Methods for Estimating Risk of Chemical Injury: Human and Non-human Biota and Ecosystems
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The Use of Epidemiological Data to Assess Human Cancer Risk

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ABSTRACT

Epidemiological studies contribute to assessment of the human cancer risk associated with exposure to chemicals through both the generation and testing of hypotheses. For chemicals now established as carcinogenic to humans, most of the evidence has come from cohort studies (particularly following occupational exposure) although case-control studies have made a contribution. Whether or not epidemiological studies will be able to detect a cancer hazard depends on the carcinogenic potency of the chemical concerned, the level of human exposure to it, the proportion of the population exposed, the duration of human exposure to the chemical and the incidence of the cancer in the absence of exposure to the chemical.

Once a hazard is detected it is desirable to model cancer risk as a function of dose of chemical, characteristics of dose delivery (including dose rate), time since first exposure and possible interacting factors. This has been rarely possible in the past because of limitations on the quality of the epidemiological data available. Quality will be improved, particularly in occupational cohort studies, when the necessary data are adequately recorded. As a minimum, industrial records should contain complete identification of each worker, details of all processes to which he has been exposed, quantitative measurements of the exposure associated with each process, and exposure to interacting or confounding variables.

1 INTRODUCTION

Epidemiological studies in humans contribute to assessment of the risk of cancer associated with exposure to chemicals in two main ways:

(1) Generation of hypotheses that particular chemicals cause cancer; this may involve *ad hoc* study or continuing epidemiological surveillance.
(2) Testing of hypotheses about carcinogenesis.

Valid quantitative assessments of human cancer risk will usually come from hypothesis testing studies.

Assessment of risk can be seen as both qualitative (Does this chemical cause cancer in humans?) and quantitative (How much cancer is caused by how much of this chemical after how long since first exposure?). Quantitative assessment will be difficult or impossible unless the data are sufficient, first of all, to support a qualitative conclusion. Thus, factors influencing both qualitative and quantitative assessments will be reviewed.

2 QUALITATIVE ASPECTS

2.1 Epidemiological Methods

Three broad types of epidemiological studies contribute data to the assessment of human cancer risk—cohort studies, case-control studies and ecological studies. In addition, purely qualitative information from case reports of cancer in humans exposed to particular chemicals is often grouped with that from epidemiological studies (notably in IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans—referred to hereafter as IARC Monographs).

Cohort and case-control studies are analytical in type, relate individual exposure to chemicals to individual risk of cancer, and give rise to an estimate of relative risk as the main measure of effect. Cohort studies can determine, in addition, the absolute risk of cancer in those exposed and not exposed to the presumed carcinogen.

In ecological studies the units of investigation are populations rather than people and exposure of the population to the agent under study is related to its aggregate experience of cancer. Examples include correlation studies (see, for example, Hoover and Fraumeni, 1975) and time-trend analysis (see, for example, Armstrong and Doll, 1974).

Case reports arise generally from the suspicion, based on clinical experience, that the concurrence of two rare events, that is, exposure to a particular agent and occurrence of a cancer, has happened rather more frequently than would be expected by chance. They are not epidemiological studies because they lack, usually, complete ascertainment of cases in any population, definition or enumeration of the population at risk and numerical estimation of the expected number of cases in the absence of exposure.

All of the above methods may be used to generate hypotheses about the causes of human cancer. Cohort and case-control studies are used most often in hypothesis testing. The uncertainties surrounding interpretation of case reports and ecological studies make it doubtful whether either one alone would be sufficient, except in rare instances, to establish a causal relationship. The rare instances might include, for case reports, the 'kangri cancer' of the skin of the

lower abdomen and thighs caused by charcoal heating pots in Kashmir (Emslie, 1866) and, for ecological studies, the geographical association of intake of aflatoxin in food with primary liver cancer (Linsell and Peers, 1977), if it could be shown that a sustained reduction in aflatoxin intake gave rise to a sustained reduction in incidence of primary liver cancer.

When taken together with analytical studies, relevant case reports or ecological studies may add materially to qualitative assessment of cancer risk. Thus, for example, evidence from case-control studies relating soft-tissue sarcomas to exposure to phenoxyacetic acids and chlorophenols in Sweden (Hardell and Sandstrom, 1979; Eriksson *et al.*, 1981) has been strengthened by reports of cases of soft-tissue sarcoma in men who worked with trichlorophenol and 2,4,5-T in the United States (Cook, 1981; Johnson *et al.*, 1981; Moses and Selikoff, 1981). The evidence, from case-control studies, that conjugated oestrogens increase risk of endometrial cancer, has been strengthened by studies showing that incidence of endometrial cancer increased in the United States over a period in which use of conjugated oestrogens was increasing (Weiss *et al.*, 1976) and has decreased in a US population in which use of conjugated oestrogens has fallen (Jick *et al.*, 1979).

