Risk Estimation Models

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ABSTRACT

Models for risk estimation are discussed in terms of time and dose as measures of exposure. The type of behaviour to be expected is shown to depend on the mode of action of the agent concerned, requiring formalization in terms of a multistage process. Straightforward dose–response curves for late-stage carcinogens may show different patterns from dose–response curves for early-stage carcinogens. In addition, the dose–response for a single agent may be strongly modified if other agents act simultaneously. The joint effect of two or more agents also depends heavily on their mode of action as multistage models would suggest. Some attention is finally given to the dose–response for protective agents which can be expected to become of increasing relevance.

1 INTRODUCTION

Qualitative descriptions of cancer risks are being increasingly recognized as inadequate as a basis for preventive measures. A rational approach to prevention can only be based on a quantitative estimate of cancer risk. Since even a qualitative association between experimental results and human risk is only tentative, it is clear that most of the data, on which assessments in humans should be based, come from epidemiology. The problem with epidemiological data is that they tend to be rather sparse, except for cigarette smoking and perhaps alcohol and asbestos. For a particular exposure it would be rare to have observations within a range of conditions wide enough to give direct measures of risk for most situations likely to be encountered. One is thus obliged first to interpolate between data points, and then perhaps to extrapolate beyond the observation range. For both purposes, some basic model is required relating risk to the characteristics of exposure. This chapter will discuss some of the models that have been proposed to describe cancer risk and the data used to justify them. It is important to note that attention will be confined to modelling risk at dose levels for which observations are available, and no attention will be given to models for risk estimation at levels for which observations are demonstrably impossible to obtain. Biological understanding of cancer may in time become

sufficiently advanced to provide a sound theoretical basis for discussing increases in relative risk of the order of 10^{-3} or less but, at present, attempts to estimate dose levels for which the risk is of this order of magnitude are unpersuasive.

We shall start by considering single agent exposures. The two major determinants of risk are dose and time. Duration of exposure, time since exposure started, time since exposure ceased and age are all aspects of the general factor 'time' which may affect risk. 'Dose' is also a complex variable, and the response may be determined by the route of administration, fractionation of dose, single shot versus continuous exposure, or the age at which the dose is applied. Rather than examine the full range of complexities, we shall confine ourselves to some exemplary situations.

2 RELATIONSHIP OF RISK TO TIME AND DOSE: GENERAL CONSIDERATIONS

Risk is best measured by tumour incidence and, given the importance of time in any quantitative approach, time-specific (often meaning age-specific) incidence rates provide the best overall measure of risk. Incidence is preferable to prevalence, since the prevalence is affected by the lethality of the tumour. If information on survival is not available, conversions from prevalence to incidence cannot be done with any accuracy. In some examples discussed below, prevalence has had to be used, and in these cases the interpretation must be treated with caution.

Experimentally, skin painting experiments have provided the most detailed information on the evolution of age-specific incidence rates in relation to exposure because one can observe the tumours directly.

A series of experiments by Lee and O'Neill (1971) demonstrated a power law dose–response. Four dose levels of benzo(a)pyrene (BP) were used (6 µg/week, 12 µg/week, 24 µg/week and 48 µg/week). The age-specific cumulative incidence rates of skin tumours were well fitted by the expression

$$\text{incidence } (d, t) \propto d^{1.78}(t - 18)^{2.95} \tag{1}$$

where d = dose and t = age.

Later skin painting experiments by the same group considered the question of whether age itself or time of exposure is the relevant time variable (Peto *et al.*, 1975). The results demonstrated unequivocally that age *per se* was unimportant. Irrespective of whether exposure started at 10, 25, 40 or 55 weeks of age (twice weekly skin painting with BP), the incidence of skin tumours increased at approximately the third power of duration of exposure less 28 weeks.

