same since Eq. (4) is not normalized to all oxides and does not contain  $\text{SiO}_2$ . The values of the coefficients in Eq. (4) are seen to be identical to the statement of Potter and Mattson, 1991, noted previously.

It is seen by comparing Eq. (4) with Eq. (3) that  $\log k_{dis}$  should be approximately linear in  $K_I$ . That this is so is shown in Figure 5, which plots the measured  $k_{dis}$  on a logarithmic scale against  $K_I$  for the set of borosilicate glass fibers used previously. The  $R^2$  statistic for the linear fit of  $K_I$  to  $\log k_{dis}$ , shown in Table 2, is large,

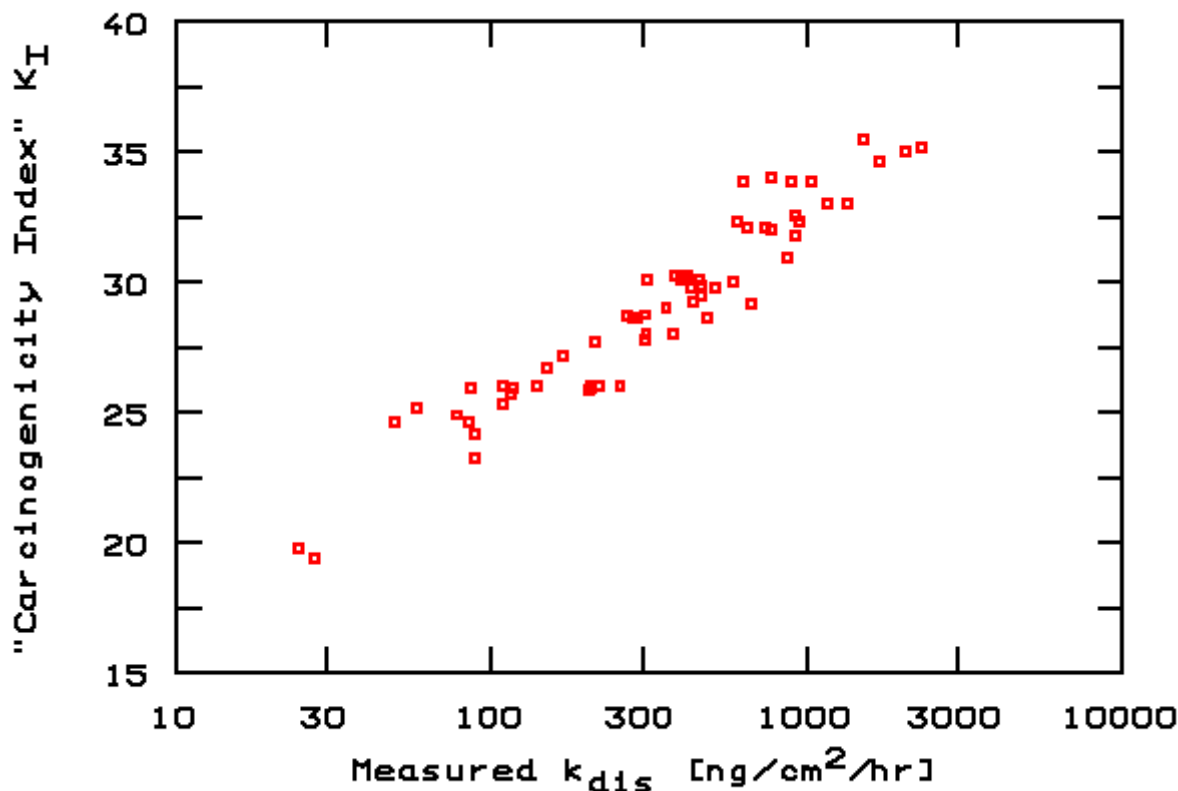


indicating a good fit. For these compositions,  $K_I$  is a reasonably good predictor of  $k_{dis}$ , which is why it is a good predictor of tumors following IP injection, as proposed in TRGS 905.

Equation (3) proposed here is a better predictor of  $k_{dis}$  than  $K_I$ , over the same range of composition, however, as seen by comparing Figure 5 with Figure 3. This comparison may be made more precise by use of the standard error of the fit, shown in Table 2 for the linear fit of  $K_I$  to  $\log k_{dis}$  and for the calculated  $k_{dis}$  of Eq. (3). The improvement in the standard error for the calculated  $k_{dis}$  by Eq. (3) over that by  $K_I$  is found to be significant at the 1% level.

