a scientific weight of evidence approach, Freedman and Zeisel propose an alternative solution: "informal argument." However, when scientific evaluations of possible human risk are replaced by a lawyer's debating skills, and regulatory decisions determined solely by who is able to "informally argue" their position more persuasively, then the ultimate loser may be our nation's public health.

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Comment

Suresh H. Moolgavkar and Anup Dewanji

"The Emperor has no clothes," say Freedman and Zeisel, and they marshal an impressive array of facts to support their conclusion.

That carcinogenic risk assessment is of enormous practical importance is a truism. It is equally obvious that, if possible, risk assessment should be performed within the framework of a biologically based model of the carcinogenic process. Indeed, if risk is to be extrapolated from high doses to low or from one species to another, then it is absolutely imperative that a biologically based model be used if the results are to be meaningful. Among the models considered by Freedman and Zeisel, the multistage model, first proposed by Armitage and Doll, is the only one that could, even remotely, be considered to be biologically based. Before discussing this model, we would like to state our view of the role of carcinogenesis modeling in the process of risk assessment. A biologically based cancer model is only one component of a rational risk assessment strategy. Such a cancer model relates fundamental biological processes at the cellular level to the incidence of tumors of specific tissues in human or animal populations. In order to relate the parameters of the model to the specific agent under investigation it is necessary to know the dose of the active metabolite responsible for the carcinogenic action in the tissue of interest. Thus, before the carcinogenesis model can be used, either direct measurements of the metabolite in question must be made in the tissue of interest or a pharmacokinetic model must be used to

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infer the tissue level of the metabolite from knowledge of the level of the agent in the environment. The importance of pharmacokinetic modeling in risk assessment is now widely appreciated (Dedrick, 1985; Hoel, Kaplan and Anderson, 1983; Krewski, Murdoch and Dewanji, 1986; Murdoch, Krewski and Crump, 1987).

The multistage model for carcinogenesis was first proposed by Armitage and Doll (1954) in the 1950s to explain the observation that the age-specific incidence rates of many human cancers increase roughly with a power of age. As Freedman and Zeisel point out, this model views carcinogenesis as the end result of a progressive deterioration of a normal cell via a number of intermediate stages to malignancy, with the sojourn time in any stage being exponentially distributed. The action of environmental agents is modeled by letting the parameters of the exponentially distributed sojourn times be functions, usually linear, of dose. Now it is widely recognized that there are, broadly speaking, two classes of agents, initiators and promoters, that facilitate carcinogenesis. Although the situation is more complicated, roughly speaking, promoters are agents that are more efficient in increasing the incidence of cancer if exposure to them occurs after exposure to initiators, rather than before. Within the context of the Armitage-Doll model, initiators are considered to be "early" stage carcinogens whereas promoters are considered to be "late" stage carcinogens. As Freedman and Zeisel note, it is not easy to reconcile this view of initiation-promotion with the results of the so-called IPI protocol, in which application of initiator followed by promoter followed again by an initiator, greatly increases the yield of malignant tumors. Further, it is known that initiators and promoters have quite different mechanisms of action. It is quite unrealistic biologically to model them in essentially the same way, i.e., as affecting the parameters of an exponential waiting time between stages.

There are other biological problems with the Armitage-Doll model that are even more fundamental. It is well known that both mutation and cell division and differentiation are important in carcinogenesis. Yet, the model takes no explicit account of the latter. The stages postulated in the model are mathematical abstractions and have no biological interpretation. The number of stages is undefined.

Even if the Armitage-Doll model is accepted at face value, the current statistical use of the model is seriously flawed. For risk assessment, the Armitage-Doll model is often used in the form (Brown and Hoel, 1986)

$$P(d, t) = 1 - \exp(-g(d)\mathrm{H}(t)),$$

$P(d, t)$ is the probability of a carcinogenic response by time t, $g(d)$ is a polynomial in dose and $H(t)$ is a power of time. This formulation depends crucially on the adequacy of a couple of approximations (Moolgavkar, 1978). These approximations are likely to be poor when the probability of tumor is high. This is typically the case in animal experiments and, thus, the formula above is inappropriate in precisely those situations in which it is most widely used, i.e., in the analysis of animal experimental data. A second problem is that (when the approximations hold) the Armitage-Doll model implies that the polynomial $g(d)$ is a product of linear terms. In the application of this formula, however, $g(d)$ is treated as a general polynomial.