The power law relating incidence to time for organs for which major changes do not take place during pre-adult and adult life and for which one might suspect fairly continuous exposure, has been one of the seminal epidemiological

bservations of the past 20 years. For most epithelial tumours, excluding those ormonally related, the age-specific incidence rises as the fourth or fifth power of ge. For one situation where incidence rates have been computed as a function of luration of exposure, namely lung cancer among cigarette smokers, and where mong the exposed the great majority of lung cancers are smoking related, one inds the same behaviour as seen for skin tumours after skin painting. Rates rise as power of the duration of exposure, in this case about the fourth power (Doll, 971).

Among cigarette smokers, the relation of lung cancer with the amount smoked s partially obscured by the fact that amount smoked changes over time and that moking histories are not completely accurate. Both factors would tend to reduce he estimated exponent of a power function relationship for dose effect. In a study n which attention was confined to stable smoking histories, a clear indication was given that the power of the dose–response curve was higher than one (Doll and Peto, 1978), in contrast to earlier findings with less stringent requirements on the moking history where a linear dose–response was suggested. For cigarette moorters, a relation for lung cancer of the form:

ung cancer incidence $\propto$ (daily amount smoked)$^\beta$ $\times$ (duration of smoking)^4 (2)

where β is between 1 and 2, is strongly supported by the available data.

The similarity between skin painting in mice and cigarette smoking in man suggests that the model has some validity, at least in the dose ranges considered. It would clearly be unjustified, however, to extrapolate to doses, say, a thousand-fold lower than the lowest doses observed in the studies described.

It is of interest to note that under rather different circumstances similar models are also of use. The induction of mesothelioma by a single intrapleural injection of asbestos type fibres has been extensively studied, and the results discussed quantitatively by Berry and Wagner (1969). A model of the form

$$incidence = c(t - w)^k \tag{3}$$

where t is the age, w is the age at the beginning of exposure and c and k are constants, fitted various sets of data closely with $k \simeq 2$. Human mesothelioma data, as for example seen in the cohort followed by Newhouse and Berry (1976), exhibit a similar relationship with time (Peto *et al.*, 1982).

3 RISK AS A FUNCTION OF TIME: EXPOSURE OF LIMITED DURATION

We shall now look more closely at the relationship between risk, dose and time, considering first the time variable.

The power relationship (3) given in the previous section refers to continuous

exposure to an agent. Since asbestos fibres remain indefinitely in the lung, even a short-term environmental exposure to asbestos might be considered as continuous exposure. When exposure is not continuous, a variety of ways in which risk can evolve has been observed. We shall consider here the effect of stopping exposure, and the effect this cessation may have on subsequent cancer risk. An example which typifies the differences that can be observed is given by the so-called ED_{01} study in which BALB/c mice were fed 2-acetylaminofluorene (2-AAF) under several different treatment regimens. Both liver and bladder tumours were induced, bladder tumours particularly at high dose levels. Several of the experimental groups were fed 2-AAF for the first 9, 12 or 15 months of life, and then followed up without further treatment. Other groups were treated throughout life. Figures 1 and 2 (Littlefield *et al.*, 1980a) compare the prevalence of bladder and liver tumours over time between groups with continuous treatment and those with treatment of limited duration. For liver tumours, the effect of stopping the treatment is minimal, tumour prevalence continues to increase after the cessation of treatment. For bladder tumours, stopping the treatment immediately freezes the prevalence of tumours found at sacrifice (Day and Brown, 1980; Littlefield *et al.*, 1980b).

Similar differences in behaviour are seen in skin painting experiments where exposure is of limited duration. In a study reported by Lee (personal communication; see also Day and Brown, 1980) two agents, benzo(a)pyrene (BP) and tobacco smoke condensate, were used. Skin painting for life was compared
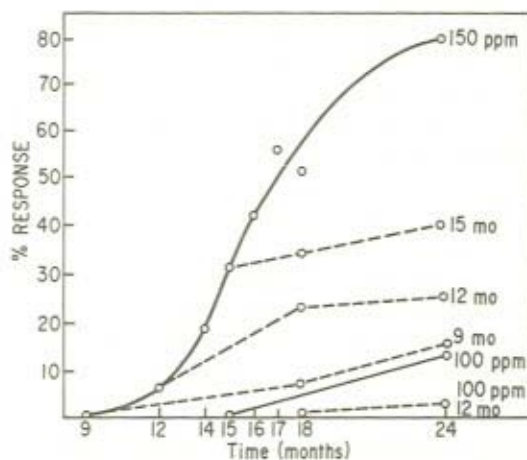

