

Quantitative assessment of human cancer risk

by John M Kaldor, PhD^{1,2}

KALDOR JM. Quantitative assessment of human cancer risk. *Scand J Work Environ Health* 1992;18 Suppl 1:90-6. Because exposure to carcinogens cannot be eliminated, it has become important to define exposure levels which are acceptable to society or are irreducible. Quantitative assessment of cancer risk is part of this process. This paper presents a definition of risk and discusses the role of epidemiologic observation in the quantitative assessment of cancer risk, the estimation of risk from epidemiologic data, and the role of animal cancer bioassays in the quantitative assessment of cancer risk. It is emphasized that quantitative risk assessment is inevitably based on multiple assumptions. Where possible, the magnitude of errors associated with these assumptions should be stated, even to the extent of an acknowledgment of complete ignorance.

Key terms: animal cancer bioassays, dose-response models, epidemiologic data, exposure, multistage models.

When carcinogenic chemical substances were first identified, it was thought that humans might avoid cancer by totally eliminating exposure to these agents. However, as the number of substances determined to be carcinogenic has increased, this goal has come to be seen as unrealistic. The attention of scientists and regulatory bodies has therefore turned towards evaluating the magnitude of carcinogenic hazard associated with specific agents with the ultimate hope of somehow defining levels of exposure which are in some sense acceptable to society, or irreducible. The two sides of this process are the measurement or quantitative estimation of hazard, and the assessment of benefit derived from the agents or process involved.

In this review, I describe the principles underlying quantitative cancer risk assessment, with particular reference to the assumptions involved.

Definition of risk

Not all people exposed to a specific carcinogenic agent develop cancer during their lifetime, even if the agent is a very potent carcinogen. Conversely, no form of cancer has been identified which only occurs in response to a single agent or group of agents. Thus the notion of cancer risk following exposure to a designated agent must take into account both the probabilistic nature of cancer occurrence and the existence of a background level of risk which is present even in the

absence of exposure to the agent. Risk is defined accordingly as the probability that cancer will occur in an exposed person during a specified period, and it is compared with the corresponding probability for an unexposed person.

If P_E is the risk following exposure, and P_O the risk in the absence of exposure, the relative risk associated with exposure can be defined as P_E/P_O , and the excess risk as $P_E - P_O$. Another measure is the attributable risk, that is, the proportion of cases in a population which would not have occurred had the exposure been absent.

The definitions of relative and excess risk following exposure to a designated agent apply to an individual (or to a single tissue if risk related to a specific tumor type is being considered) at a particular time. However, the risk may well vary from one person to the next, depending on characteristics such as gender, age at exposure, exposures other than the agent in question, and biological factors which could affect individual susceptibility to carcinogenesis. In its ideal form, quantitative risk assessment would involve estimating risk separately for each person, in a way which would take account of all these individual characteristics. Furthermore, the estimation process would need to allow for different patterns of exposure and the evolution of risk with time since exposure. As an illustration, figure 1 shows a hypothetical exposure pattern for someone who came into contact with an occupational carcinogen at the age of 20 years, had varying levels of exposure during the working lifetime, and eventually left exposure at the age of 65 years. The incidence of cancer, which is equivalent to the probability of cancer occurrence within short time intervals, is shown to increase sharply with age, as is the case for many epithelial tumors, for both exposed persons and unexposed persons. The increment for the exposed and unexposed persons could differ according to the exposure pattern over time and characteristics of the individual such as those that have already been noted.

¹ International Agency for Research on Cancer, Lyon, France.

² Current address: National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia.

Reprint requests to: Dr JM Kaldor, National Centre in HIV Epidemiology and Clinical Research, St Vincent's Medical Centre, 376 Victoria Street, Sydney, NSW 2010, Australia.

