Chemical Carcinogenesis: Dose-Response Extrapolation

Marvin A. Schneiderman (Letters, 16 Feb., p. 603) implies that if you can devise an appropriate biological model for chemical carcinogenesis, you can devise a theoretical dose-response curve that will enable a meaningful extrapolation to be made to very low carcinogen doses. This may be good theory, but practically it is grossly error-prone.) My figure, used by Thomas H. Maugh II (Research News, 6 Oct. 1978, p. 37) is meant to illustrate the point that the further you extrapolate from the data base, the greater the level of uncertainty in the predictions. Significant tumor yields in animal experiments usually range from 5 to 100 percent. Vast numbers of animals have to be used to establish a 1 percent tumor yield, and much below this level adequate facilities are not available even on a worldwide basis. Therefore extrapolation to dose levels including one tumor in a population of 10^6 or 10^8 cannot be confirmed experimentally. In cancer induction the uncertainties in extrapolation are compounded by the complexity of the process and the vase number of factors, such as promoting agents, which may drastically affect tumor yield.

Schneiderman draws attention to the fact that the figure does not show the incidence of tumors occurring in a population not exposed to the carcinogen. As a logarithmic scale was, in fact, used, this incidence would not appear in the figure if the spontaneous tumor incidence was zero. More realistically, most spontaneous tumor incidences range from a fraction of 1 percent to several percent both in humans and in rodents. The uncertainty of establishing an *induced* tumor incidence at a level of one tumor in a population of 10^6 or 10^8 against a background incidence of, say, 1 percent is very considerable, especially if you realize that the actual human population (the real objective) is genetically heterozygous and diverse in its habits, so that spontaneous incidence will vary from one subset of the control population to another. The real or theoretical shape of the dose-response curve is quite irrelevant to my argument.

It is becoming clear that many chemical carcinogens must remain in low levels in our environment, despite the best efforts of regulatory agencies. Let us not pretend at this time that efforts at dose-response extrapolation for carcinogens is any better than pragmatic level-setting. Only a more complete understanding of the many factors involved in carcinogen-

esis can lead to a rational appreciation of the effects of low levels of specific chemical carcinogens.

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Chimpanzee Task Force Report

The Interagency Primate Steering Committee (IPSC) of the National Institutes of Health has recently published a report (*1*) on the current and future needs for chimpanzees in biomedical programs in the United States. The report contains a number of errors, which is surprising when one considers the source of the publication and the expertise represented by the many primatologists consulted. In addition, there are apparently no detailed position papers supporting the statements and claims made in the report that are available for public scrutiny. It is therefore impossible to check the source of and justification for some of the questionable statements.

The report states that 200 chimpanzees are currently being used in toxicology and pharmacology programs and that future demands will require about 100 animals per year. However, there are few, if any, good reasons for using chimpanzees in terminal toxicological studies. It is also stated that 150 animals are currently being used in the field of hematology, immunology, and immunogenetics and that approximately 50 additional animals will be required every year. However, the World Health Organization Collaborating Center on Hematology in Primate Animals estimates that the actual figures are considerably lower than this (*2*). This raises the possibility that some of the other figures in the report are also inflated. Certainly the draft of the National Primate Plan published in 1977 gave a much lower estimate than the task-force report for the total number of chimpanzees currently being used in research and testing. It is estimated in the section on "Other research areas" that about 80 animals a year will be required, including ten for molecular biology projects. Presumably, the animals for this program will be passed on from other research projects involving necropsies, since it is inconceivable that these animals will be killed (or maintained) solely as a source of material for studies on the molecular biology of chimpanzee macromolecules.

The report suffers from a number of other shortcomings. First, the task force states that its evaluation has "clearly shown that [the chimpanzee] is absolutely essential for research on several important human diseases." While it is true that the chimpanzee is an important research model in some areas, the report does not substantiate the above quotation. In addition, the task force does little to demonstrate concern for conservation issues and does not emphasize the need to develop other research models that might eliminate the demand for chimpanzees in particular fields. For example, there may well be other satisfactory models in hepatitis research.

Second, the task force does not adequately consider the implications of its projected demand of 300 to 350 chimpanzees per year. Current U.S. breeding programs produce only about 40 to 50 animals a year (the major chimpanzee facilities contain about 750 animals altogether), leaving an annual import demand of 250 to 300 animals. In the 5 years up to 1977, the West African dealers were exporting between 200 and 250 animals every year to the whole world (not just the United States) (*3*). Because of increased restrictions on this trade as a result of the threat posed to wild chimpanzee populations, the numbers exported have fallen considerably in the last year or two, and apparently the main traders have now stopped operations altogether. Presumably, some attempt may be made to tap the Central African chimpanzee population, but this is likely to run into the same problems that have developed in the West African trade.

Third, the bibliography is most unsatisfactory. Only a few references are provided, many of which are not particularly current. Fourth, the report should have considered some of the ethical aspects of chimpanzee use and caging.

The IPSC has the prestige of the National Institutes of Health backing its publications, but that is no excuse for the production of this document. The chimpanzee, and those who are concerned about its use in biomedical laboratories, deserve detailed arguments and justifications as to why this animal in particular is required for *specific* research needs.

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References

1. *Report of the Task Force on the Use of and Need for Chimpanzees*, (National Institutes of Health, Washington, D.C., 1978).
2. J. Moor-Janowski, personal communication.
3. *IPPL Newsl.* **5** (No. 3), 15 (1978).