Figure 1   The prevalence of bladder neoplasms in mice fed 2-AAF for 9, 12 and 15 months and sacrificed at 18 and 24 months. Reproduced by permission of Pathotox Publishers Inc. from Littlefield *et al.*, 1980a
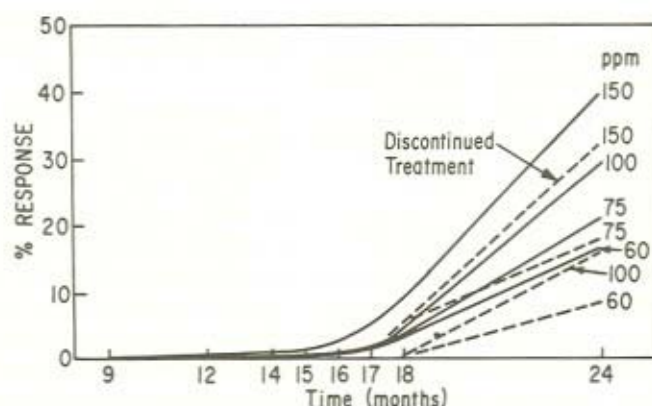
Figure 2 The prevalence of liver neoplasms in mice fed 2-AAF for 12 months and sacrificed at 18 and 24 months. Reproduced by permission of Pathotox Publishers Inc. from Littlefield *et al.*, 1980a

with exposure limited to 20–50 weeks. For BP, stopping exposure had relatively little effect on the subsequent appearance of skin tumours, whereas with tobacco smoke residues, stopping exposure led to a rapid reduction in risk relative to continuous exposure.

These differences in behaviour would be difficult to model if the mode of action of each agent were the same. They are exactly the differences we should predict, however, if one were to consider carcinogenesis as a multistage process, and one imagines different agents acting principally at different stages. In these terms, one can describe the action of 2-AAF on bladder tumour induction and the action of tobacco smoke condensate on skin tumour induction as being primarily late stage. In contrast, the action of 2-AAF on liver tumour induction, or BP on skin tumour induction, appears to be primarily early stage (Day and Brown, 1980).

Models for continuous exposure, with incidence related to a power of duration of exposure, although arising empirically as satisfactory descriptions both of human cancer incidence data and of experimental data, were first proposed on theoretical grounds as the behaviour to be expected if cancer were a multistage process, relatively homogeneous in time (Armitage and Doll, 1954). The extension of these multistage models to risk associated with short-term exposure fits the relevant experimental data and, in terms of the type of behaviour observed, provides a classification of the mode of action of each agent based on incidence. This classification is given support by independent experimental data, such as the identification of mouse skin tumour-promoting agents in tobacco smoke, the hyperplasia of bladder epithelium during 2-AAF treatment which regresses when treatment stops, or the demonstration of initiating action on mouse liver by short-term exposure to 2-AAF. This last experiment also demonstrated the

promoting or late-stage action of DDT on mouse liver following initiation by 2-AAF, in agreement with the interpretation put on the results of short-term as opposed to continuous exposure to DDT.

Multistage models appear, therefore, to be successful in describing cancer risk as a function of time. They also underline the importance of time as a determinant of risk. These models demonstrate moreover that attempts to quantify and to model the effect of a particular agent must be based on some knowledge of its mode of action. It is probably sufficient for the purpose of describing risk simply to be able to characterize an agent as primarily early stage or primarily late stage. The more detailed demarcation of stages in cancer induction, based on *in vitro* experimentation, is too fine for the basically rather crude measures of incidence to distinguish. The predictions of cancer incidence are similar whether they are based on a five- or six-stage model, homogeneous in time, or on a two-stage model allowing a differential increase in the growth of the population of intermediate cells.

