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Letter to the Editor

Biologically Based Models for Cancer Risk Assessment: A Cautionary Note[1]

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Biologically based models of carcinogenesis are becoming increasingly popular for risk assessment.[1-3] The multistage model, proposed by Armitage and Doll[4] to explain the observation that the age-specific incidence rates of many cancers increase with a power of age, views the process of carcinogenesis as the progressive deterioration of a normal cell through a sequence of intermediate stages to malignancy. When a couple of crucial approximations are made, the Armitage–Doll model generates an incidence function that increases with a power of age. These approximations have been examined in detail in a previous publication[5] and will not be reviewed here. Suffice it to say that the approximations are unlikely to hold in animal experiments in which, typically, a large proportion of animals develops tumors. For risk assessment the multistage model is often used in the form

$$P(d,t) = 1 - \exp[-g(d)H(t)]$$

where $P(d,t)$ is the probability of a carcinogenic response by time t, $g(d)$ is a polynomial in dose, and $H(t)$ is a power of time. This formulation depends crucially on the adequacy of the approximations alluded to above, and may, thus, be inappropriate in precisely those situations in which it is most widely used, viz., in the analysis of animal experimental data.

More recently Thorslund *et al.*[3] have proposed that risk assessment be based on a two-stage model for carcinogenesis developed by Moolgavkar and Venzon[6] and shown to be consistent with a large body of epidemiologic and experimental data by Moolgavkar and Knudson.[7] In the original mathematical development of the model[6] the parameters of the model were assumed to be independent of time. Thorslund *et al.*[3] present an expression for the incidence function generated by the model when the parameters are made time dependent. This allows the use of the model for the analysis of carcinogenesis experiments with time-dependent dosing patterns. Thorslund *et al.*[3] do not present a derivation of the expression for the incidence function. We would like to point out that the derivation depends upon the adequacy of an approximation. As in the case of the Armitage–Doll model, this approximation is unlikely to be adequate when dealing with animal experiments in which the probability of tumor is high. Specifically, let $Y(t)$ and $Z(t)$ represent the number of intermediate (premalignant) and malignant cells at time t, and let $\mu_2(t)$ represent the second event (mutation) rate. Then the incidence function predicted by the model is

$$h(t) = \mu_2(t) E[Y(t) \mid Z(t) = 0]$$

where E is the expectation. When the probability of tumor is small, it is reasonable to make the approximation

$$E[Y(t) \mid Z(t) = 0] \approx E[Y(t)]$$

That is, the *conditional* expectation may be replaced to a good approximation by the *unconditional* expectation of the random variable $Y(t)$. This approximation is essential for the expression presented by

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Thorslund *et al.*[3] and is identical to the approximation presented in the appendix to Moolgavkar *et al.*[8] When the approximation does not hold, the expression for the incidence is considerably more complicated than that in Thorslund *et al.* A complete mathematical treatment of the two-stage model with time-dependent parameters will appear elsewhere.[9]

The use of biologically based models of carcinogenesis for risk assessment is desirable. However, it is incumbent upon the investigator using these models to appreciate the conditions under which the assumptions and approximations implicit in the mathematical formulation are violated.

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