A RATIONALE FOR ASSESSING EXPOSURE-DOSE-RESPONSE RELATIONSHIPS FOR OCCUPATIONAL DUST-RELATED LUNG DISEASE

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INTRODUCTION

The complex chain of processes linking occupational exposure to airborne particles with the occurrence of related lung disease is summarized in Figure 1. Epidemiology is usually concerned with relating the two ends since it is the disease on the one hand which is the 'problem' and exposure at the other which can be monitored and controlled. However, it has long been held that, by a proper understanding of the intermediate processes and its incorporation into the epidemiological framework, substantial further advances will be made possible in epidemiology and risk assessment. From multidisciplinary studies carried out worldwide into (a) the physical nature of the aerodynamic transport of airborne particles in the respiratory tract and their deposition in the lung, (b) the kinetics of their redistribution, clearance and storage, (c) the cellular and pathological responses to the presence of particles in the lung, and (d) epidemiology itself, such understanding is now available. The task now is to bring together and apply the knowledge which has been acquired.

This paper reviews the factors to be considered, including not only the level of initial challenge (i.e., involving considerations of the intensity of exposure, rate of deposition in the lung) but also the time-dependent history of exposure (involving considerations of sampling strategy), chemical composition and indices of biological response. The ultimate objective is a dosimetric approach to the problem. What is presented here is a hypothesis upon which such an approach can be built.

THE CONCEPT OF 'DOSE'

The concept of 'dose' is a fundamental issue. In the first instance, it involves the mass rate of deposition in the respiratory tract. The usual approach to this is to assume a conventionalized deposition fraction of the airborne particulate and to measure exposure in terms of that fraction. For the alveolar fraction, a number of quantitative definitions have been widely used, notably that recommended by the British Medical Research Council.[1] In risk assessment, however, it is worth noting that such an approach does not allow for possible differences in deposition for workers engaged in different levels of physical activity (where breathing parameters might vary). Some of our estimates for underground mineworkers in different occupational groups (based on previous measurements of breathing patterns for similar groups of workers and on published lung deposition data) suggest that such effects could lead to differences in alveolar deposition by as much as x2, as compared with exposure measured according to a conventionalized deposition fraction. This suggests in turn that, at least in some epidemiological research, a more flexible approach to dust sampling may be desirable using instruments capable of providing a wider range of information (including particle size distribution and composition). Instruments suitable for this purpose, including dust 'spectrometers', are now available. Some have been the subjects of recent comparative studies carried out in several European laboratories, as reported elsewhere at this Conference by Vincent.

As far as 'dose' is concerned, however, the relationship between exposure and the rate of mass deposition in the lung is just the first stage in the process. The next step is to consider what happens after material has been deposited. In order to express dose in the context of potentially-hazardous inhaled particulate material, a useful starting point is the approach which is widely used for dealing with the dosimetry of inhaled radioactive particles.[2] Thus the hazard-related dose received by lung tissue is equivalent to the integral over time of the amount of particulate material present combined with some modifying 'harmfulness' (or 'damage') function. The latter describes the rate at which the intrinsic property associated with the hazard is transmitted from the material to the tissue and how it changes with the time during which the material is in contact.

In setting out to construct a quantitative dosimetric model, consider first the exposure history. This may be expressed as E_n, reflecting the mass deposited in the lung during the N^{th} day since exposure began. From this, cumulative exposure (C) at the n^{th} day is

$$C(N) = \sum_{n=1}^{N} E_n \qquad (1)$$

which is the form widely employed in epidemiological studies (where E_n is usually obtained in terms of the measured concentration of an appropriate dust fraction, time weighted over the working shift).

