

**SESSION IV: Regulatory Issues Affecting Canada and
the United States**

Assessment of Carcinogenicity

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The assessment of carcinogenicity has been a major preoccupation of many scientists and agencies for some time. Indeed, the International Agency for Research on Cancer (IARC), an agency of the World Health Organization (WHO), has as its principle function the assessment of carcinogenicity of a broad range of chemicals both in experimental animals as well as directly in human populations. Regulatory components of government have also reflected this societal concern through the creation of agencies such as the National Cancer Institute in both Canada and the U.S., the Carcinogen Assessment Group in the U.S. and the recent publication of a guidance document on carcinogenicity assessment by the Health Protection Branch of Health and Welfare Canada. Further, the requirement to, and the process by which carcinogens are to be assessed are well established in both Canadian and US regulatory organizations.

Considerable debate within the scientific community has focused on the most appropriate models and methods which are available to assess potential carcinogenicity of chemicals and the means by which this potential might be predicted and estimated in man. In recent years, within regulatory circles, two principle approaches have emerged. In Canada, general support has emerged for a qualitative approach for the assessment of carcinogens in which the nature, rather than the frequency, of the response forms the basis of the assessment. This evaluation might include consideration of the incidence of an appropriate combination of benign and malignant neoplasms, the number of species and studies in which the response has been observed and to what extent malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset. In this regard, the approach taken by the Bureau of Veterinary Drugs is most closely aligned to the philosophy of IARC. Noteworthy, is that a recent review of an important Canadian regulatory decision on the potential carcinogenicity of a commercial herbicide generally supported the biologically driven weight of evidence approach taken by Canadian authorities in their decision.

An approach to the assessment of carcinogens which relies more heavily on mathematical models has developed in the United States. Biological assessment continues

to be a central component of U.S. procedure, and the pivotal role of mathematical models is well established and entrenched in U.S. practice. While many models are available for the estimation and prediction of risk in man, many regulatory agencies, including our own, favour the use of models which incorporate a low dose linear component. Indeed, in 1985 the U.S. office of Science and Technology Policy noted that ". . . when data and information are limited . . . and when much uncertainty exists regarding the mechanism of carcinogenic action, models or procedures which incorporate linearity are preferred . . .".

The principle of linearity incorporates the view that a dose response relationship can be predicted for low doses to which human populations might be exposed, but for which no direct experimental evidence is available. At the "virtually safe dose", the probability of a response is "diminimus" or within the range considered to fall within a background response. A linear response presumes that every dose has an associated probability of response, however small, and the essential relationship favoured by the U.S. Office of Science and Technology Policy.

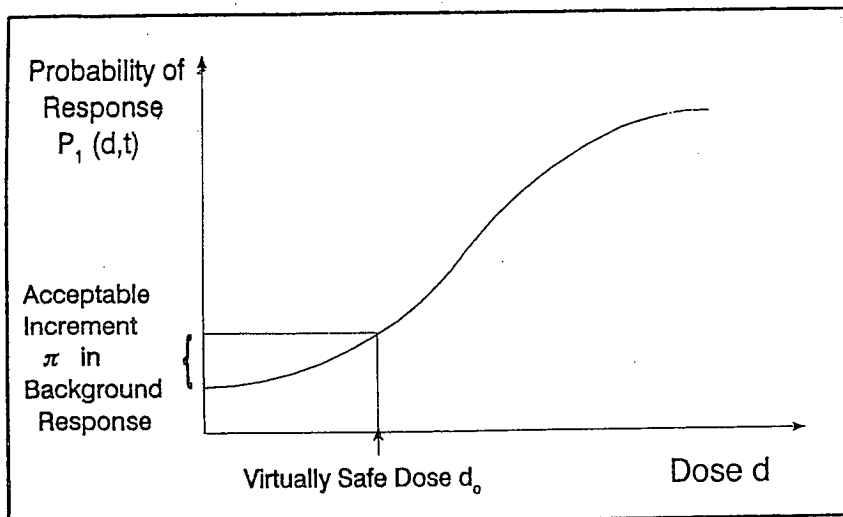
In order to explore the inherent weakness of this approach one can examine the relationship between the q^* cancer potency and the TD_{50} , in which the TD_{50} can be defined as the dose causing an excess tumour risk of 50% in exposed animals and the q^* cancer potency is the largest risk that is consistent with the data and is obtained from the linearized multi-staged model. As the TD_{50} dose increases, the cancer potency (q^*) declines accordingly. Noteworthy as well is the fact that this empirical relationship is insensitive to the biological relevance of the induced neoplastic response, and may therefore ignore critical biological function which, from a mathematical perspective, cannot be considered.

This maximum tolerated dose (MAD) can be defined as a dose level that provides the highest probability of demonstrating tumours without shortening the lifespan or depressing the clinical condition of the test animal, and at the same time, is the highest dose possible to fulfil these conditions. In reviewing this definition, it is important to note that the MAD is estimated and predicted on the basis of toxicological end points observed in short term studies, up to and including 90 days in duration and not from chronic toxicity or carcinogenicity studies directly. The TD_{50} can be predicted from the MAD alone and is not based on direct observations from the carcinogenicity study. As excess risk can be estimated from the MAD alone, design of bioassay appears to provide little additional information on low dose risk.

