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Discussion Session 2, March 25th, 1976 – Summary

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(1) Is the Mantel-Bryan procedure biologically justified?

The Mantel-Bryan method assumes that the population at risk has a log normal probability distribution of tolerances to a carcinogenic agent. Each individual has its own tolerance to the agent, i. e. some level below which it does not respond and above which it will respond. Only when this assumption about the tolerance distribution is true, the procedure is biologically valid. The Mantel-Bryan approach assumes a slope of 1.0 for a dose-response relationship.

Experimental results presented at the meeting, however, suggest a slope of about 0.4.

(2) Are modifying factors taken into consideration, which influence the effective dose?

Many factors contribute, e. g. distribution, metabolism, excretion, the heterogeneity of the population at risk, enzyme induction or inhibition. A carcinogen is often applied experimentally at such a high dose level, that the cell economy is imbalanced. There is clearly a need for more research on basic pharmacological and toxicological mechanisms.

(3) How would information on tumor induction time fit into the Mantel-Bryan procedure?

There is a mathematical equivalency between extrapolations on the basis of latency and on the basis of lifetime risk. Therefore, information on tumor induction time is easily added to these mathematical models and should be used when the data are available. The assumption, that the latency periods are log-normally distributed, leads to the probit model for dichotomous response data.

(4) Is the Mantel-Bryan model also applicable to one-hit events?

A one-hit model should be correct for only a few carcinogenic agents. A multi-event hypothesis probably more often reflects the true situation. However, at low dose levels, both the one-hit and multi-event models are linear with respect to dose.

Complexities adhering to animal experiments must be taken into consideration when mathematical models are used to establish safe levels for man. Among these are: the role of species differences, route of administration, qualitative and quantitative changes with changing dosage, the influence of dose distribution over specified time intervals and other factors that might influence dose-response relationships.

It was suggested to carry out a practical test to examine the validity of the Mantel-Bryan procedure on the basis of available data for aflatoxin. By taking animal data and applying the Mantel-Bryan method at several risk levels, how do resultant dose levels compare with those derived from human epidemiological surveys?

Concluding remark: Although the mathematical models presently available give only rough approximations they still allow a better risk evaluation than the conservative approach of establishing a no-effect dose and applying a safety factor.