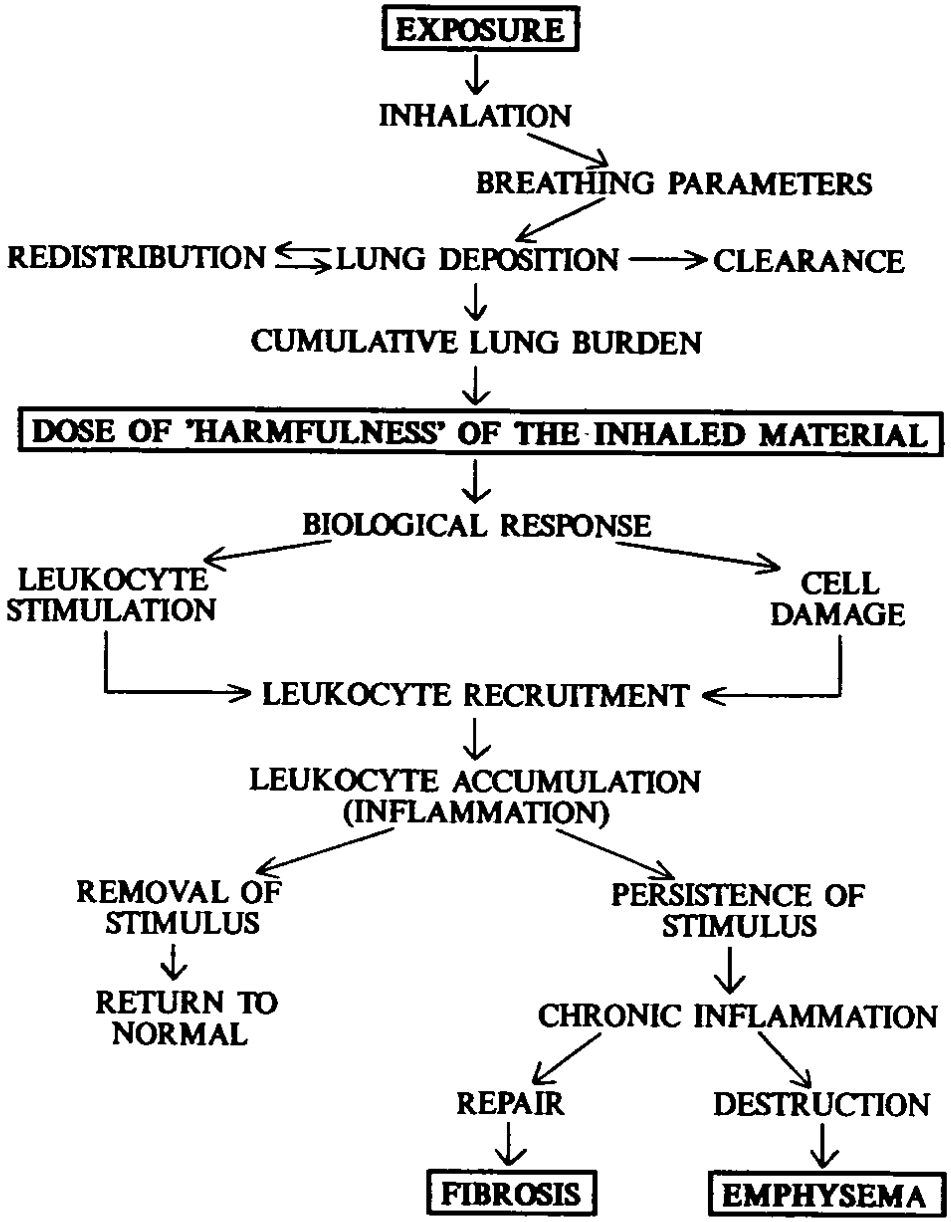

Figure 1. Processes linking exposure, dose and response associated with health effects due to mineral dusts in the deep lung.