The reality of quantitative risk assessment differs from this idealized scenario. Even the most sophisticated attempts at risk estimation have generally produced a single number to summarize the carcinogenic effect of the agent under investigation, and they have effectively ignored the possibility of individual variation and temporal evolution in the risk of cancer. Indices which have been used are the increase in the number of cancer cases or deaths in an exposed population of a given size, the increment in risk per unit of cumulative exposure, and the cumulative dose required to cause a specified increase in cancer risk. The use of a single number is an admission that the available empirical information on human cancer risk is insufficient to permit idealized risk assessment which would account for all combinations of individual characteristics and a range of exposure patterns. If it were known, for example, that risk did not depend on age, gender, or other individual characteristics, that it increased linearly with dose level, and that only cumulative dose was relevant, then a single number to quantify risk would be perfectly valid. In practice, however, simplifications of this kind cannot be supported by observational data. Instead, they are invoked as assumptions, either explicitly or implicitly, which have not been tested.

Role of epidemiologic observation in quantitative cancer risk assessment

If the goal is to quantify human cancer risk, the most appropriate source of information is observation of exposed humans and of appropriate unexposed comparison groups. However, most human cancer risk assessment must be carried out in the absence of epidemiologic data. For many agents there has simply not been enough accumulated exposure for potential carcinogenic effects to be manifested, so that an epidemiologic study would not even be expected to detect a carcinogenic effect, let alone adequately measure its magnitude. For other agents, a substantial number of people may have been exposed for a long time without being subject to formal study of cancer occurrence, sometimes because the necessary resources have not been made available, but also because exposure may have taken place in populations on which research on cancer risk could not be carried out. For example, transient workers may have been exposed during employment but can no longer be traced. Even when epidemiologic studies of cancer risk have been carried out, quantitative interpretation of the results is often limited by difficulties in quantifying exposure levels (especially in regard to exposure which occurred years in the past) the potentially confounding effects of other exposures such as cigarette smoking, and the limited number of subjects available for study. Thus, even if a well-executed epidemiologic study clearly demonstrates an increased rate of cancer for exposed

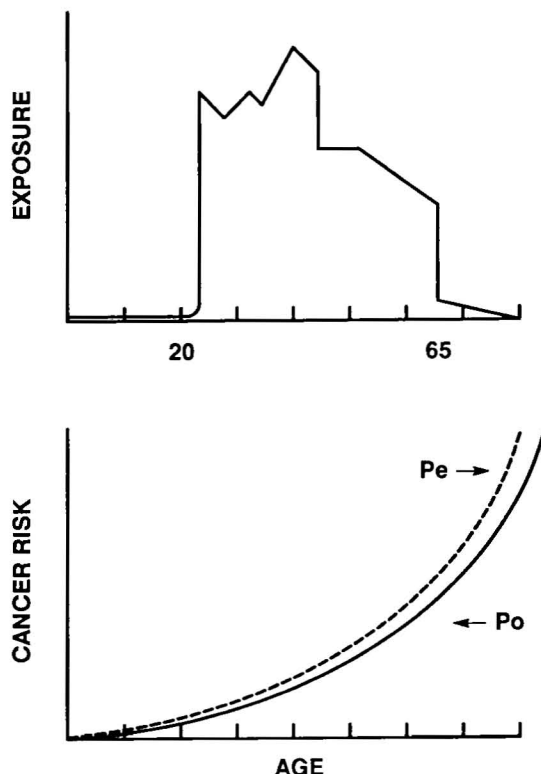


Figure 1. Upper figure: Theoretical exposure to an occupational agent over a lifetime. Lower figure: p_0 : incidence of cancer over a lifetime in the absence of exposure to the agent; p_e : incidence of cancer over a lifetime in a person exposed as above.

individuals, it is generally very difficult to make the next step into quantifying the amount of exposure associated with specific levels of risk.