In terms of human exposure, late-stage effects can be seen reflected roughly in the constant lung cancer incidence among ex-cigarette smokers (in contrast to the continuing increase among continuing smokers) (Doll and Peto, 1976), the reduction in risk for endometrial cancer on ceasing to take exogenous oestrogens (Jick *et al.*, 1979), or the reduction in the rate of increase of breast cancer incidence in the menopausal and immediately post-menopausal age range (Moolgavkar *et al.*, 1980). Early-stage effects might be proposed for asbestos, particularly for mesothelioma, where short-term exposure leads to a long-term continuing increase in risk (Seidman *et al.*, 1977), and for nickel-related exposures among nickel refinery workers, at least for nasal sinus cancers. The lung cancer experience of the nickel refinery workers suggested that the excess absolute risk remained constant after exposure stops (Doll *et al.*, 1970), a further example of the same agent apparently affecting different stages for different cancers.

4 MULTISTAGE MODELS AND DOSE–RESPONSE RELATIONSHIPS

The importance of mode of action is not, however, limited to the effect of time on risk. Basic dose–response models also appear to depend heavily on the role the agent plays in carcinogenesis. For agents whose main effect appears to be early stage, dose–response relationships appear to be between linear and quadratic, over the dose range at which observations have been made. The effect of BP on mouse skin (as discussed earlier, Lee and O'Neill, 1971), 2-AAF (Figure 3) or of aflatoxin on mouse liver, and of asbestos on the pleura, give clear examples of such behaviour. For agents for which a major part of their effect is late stage, there appear to be a wide range of dose–responses. We shall consider the effect of DDT on mouse liver in males (Turusov *et al.*, 1973) and 2-AAF on mouse bladder. The two dose–responses are shown in Figures 4 and 5. Both of them differ markedly
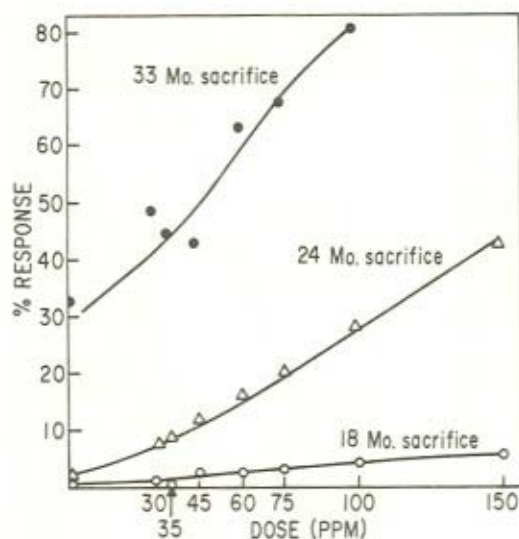
Figure 3 The prevalence of liver neoplasms in sacrificed mice in respect to dose of 2-AAF. Reproduced by permission of Pathotox Publishers Inc. from Littlefield *et al.*, 1980a
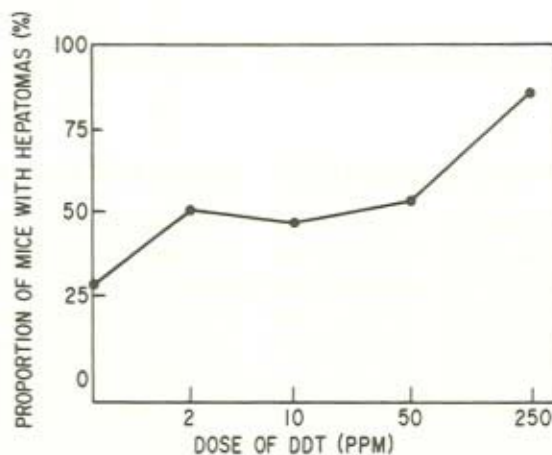