Next consider the time-dependent retention of particulate material in the lung. The function R_m describes the proportion remaining of a particular 'packet' of material at the m^{th} day after it has been deposited. The distinction is drawn between n (which refers to the overall time elapsed since exposure began) and m (which refers to the time elapsed since a particular packet of material has been deposited in the lung). The value of R_m (between 0 and 1) is determined by the kinetics of redistribution, clearance and storage of the deposited particles. By combining E_n and R_m, the accumulated mass (M) after N days have elapsed may be shown to be

$$M(N) = \sum_{n=1}^{N} E_n R_{N-n+1} \qquad (2)$$

We now introduce the damage function G_m, which defines the rate per unit mass at which harmfulness is being transmitted to the tissue at the m^{th} day after is has been deposited. It may thus be regarded as a hazard-related 'fingerprint' for the material in question. The transferred property which is responsible for initiating the cell damage may be physical, mineralogical or biochemical.

We now have the three essential elements for constructing a dosimetric model. Hypothetical examples are given in Figure 2. These may be combined as follows:

Day	Dose received
1	$E_1R_1G_1$
2	$E_1R_2G_2 + E_2R_1G_1$
3	$E_1R_3G_3 + E_2R_2G_2 + E_3R_1G_1$

and so on. The cumulative dose of harmfulness is equivalent to the sum of all the contributions indicated. Thus at the N^{th} day, we have

$$H(N) = \sum_{n=1}^{N} E_n \left\{ \sum_{m=1}^{N-n+1} R_m G_m \right\} \qquad (3)$$

In relation to the epidemiology of dust-related lung disease, it is suggested that Equation (3) should replace Equation (1) and other simplistic forms of dose assessment.

PRACTICAL CONSIDERATIONS

Practical implementation of the proposed rationale involves quantitative description of the three key elements; E, R and G.

The first of these is derived from measurements of dust concentration in a way such that the life-time dust exposures of individual workers may be described. This is a complex task. In the first place, it involves choosing a sampling instrument that provides a measurement of the airborne concentration of a dust fraction relevant to the disease in question. In the case of pneumoconiosis, this is the respirable fraction (although there may still be some debate about the particular quantitative criterion by which this should be defined). In turn, there are many instruments available which can provide the required information. In choosing the instrument, considerations of how best to make the measurement relevant to the true exposure of the individual worker raises questions of personal versus static (fixed point) sampling which have been discussed elsewhere.[3] Both types provide the time-weighted shift average of the exposure concentration. The frequency of sampling and its relevance to the assessment of long-term exposure are a matter of sampling strategy, involving considerations of the 'smoothing' that takes place in the body after particles have been deposited (which, in turn, is dependent on R).[4] Furthermore, since the exposure history, if it is to be useful, must reflect the life-time experience of the individual worker, and since he (or she) may move around the workplace from time to time, a record of time worked in particular occupations is an important ingredient towards construction of exposure history. Finally, since it is likely that epidemiology will be desirable for workers for whom exposure records in the early years are either non-existent or imperfect, it may be necessary in many cases to retrospectively estimate exposure histories on the basis of intelligent extrapolations backwards, taking into account more recent measurements and engineering histories of the industries in question.[5,6]

As far as R is concerned, substantial progress in understanding has been made in recent years, mostly based on inhalation studies with animals.[7,8,9] Therefore we now have pharmacokinetic models which are applicable to various toxic and non-toxic, fibrous and non-fibrous materials over wide ranges of exposure level. It is, however, important to note, that such models are relevant strictly only to the animals in question, and need to be validated with respect to humans. Data obtained during epidemiological research in the British coal industry, in particular information from autopsy studies on the lung burdens of mineworkers for whom exposure histories are known, are at present being examined in order to explore the feasibility of establishing such a link.

Although the third quantity, G, is just as important in relation to dose, it is still more difficult to quantify. In the case of radioactive particulate matter (the starting point for the dosimetric hypothesis), the harmful property which is transferred between the particulate matter and the lung tissue is relatively easy to identify (e.g., ionizing radiation of a well-defined type). For mineral dusts, however, like those encountered in many industrial workplaces, the nature of the property is not known. Quartz is one example where, although there are well-known health hazards associated with inhaling respirable particles, somewhat inconsistent epidemiological findings have emerged, especially when other materials are present. As a result, attempts to determine the basic nature of the harmfulness of quartz have not

yet provided definitive answers. European research, involving several laboratories, is presently in progress to address this question, as described elsewhere at this Conference by Robock.

