Methods for Estimating Risk of Chemical Injury: Human and Non-human Biota and Ecosystems
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Some Problems in Dose–Response Estimation in Cancer Epidemiology

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ABSTRACT

The effects on cancer incidence of dose level, duration of exposure to a carcinogen and age should always be analysed separately. Errors that have led to misinterpretation of such data include the inappropriate combination of dose level and duration in a single 'cumulative dose' index, analysis of prevalence rather than incidence, and misuse of the term 'latency', which is used in at least four quite different senses. These and other statistical difficulties in dose–response analysis are illustrated with examples from studies on asbestos, ionizing radiation and smoking, and discussed in relation to low-dose extrapolation and industrial surveillance.

1 INTRODUCTION

Quite accurate quantitative data either have been or could be obtained on various 'life-style' factors that have a marked influence on cancer risk, such as cigarette smoking, age at first pregnancy, promiscuity and alcohol consumption, and it seems likely that several dietary factors with large effects that can be measured with similar accuracy will soon be identified. This may never be true of industrial carcinogens, however. Age, time since first exposure and duration of exposure can be measured accurately, but existing data on the intensity of heavy exposures that have produced large cancer risks are usually too crude to provide good estimates of dose–response relationships, and a moderate increase in relative risk due to a new carcinogen is likely to be difficult to detect at all and impossible to estimate accurately by conventional epidemiological methods. Many people at this meeting may therefore feel that the most useful future developments in both surveillance and dose–response estimation will come from advances in biological understanding leading to a firmer basis for extrapolation from *in vitro* or animal testing to human risk assessment. Epidemiology has, however, made substantial contributions to the understanding of carcinogenesis, particularly in relation to multistage processes and the age and time dependence

of cancer risk, and developments in biological knowledge should complement rather than supplant such research. For example, metabolites or inhibitors of carcinogens, and cytogenetic and chemical indicators of exposure such as alkylated base concentrations or sister-chromatid exchange rates, can be measured in case-control and prospective studies, and may provide direct and quite precise measures of 'effective exposure' that can be related both to environmental factors and to cancer risk.

2 THE ASSUMPTION OF LINEAR DOSE–RESPONSE

A linear dose–response relationship is now usually assumed for the practical purpose of extrapolating from the observed effects of intense exposure to a carcinogen to predict the effects of lower exposure levels. This is more prudent and scientifically more reasonable than using models which implicitly assume a safe or virtually safe threshold, although there are carcinogens for which linear extrapolation would substantially overestimate the risk and some for which the opposite would hold. One human carcinogen for which there is suggestive evidence of a higher than linear dose–response relationship is cigarette smoke. Smoking appears to both initiate and promote lung cancer, so if the dose effect at

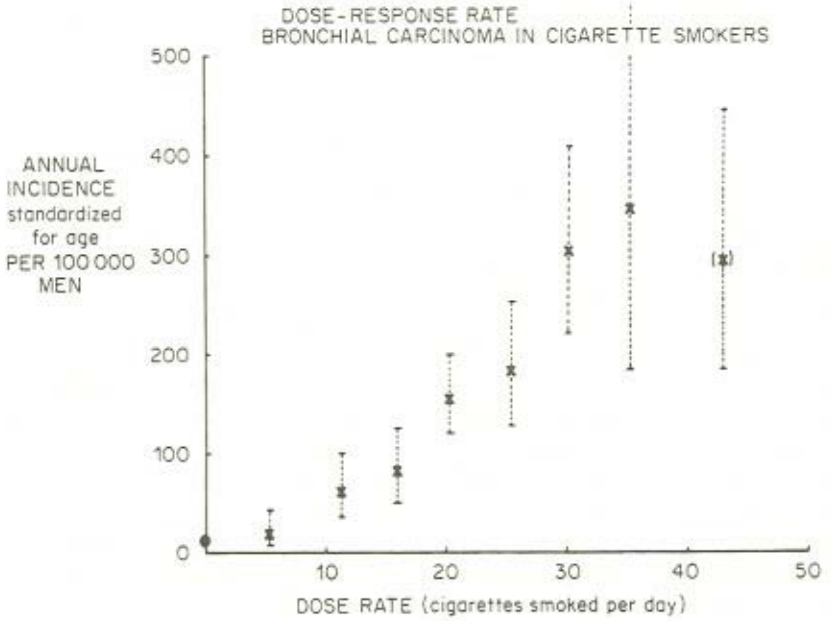

Figure 1 Dose–response relationship between lung cancer incidence and cigarette consumption, showing upward curvature. Reproduced by permission of *Cancer Research* from Doll (1978)

each stage were roughly linear the overall dose–response relationship should be approximately quadratic, and data on continuing cigarette smokers do suggest some upward curvature (Figure 1, Doll, 1978). Linear extrapolation from the risk to heavy smokers may therefore overestimate the risk to light smokers. Leukaemia mortality caused by ionizing radiation (Figure 2, Smith and Doll, 1982) and tumour incidence in mice initiated with DMBA and promoted with TPA (Figure 3, Stenback *et al.*, 1981) show the opposite effect, with marked downward curvature in dose–response. Linear extrapolation from the observed risk at higher doses could thus underestimate the risk at lower doses by an order of magnitude for these agents.