Figure 4 The prevalence of liver neoplasms among male CF-1 mice fed differing doses of DDT

from a linear to quadratic response, but in opposite directions. The 2-AAF dose–response is more convex and the DDT response more concave (at least up to 50 ppm) than one would expect from a linear to quadratic response. The DDT example suggests that the speculation that late-stage agents may have thresholds,
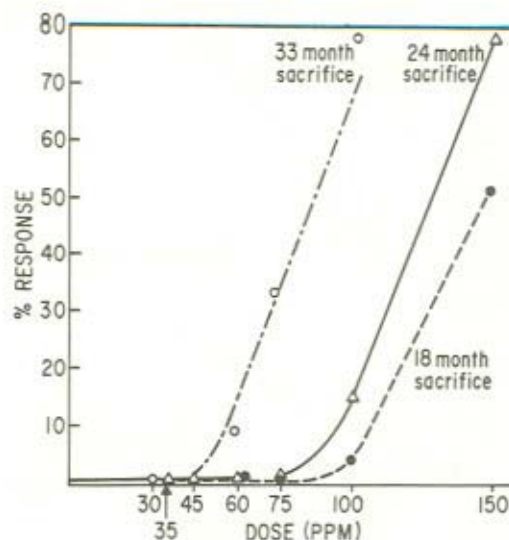
Figure 5   The prevalence of bladder neoplasms in sacrificed mice in respect to dose of 2-AAF. Reproduced by permission of Pathotox Publishers Inc. from Littlefield *et al.*, 1980a

even assuming that it has some validity, applies only to a certain class of late-stage agents.

5 MULTISTAGE MODELS: MODIFYING EFFECTS

Multistage considerations are also relevant when considering the joint action of two or more agents. The combined action of different agents would be expected to depend on whether the agents were primarily acting on the same, rather than different, stages. Before considering combined action, however, one should note that the dose–response for a single agent may be considerably modified if acting in the presence of a second factor. *In vitro* transformation of mouse C3H 10T1/2 cells by ionizing radiation provides an informative example (Little and Kennedy, 1982). One could suggest that if ionizing radiation acts alone, the dose–response approaches the quadratic form. In the presence of 12-*O*-tetradecanoylphorbol-13-acetate (TPA), the dose–response is linear (Figure 6). This difference is perhaps explicable in terms of a multistage process. Alone, radiation may have to effect two changes to cause transformation, and if the dose–response for each change were linear, the overall dose–response would be quadratic. If, however, TPA brings about one of the two changes, then the single change effected by radiation would imply a linear dose–response.
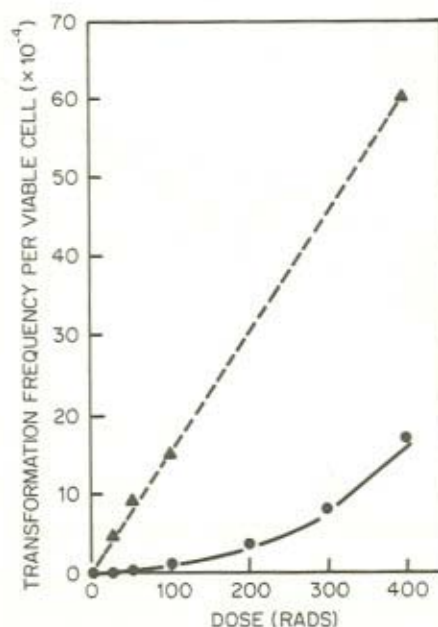
Figure 6 *In vitro* transformation of C3H 10T1/2 cells by varying doses of X-rays, with or without TPA treatment. Reproduced with permission from Little and Kennedy in Hecker et al., *Cocarcinogenesis and Biological Effects of Tumor Promoters.* Copyright 1982 Raven Press, New York