In setting out to quantify G, mineralogical assessment alone does not provide all that is required. Neither (necessarily) does toxicity evaluation based on in vitro cell viability tests. In our own Institute, we are at present exploring how progress might be achieved by direct reference to the cellular response in the lung itself.[10] Bronchoalveolar lavage studies in rats exposed to dusts known to produce contrasting health effects (relatively-innocuous titanium dioxide and highly toxic quartz, for example) have been carried out. These have involved measurements of responses reflecting lung injury (e.g., leukocyte recruitment). Some of the results are particularly relevant in the present context—although the conclusions are preliminary at this stage. Some examples are shown in Figure 3, where the dusts were delivered into the lungs of the rats by inhalation and the leukocyte recruitment assessed subsequently (in terms of neutrophil counts). For the titanium dioxide, the results suggest a biological response is provoked which falls after the cessation of exposure. This in turn suggests that the intrinsic 'harmfulness' of the ma-

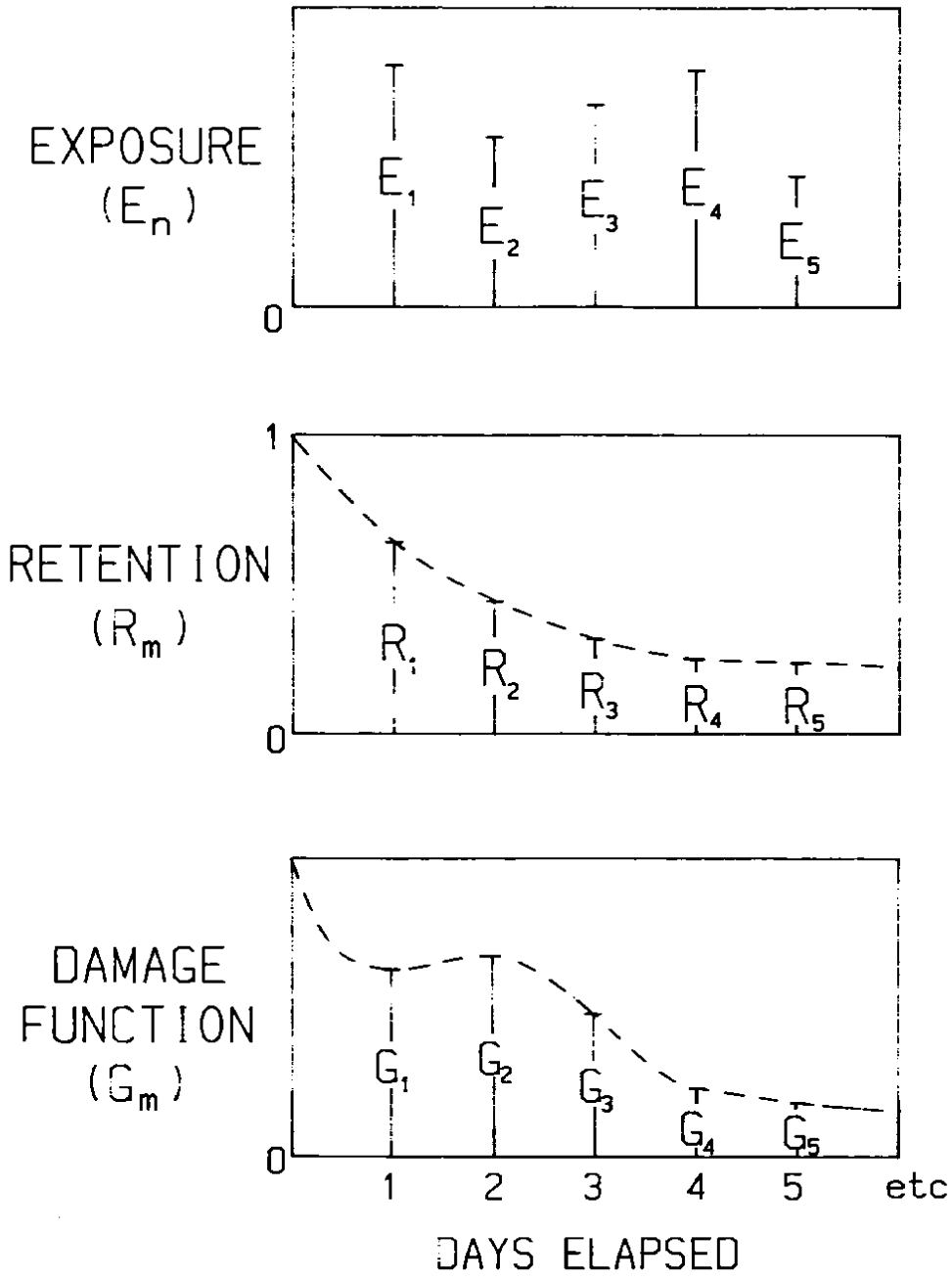

Figure 2. Hypothetical examples to illustrate the quantitative nature of exposure (E), retention (R) and damage function (G).