One possible explanation of such downward curvature in dose–response is that even at moderate doses a high proportion of cells are affected, as has been observed in *in vitro* systems for both chemical and radiation-induced transform-

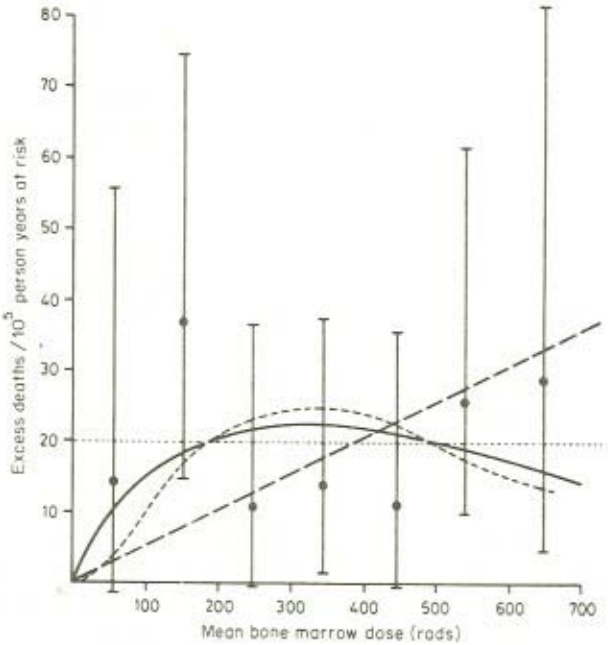

Figure 2 Dose–response relationship between excess leukaemia risk and mean marrow dose D of irradiation given as treatment for ankylosing spondylitis. The heavy line, the best-fitting model considered by the authors (Smith and Doll, 1982) is proportional to $d.\exp(-kd^2)$. The corresponding low-dose risk estimate is 2.0 per million person years per rad. Reproduced by permission of the *British Medical Journal* from Smith and Doll (1982)

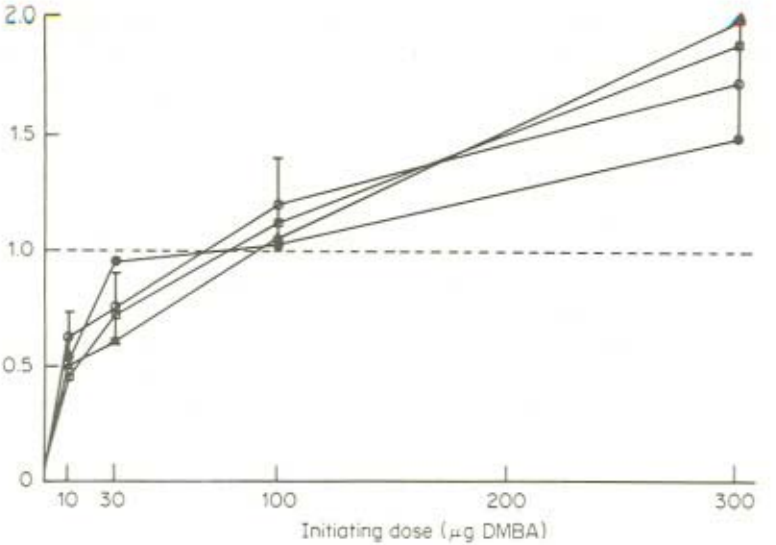

Figure 3 Tumour response in mice initiated with DMBA and promoted with TPA, showing downward curvature in relation to initiating dose. Reproduced by permission of *Macmillan Journals Ltd.* from Stenback *et al.* (1981)

ation (Kennedy *et al.*, 1984). An observation that suggests that this can occur *in vivo*, at least for radiation, is the high tumour incidence in the offspring of mice whose germ cells have been irradiated (Nomura, 1982). At the highest doses ($\sim$500 rad) the proportion of offspring that developed tumours within 8 months was increased by about 10–20%, which suggested that at least this proportion, and probably considerably more, of surviving irradiated germ cells suffered heritable alteration predisposing to carcinogenesis. It is possible that certain heavily exposed industrial populations have also suffered such 'saturation exposure' to carcinogens, and that extrapolation from their experience could therefore underestimate the risk at lower levels. In this context, 'saturation exposure' does not necessarily mean that the cancer risk is enormous, but that a high proportion of cells are altered, and neither this proportion nor the risk per affected cell of becoming fully malignant will increase in proportion to further increases in dose.

3 CURRENT PROBLEMS AND FUTURE DEVELOPMENTS

The study of dose–response relationships raises several interrelated but separate problems, some of which are listed below. Certain issues are discussed in more detail in later sections, including latent period, which is one of the most

frequently abused concepts in epidemiology; total dose and the confusion of dose and time in dose–response relationships; factors that may affect dose–response for ionizing radiation; and the errors that can arise when prevalence rather than incidence is analysed.

3.1 The Appropriate Statistical Approach to Analysis, Extrapolation and Interpretation

The importance of formal separation and separate analysis of dose and time effects and temporal differences in the effects of carcinogens acting at different stages (initiators and intermediate or late-stage promoters) is still not universally appreciated. Errors of analysis usually arise as a result of failure to formulate a sensible model or by using intuitively appealing but inappropriate measures of response (prevalence or latent period rather than incidence) or exposure (confusion or combination of dose rate and duration of exposure). Several examples of such errors are given in a later section.