A few human carcinogens have lent themselves more readily than others to epidemiologic risk assessment. Cigarette smoking, the most important identified carcinogenic exposure in developed countries, has been quantitatively investigated in several large studies, which have provided information on the risk increment for various types of cancer. The carcinogenic effect of ionizing radiation has also been subject to a great deal of epidemiologic scrutiny, largely with a view to setting limits for occupational and environmental exposure. Several carcinogenic pharmaceutical drugs have been quantitatively evaluated for carcinogenic potential from human observations, as have asbestos and some industrial chemicals, including benzene.

Even for these agents, epidemiologic data have only provided a limited basis for quantitative cancer risk assessment. The evaluation of the carcinogenic effect of cigarette smoking was made on the basis of past formulations of cigarettes, and extrapolation to estimate the risk associated with current, lower tar cigarettes is not straightforward. The carcinogenic effect of ionizing radiation has been largely estimated

from observations on survivors of the atomic bombings in Japan, and the relevance of this instantaneous, high-dose exposure to risk estimation for, say, nuclear power workers exposed to very low doses for long periods is unknown.

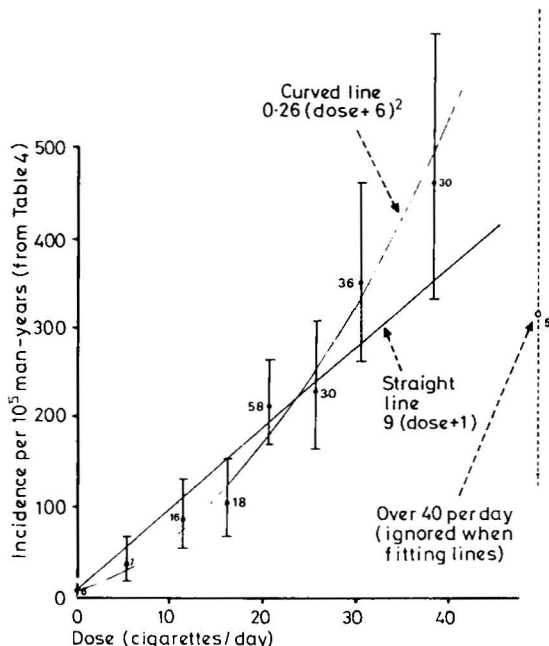


Figure 2. Observed incidence of lung cancer among male British doctors (with 90% confidence limits) by smoking dose, and fitted linear (straight line) and quadratic (curved line) dose-response models [reprinted with permission from Doll & Peto (13)].

Estimation of risk from epidemiologic data

The process of risk estimation involves defining a mathematical model or formulation of the relationship between exposure to the agent under study and the probability of cancer occurrence.

The model is of the form $P_E = f(E, X, B)$, expressing the dependence of cancer risk P_E on exposure level E ; other measured variables, such as age and gender, which influence cancer occurrence; and unknown parameters B , which relate E and X to P_E . Quantitative risk estimation requires specification of the parameters B , so that for any given values of E and X , the corresponding cancer risk P_E can be predicted via f . A very simple model might be

$$P_E = B_0 + B_1 E, \quad (\text{equation 1})$$

where E is defined as cumulative exposure to the agent under study, expressing a linear dependence of cancer risk on E and no dependence of risk on variables other than E . Given a set of observations on cancer occurrence in people exposed to various levels of the agent under study, the unknown parameter B can be estimated with standard statistical procedures. This process, which in general terms involves identifying the value of B for which f is as close as possible to P_E , is known as "fitting the model." It produces both an estimate of B and an estimate of how precisely B has been estimated, that is, the standard error. Figures 2 and 3 illustrate two well-known examples of model-fitting with epidemiologic data. In figure 2 the risk of lung cancer is plotted for smokers against the number of cigarettes smoked per day. The figure also shows

