[CANCER RESEARCH 35, 3212–3213, November 1975]

Correspondence

After a long and generally cogent discussion of the problem of estimating "safe" levels of potential carcinogens, Mantel and Schneiderman (4) stop short of the conclusion for which they are clearly heading. In view of the many difficulties that are pointed out in the sections titled "Problems Not Covered by Mantel-Bryan Procedure" and "Further Problems" it is merely wishful thinking to conclude that "there is a need for" or "it should be possible to develop" the "reasonable, objective ways of finding 'safe' levels" that everyone would like. The clear conclusion is that there is no procedure at hand or in sight which can serve the purposes of the much-criticized Delaney clause.

The Delaney clause says, in effect, that when it is known that something can produce cancer in any species, then it is only prudent to avoid exposing humans to it. The objections to this common-sense guideline hinge on the apparent "unfairness" of the rule in the following sense. It is relatively simple and straightforward to show that something produces cancer in a species, but it is extremely complex and convoluted to give a scientific demonstration that anything is safe. But this is not the "fault" of the Delaney clause; it is a scientific "fact of life." Much of the Mantel and Schneiderman paper consists of illustrations of this "fact of life."

The plain fact is that we do not have the deep scientific understanding of the underlying mechanisms of potential carcinogens that would entitle us to state with genuine assurance just what is or what is not a "safe" level. A public recognition of this by cancer scientists is long overdue. Anyone who claims to have such assurance simply does not understand the scientific and statistical problems and is deluding himself and the public (2). The authors of the article are well aware of the problems but try to substitute what might be called "equitable ignorance" for scientific knowledge. However, there is no substitute.

The Mantel-Bryan procedure is put forward here with the supposed virtue that it uses "one rule of extrapolation for all circumstances." This is a fatal defect. If the dosage-response curves were derived from the deep scientific structure of the problem (*e.g.*, a precise mathematical characterization of the mechanism of carcinogenesis), there might be some justification for extrapolation beyond the range of the data (1). In practice, however, the dosage-response curves are merely arbitrarily fitted mathematical functions that can legitimately be used only for *interpolation* in the range of the data.

This point can easily be seen by fitting several mathematical functions, all arbitrary, to the same data set. An equivalent method is to use several transformations, *e.g.*, probit, logit, or angit, to linearize the data. Usually, there will be 2 or more different functions that give a satisfactory fit in the range of the data and will give about the same results when used for interpolation. With the extreme extrapolations used to find "safe" levels, the results will be entirely different, and there is no guarantee that any of the arbitrary functions are giving scientifically meaningful results.

If the extrapolation is bad from a statistical standpoint, it is even worse from a scientific one. When the dosage range is changed, the mechanism of action is likely to change as well. For example, at high levels of ionizing radiation, the gross structure and function of a cell can be disrupted and the end result may be death. However, for low levels of ionizing radiation where death is again the eventual end result, the damage may be confined to biochemical lesions that put misinformation into the genetic material of the cell (3). Misguided efforts to extrapolate back both for animal and human data have led to a long series of erroneous estimates of "safe levels" for low-level radiation that extend over a period of at least 20 years. These levels have repeatedly been "corrected" downward by an order of magnitude.

I do not think any general-purpose statistical gimmick can solve the problem. If there is any hope of solution, it would lie in gradually evolving techniques that exploit what is known about the underlying mechanisms of carcinogenesis and that are appropriate for specific compounds. There are no shortcuts to safety.

Irwin D. J. Bross

Roswell Park Memorial Institute
Buffalo, New York 14263

REFERENCES

1. Bross, I. D. J. Scientific Strategies in Human Affairs: Use of Deep Mathematical Models. Trans. N. Y. Acad. Sci. Ser. II, *34:* 187–199, 1972.
2. Bross, I. D. J. Scientific Strategies in Human Affairs: To Tell the Truth. Jericho, N. Y.: Exposition Press, Inc., 1975.
3. Bross, I. D. J., and Natarajan, N. Risk of Leukemia in Susceptible Children Exposed to Preconception, In-Utero and Postnatal Radiation. Prevent. Med., *3:* 361–369, 1974.
4. Mantel, N., and Schneiderman, M. A. Estimating "Safe" Levels, a Hazardous Undertaking. Cancer Res., *35:* 1379–1386, 1975.

Dr. Bross is probably correct in his thinking that there is today no real substitute for the Delaney Amendment. We agree that there are no shortcuts to safety. Some people imply (1, 2) that the Delaney Amendment is a shortcut. We are concerned about procedures that accept the appearance of safety as proof of safety under a requirement of zero risk. In an earlier paper (6) we said, "We look upon our proposal as not in conflict with, nor as a substitute for, the Delaney clause." We have not retracted that statement. And, of course, there are risks in things other than food additives. No Delaney clause applies to those risks.

As mathematical models in biology reflect more and more of the underlying mechanisms, the less likely they are to mislead us. We have suggested an extrapolation procedure that we think reflects the realities of how much (or how little) we know. Our procedure is strictly an extrapolation procedure and not for interpolation. It is not curve fitting. There is a real need for better ways to estimate responses

outside the range of observation and to take into account that mechanisms may be different at different doses. We think, however, that before mechanisms can be known for each separate material and all the combinations of materials, some conservative extrapolation procedure is needed. After mechanisms have been determined, "safe" levels could be vastly changed even as in the radiation example.

Our approach is clearly a stopgap. Our use of the probit scaling was only illustrative, rather than binding. We were not closing the door on the use of other scalings like those Dr. Bross now notes. Our claim, after all, was only that we might have an approach to a problem with no seeming solution (3–5).

One of our concerns is that without some operating rule to establish "virtually safe" levels, there may be no safe levels established; *i.e.*, people might wait for the full elucidation of a mechanism before setting any limits, thus permitting possibly excessive exposures for a long time. One sees this sort of thing from time to time, particularly with exposures in industry, where there is no Delaney clause.

We do not agree that nothing better than the Delaney clause will ever be developed to protect people. That may be the current state of affairs, but we do not think it will be true forever. However, if a problem is not discussable, it will not be solved. We would like to start discussions as part of the route to solutions.

Nathan Mantel

Biostatistics Center
George Washington University
7979 Old Georgetown Road
Bethesda, Maryland

Marvin A. Schneiderman

Field Studies and Statistics
Division of Cancer Cause & Prevention
National Cancer Institute
Bethesda, Maryland 20014

REFERENCES

1. Coon, J. M. The Delaney Amendment. Prevent. Med., *2:* 150–155, 1973.
2. Jukes, T. H. The Delaney "Anti-Cancer" Clause: The Delaney Amendment. Prevent. Med., *2:* 133–139, 1973.
3. Mantel, N. The Concept of Threshold in Carcinogenesis. Clin. Pharmacol. Therap., *4:* 104–109, 1963.
4. Mantel, W., Bohidar, N. R., Brown, C. C., Ciminera, J. L., and Tukey, J. W. An Improved Mantel-Bryan Procedure for "Safety" Testing of Carcinogens. Cancer Res., *35:* 865–872, 1975.
5. Mantel, N., and Bryan, W. R. "Safety" Testing of Carcinogenic Agents. J. Natl. Cancer Inst., *27:* 455–470, 1961.
6. Schneiderman, M. A., and Mantel, N. The Delaney Clause and a Scheme for Rewarding Good Experimentation. Prevent. Med., *2:* 165–170, 1973.