3.2 The Effects of Measurement Error

These systematically flatten dose–response curves and reduce the exponent of dose. Quadratic dose–response relationships appear linear, and linear relationships appear sublinear when doses are estimated inaccurately.

3.3 Biological Hypotheses Relating to Mechanisms of Carcinogenesis

The studies mentioned in the previous section suggest that both radiation and chemical carcinogens can sometimes predispose a high proportion of cells to become transformed or malignant, and the simplest multistage model, which predicts that only a small fraction of cells are affected, may require substantial modification to accommodate these observations. Another anomaly which might be discussed at this meeting is the fact that certain carcinogens appear to act as initiators for certain tumours and as promoters for others (Day and Brown, 1980; Peto *et al.*, 1982). It seems unlikely that fundamentally different carcinogenic processes should happen to be caused by the same agent, but both initiators (Hennings *et al.*, 1983) and promoters (Slaga *et al.*, 1980) can act at two or more stages in experimental carcinogenesis.

3.4 Future Developments in Industrial Surveillance

Monitoring biochemical and genetic effects in industrial cohorts should complement rather than replace the measurement of incidence or death rates in future studies, and the establishment of a large data base for future research is one

important practical issue that this meeting should address. For example, blood, urine and perhaps stool samples, together with environmental air samples from which gaseous and particulate exposure can be measured, could be collected on a million or more workers every five years or so. The approach which seems to me likely to prove the most economical and fruitful is to store both biological and environmental samples for future case-control or cohort analysis rather than to attempt to measure a large number of factors immediately. The sampling and storage techniques should ideally preserve carcinogens and their metabolites, alkylated bases, factors such as beta-carotene and aryl hydrocarbon hydroxylase and possibly even the entire genome. This is easy to suggest but difficult to do, but the benefits could be substantial. For example, the problem of linking the moderate cancer risk in certain rubber workers to one or more of the large number of chemicals to which they are exposed could be approached more systematically through such a data base. 'Job-exposure' matrices based on employment records are at best only semiquantitative, and premalignant effects of exposure may be very much more common and appear much earlier than overt cancer. A moderate risk in men exposed to many possible carcinogens is probably typical of future problems in industrial surveillance.

Such a data base, together with detailed dietary, smoking, medical and reproductive histories, would of course also be of great value in other areas of cancer research.

3.5 Statistical Methodology and Model-Fitting

Standard programmes are already available for the analysis of multiplicative effects on simple absolute or relative risk data, but there are many situations in which more complex temporal models may be useful. For example, the relative risk of epithelial cancer caused by ionizing radiation, and of lung cancer caused by brief intense asbestos exposure, increases for some years after exposure, and then either remains roughly constant or eventually falls (Day and Brown, 1980). It is well known that such effects correspond qualitatively to the predictions of a multistage model in which an intermediate or late stage is affected, but most epidemiologists have been reluctant to fit very specific models to such data. Among the few examples of such analysis, however, several have already proved useful:

(1) Knudson's two-stage model for heritable susceptibility to retinoblastoma (Knudson, 1971) has recently received strong experimental support (Cavenee *et al.*, 1983).
(2) The suggestion that cigarette smoking affects the first and penultimate stages in the development of lung cancer seemed anomalous in 1971 (Doll, 1971), as a two-stage effect would be expected to produce a quadratic rather than linear dose–response; but further data suggest that this prediction was

probably correct, and that the apparent dose linearity in earlier studies reflected the inaccuracy of smoking histories as a measure of bronchial exposure (Doll and Peto, 1978).

(3) Mole and Major fitted specific linear and quadratic dose–response models incorporating cell-killing effects to explain leukaemia rates in irradiated animals (Major and Mole, 1978), and such a model may explain the apparently anomalous leukaemia dose–response relationship for patients irradiated as a treatment for ankylosing spondylitis (Smith and Doll, 1982).

None of these models is likely to provide a complete explanation of the phenomena analysed, and some may be completely wrong. They are still useful, however, both as a basis for tentative theories, and as a stimulus to further analysis of existing studies and the collection of more extensive and accurate data. A standard computer programme incorporating both additive and multiplicative dose effects at various stages in a multistage model would be a useful addition to the tools of cancer epidemiology. Ideally, the programme should be capable of analysing both absolute incidence rates, and relative (observed/expected) or excess (observed minus expected) rates compared with the age-specific rates of a standard population. It would be silly to expect such a programme to determine the exact stage or sequence of different effects, but it might facilitate the criticism and further development of such models. At a simpler level, industrial studies in which exposures at different times and intensities are estimated for a single carcinogen require an additive model for the combined effects of separate exposures, which are difficult to incorporate into the conventional proportional hazards model in which separate effects act multiplicatively.

4 USE AND ABUSE OF THE CONCEPT OF LATENCY

The long delay between first exposure and any detectable increase in cancer incidence that is observed for many carcinogens is predicted by the equation

$$I = b \cdot t^k$$

which describes, at least approximately, the incidence pattern of various human and animal tumours caused by chronic low-dose exposure (Doll, 1971). I denotes cancer incidence, t is either duration of exposure or time since first exposure to the carcinogen, and b is constant for a given dose level. The exponent k is usually 3 or more, and a potent carcinogen which causes cancer in 10% of exposed individuals within 40 years of first exposure will therefore produce a cumulative risk of less than 0.04% within 10 years. In a cohort of 1000 workers in which 100 cancers are caused within 40 years of first exposure, it will thus be unusual for

any cases to occur within 10 years of first exposure, although several may occur between 15 and 20 years after the first exposure.