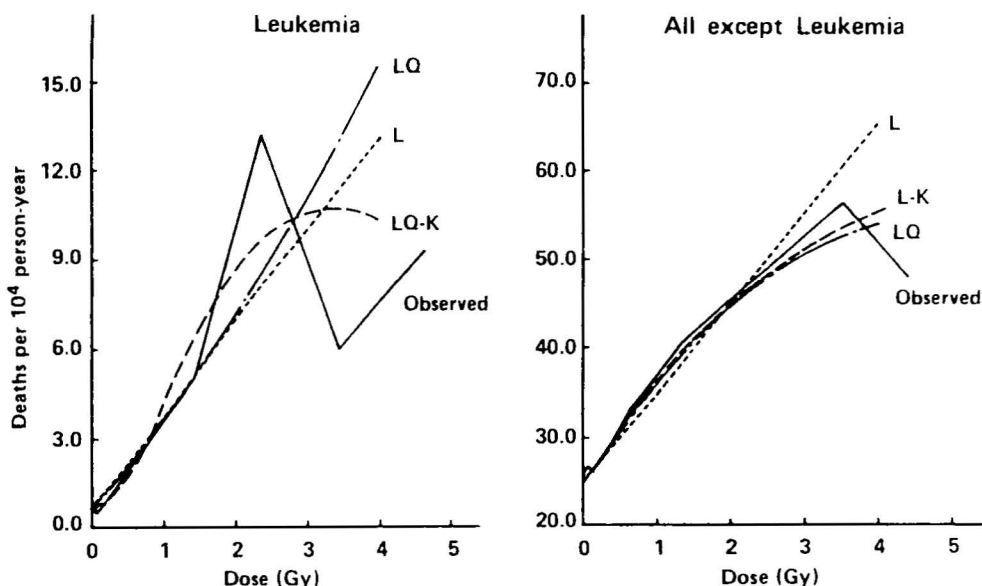


Figure 3. Observed mortality from leukemia and all cancer except leukemia, among survivors of the Japanese atomic bombings of 1945, by estimated radiation dose and fitted linear (L), lined-quadratic (LQ), and cell killing (K) dose-response models [reprinted with permission Shimizu et al (14)].

the fitted linear model, as in equation 1, and a quadratic model, relating the number of cigarettes to the risk of lung cancer. Note that in fitting the quadratic model the authors chose to exclude the highest smoking category, on the grounds that biological mechanisms are different in heavy smokers and that a different model should apply. In figure 3 the risk of leukemia in survivors of the Japanese atomic bombings is plotted against estimated radiation dose, accompanied by the fitted linear model. Under the linear model, B_1 is the increase in cancer risk per unit dose, or, conversely, it can be stated that a specified increase, $P_E - P_O$, in cancer risk occurs at dose $(P_E - P_O)/B_1$.

Risk estimation can appear to be a rather routine affair, until one realizes how much it relies on the specification of the model and begins to question the validity of the model and why it was chosen to express the relationship between exposure and cancer risk. Two broad classes of models have played the role of f in cancer risk estimation. The first class can be referred to as empirical models and includes the linear and quadratic relationships of figures 2 and 3. These models can be characterized as well-known statistical entities which have been used extensively in both biological and nonbiological applications. They can be extended to include time and other effects, in addition to the dependence of cancer risk on dose. Perhaps the most widely used of the empirical models in cancer epidemiology is the logarithmic regression model, in which the effects of different factors are supposed to combine multiplicatively to influence cancer risk. In table 1 the estimated effects (expressed as relative risks) of several determinants of nasal sinus cancer risk among nickel workers are presented, as estimated from a multiplicative model.

Models in the second class are built on hypotheses about biological processes, the aim being to produce a realistic representation of the carcinogenic process. The multistage model, first proposed in the 1950s, is the most well-known mechanistic model of carcinogenesis. It has undergone a series of modifications over the years to incorporate cellular proliferation, of both normal and partially transformed cells, and the effects of dose on mutation and proliferation (4). The model has been used to estimate various aspects of the relationship between lung cancer and cigarette smoking, as shown in table 2.

