Models of Carcinogenesis

Nicholas A. Ashford *et al.*, in their response to comments on their article (Letters, 11 May, p. 554), raise several important issues about low-dose extrapolation models for carcinogens. I would like to comment on an additional and critical element of no-threshold models, using the one-hit, no-threshold model as an example.

The one-hit, no-threshold model for low-dose extrapolation of the dose-response relationship for carcinogens predicts a finite probability that a single molecule can evade the body's defenses and produce an event that triggers cancer. A toxicological threshold is a dosage at or below which no adverse response is observed.

This "no-threshold" concept has received widespread publicity in both the popular and scientific literature and has served as a focal point for criticism of the model. Reduction of this argument ad absurdum has resulted in legislation such as the Delaney clause of the Federal Food, Drug, and Cosmetic Act (*1*). This clause requires that any substance used as a food additive and demonstrated to be a carcinogen in either an animal bioassay or human study must be banned from all food products.

It is critical that the one-hit, no-threshold model be placed in the context of the stochastic (probabilistic) relationship in which it was developed. Although it is theoretically possible that a single molecule of a carcinogen could induce cancer, the probability of this occurrence is vanishingly small. The carcinogenic potential of a chemical substance is a function of both potency and dose. According to the one-hit theory, both of these variables directly and proportionally affect the derived probability that a carcinogenic event will occur. Carcinogens vary in potency by approximately 12 orders of magnitude, and hence there is a wide range of carcinogenic probabilities for any specified dosage of different carcinogens.

For example, benzene is a moderately potent, proven human and animal carcinogen. Low-dose extrapolation from occupational studies using the one-hit, no-threshold model suggests that persons drinking water containing 1 part per billion (weight to volume) (1.0 microgram per liter) of benzene throughout their lives might have an added risk of cancer (excess cancer risk) as high as approximately 2×10^{-6} (*2*) (two additional cases of cancer for every million people so exposed).

The probability of cancer from a single molecule of benzene per liter of drinking water is readily calculable by using this model. If one assumes that the average person weighs 70 kilograms and drinks 2 liters of water per day for a lifetime, the excess carcinogenic risk of drinking water contaminated with one molecule of benzene per liter, a lifetime consumption of about 51,000 molecules of benzene, is approximately 10^{-22}. This risk is more than 16 orders of magnitude smaller than the most stringent state or federal regulatory standard for an allowable risk level of 1×10^{-6} (one in a million excess lifetime risk of cancer). Assuming that the present total world population is 5 billion people and that it consumes this "contaminated" water, one would not expect even one additional case of cancer from this contaminated water, since the probability of one excess case of cancer's occurring in the world's population is 5×10^{-13}.

The fact is that both factions in this argument are correct. According to the no-threshold, one-hit model, there is a finite probability that one molecule of a carcinogen could cause cancer; however, the opponents of this theory are also correct in expressing their incredulity at this possibility. For all practical purposes, the probability of this occurring is so slight as to make this skepticism reasonable. The fact that this model allows for the possibility that one molecule of a carcinogen can induce cancer does not invalidate the model. On the contrary, because the model itself predicts that the occurrence of even a single cancer case from a single molecule of a carcinogen is highly unlikely, the model is able to reflect the known pharmacokinetics and enzymology at extremely low doses rather than totally dismissing this carcinogenic potential by assuming an absolute threshold.

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References and Notes

1. Public Law 85-929, 72 Stat. 1784 (1958).
2. Environmental Protection Agency value for the low-dose slope of 0.052 (milligrams per kilogram per day)$^{-1}$ based on R. A. Rinsky, R. J. Young, and A. B. Smith ["Leukemia in benzene workers," *Am. J. Ind. Med.* **2**, 217 (1981)] and provided in *Health Assessment Document for Acrylonitrile* [(EPA-600/8-82-007, Environmental Protection Agency, Washington, D.C., 1983), p. 13-165].