A somewhat analogous situation is seen with tobacco smoke-related risks. Most lung cancers appear related solely to cigerette smoking, and consideration of the epidemiological data would suggest that cigarette smoke has both early- and late-stage effects. Taking account of the biases introduced by imprecision of measurement, and restricting attention to those with a constant pattern of smoking, it would appear that for lung cancer the dose–response curve for cigarette smoking approaches the quadratic form. For cancers of the oesophagus, however, the situation is completely different. In western countries, risk is related both to tobacco and to alcohol. The risk associated with tobacco smoking appears closely related to the square root of daily cigarette consumption (Figure 7) (Breslow and Day, 1980). Interestingly, a similar relationship appears for cancer of the bladder (Howe *et al.*, 1980), where cigarette smoking is one component in what appears to be a multifactorial aetiology. The dose–response is sublinear, close to a square root relationship.
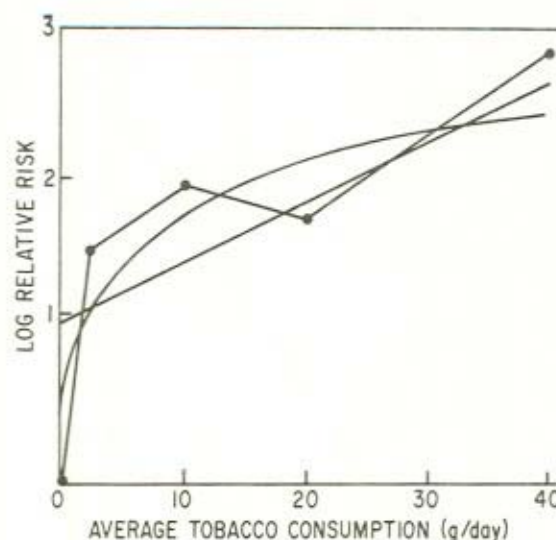
Figure 7   The relative risk for oesophageal cancer as a function of tobacco consumption. Reproduced by permission of the International Agency for Research on Cancer from Breslow and Day, 1980

For cancer of the oesophagus, the dose–response for the second agent, alcohol, is in marked contrast to the dose–response relationship for tobacco. The role of alcohol is not clear, and it has been proposed both as a late-stage carcinogen and as a transport vehicle for the tobacco-related carcinogens. The dose–response has been well-defined in case-control studies and is close to exponential (Breslow and Day, 1980), probably the steepest well-documented dose–response seen in humans (see Figure 8). It resembles the 2-AAF dose–response for bladder tumours in mice.

The difference in the dose–response relationship for oesophageal cancer between alcohol and tobacco illustrates the importance of the mode of action; the differences in the cigarette-related dose–response between lung and oesophageal cancer illustrate the importance of single or joint action.

6 MULTISTAGE MODELS: JOINT ACTION

The utility of multistage considerations in providing a framework for describing joint action has recently been discussed by Siemiatycki and Thomas (1981). If the mode of action of two agents is thought to act on different stages in the carcinogenic process, then a multiplicative combination of risk might be proposed. Multiplicative combined action is observed with alcohol and tobacco
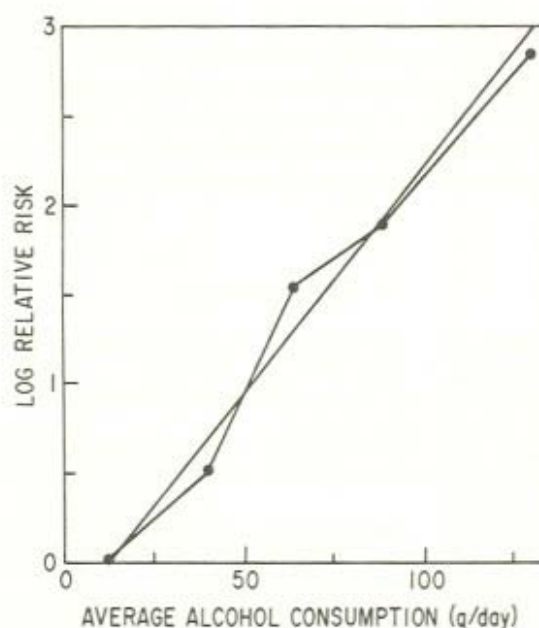
Figure 8 The relative risk for oesophageal cancer as a function of alcohol consumption. Reproduced by permission of the International Agency for Research on Cancer from Breslow and Day, 1980