2.2 The Use of Epidemiological Data in IARC Evaluations

The IARC Monographs provide a practical illustration of the use of epidemiological data in qualitative assessments of cancer risk due to exposure to chemicals. Supplement 1 to the Monographs (IARC, 1979) reviewed all available evidence relating to carcinogenicity of 54 chemicals or industrial processes which had been reviewed in volumes 1–20 of the series and for which there were some human data. This review has been brought up to date (IARC, 1982) for the 153 chemicals or industrial processes with human data (including the original 54) covered in volumes 1–29, but, as it has become available only recently, this analysis is based on the original 54.

The evidence for carcinogenicity of each chemical in humans was classified by an expert working group as follows:

(1) *Sufficient evidence*—indicates a causal association between exposure to the agent and human cancer;
(2) *Limited evidence*—indicates a possible carcinogenic effect in humans, although the data are not sufficient to demonstrate a causal association;
(3) *Inadequate evidence*—indicates that the data are qualitatively or quantitatively insufficient to allow any conclusion regarding carcinogenicity for humans.

Table 1 summarizes the evaluation of human evidence for carcinogenicity of the 54 chemicals and processes in Supplement 1 and the epidemiological evidence which contributed to each. Data from cohort studies were available for 47 of the

Table 1 Numbers of chemicals or industrial processes by types of epidemiological data contributing to assessment of their carcinogenic risk in humans among 54 chemicals or industrial processes reviewed in Supplement 1 to the IARC Monographs (IARC, 1979)

Types of data	Classification of evidence for carcinogenicity in humans			
	Sufficient	Limited	Inadequate	Total
Cohort studies	18	13	16	47
Case-control studies	3	4	4	11
Ecological studies	3	1	0	4
Case reports	11	10	8	29
All types	18	14	22	54

54 agents and for all 18 of those for which there was 'sufficient evidence' of carcinogenicity. Cohort studies were the major source of evidence; this is partly due to selection of the agents for the monographs but also illustrates the predominance of the retrospective or non-concurrent cohort study in studies of occupational carcinogenesis (Armstrong, 1981)—37 of the 54 agents involved mainly industrial exposure. Cohort studies lend themselves to situations in which a small, readily identifiable group of workers has been exposed heavily to the chemical in question and it is desired to study the development of all forms of cancer rather than a specific cancer type.

Table 1 also shows that the evidence for carcinogenicity was classified as limited in 12 instances and inadequate in 16 instances in the presence of data from cohort studies. The reasons for these limitations on the evidence are summarized in Table 2. The main reason was difficulty in, or impossibility of, distinguishing exposure to the index chemical from exposure to other chemicals in the workplace (sometimes known and sometimes unknown or not described). This was responsible for 16 of the 28 'limited' or 'inadequate' classifications. Possible

Table 2 Main reasons for designation of evidence of carcinogenicity as 'limited' or 'inadequate', in the presence of data from cohort studies, in 29 chemicals reviewed in Supplement 1 to the IARC Monographs (IARC, 1979)

Main reason for limitation on evidence	Classification of evidence	
	Limited	Inadequate
Exposure to index chemical could not be separated from exposure to other chemicals	9	7
Other possible confounding factors	2	1
Cohort too small or follow-up time too short	2	6
Other reasons (difficulty in interpretation of results, multiple weakness, etc.)	0	2

or undocumented exposure to other confounding factors (particularly cigarette smoking in studies of lung cancer) was a less frequent limitation. The small size of the cohort or a short follow-up time (important both with respect to accumulation of person years and passage of some minimum induction period before tumours are likely to appear) were more important in 'inadequate' than 'limited' classifications.

Case-control studies made surprisingly little contribution to assessment of the carcinogenicity of these 54 agents (Table 1). They contributed to sufficient evidence of carcinogenicity of three compounds—diethylstilboestrol (DES), asbestos and benzene. They were the main source of data for DES. They contributed, with cohort studies, to four 'limited' classifications (cadmium and cadmium compounds, phenacetin, phenobarbitone and phenytoin) and to four 'inadequate' classifications. The most notable of the latter was the classification of the evidence for carcinogenicity of reserpine; there were 13 relevant case-control studies with relative risks varying from 0.6 to 3.5 (IARC, 1980). The inadequate classification was a compromise drawn between those who favoured a 'negative evidence' classification (possible but not used) and those who favoured 'limited evidence' (in consideration of some statistically significant positive results not clearly explained by bias or confounding).