Although the incorporation of biological knowledge is certainly an important aspect of the development of mathematical models of carcinogenesis, proponents of the biological models often appear to be satisfied by the fact that a model is intended to be realistic, even if there is no empirical evidence that it actually achieves this goal. Until the process of carcinogenesis is understood more clearly, it will be difficult to have any greater confidence in biologically based models than in their simpler empirical relatives. In either case, the statistical criteria for a good model are a close fit to the observed data, a small number of unknown pa-

rameters to be estimated, and, ideally, an ability to predict cancer risk accurately when applied to populations other than the one from which its unknown parameters were estimated. These criteria should apply regardless of which form of model is used.

An example of the process of fitting models to epidemiologic data for the assessment of cancer risk was provided by Rinsky et al (6) in a quantitative evaluation of the leukemogenicity of benzene. The study cohort consisted of 1165 workers, of whom 15 were reported to have died from cancer of the lymphatic or hematopoietic system, including nine cases of leukemia. Table 3 summarizes these cases according to cumulative exposure levels and the time between first exposure and death. On the basis of these observations, the authors decided to fit an exponential relationship between dose, as expressed in parts per million multi-

Table 1. Estimated relative risks for lung and nasal sinus cancer mortality among nickel workers according to selected variables (3).

Variable	Lung cancer	Nasal sinus cancer
Age at first employment (years)		
< 20 ^a	1.0	1.0
20–27.5	1.4	3.3
27.5–35	1.3	5.0
> 35	0.93	10.6
Year of first employment		
< 1910 ^a	1.0	1.0
1910–1914	1.1	2.4
1915–1919	0.57	2.9
1920–1924	0.65	0.91
Exposure index ^b		
< 1 ^a	1.0	1.0
1–4	1.9	4.7
5–9	3.1	4.0
10–14	2.6	12.7
≥ 15	4.2	2.5
Time since first employment (years)		
< 20 ^a	1.0	1.0
20–29	0.74	2.8
30–39	0.47	2.4
40–49	0.22	3.1
≥ 50	0.11	3.4

^a Reference category.

^b Defined as years in high exposure areas.

Table 2. Parameter estimates from a two-stage model of lung cancer in British doctors (5).

Parameter	Interpretation	Magnitude
C_0	Background mutation rate	$6.5 \cdot 10^{-8}$
C_1	Increase per daily cigarette in first mutation rate	$8.3 \cdot 10^{-8}$
C_2	Increase per daily cigarette in second mutation rate	$6.5 \cdot 10^{-8}$
a	Background proliferation rate for intermediate cells	0.114
b	Increase per daily cigarette in proliferation rate	0

plied by the number of years exposed, and the relative risk of leukemia (figure 4). The authors reported that alternative models were investigated and rejected, but some factors of potential importance, including the effect of time since exposure and age at exposure, on risk were not reported as having been included in the modeling process. In any case, with only nine cases

of leukemia available for study, the analysis would have had only a limited ability to distinguish competing models statistically.

Subsequent writers (7) commented on the uncritical use of model assumptions in the estimation of cancer risk associated with benzene exposure. Although benzene is one of the most widely produced chemicals in the world and millions of people are exposed every day, this attempt at quantitative estimation of the associated leukemia risk comes down to the deaths of nine men in a single plant in the United States. Although as an indication of the leukemogenicity of benzene the study of these workers is virtually unchallenged, the shaky foundations of quantitative cancer risk assessment are clearly revealed.

Table 3. Leukemia in workers exposed to benzene (6).