for cancers of the oesophagus (Tuyns *et al.*, 1977) and of the mouth (Wynder *et al.*, 1957; Rothman and Keller, 1972), cancers for which the mode of action of the two agents would seem to be quite different. Asbestos and cigarette smoking combine multiplicatively to increase lung cancer risk (Saracci, 1977).

If two agents both act at several stages, i.e., both early and late stages, then a combined effect between additive and multiplicative might be expected. The joint effect of radon daughters and cigarette smoking on lung cancer risk appears to fit into this category (Archer *et al.*, 1973). That radiation may have late-stage effects apart from the evident early-stage effects has been pointed out recently on several occasions (Fry *et al.*, 1982).

If two agents act in a similar way, then their effect might be expected to be additive. The joint action of obesity and exogenous oestrogens in increasing risk for endometrial cancer could be cited as an example (Smith *et al.*, 1975).

7 PROTECTIVE AGENTS

Risk estimation as commonly understood and as discussed in this paper does not consider an area of research which has at present great interest, namely,

protective agents. The role of fibre in large bowel cancer, vitamin A and its precursors in lung cancer, riboflavin and perhaps vitamin A in oesophageal and oral cancer, hold promise of providing more effective means of prevention than identification and control of positive risk factors. The form of the dose–response, or dose–protection, curves for such agents can only be speculated on, but may well demonstrate strong non-linearity and the appearance of threshold effects.

8 REFERENCES

Archer, V. E., Wagoner, J. K., and Lundin, F. E. (1973). Uranium mining and cigarette smoking effects on man. *J. occup. Med.*, **15**, 204–211.

Armitage, P., and Doll, R. (1954). The age distribution of cancer and a multistage theory of carcinogenesis. *Br. J. Cancer*, **8**, 1–12.

Berry, G., and Wagner, J. C. (1969). The application of a mathematical model describing the times of occurrence of mesotheliomas in rats following innoculation with asbestos. *Br. J. Cancer*, **23**, 582–586.

Breslow, N. E., and Day, N. E. (1980). *Statistical Methods in Cancer Research, Vol. 1. The Analysis of Case-Control Studies*, IARC Scientific Publications No. 32. International Agency for Research on Cancer, Lyon: 338 pages.

Day, N. E., and Brown, C. C. (1980). Multistage models and primary prevention of cancer. *J. natn. Cancer Inst.*, **64**, 977–989.

Doll, R. (1971). The age distribution of cancer. *J R. statis. Soc. A*, **134**, 133–155.

Doll, R., Morgan, L. G., and Speizer, F. E. (1970). Cancers of the lung and nasal sinuses in nickel workers. *Br. J. Cancer*, **24**, 623–632.

Doll, R., and Peto, R. (1976). Mortality in relation to smoking: 20 years observation on male British doctors. *Br. med. J.*, **2**, 1525–1536.

Doll, R., and Peto, R. (1978). Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and life-long non-smokers. *J. Epidem. Community Hlth*, **32**, 303–313.

Fry, R. J. M., Lay, R. D., Grube, D., and Staffeldt, D. (1982). Studies on the multistage nature of radiation carcinogenesis. In Hecker, E., Fusenig, N. E., King, F., Marks, F., and Thielmann, H. W. (Eds.) *Cocarcinogenesis and Biological Effects of Tumor Promoters*, pp. 155–165. Raven Press, New York.

Howe, G. R., Burch, J. D., Miller, A. B., Cook, G. M., Esteve, J., Morrison, B., Gordon, P., Chambers, L. W., Fodor, G., and Winsor, G. M. (1980). Tobacco use, occupation, coffee, various nutrients and bladder cancer. *J. natn. Cancer Inst.*, **64**, 701–713.