**Table 2.** Comparison of fit statistics for  $k_{dis}$  obtained by calculating it from Eq. (3) and from  $K_I$ .

Statistic	Calculated $k_{dis}$	$K_I$
$R^2$	0.96	0.91
Standard error	0.095	0.132



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**Figure 5.** "Carcinogenicity Index"  $K_I$  plotted against the measured dissolution rate constant  $k_{dis}$  for a series of glass compositions. The correlation is not so good as that of the method of this paper, shown for the same glass compositions in Figure 3.

It is seen then that Eq. (3), along with the coefficients given in Table 1, provide a reasonably accurate method for estimating the dissolution rate constant  $k_{dis}$  for a borosilicate glass fiber if its composition in oxide weight percent is known. A computer program that runs in a web page is available to perform this calculation for any

given borosilicate glass composition. This program may be started by [clicking here](#). The range of composition over which the compute estimate is accurate is shown in Figures 1 and 2. From the dissolution rate constant, it is then feasible to estimate whether disease would ensue following animal inhalation or intraperitoneal studies, as shown previously ([Eastes and Hadley, 1996](#)).

The ability to determine  $k_{dis}$  simply from the composition of a glass fiber should be useful both to fiber manufacturers and to researchers who are interested in the dissolution rate of glass fibers. Additionally, it provides a tool by which interested regulatory bodies may monitor the dissolution rate of insulation glass wools simply by monitoring their composition without expensive and time-consuming animal tests.

So far, this work has focused exclusively on  $k_{dis}$  as the measure of dissolution rate in vitro and in vivo because it is a conventional parameter. However, dissolution rate, especially when expressed in the conventional units of  $\text{ng}/\text{cm}^2/\text{hr}$ , does not relate in any intuitive way to the clearance of fibers from the lung. To make the connection between dissolution and fiber removal more obvious, the authors recommend that the parameter *dissolution time*  $t_{dis}$  in units of  $\text{days}/\mu\text{m}$  be used instead of  $k_{dis}$ . The relation between these two measures of dissolution ([Eastes and Hadley, 1996](#)) is

$$t_{dis} = \frac{\rho}{2k_{dis}}, \quad (6)$$

where  $\rho$  is the density of the fiber. In physical terms,  $t_{dis}$  in  $\text{days}/\mu\text{m}$  is the time required to dissolve a  $1 \mu\text{m}$  diameter fiber. It would be the time to eliminate this fiber from the lung if dissolution were the only process operating on the fiber. Of course there are other mechanisms besides dissolution that serve to remove fibers, and dissolution mostly affects the long, extracellular fibers in any case. For these reasons,  $t_{dis}$  cannot be equated to the clearance time, but rather indicates the time for one of the clearance mechanisms, long fiber dissolution, to happen. The parameter  $t_{dis}$  should not be confused with the half life often used to describe particle clearance. The  $t_{dis}$  is appropriate for a zero order fiber dissolution reaction, whereas a half life is appropriate for a first order clearance mechanism ([Scholze, 1988](#)).

A comparison of  $t_{dis}$  with the equivalent value of  $k_{dis}$  is given in Table 3 for a typical glass fiber density. One important result of expressing dissolution as  $t_{dis}$  rather than  $k_{dis}$  is that it illustrates the unlikely biological relevance for inhaled fibers of increasing  $k_{dis}$  much above  $100 \text{ ng}/\text{cm}^2/\text{hr}$ . At this rate, long fibers would undergo complete dissolution and hence removal more rapidly than macrophage-mediated clearance generally removes inhaled particles or short fibers. Indeed, Table 3 shows that many of the large  $k_{dis}$  values exhibited in Figures 3 and 4 have dissolution times less than a few days, which is unlikely to have a biological impact in the lung.

**Table 3.** Comparison of two different parameters for expressing dissolution.

$t_{dis}$ [days/ $\mu\text{m}$ ]	$k_{dis}$ [ng/cm <sup>2</sup> /hr]
5	1000
10	500
25	200
50	100
100	50

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