One item which I miss in Cornfield's approach is the recognition that the response to a carcinogenic agent depends on the rate of exposure. For the radioactive agents the priority for the study of the so-called dose-rate effects appears to belong to Upton (3). A review (4) indicates that important dose-rate effects exist also for certain chemical carcinogens.

Another item that I miss in Cornfield's approach is the phenomenon of synergisms. The importance of this phenomenon is dramatically emphasized by the title of a recent symposium (March 1977) organized by the Biology Division of Oak Ridge National Laboratory, namely, Symposium on Mechanisms of Tumor Promotion and Co-Carcinogenesis. The subjects discussed at that conference are marked by tale-telling terms: initiator, tumor promoter, and inhibitor. In view of these developments, the problem of the FDA regarding some chemicals C1, C2, C3 is not limited to its possible carcinogenic effects when administered singly, but also in combinations such as C1 and C2, C1 and C2 and C3. Statistical methodologies relating to such problems—the so-called multiple comparison problems—were summarized by Miller, first in a monograph and then in the Journal of the American Statistical Association (5). However, the problem of an optimal methodology does not appear to have been solved and represents an inspiring challenge to mathematical statisticians [see (6)].

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2. J. Cornfield, ibid., p. 693.

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Risk assessment at very low doses of carcinogen is faced with the problem of whether or not a threshold dose is zero. In biochemical terms the question is whether the molecular fate of a carcinogen is proportional or disproportional to dose. Cornfield (1) concluded that with decreasing dose a relatively higher percentage of carcinogen (C in our Fig. 1), its activated derivative (or derivatives) (C*), and relevant DNA adduct (or adducts) (C*-DNA) would be eliminated (C) by the cells' protective mechanisms (deactivation, DNA repair, for example) leading to zero relevant interaction at very low doses. Only if the protective mechanisms were saturated or overwhelmed by sheer numbers of carcinogenic molecules would carcinogenically relevant interactions occur.

In Cornfield's model all the reactions in which carcinogen participates are considered to be reversible, except at least one irreversible protective reaction. Furthermore, the model is analyzed for steady-state condition and apparently, though this is not mentioned, for a single-dose exposure. In such a system in steady state the amount of C*-DNA will be zero and all carcinogen will have been detoxified.

It should be noted that in this model, steady state is, by definition, only reached if all carcinogen is converted irreversibly into detoxified products C*, and that before this state is reached the amount of C*-DNA will have been greater than zero (Fig. 1). Now, as long as C*-DNA, the promotogenic lesion, is present it has a certain chance of being fixed genetically (during DNA synthesis or by misrepair) leading to an irreversible effect (mutation) (2). Moreover, the less reversible the pertinent reactions are, the longer will C*-DNA exist in higher concentration and the greater is the chance that an irreversible effect will ensue. In fact, the reactions in which chemical carcinogens are involved can be considered as virtually irreversible; persistent C*-DNA lesions have also been identified (3).

If carcinogen is applied continuously to this model, the amount of C*-DNA will be greater than zero under steady-state conditions.

Cornfield's "hockey-stick" kinetics (zero carcinogenic response at low doses, followed by a steep increase at higher doses, linear plot) do not correspond to the results of calculations of Gehring (4) on C*-DNA formation as a function of dose [see figure 5 in (4)]. According to Gehring, the normalized quantity (ratio between C*-DNA and dose) is plotted against dose (on a double logarithmic scale). The horizontal part of that curve in the low-dose range thus indicates a direct proportionality between the amount of C*-DNA formed and the dose.

The demonstration by Cornfield of fit of the Bryan and Shimkin data to this model is unconvincing because the data may be inappropriate for this purpose and the model contains too many free parameters. Since tumor incidence is a function of dose rate and time (5), tumor responses should be measured at a fixed time for all doses employed if a kinetically meaningful result is to be obtained. In the above experiments, however, the mean latent period was 2.4 months for the highest and 6.96 months for the lowest effective dose group.

We therefore maintain that Cornfield's data do not support threshold kinetics in chemical carcinogenesis.

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An author cannot escape complete responsibility for misinterpretation of his writings, but I nevertheless suggest that only a misreading of my article could have led to characterizing the model given there as a threshold model. The threshold holds for the special case of a steady-state model in which the deactivation reaction is irreversible and will not hold, as several of the correspondents have pointed out, when the time course of the reaction is taken into account. But once the irreversibility assumption is relaxed, as it is in the page-
Models for Carcinogenic Risk Assessment

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