It is clear from the above discussion that we share Freedman and Zeisel's bleak view of the current state of affairs in risk assessment. However, we believe that it is possible to devise a more rational risk assessment strategy based on recent progress in understanding the biology of cancer.

Perhaps the most important discovery in the past decade is that there appear to be two classes of genes important in the process of malignant transformation. Inappropriate activation of genes belonging to one of these classes, the oncogenes, could well be the final common pathway in carcinogenesis. In contrast to the oncogenes, genes belonging to the other class, the so-called antioncogenes, lead to cancer when they are inappropriately *inactivated* (Knudson, 1985). A stochastic model for carcinogenesis that incorporates these two classes of genes and explicitly considers tissue growth and differentiation has been proposed (Moolgavkar and Knudson, 1981; Moolgavkar, 1986). This two-stage model for carcinogenesis has been shown to be consistent with a large body of epidemiologic and experimental data. The stages and parameters of the model are explicitly interpretable in biological terms. The model provides a natural framework for understanding initiation and promotion. For example, the model predicted the results of the IPI experiment before it was performed. Thus, the model does not share the deficiencies of the Armitage-Doll model. Further, the fact that the parameters of the model are interpretable in terms of biological quantities that can be measured in the laboratory, makes the model particularly suitable for interspecies and low-dose extrapolation. The use of this model for risk assessment has recently been proposed (Wilson, 1986; Thorslund, Brown and Charnley, 1987).

With the increasing appreciation of the role of pharmacokinetics, the discovery of sensitive methods for the measurement of delivered tissue dose, and the development of more realistic carcinogenesis models, we believe we are now in a position to begin a systematic scientific assault on the problems posed by quantitative risk assessment. The Emperor may have no clothes but the time is ripe to provide him with a fig leaf.

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Comment: The Use of Animal Experiments in Cancer Risk Assessment

J. Kaldor and L. Tomatis

Among the agents which have been demonstrated to cause cancer in humans, environmental chemicals have been the major focus of public and regulatory concern over the past several decades. In the case of artificially synthesized compounds, particularly strong sentiments can be aroused: why should proven, or even suspected causes of cancer, be allowed to contaminate the human environment? The answer often given is that many manmade carcinogens have become of substantial economic benefit, and the risks which they represent are to be weighed against the costs of their removal from the environment. It has long been recognized that the quantification of both risk and benefit presents major difficulties, and Freedman and Zeisel are only the most recent commentators to conclude that, in particular, the quantitative assessment of cancer risk entails a number of biological assumptions that have not been verified empirically. In reaching this conclusion, with which we are in general agreement, Freedman and Zeisel sidestep into areas where they appear to be out of their depth, and manage to distort several important issues concerning the use of animal experiments as indicators of potential human hazard.

The sine qua non for establishing a chemical as a human carcinogen is undoubtedly the epidemiological finding that, after eliminating as far as possible the effects of bias, confounding or chance, those exposed to the chemical have a higher risk of cancer than those unexposed. Although laboratory experiments and information on chemical structure, metabolism and pharmacokinetics all play an important role in the evaluation process, some grounds can always be found to challenge their relevance if epidemiological data are absent.

The current reality, however, is that for most environmental chemicals, studies of cancer risk in exposed humans are not available. In a few cases, this can be attributed to a lack of resources for studying an appropriate, exposed population. For the overwhelming number of chemicals, however, such a population does not exist, either because it is too difficult to define who is exposed, because when exposure does occur it is in conjunction with other chemicals or because not enough time has elapsed to be able to evaluate the cancer risk in exposed populations. For a number of major classes of chemicals such as the *N*-nitrosamines, which are both animal carcinogens and widespread in the human environment, direct epidemiological evidence of carcinogenicity is still lacking.

In this situation, the process of cancer risk assessment, whether qualitative or quantitative, must rely entirely on experimental data, perhaps combined with some information on human metabolism or other relevant parameters. Although each chemical should be evaluated independently, it is only on examination of results across chemicals that one can evaluate the validity and long term performance of experimental data in predicting human risk. In their critique of risk

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