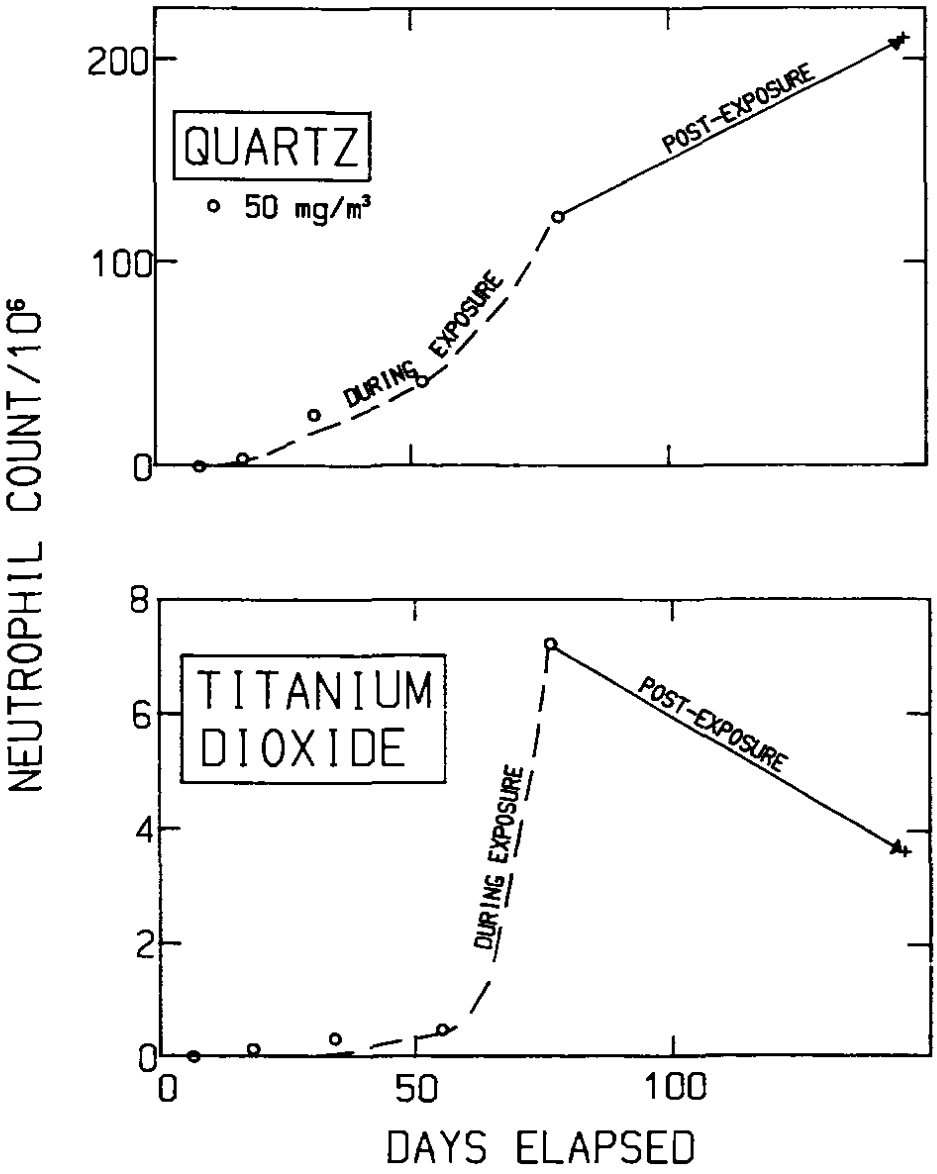

Figure 3. Typical results of cell-lavage study, showing neutrophil response during exposure- and post-exposure for quartz and titanium dioxide inhaled by rats at 50 mg/m³ (respirable). The results shown are means for four rats.

terial is not persistent but rather the damage function, G, decays with time. Throughout, its magnitude is relatively small. In contrast, the biological response to the inhaled quartz is much greater in magnitude and is much more persistent. That is, G is high upon arrival in the lung, and—unlike titanium dioxide—does not decline, even post-exposure. From these findings, the dosimetric implications are clearly consistent with what is known about the contrasting hazards associated with inhaling each of these two materials. Further work is now needed to place such ideas on a more quantitative footing, and to extend them to other, more-realistic mineral dusts.

CONCLUDING REMARKS

In the preceding, we have discussed the main ingredients of a dosimetric model for assessing the risk associated with inhaling airborne particles. The rationale for its development is summarised in Figure 4. At this stage, it is no more than an initial hypothesis. Before it can be proposed as a working model, it is necessary, (a) to establish the validity of pharmacokinetic models, derived originally from the results of animal inhalation studies, for describing retention in humans, and (b) to establish the validity of (and extend) the biological assays aimed at quantifying G for dusts relevant to work-

