Conservatism in Carcinogen Risk Assessments?

John C. Bailar, III

McGill University Faculty of Medicine, 1020 Pine Avenue West, Montreal, Quebec H3A 1A2, Canada

The following is the abstract of the presentation by Mr. Bailar. His paper is not available for publication at this time.

Present methods of assessing the human health risks of carcinogens at low exposure levels are likely, on the whole, to underestimate those risks. In this context, "low exposure levels" means exposures where the assessed risks are 10^{-5} or lower. The process of risk assessment in this range is widely recognized, especially by its practitioners, to be subject to much uncertainty, often orders of magnitude. Neither supporters nor critics have a "gold standard" to assess the performance of various steps in the process. There are several strong reasons, however, for believing that risks overall may well be greater than estimated.

First, there are at least six plausible biologic mechanisms that produce supralinear dose–response curves. Each of these has been shown in practice to be important at higher risk levels in some risk assessments, and none has been ruled out as being of broad importance. In fact, data from the National Toxicology Program show that underestimates with the one-hit model are almost as common as overestimates.

Second, uncertainty in risk assessment is commonly expressed on geometric (logarithmic) scale, such as "within an order of magnitude," but what matters for the protection of human health is risk on a linear scale. For example, the consequences of underestimating risk by a factor of 10 or 100 are 9 or 99 times greater than the consequences of similar overestimation. Thus, an argument that overestimation is more common, even (contrary to evidence) by a wide margin, is compatible with an overall result that is far from conservative.

Third, when the data as a whole are deemed to be compatible with a supralinear model (not just a matter of showing that a linear or one-hit model fails to fit), one generally has no way to estimate where the curve starts to "flatten out" and hence no way to derive an upper bound on risk at much lower levels. This situation seems to be quite common: A linear model fitted to one high-dose point, or even two if there is some evidence of flattening at the upper end, is compatible with very large risks at lower doses even if those risks are sublinear because an upper bound in that range cannot be calculated.

Fourth, we do have a human health problem. Cancer incidence rates are known to be rising everywhere that adequate epidemiologic data exist; cancer death rates at older ages are rising even when lung cancer is excluded from the data, and geographic differences in risk cannot be explained by inherent differences in susceptibility. A high proportion of persons now get at least one cancer at some time during their lives, and something external is causing most of them (perhaps 85%) or we would not find such large variations in risk over space and time.

Recent arguments that risk assessment methods on the whole overestimate hazards to human health are not and will not become credible unless they can be revised to respond to the concerns expressed above. On the basis of current evidence, it is more likely that standard methods underestimate risk, despite some recent and well-publicized exceptions.