Jick, H., Watkins, R. N., Hunter, J. R., Dinan, B. J., Madsen, S., Rothman, K. J., and Walker, A. M. (1979). Replacement estrogens and endometrial cancer. *New Engl. J. Med.*, **300**, 218–222.

Lee, P. N., and O'Neill, J. A. (1971). The effect of both time and dose applied on tumor incidence rates in benzpyrene skin painting experiments. *Br. J. Cancer*, **25**, 759–771.

Little, J. B., and Kennedy, A. R. (1982). Promotion of X-ray transformation in vitro. In Hecker, E., Fusening, N. E., King, F., Marks, F., and Thielmann, H. W. (Eds.) *Cocarcinogenesis and Biological Effects of Tumor Promoters*, pp. 243–257. Raven Press, New York.

Littlefield, N. A., Farmer, J. H., and Gaylor D. W. (1980a). Effects of dose and time in a long-term, low-dose carcinogenic study. *J. envir. Path. Tox.*, **3**, 17–34.

Littlefield, N. A., Greenman, D. L., Farmer, J. H., and Sheldon, W. G. (1980b). Effects of

continuous and discontinuous exposure to 2-AAF on urinary bladder hyperplasia and neoplasia. *J. envir. Path. Tox.*, **3**, 35–55.

Moolgavkar, S. H., Day, N. E., and Stevens, R. G. (1980). Two stage model for carcinogenesis: the epidemiology of breast cancer in females. *J. natn. Cancer Inst.*, **65**, 559–569.

Newhouse, M. L., and Berry, G. (1976). Predictions of mortality from mesothelial tumours in asbestos factory workers. *Br. J. ind. Med.*, **33**, 147–151.

Peto, J., Seidman, H., and Selikoff, I. J. (1982). Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. *Br. J. Cancer*, **45**, 124–136.

Peto, R., Roe, F. J. C., Lee, P. N., Levy, L., and Clark, J. (1975). Cancer and ageing in mice and men. *Br. J. Cancer*, **32**, 411–426.

Rothman, K. J., and Keller, R. F. (1972). The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J. chron. Dis.*, **25**, 711–716.

Saracci, R. (1977). Asbestos and lung cancer: an analysis of the epidemiological evidence on the asbestos – smoking interaction. *Int. J. Cancer*, **20**, 323–331.

Seidman, H., Lilis, R., and Selikoff, I. J. (1977). Short term asbestos exposure and delayed cancer risk. In Nieburgs, H. E. (Ed.) *Preventon and Detection of Cancer. Part I, Prevention*, pp. 943–960. Marcel Dekker, New York.

Siemiatycki, J., and Thomas, C. D. (1981). Biological models and statistical interactions: an example from multistage carcinogenesis. *Int. J. Epidem.*, **10**, 383–377.

Smith, D. C., Prentice, R., Thompson, D. J., and Hermann, W. L. (1975). Association of exogenous oestrogen and endometrial carcinoma. *New Engl. J. Med.*, **293**, 1164–1167.

Turusov, V., Day, N. E., Tomatis, L., Gati, E., and Charles, R. T. (1973). Tumors in CF-1 mice exposed for six consecutive generations to DDT. *J. natn. Cancer Inst.*, **51**, 983–997.

Tuyns, A. J., Pequignot, G., and Jensen, O. M. (1977). Le cancer de l'oesophage en Ille-et-Vilaine en fonction des niveaux de consommation d'alcool et de tabac. [Cancer of the oesophagus in Ille-et-Vilaire as a function of the level of alcohol and tobacco consumption]. *Bull. Cancer*, **64**, 45–60 (in French).

Wynder, E. L., Bross, I. J., and Feldman, R. M. (1957). A study of etiological factors in cancer of the mouth. *Cancer*, **10**, 1300–1323.