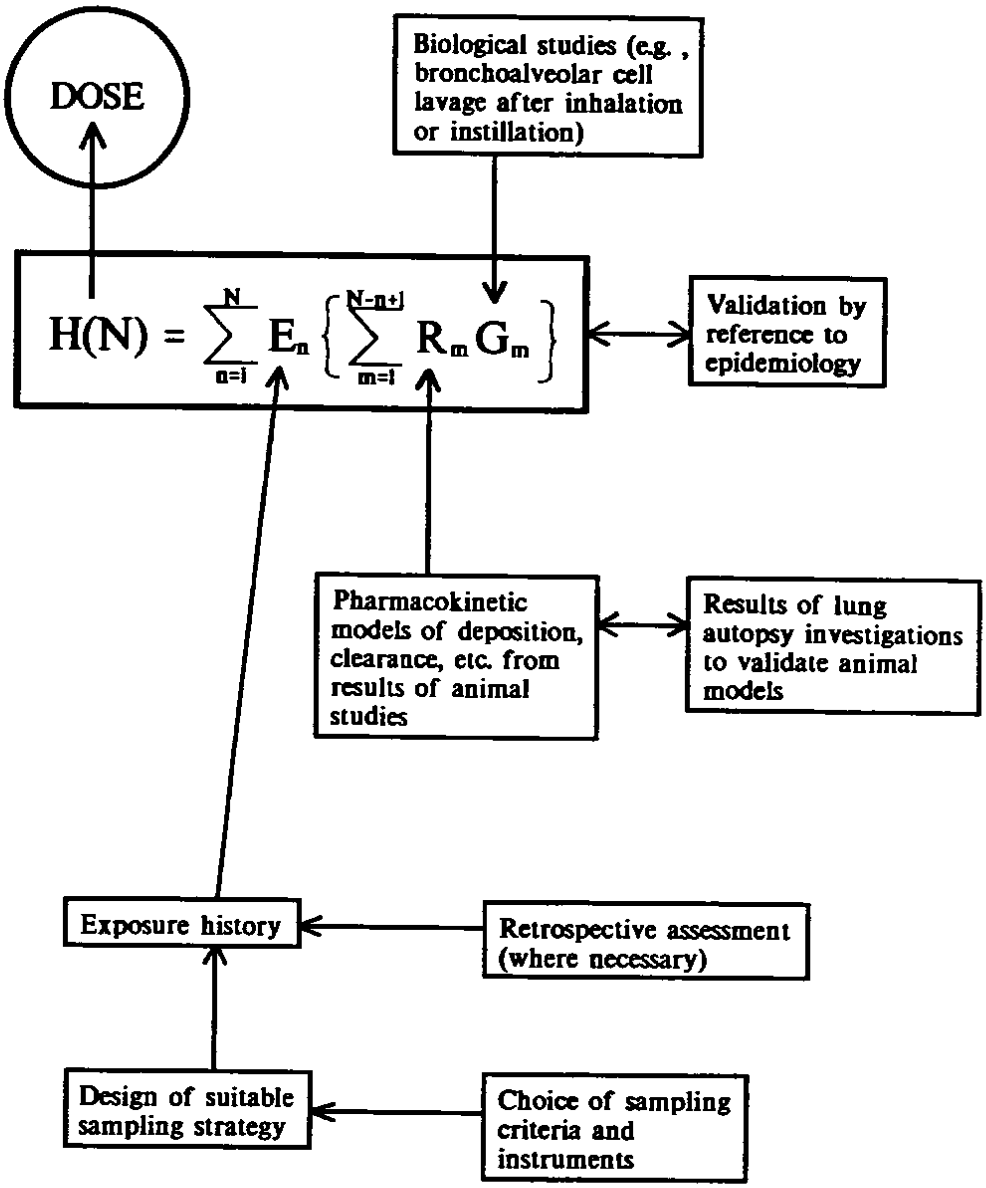

Figure 4. Summary of the rationale for the development of a dosimetric model.

place exposures. Some such studies are in progress. Having once established the working hypothesis, the next step is to validate it with respect to epidemiology for working populations whose exposure and occupational histories are sufficiently well-known. From this scenario, it may therefore be assumed that the emergence of an actual working dosimetric model is still some years away.