4.1 Definitions of Latency in Common Use

This lag between first exposure and an appreciable increase in cancer risk is of considerable practical importance. It determines the delay between the introduction of a new carcinogen and its epidemiological detection, and the loss of expected life of a cancer victim will be less if the latent period is long. The widespread belief that latency increases as exposure is reduced is not in general true, however; indeed, it is shown below that the average age at diagnosis or death for lung cancers caused by moderate exposure to cigarette smoke or asbestos may well be slightly older than for lung cancers among non-smokers not exposed to asbestos. Heavy exposure to a carcinogen can produce the opposite effect, although this is usually due to the shortening of life, not to changes in the age-specific incidence pattern. This confusion is due largely to the fact that the term 'latent period' is used in at least four quite different senses.

4.1.1 A Period of Absolute Immunity

By an irritating quirk of statistics, a cancer incidence rate that is approximately proportional to a power of age or time since first exposure can also be described by the equation

$$I = b.\ (t-d)^k$$

Thus, for example, the lung cancer rate among life-long smokers can be equally well fitted either by the seventh power of age or the fourth power of duration of smoking (Doll, 1971; Doll and Peto, 1978). Duration of smoking is roughly equal to age minus 20 years, and in this instance the 'lag' of 20 years is merely the age by which the habit of regular smoking is established. There is probably also a lag of a few weeks in mice and a year or more in humans between the existence of the first fully malignant cell and diagnosis of cancer.

Such a period of absolute immunity is a useful and meaningful concept, but its duration cannot usually be estimated with any precision, except in large experiments in which a high proportion of animals develop cancer.

4.1.2 The Average Interval Between First Exposure and Diagnosis

This varies grossly with age at exposure, duration of follow-up and mortality due to other causes, and is only weakly and inconsistently related to intensity of exposure, unless doses are so high that a high proportion of individuals (usually experimental animals) develop cancer or die of toxic effects.

4.1.3 The Time From First Exposure to the First Observed Cancer in a Particular Cohort

This is determined as much by the size of the cohort as by the intensity of exposure, and is merely a crude measure of the point at which the product of cumulative risk and cohort size is of the order of unity.

4.1.4 The Time by Which a Fixed Proportion of Animals in a High-dose Carcinogenesis Experiment Have Developed Cancer

This is of course strongly related to dose, but Druckrey's study (Druckrey, 1967) which showed this is still incorrectly cited as evidence that 'latent period' in one of the senses defined above will be dose-related.

4.2 Errors Due to Inconsistent Definition of Latency

It is most unsatisfactory that the same term should be used, usually without formal definition, in four quite different senses. The need for a better understanding and definition of the concept of latency is illustrated by the following examples. In each case the 'observation' is a necessary consequence of the particular definition of latency that was implicitly used, and the resulting inference is circular or false.

A draft report on the effects of asbestos written for a US Government agency noted that the interval between first asbestos exposure and diagnosis of pleural mesothelioma is inversely related to age at first exposure. This is hardly surprising; those first exposed at age 50 or later are unlikely to live long enough to develop mesothelioma, but if they do the 'latent period' cannot much exceed 30 years. The inference that was drawn from this observation, that the pleural mesothelioma risk may be lower when persons are exposed at younger ages, is of course the opposite of the truth.

A review of case reports of childhood mesotheliomas (defined as cases diagnosed below age 15) observed that 'the most conspicuous difference between the characteristics of mesothelioma in children and in adults is the length of the latent period of this tumour (up to 14 years in children and from 20–55 years in adults)'. Here again, the tautology that exposure cannot begin before birth (or conception, for *in utero* exposure) and cancer cannot develop after death is presented as a significant epidemiological finding. Long follow-up of a cohort of individuals exposed to asbestos in childhood would be required to demonstrate that the resulting pattern of mesothelioma incidence differs from that caused by later exposure.

It is often suggested that the latent period increases as the exposure level falls, and that this provides an effective safe threshold for carcinogens, as below a certain level the latent period will exceed the human life-span. This mis-

understanding is common even among epidemiologists, and is worth considering in more detail.

4.3 Comparison of Various Definitions of Latency

Suppose that a cohort of industrial workers is first exposed to a carcinogen at age 25 and that their relative lung cancer risk is 1.0 up to age 35, increases steadily to a maximum age of 65, and remains at this level thereafter. The effects of varying intensity of exposure, duration of follow-up and the size of the cohort on different measures of 'latent period' are shown in Table 1, which is calculated from British male death rates for lung cancer and other causes. Ages rather than latent periods are shown, but as the cohorts are all first exposed at age 25 (except, of course, the unexposed cohort) the corresponding latent periods are simply age minus 25 years, whatever definition of latency is adopted.

The age at which the first lung cancer death occurs, and the age by which a certain proportion (5% in Table 1) have died of lung cancer, both fall with increasing intensity of exposure, although the former is also grossly affected by the size of the cohort; but the average age at death of those who die of lung cancer is virtually unaltered until the risk is so high that a substantial proportion of the cohort is eliminated by the hazard. Table 1 also shows that this average age is grossly underestimated if the cohort is not followed to extinction; it must be estimated by extrapolation, not, as is often done, by merely averaging the ages at death observed in a study. Although the effect is small, it is perhaps worth emphasizing that the average age at death from lung cancer is actually increased by moderate exposure, from 68.1 years in the unexposed general population to 68.4 years in moderately exposed workers whose lung cancer risk is doubled in old age. The effect of carcinogens such as cigarette smoke and asbestos that produce this sort of risk pattern is thus to increase the probability of developing cancer, but not to make it occur earlier.