The lack of impact of case-control studies on these evaluations is due partly to historical reasons which include the novelty of using case-control studies and the small number of chemicals to which substantial numbers of individuals are exposed. More use of case-control studies, however, is now being made in industrial situations to refine the details of the relevant exposure, once the presence of an increased risk of cancer has been established in a cohort of workers (see, for example, Checkoway *et al.*, 1981).

Ecological studies contributed evidence along with cohort and, sometimes, case-control studies to three classifications of 'sufficient evidence' (arsenic, asbestos and vinyl chloride). In two, the ecological associations contributed materially to the evidence (the associations between arsenic in water supplies, arsenicism and skin cancer (IARC, 1973); and between increasing use of melphalan for treatment of multiple myeloma and incidence of acute leukaemia (Adamson and Sieber, 1977)). Ecological data, essentially alone, gave rise to the 'limited' classification of the evidence relating aflatoxin intake to human primary liver cancer which is based entirely on geographical correlation (Linsell and Peers, 1977). Although the data are all consistent with this association, the evidence was considered 'limited' because confounding, particularly with hepatitis B virus infection, could not be ruled out.

Case reports alone permitted a classification of 'limited evidence' in one instance—the association between oxymetholone and primary liver cancer. There were reports of ten cases of liver cell tumour in patients who had received long-term therapy with oxymetholone. This is the classical association of a rare condition with a rare exposure which excites suspicion.

2.3 The Power of Epidemiological Methods

Whether or not epidemiological methods will be able to provide data for assessment of human cancer risk following exposure to a particular chemical will depend on the following innate characteristics of the study situation.

(1) The carcinogenic potency of the chemical concerned—in simple terms, the change in cancer incidence induced by unit change in dose of the chemical. The higher the potency, the higher will be the relative risk associated with a particular level of exposure and the greater will be the probability that epidemiological methods will be able to detect it.
(2) The level of human exposure to the chemical (i.e. the range of possible doses).
(3) The proportion of the human population exposed to the chemical. In this context, there are two issues: (a) The absolute number of people exposed—if the number is too small (how small is too small will depend on carcinogenic potency, exposure level, etc.) it may not be possible to accumulate sufficient experience of the exposure to distinguish an increased rate of cancer in those exposed from that prevailing in the unexposed; (b) The ubiquity of the exposure—epidemiological studies depend on heterogeneity of exposure; if exposure is ubiquitous they will have difficulty in detecting any consequent increase in risk of cancer.
(4) The duration of human exposure to the chemical. There is an obligatory induction period from first exposure to the carcinogen to the time at which cancers may appear clinically. This period, particularly for initiating carcinogens (perhaps much less so for promoters) is usually measured in tens of years. It will be impossible to detect an increased risk of cancer in less than the minimum induction period, and the likelihood that it will be detected increases as the period since first exposure increases, provided that exposure continues.
(5) The incidence of the cancer in the absence of exposure to the chemical. If the underlying incidence of the cancer is high, the increment due to a particular dose of carcinogen will produce a smaller increase in relative risk than if the cancer is rare. Thus, the more common the cancer, the harder will it be for epidemiological methods to detect an effect of the carcinogen.

Assuming that human exposure to a carcinogen has persisted for a generation or more, two extremes may be defined with respect to ability of epidemiological studies to detect an increased risk of cancer.

Extreme 1

(a) The chemical is a strong carcinogen;
(b) The cancer is rare in the absence of exposure to the chemical;
(c) A substantial, readily identifiable group of individuals has been exposed to the chemical at high levels;

(d) The population in general is relatively unexposed to the chemical.

This extreme is exemplified by occupational cancers such as mesothelioma associated with asbestos, angiosarcoma of the liver associated with vinyl chloride and bladder cancer associated with 2-napthylamine. These associations are comparatively easy to detect by epidemiological methods and figure prominently among those for which there is 'sufficient evidence' of carcinogenicity in humans (IARC, 1979).

Extreme 2

(a) The chemical is a weak carcinogen;
(b) The cancer is common in the absence of exposure to the chemical;
(c) The majority of the population is exposed to the chemical in small amounts and to about the same degree.

This extreme is exemplified by the postulated relationship between dietary meat and colon cancer (Armstrong *et al.*, 1982). In it the problem of ubiquity of exposure has been overcome, to some extent, by the identification of populations which do show substantial heterogeneity in individual meat intake (Hawaiian Japanese, Haenszel *et al.*, 1973; Seventh-day Adventists, Phillips, 1975) or by following a cohort with low rather than high exposure to meat (Seventh-day Adventist vegetarians, Phillips, 1975). In this situation associations may be more evident in ecological studies than cohort or case-control studies because there may be more heterogeneity in exposure between populations than within populations (as is probably the case for aflatoxin contamination of food).