The broad benefits of the dosimetric approach to epidemiology have already been mentioned. Notably, as far as epidemiology is concerned, it is anticipated that improved sensitivity (and specificity) and reduced variability in explaining the relationships between the environment and health will be achieved. In turn, improved standards setting, more representative dust sampling strategies, and more effective control procedures (through appropriate worker deployment strategies, technical measures, etc.) will be made possible.

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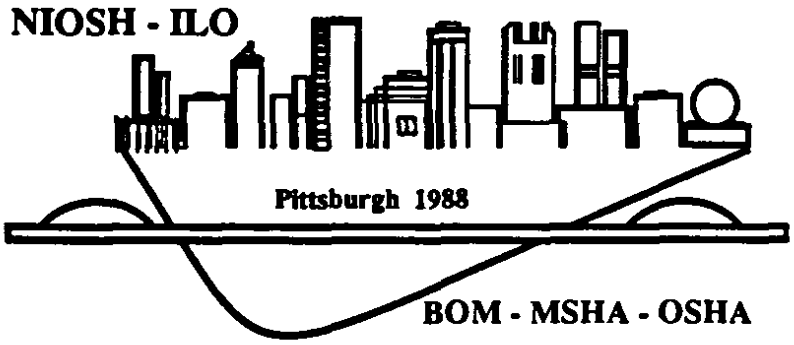

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