5 TOTAL DOSE AS A MEASURE OF RADIATION OR ASBESTOS EXPOSURE

Asbestos and ionizing radiation are the two most important industrial carcinogens for which there are some dose–response data and reasonably accurate data on temporal effects, but the mechanisms by which they act may be quite unlike those of the major environmental causes of cancer or of chemical carcinogens in industry. The carcinogenic effects of asbestos may be entirely due to physical rather than chemical properties, and dose–response data are difficult to interpret, as the effects of asbestos appear to vary with fibre length and diameter, and with residence and transport differences between different fibres. The effects of radiation are complicated by cell killing and perhaps DNA repair mechanisms, and depend on fractionation and scattering in ways which are not

Table 1 Measures corresponding to different definitions of 'latent period' in a cohort of workers followed up since first exposure to a lung carcinogen at age 25

Exposure level (max. rel. risk) and cohort size	Follow-up in years	Average age of lung cancer deaths	% of cohort dying of lung cancer	Age by which 5% die of lung cancer	Age of first lung cancer death*	Life expectancy
Unexposed (RR = 1) 500 men	25 (to age 50)	44.4	0.3%	Not reached	46	
	50 (to age 75)	64.1	7%	71	46	71.3
	To extinction	68.1	9%	71	46	
Moderate (RR = 2) 500 men	25 (to age 50)	44.9	0.5%	Not reached	45	
	50 (to age 75)	64.6	12%	65	45	70.5
	To extinction	68.4	16%	65	45	
Heavy (RR = 10) 500 men	25 (to age 50)	46.0	1.4%	Not reached	42	
	50 (to age 75)	64.0	43%	56	42	66.0
	To extinction	66.2	50%	56	42	
Heavy (RR = 10) 100 men	25 (to age 50)	46.0	1.4%	Not reached	47	
	50 (to age 75)	64.0	43%	56	47	66.0
	To extinction	66.2	50%	56	47	

* Age of first death is defined as the age by which the probability that at least one lung cancer death has occurred in the cohort exceeds 50%. It is assumed that the relative risk for lung cancer is 1.0 up to age 35 and rises uniformly from 1.0 at age 35 to a maximum at age 65, and remains constant thereafter.

yet understood. These two agents are major carcinogens in their own right, however, and the age and time dependence of the cancers they produce, like those caused by chemical carcinogens, can be explained, at least qualitatively, within the general framework of the multistage model.

5.1 Cumulative Asbestos Exposure—Confusion of Exposure Level and Duration

There is an almost perfectly linear relationship among asbestos miners and millers between the relative risk for lung cancer and estimated 'cumulative dose', the product of average estimated exposure level and duration of exposure (Figure 4, Peto, 1978; McDonald *et al.*, 1980). The eventual relative risk for lung cancer also increases with increasing duration of exposure, however, which can of course be measured extremely accurately, and results similar to those shown in Figure 4 would therefore be obtained if the exposure level of the entire cohort were the same, or even, for that matter, if exposure level estimates were assigned to individuals at random. The critical test of exposure level estimates is the dose–response for average estimated exposure levels among workers exposed for similar durations.

One important implication of the far greater accuracy of measurement of

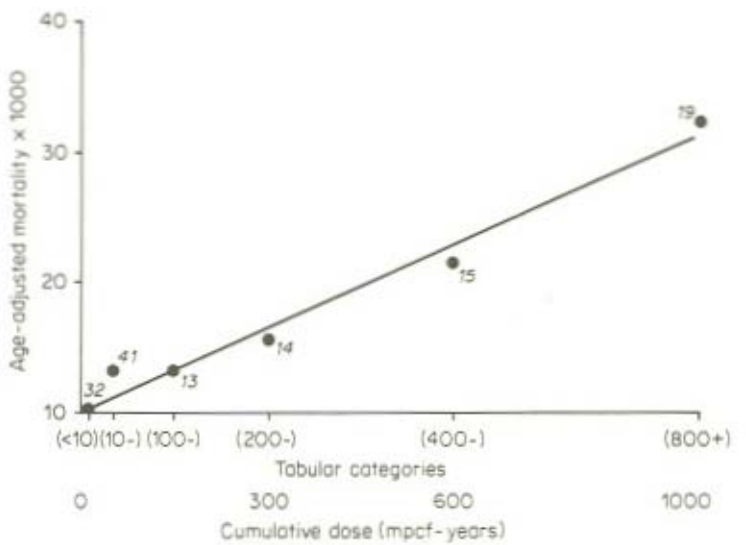

Figure 4 Linear relationship between age-adjusted mortality (and hence relative risk) for lung cancer and cumulative asbestos exposure. Reproduced by permission of *The Lancet* from Peto (1978), based on the study of McDonald *et al.* (1980)

duration than of dose is that the best strategy for detecting industrial carcinogens may be to depend entirely on duration, particularly in case-control studies. A case-control study in which controls from the same factory are matched for duration of employment would fail to detect a potent carcinogen if no large job category involved exceptional exposure. Once the carcinogen has been detected, however, a clear relationship between exposure level and risk is required to demonstrate that the exposure estimates provide a satisfactory basis for dose–response estimation and extrapolation.