Between these two extremes identification of carcinogenicity will be more or less difficult, depending on the exact situation, and case-control or cohort studies will be more or less efficient. Case-control studies are most efficient when about equal proportions of the population are exposed and not exposed to the chemical. The relative absence of case-control studies from Table 1, although partly due to selection, may indicate that frequent exposure to measurable levels of chemical carcinogens is unusual.

2.4 The Quality of Epidemiological Studies

Several factors, more or less under the investigator's control, will influence the likelihood that a study will contribute useful evidence bearing on the carcinogenicity of a chemical. They include:

(1) Study size. Size refers to numbers of cases and controls or size of exposed and unexposed cohorts and duration of follow-up—the bigger the study the more likely it is to detect an increased risk of cancer.
(2) Existence of appreciable numbers of subjects in the study who have been

exposed for more than the minimum induction period (see section 2.3 above).

(3) Valid and quantitative documentation of exposure to the chemical. Random misclassification of subjects with respect to exposure will bias the relative risk towards unity.
(4) Identification, quantitation and control of all relevant confounding factors, including other chemicals in the work situation (when an industrial chemical is under study), and life-style factors which may be relevant to the cancer in question.
(5) Minimization where possible and, otherwise, documentation and control of factors which may bias the estimate of relative risk (e.g. the 'healthy worker' bias in occupationally defined cohort studies, McMichael, 1976).

Some of these issues have been summarized in the OSHA recommendation that an adequate study demonstrating the absence of a substantial cancer hazard should involve 20 years of exposure (duration of exposure is often taken as a surrogate for total dose because data on the dose rate are not usually available), 30 years of observation following first exposure (the induction period) and a population of sufficient size to show at least a 50 % increase in cancer occurrence, were it present, with 95 % certainty (Nelson, 1981).

3 QUANTITATIVE ASPECTS

3.1 Statistical Modelling of Cancer Risk

The ultimate objective of quantitative assessment of human cancer risk in relation to exposure to a particular chemical is the statistical modelling of absolute risk of cancer as a function of:

(1) dose of chemical;
(2) characteristics of dose delivery (for example, dose rate, whether continuous or intermittent);
(3) time since first exposure;
(4) possible interacting factors such as sex, age, ethnic origin, exposure to other chemicals.

Adequate modelling will not be possible unless:

(1) the study situation, design and conduct are such as to permit qualitative assessment of carcinogenicity (see sections 2.3 and 2.4 above);
(2) the study design and analysis are such as to account fully and quantitatively for any likely biasing or confounding factors;
(3) data on dose of carcinogen, date of first exposure, duration of exposure and characteristics of dose delivery are of high quality;
(4) data of similar quality are available on possible interacting factors.

Peto *et al.* (1982) provide an illustration of quantitative assessment of risk, from epidemiological data, in their modelling of mesothelioma mortality in four cohorts of workers exposed to asbestos. They showed that mortality from mesothelioma is approximately related to time since first occupational exposure to asbestos in the following way:

$$m = bt^k$$

where m = mortality from the mesothelioma, t = time since first exposure, and $k = 3.2$ (derived empirically). The constant b (also derived empirically) varied somewhat between the four studies (2.94–5.15) and is presumably a function of the nature of the fibre to which the men were exposed, the total dose of fibre, etc. It appeared that risk of mesothelioma at any time since first exposure to asbestos was independent of age at first exposure.

Whether or not absolute or only relative risk of cancer can be modelled will depend on whether the data are provided by cohort or case-control studies. Only relative risk is available directly from case-control studies although, if the incidence of the cancer is known in the population giving rise to the cases and controls, and the cases and controls are representative, respectively, in relevant respects, of all cases and non-cases in the population, the absolute risk of cancer in exposed individuals may be computed from the relative risk.

Recently, attention has been drawn to the possibility of estimating relative risk from ecological studies (Beral *et al.*, 1979). The method involves the assumption that risk is related linearly to exposure over the different population units (defined temporally, geographically, etc.), although other mathematical models might be assumed equally well, and, more important, that all the variation in disease frequency is explained causally by variation in the measured exposure. Neither assumption is necessarily valid; the former can be tested in the data but the latter cannot be substantiated from ecological data alone. The method may be useful, however, in demonstrating coherence between analytical and epidemiological data. Thus, for example, Beral *et al.* (1979) showed that relative risk of death from ovarian cancer in women with one or two pregnancies, compared with women with three or four pregnancies, was 1.8 when estimated from trends in ovarian cancer mortality in succeeding birth cohorts of women in England and Wales, 2.4 when estimated from correlation, internationally, of ovarian cancer mortality with average family sizes, and 1.6–2.3 in a case-control study. This coherence adds materially to the inference that cancer of the ovary is causally related, inversely, to child bearing.