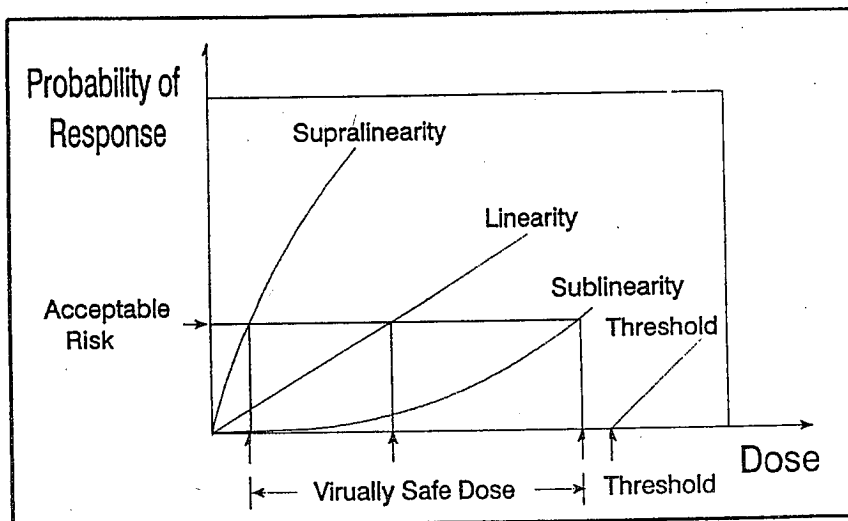
The insensitivity of mathematical models to the biological response is evident in the relationship between extremely low doses and estimated excess risk. Excess risk predicted is highly dependent on the specific model selected and may range well within or far beyond acceptable limits without regard whatsoever for the nature and importance of the biological response under investigation.

In summary, evaluation of carcinogenic potential is a highly complex undertaking fraught with uncertainty. While mathematical models can be useful tools for assessing and comparing similar test results; these models are generally insensitive to biological criteria and must be utilized with caution in predicting human carcinogenic risks on the basis of experimental animal data alone.

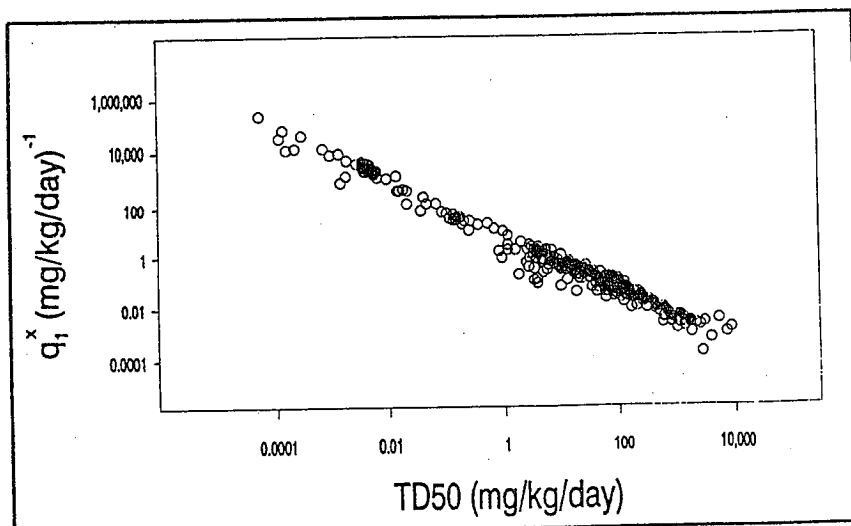
BVD/BMV



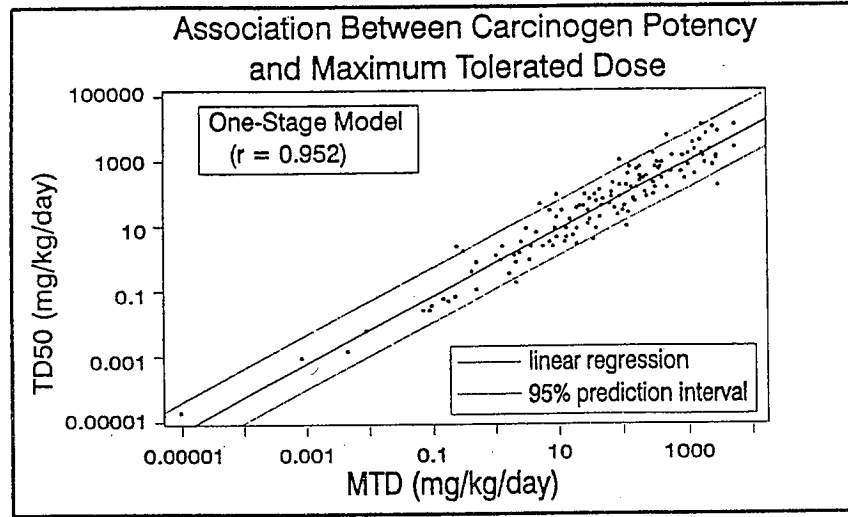
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