5.2 Total Irradiation Dose and Leukaemia Risk

For practical purposes, the most important outstanding question in relation to radiation carcinogenesis is the likely effect of low-dose exposures to workers in certain industries, to the general population from ambient levels or accidents involving release of radioactive material, and to patients in routine radiography. The carcinogenic hazard of brief intense radiation is insignificant in comparison with the hazards of most diseases for which radiotherapy is now given, or the more immediate consequences of nuclear war. Unfortunately, however, the best dose–response data so far obtained relate to the effects of radiotherapy or nuclear weapons, and there is still considerable uncertainty in the reliability of low-dose predictions derived from such data, which are not sufficiently detailed or extensive to provide an adequate test of the assumptions implicit in such extrapolation. Some of these difficulties are illustrated by the data on leukaemia mortality among patients irradiated as a treatment for ankylosing spondylitis (Figure 2, Smith and Doll, 1982).

For medical irradiation, the effects of scattering and cell killing may substantially affect the dose–response curve. It is not possible in practice to estimate accurately the distribution of doses delivered to all susceptible cells by scattering from a focused beam, but the following simple model gives some idea of the type of effects that might occur. The three curves shown in Figure 5 show the relationship between risk and total dose for three different beam patterns, assuming a linear dose effect with cell killing. The risk R is thus proportional to $d.\exp(-kd).v$, where d is dose per unit volume, v is the volume of marrow irradiated, and the constant k is chosen to correspond to 50% cell killing at 100 rad. Up to a total dose of 50 rad, the effects of increasing the intensity of irradiation to unit volume of marrow (line C) or of increasing the volume uniformly irradiated at 50 rad (line A) are approximately equal, but at higher total doses they differ markedly. Line B shows the effect of scattering. The beam intensity is normally distributed along a length of marrow, with the same intensity in the centre of the beam and the same total dose as for C. At high doses the risk is still substantial, because irradiated cells at the edge of the beam survive. If the assumption of dose linearity is correct, the dose–response relationship shown in Figure 2 is presumably a weighted average of such patterns, but their

relative contributions are difficult to assess, and probably vary at different total doses. Data on patients exposed to maximum doses per unit volume much exceeding the 50 % cell-killing dose are thus of little value in assessing the risk of whole-body irradiation at low levels unless the distribution of irradiation is known in great detail, and a better estimate might be obtained if they were ignored, and the model $d.\exp(-kd).v$ fitted to the data on patients whose intensity of irradiation did not exceed 200 rad or so. These difficulties were recognized by Smith and Doll, who emphasized the questionable validity of their model-fitting and resulting extrapolation based on mean marrow doses, and pointed out that they obtained a surprisingly high estimate of the 50 % cell-killing dose (a mean dose of 210 rad, corresponding to a dose to irradiated marrow of about 400 rad). They were unable, with the data available, to separate intensity of irradiation and volume of marrow irradiated, but such analysis might substantially alter their results. If the data in Figure 2 at mean doses exceeding 200 rad could be dismissed as uninterpretable artefacts of scattering and cell killing, for example, a more plausible 50 % cell-killing level of about 100 rad could be fitted to the first two data points, although it could obviously not be estimated with any precision from these data alone. Restricting analysis to the two lowest dose levels could also either increase or reduce the estimated risk at lower doses. The fitted curve in Figure 2 would no longer be constrained to lie below the observed risks at mean doses below 200 rad, and if the mean dose of 100–200 rad corresponded

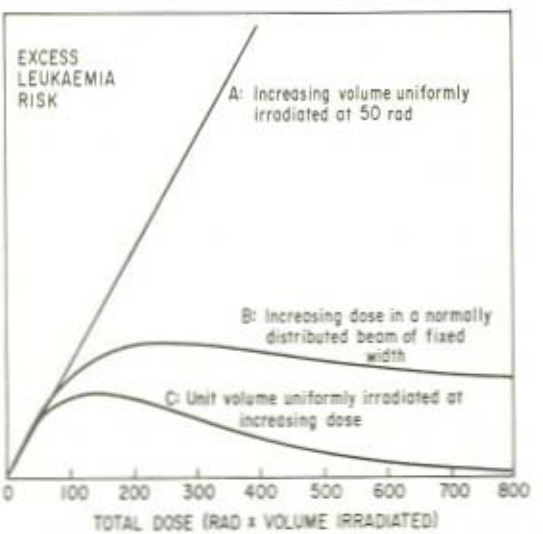

Figure 5 Predicted relationships between total marrow dose of irradiation and leukaemia risk, assuming a linear effect, and 50 % cell killing at 100 rad

approximately to a dose of 300 rad to half the marrow and the 50% cell-killing dose were 100 rad, the risk caused by 150 rad of whole-body irradiation could be up to three times greater than the observed risk plotted at 150 rad in Figure 2, depending on the degree of scattering. The linear model $d.\exp(-kd)$ would then predict a leukaemia risk at low doses up to an order of magnitude higher than the figure of about 2 per million per year per rad derived from these data; but the quadratic model $d^2.\exp(-kd)$ would fit the first two points in Figure 2 better than the linear model and would predict a negligible risk at low doses. Estimates based on the experience of atomic bomb survivors who received whole-body irradiation of under 100 rad suggest that the estimate of 2 per million per year per rad cannot be much to low (Beebe *et al.*, 1978), so the dose–response may well be quadratic, perhaps with a linear component. There is evidence of gross differences between the effects per unit dose of brief and protracted irradiation, however, at least in mice, and there are several other uncertainties in such comparisons, including problems of dosimetry and the relative effects of different wavelengths and other particles. Further data, preferably from direct observation of cohorts exposed to levels of 100 rad or less, are required to provide reliable estimates of the likely effects at lower levels.