Linsell and Peers (1977) took a similar approach, without computation of relative risk, in summarizing data relating average aflatoxin intake to incidence of primary liver cancer. While there are no data from analytical studies with which these results can be compared, they imply a much lower susceptibility to aflatoxin carcinogenesis in women than men. This is consistent with the

uniformly lower rates or primary liver cancer in women than men (Waterhouse *et al.*, 1976) and the lower susceptibility of female than male rodents to experimental hepatocarcinogenesis.

3.2 Measurement of the Induction Period

The length of the induction period of cancer (defined, empirically, as the time from first exposure to carcinogen to clinical diagnosis of cancer, Rothman, 1981) has received little explicit consideration in analytical studies in cancer epidemiology although it may be incorporated readily in a complete risk model. Rothman (1981) has drawn attention recently to the possible consequences of inappropriate assumptions, in study design or analysis, about the length of the induction period. In particular, if exposures which lie outside the time span of the range of the induction period are included in the analysis, measures of relative risk will be attenuated. Rothman (1981) has suggested that a range of induction periods should be examined to determine the one which maximizes the estimate of effect. Procedures of this type were used by Goldsmith *et al.* (1980) in the analysis of a case-control study of cancer of the prostate in a cohort of rubber workers (the analysis suggested a modal induction period of 29 years with a range of 15–38 years) and Labarthe and O'Fallon (1980) in a study of reserpine and breast cancer (apparent induction period of 3 years or less).

Smith *et al.* (1980) have proposed a further sophistication in their serially additive expected dose model of analysis of either case-control or cohort study data. This method contrasts mean cumulative doses of carcinogen between cases and non-cases while stratifying by age, year and interval between first exposure and the event. The method permits estimation of the induction period and description of the shape of the dose–effect curve but does not lead to the usual estimates of effect such as the ratio or difference of incidence rates between compared levels of exposure.

For initiating carcinogens the most important measurement is probably the minimum induction period. The mode and apparent maximum induction period will, in many instances, be artefacts of limitation in the upper bound of post-exposure observation periods or of mortality from other causes. The model of mesothelioma mortality following asbestos exposure given by Peto *et al.* (1982) implies, for the study of Selikoff *et al.* (1979), a minimum induction period of about 15 years with an exponential increase in mesothelioma mortality, in the absence of other causes of death, with increasing induction period thereafter.

For cancer promoters the period from last exposure to the agent may be as, or more, relevant in risk modelling than the period from first exposure. Thus, for example, the relative risk of endometrial cancer associated with use of conjugated oestrogens begins to fall quite rapidly after cessation of use (see, for example, Weiss *et al.*, 1979).

3.3 Improvement of Data Quality

Quantitative assessment of risk has generally been limited by the quality of the data available. In non-concurrent cohort studies of men exposed to carcinogens in the workplace, date of first and last exposure are usually known but level of exposure (dose per unit time) and its variation over time have rarely been known, except qualitatively. Likewise, quantitative control of confounding or interacting factors has rarely been possible. In case-control studies which rely on subjective recall, data on confounding or interacting factors may be obtained but details of dates, duration of exposure, dose and variation in dose rate may be of doubtful validity. Where exposure information for case-control studies has been obtained from records, the problems of detail seen in non-concurrent cohort studies have usually applied.

Assuming that much of the future action will be in studies of occupational exposure to chemicals, recommendations or regulations regarding documentation of the exposure of individual workers could be made. They would require:

(1) complete identification of each worker—including full name, maiden family name where relevant, date and place of birth, current address and next of kin (preferably a person of the same age or younger);
(2) details of all processes to which the worker has been exposed, including date of first and last exposure to the process, an indication of intensity of exposure and its variation over time; intensity might include proximity of the usual workplace to source of any chemical effluent and the number of working hours per day at that site;
(3) for each process actual measurements of average concentrations over a working day of all relevant chemicals in the working environment and their variation with distance from the source of chemical effluent and with calendar time;
(4) details for each worker of exposure to other confounding or interacting agents including, in particular, past and present smoking habits and their variation during employment, previous employment in industries involving chemical exposures, etc.

Such records would greatly facilitate future quantitative assessment of cancer risk from epidemiological studies of chemical exposure.

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