Latency (year)	Cumulative exposure (ppm-years)			
	< 40	< 200	< 400	> 400
<5	2	—	—	—
<10	—	—	—	—
<15	—	1	1	—
<20	—	1	—	2
<25	—	—	—	1
<30	—	—	—	—
>30	—	—	1	—
Total	2	2	2	3
Relative risk	1.1	3.2	12	66

Role of animal cancer bioassays in quantitative cancer risk assessment

For most carcinogenic agents, epidemiologic data are unavailable or unsuitable for quantitative analysis. The

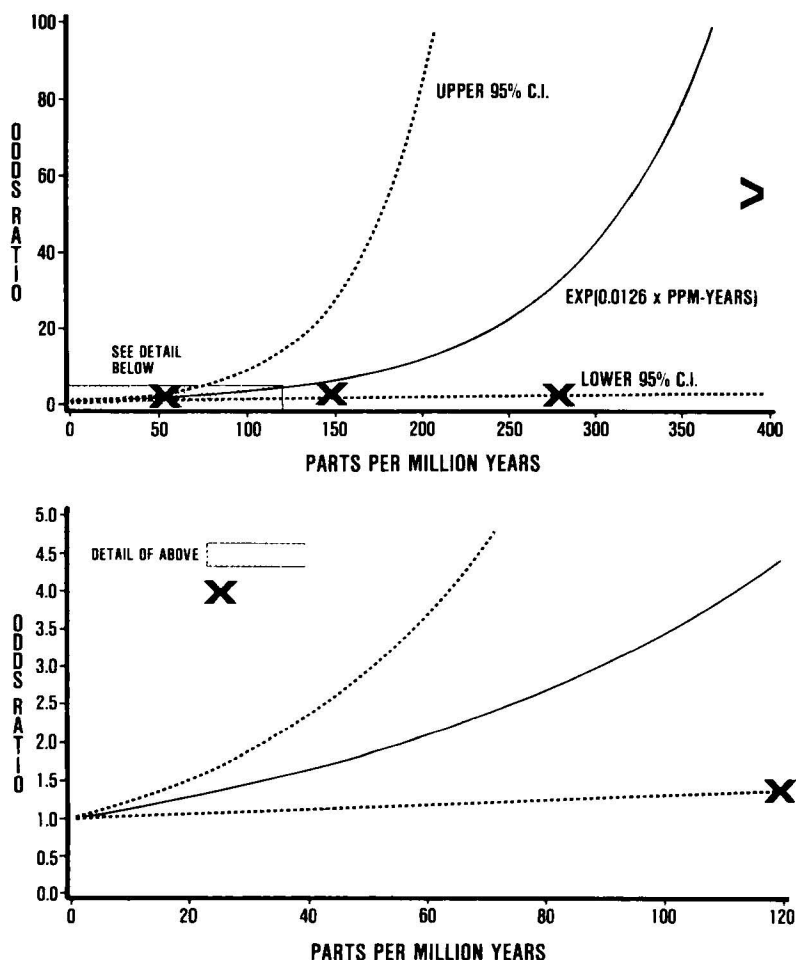


Figure 4. Observed relative risk (or odds ratio) of leukemia in workers exposed to benzene, by benzene dose, and fitted exponential dose-response models with 95% confidence limits [reprinted with permission from Rinsky et al (2)].

supposition that rodent carcinogens are potential human carcinogens has general support from the high degree of biological similarity among mammalian species, but there is nonetheless a sufficient number of differences to throw considerable doubt on the validity of quantitatively predicting risk for one species, namely, humans, on the basis of observations of cancer occurrence in other species. The target tissue in animals may not be the same as that in humans, and differences in metabolism, deoxyribonucleic acid repair enzymes, and other factors can produce discrepancies in the dose delivered to target tissues.