6 INAPPROPRIATE MEASURES OF RISK AND DOSE

6.1 Incidence and Prevalence

One reason for analysing cancer incidence (rate of appearance of new cases) rather than prevalence (cumulative risk of developing cancer) is that incidence is likely to be roughly proportional to the number of cells that have undergone all but the last stage of carcinogenesis, and is thus a more direct measure of current biological condition. The formula for incidence is therefore likely to be scientifically more informative and mathematically more tractable. Prevalence is socially and clinically more important, however, and more readily understood. Survival data are therefore often displayed by plotting survival curves, which measure prevalence, but should be analysed in terms of the underlying incidence pattern.

The crudest measure of prevalence is the proportion of individuals who have developed cancer. This is a virtually meaningless statistic unless it is calculated 'in the absence of other causes of death' by proper actuarial methods at a specified time after first exposure. Animal carcinogenicity tests are still often reported in this crude way, however, in spite of the fact that a potent carcinogen that is also directly toxic can actually reduce the probability of developing cancer by killing animals before the tumour has had time to develop. The same mistake is still sometimes made by epidemiologists. The three scientific reports described below, commissioned by or submitted to government agencies for the purpose of assessing and revising hygiene standards for asbestos, examined prevalence

without taking adequate account of dose and time dependence. In each case, conventional analysis of dose, time and incidence rates would have avoided the resulting misinterpretation.

6.2 Three Examples Involving Asbestos-related Disease

6.2.1 Prevalence of Asbestos-related Signs and Cumulative Dose

This example involves crepitations (an early sign of asbestos exposure) rather than cancer incidence, and is thus not directly relevant to the subject of this paper. The 2 fibre/ml hygiene standard for asbestos introduced more than 10 years ago in Britain and subsequently in several other countries was based on this analysis, however, and it therefore seems worth including, both for methodological reasons, and as a background to the other examples described below.

Workers were classified according to their cumulative asbestos exposure in fibre/ml · years (average exposure in each year summed over all years of employment), and the proportion suffering from crepitations plotted against this index (Berry, 1973). A log-normal curve fitted the data adequately (Figure 6), leading to the prediction that the risk at 100 fibre/ml · years would be less than 1 %. Lifetime (50 years) exposure at 2 fibre/ml gives a cumulative exposure of 100 fibre/ml · years, and it was therefore concluded that the resulting risk would be less than 1 %, so that 2 fibre/ml would be an acceptable standard. Several

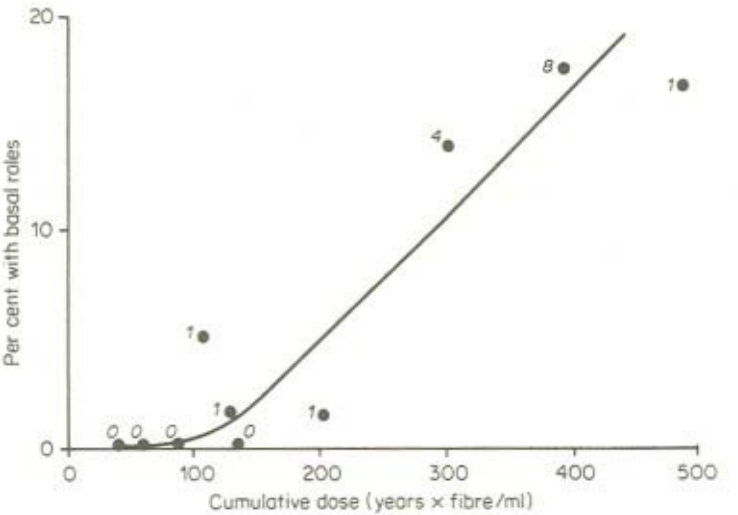

Figure 6 Prevalence of basal râles (crepitations) related to cumulative asbestos exposure. Peto (1978), redrawn from Berry (1973) by permission of the International Agency for Research on Cancer

questionable assumptions are implicit in this calculation (Peto, 1978). The cumulative dose cannot by definition increase after exposure has ceased, but the prevalence of crepitations certainly does, and the same cohort examined 10 years later would inevitably show a higher risk at each dose level. The average exposure level of this cohort was of the order of 10 fibre/ml, and a more plausible interpretation of Figure 6 is that the prevalence was zero up to about 10 years and then rose sharply with time. The absence of cases below 100 fibre/ml · years would then reflect a delay between first exposure and the appearance of symptoms and signs rather than a non-linear dose–response. The incidence of crepitations during further follow-up of these workers (Acheson and Gardner, 1979) was in fact roughly proportional to cumulative dose even at the lowest levels, suggesting that the life-long risk at 2 fibre/ml may be 20 or more times greater than the 1 % or less predicted from the original analysis. This error seems to be directly attributable to the use of prevalence as the primary response measure and the confusion of dose and time, which obscured the biological implausibility of the model.

