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ABSTRACT

# EXTRAPOLATION OF RISK FROM LOW POTENCY ANIMAL CARCINOGENS

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The term "low potency animal carcinogen" has no precise meaning. Therefore, there can be no universally valid formula for extrapolating from positive results in animal carcinogenicity tests to man.

For agents which produce cancers in animals because they react with DNA in such a way as to produce mutations, it is generally prudent to assume that humans exposed in the same way may be at increased cancer risk. Moreover, in this situation, if there are no reliable epidemiological data for humans, then the extent of the increased risk to man may best be judged by quantitative extrapolation from the available animal data. However, before such extrapolation is made, account should be taken of all the available toxicological information particularly those from comparative metabolism and pharmacokinetic studies.

By contrast, where an agent increases cancer risk in animals by a non-genotoxic mechanism, extrapolation to man is far more problematical because of the multiplicity of possible mechanisms and because many of the mechanisms are species- or strain-dependent or dependent on artifacts associated with the unnatural way in which laboratory animals are traditionally maintained. Over-feeding, lack of exercise and enforced celibacy predispose to high incidences of mixed endocrine disturbances, including high incidences of neoplasms of endocrine glands and hormone-influenced tissues. Further increases in the incidence of tumours of these same kinds in response to exposure to a xenobiotic agent is uninterpretable as far as man is concerned. Thus, it is nonsensical to use simple mathematical formulae for calculating risks to man from animal studies on non-genotoxic carcinogens.

The greatest problems of all, however, relate to xenobiotic agents which are not only marginally genotoxic but which can also increase tumour incidence in animals by a non-genotoxic mechanism. Data from studies on such agents confuse and confound the carcinogenesis literature.

It is overdue that we now return to the situation wherein mathematics is regarded as a tool of toxicological science and not vice versa.

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