The value of animal cancer bioassays has, in the past, been questioned on the grounds that they employ very high dose levels that may not be relevant to low-dose human exposure (8). In the absence of supporting evidence, this argument has generally not been successful in excluding the results of animal bioassays from the qualitative evaluation of human carcinogenic hazard. However, it carries considerably more weight when quantitative extrapolation across species is being considered. Even prediction of risk at low doses for the very animal species used in the bioassay is problematic because a wide range of different mathematical models can agree equally well with the high dose data but differ by several orders of magnitude in their predictions of risk at low doses (figure 5). Whittemore (9) has reviewed the issues surrounding quantitative risk assessment from animal cancer bioassays with particular reference to formaldehyde. Human epidemiologic data on the carcinogenicity of formaldehyde to the lung have so far been equivocal, and are certainly not suitable for risk quantification. The compound does not appear to be carcinogenic in the mouse, but in the rat it produces nasal tumors, with a sharply non-linear dose-response curve (10). Clearly any attempt to use the rodent studies to predict human lung cancer risk is fraught with uncertainty about species difference, organ specificity, and dose-response shape.

In the face of these difficulties, some authors have examined the correlation between quantitative indices of carcinogenic effect in humans and rodents. Most of the indices used have been analogous to the TD_{50} (11) (ie, the daily dose in animal experiments required to reduce the proportion of animals remaining tumor-free by 50%, estimated under the assumption of a linear dose-response curve). Allen et al (12) and Kaldor et al (13) found a relationship between human and rodent indices of carcinogenic potency, but their findings should be considered in light of the possibility that the relationship is simply due to a correlation across species in the exposure levels which have been studied.

Other authors have considered ways of improving cross-species extrapolation of carcinogenic effect by estimating the magnitude of metabolic and other species differences that may affect the carcinogenicity of specific agents in humans and animals. The principle underlying this approach is that, at the level of the ultimate target molecule for carcinogenesis, humans

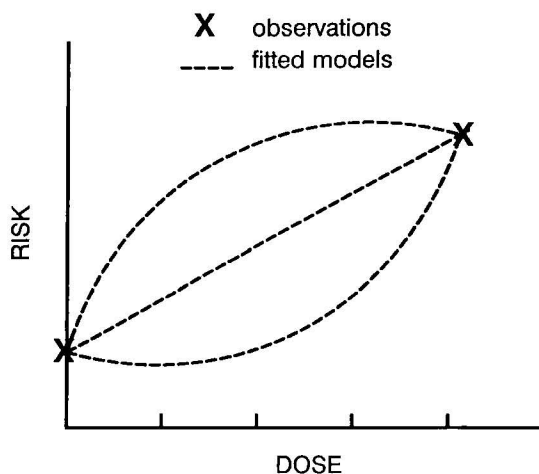


Figure 5. Theoretical results of animal cancer bioassay, showing the observation (X) at two dose levels and a range of models which could plausibly fit the observation.

do not differ substantially from animals. Therefore, if the relationship between the dose delivered to the target molecule and the risk of cancer were known from animal studies, this information could be directly applied to human cancer risk, provided the relationship between the applied or external dose and the dose to the target molecule were also known for both humans and the animal species used in the bioassay. These relationships in turn depend on factors such as the absorption, metabolism and elimination of the agent, its distribution to different tissues, and its interaction with specific cell types. While conceptually attractive, this approach is so far restricted by the limitation in knowledge about these factors and the ethical difficulties in carrying out the necessary exposure studies in humans. Furthermore, estimation of the relationships between applied and target molecule dose to humans generally requires the application of mathematical models, for which the underlying assumptions are as tenuous as they are for the more general carcinogenesis models. The risk estimation for methylene chloride has been promoted as a successful application of the method (14). It was proposed that methylene chloride, while carcinogenic to rodents, would be much less carcinogenic to humans because a specific pathway for the metabolism of methylene chloride to a carcinogenic form was present in rodents, but not in humans. This argument would have been more convincing if all possible metabolism pathways, as well as other relevant differences between humans and rodents, had also been considered.

Concluding remarks

The process of quantitatively assessing cancer risk is based on many assumptions, most of which are in-

herently extremely difficult to test. Where possible, errors associated with these assumptions should be stated, even to the extent of an acknowledgment of complete ignorance. The choice of assumptions is not a mechanical process, and it must be recognized as being inextricably linked to both politics and policy.

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