6.2.2 Mesothelioma 'Prevalence'

An issue of some importance in the current debate on asbestos control is the mesothelioma risk caused by different types of asbestos, notably chrysotile, which is now the predominant type in many countries, including Britain. The epidemiological review (Acheson and Gardner, 1979) on which the recommended revision of the British hygiene standard from 2 fibre/ml to 1 fibre/ml was based concluded that 'up to the present time chrysotile has rarely caused mesothelioma', an inference based principally on the mortality experience of chrysotile miners and millers in Canada. After reviewing case reports of mesothelioma among miners in South Africa, where almost all cases have occurred among miners exposed to crocidolite rather than chrysotile, the Report continues:

> '. . . the evidence from South Africa . . . cannot on its own be regarded as conclusive. . . . Fortunately, however, support for a relatively low risk of mesothelioma associated with chrysotile mining can be found in other countries, particularly Canada. . . . According to McDonald, a study of deaths in 11,379 chrysotile miners and millers . . . has revealed only 11 mesotheliomas. . . .'

On the basis of this observation it was apparently assumed that the mesothelioma risk due to chrysotile is negligible, and this cancer was ignored in the risk calculations. Apart from the statistical impropriety of this approach, other data suggest that the conclusion may be false, as the ratio of pleural mesothelioma to excess lung cancer does not seem to be consistently dependent on fibre type, and even in this cohort of chrysotile miners (McDonald *et al.*, 1980)

Table 2 Inappropriate dose and response comparisons of cohorts of asbestos workers. Reproduced by permission of Dietrich Reimer Verlag and Bundesgesundheits amt from Schneiderman *et al.*, 1981

Study group	Type of asbestos	Duration of study from onset of exposure	Subgroup categorized by exposure	Cumulative frequency of mesothelimas (%)	Estimated cumulative exposure (f-y/ml)	Response per unit dose (% per f-y/ml)	Mesotheliomas as % of lung cancers
1 Insulation manufacturing	Amosite	35 y (short exposures)	< 9 month	0.4% (2/481)	11	0.04	6% (2/36)
			> 9 month	3.5% (12/339)	70	0.05	21% (12/57)
2 Asbestos products manufacturing	Crocidolite, later chrysotile and amosite	M, 11–42 y	Low	0.8% (11/1438)	30	0.03	38% (11/29)
			High	2.4%	120	0.02	47% (35/74)
		F, 33–40 y	Low	1% (1/98)	30	0.03	50% (1/2)
			High	3.4% (20/595)	120	0.03	80% (20/25)
4 Asbestos products manufacturing	Chrysotile, some crocidolite and amosite	37 + y	Low	4.1% (12/293)	100	0.04	71% (12/17)
			Medium	4.1% (10/244)	200	0.02	83% (10/12)
			High	5% (4/81)	400	0.03	100% (4/4)
6 Textile production	Chrysolite	10–35 + y	Pre-1951 only	1.65% (7/424)	230	0.007	25% (7/28)
7 Insulation application	Chrysotile and amosite	10–50 + y, median 24 y	—	1.4% (170/12051)	225	0.006	38% (170/450)
8 Mining and milling	Chrysotile	10–64 y	—	0.09% (10/10939)	900	0.0001	4% (10/250)
9 Mining and milling	Chrysotile	36–56 + y	—	0.2% (1/544)	900	0.0002	4% (1/28)

the ratio (10 pleural mesotheliomas to 46 excess lung cancers in men) was not strikingly lower than that observed in certain cohorts of men who had been heavily exposed to other forms of asbestos.

Mesothelioma incidence rises as the third or fourth power of time since first asbestos exposure (Peto *et al.*, 1982), and more than 99 % of cases may therefore occur more than 15 years after first exposure. The percentage of asbestos workers in a cohort who have so far developed mesothelioma can thus vary by more than two orders of magnitude, depending on the duration of follow-up, and this crude statistic is almost uninterpretable.

6.2.3 Lung Cancer and Mesothelioma 'Prevalence', and Cumulative Dose

The ratio of the total number of lung cancers to the total number of mesotheliomas in different industrial cohorts can vary from well over 100:1 among heavy smokers not occupationally exposed to asbestos to 0.3:1 among non-smokers heavily exposed to asbestos, as the mesothelioma risk is hardly affected by smoking. Differences in this ratio between cohorts are therefore probably due more to differences in intensity of asbestos exposure and smoking than to differences between different types of asbestos. None the less, such a comparison was cited as evidence of large differences in the relative effects on these tumours of different fibre types in a recent review commissioned by the West German Government (Table 2, Schneiderman *et al.*, 1981). These authors also calculated 'dose–response' rates for mesothelioma in each cohort in per cent per fibre/ml · years, dividing the crude percentage of the total cohort that had died of mesothelioma by the average cumulative exposure of the cohort. If, as seems likely, mesothelioma incidence t years after the beginning of continuous asbestos exposure at a level of d fibre/ml is roughly proportional to $d \cdot t^{3.5}$, a 'cumulative dose' of 100 fibre/ml · years at the end of 50 years' exposure at 2 fibres/ml will produce an incidence more than 50 times greater than a dose of 100 fibre/ml · years at the end of 10 years' exposure at 10 fibre/ml, and an even larger difference in prevalence.

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