data into model-fitting approaches. Whenever a chemical is unequivocally carcinogenic in at least one species (this would have to be true before Squire's ranking method would be employed), a model-fitting approach that utilizes both positive and negative data could objectively account for negative data. This seems preferable to simply awarding a score based upon whether one or two species are affected, particularly since negative findings can be due to limitations in experimental design.

Regulatory action must take account of not only the carcinogenic potency of a chemical but also the numbers of humans exposed and their exposure levels. With a model-fitting approach there is a built-in procedure for doing this; the ranking system approach would require still further arbitrary rules. A related problem is the fact that the regulatory actions recommended by Squire for different classes of carcinogens are stated very generally; examples include "restrict or ban," "no action," "labeling," and "public education." These recommendations beg the issue; regulatory agencies need to know *how much* to restrict use. To answer this question regulators would undoubtedly be led back to a model-fitting approach.

The chief criticism of the model-fitting approach—and a valid one—is that the shape of the dose-response curve at low doses is impossible to determine experimentally, and different models, fit to experimental carcinogenicity data, often lead to vastly different estimates of low dose risks. Perhaps this difficulty could be mitigated by admitting that we don't know how to protect human health to the levels of 10^{-6} or 10^{-5} lifetime risks and to begin paying more attention to comparisons of carcinogenic potencies rather than absolute levels of risk. At any rate, the data ranking system proposed by Squire doesn't solve this problem; instead, it appears to create some additional ones. It seems likely that any such formula for ranking data would be subject to similar criticisms.

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We consider the validity of the scoring system proposed by Squire for the purpose of ranking the tumorigenic potential of known animal carcinogens to be questionable; this is due to an inherent weakness which, in many cases, will cause it to fail.

Briefly, a scoring system is applied by the author to six factors which are considered to be relevant parameters of the carcinogenicity of a substance; the final score is then derived by summing up the six scores arithmetically. It must be stressed that, although a set of six individual scores can adequately describe the biological behavior of a carcinogen, their sum does not. Several different combinations of them (each of these combinations representing a carcinogen with defined biological properties) will yield an identical final score if the proposed procedure is applied. Consequently, substances whose carcinogenicity varies greatly in nature and degree will be merged into a seemingly homogeneous class so that their individual qualities are blurred.

For the proposed ranking procedure, an unequivocal assignment of a single rank to a given set of relevant individual scores apparently does not exist.

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The comments by Crump and by Fröhlich and Hess about my ranking system approach for animal carcinogens are among several constructive opinions I have received. A major reason for my devising a ranking scheme is the fact that mathematical models utilize only dose-response data and ignore most of the biological information derived from animal tests that is relevant to risk assessment. If, indeed, other biological factors can be incorporated into mathematical models, this may be the optimal approach. However, in my experience, statisticians have been reluctant to consider graduated observations.

Crump's point about carcinogenic potency receiving inadequate attention is based upon the possibility of two chemicals having an identical effect in all the factors included in my system, except dose-response. This has never occurred in my experience, and precisely because chemicals vary so widely in all their effects, not only in dose-response, the model approach as currently employed is inadequate for risk assessment.

Crump's second point on absolute numbers of neoplasms (or animals with specific neoplasms) is well taken, and I agree that this is an important oversight. I have tentatively modified the system since publication to include an additional factor based upon the proportion of animals with the neoplasms in question in treated versus control groups. The P value resulting from statistical analysis of the tumor incidences may be a useful way to handle this. For example, a very low P value of $< .001$ would receive more weight than a P value of $< .05$. The number of animals affected by a carcinogen, the degree of tumor progression (malignancy), and the dose-response relationship are all reflections of carcinogenic potency in the test animals and, I agree, should be represented in the system.

Crump's comment on human exposure is an important one, and this factor could be incorporated into a ranking system. However, I considered it to be part of the next step, that is, the regulatory decision. As Crump points out, "how much to restrict" is a critical question, but it is a judgment based not only on risk but also on populations affected, patterns of use, benefits, economic considerations, and other factors that are not addressed in my article.

As indicated by Crump, a weakness of the model-fitting approach is the lack of information at low dose exposure. However, a greater weakness, as indicated above, is that models ignore much of the relevant biological information derived from animal tests. I am not opposed to the use of mathematical models. However, they are currently based on too limited data, and I would prefer their use in conjunction with the weight of biological evidence.

The letter by Fröhlich and Hess raises a question fundamental to any such systematic approach. I agree that, if each of the factors were independent variables, the sum total might be meaningless. However, the factors are probably not independent. They, in fact, generally correlate in their direction of severity and their "sum" reflects the weight of evidence for estimation of carcinogenic potential in an untested species. I do not necessarily believe the factors should be given equal weight, as most are in my article, or that the figures I have assigned have any intrinsic value. They are largely arbitrary. However, I believe it is the *cumulative* evidence that must be evaluated in carcinogenesis risk assessment, and the system I proposed is merely an example of an approach that could be considered.

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Erratum: In the issue of 9 August 1968 (p. 541), *Science* printed the Nobel lecture of Hans A. Bethe on "Energy production in stars." Eddington had at one time hypothesized that stellar energy arises from complete annihilation of matter. The energy to be set free by such a process, if it could occur, would be enough to supply the sun's radiation for 15,000 billion years. In the lecture, this number was erroneously given as 1500 billion years.