CORRELATION OF NCI AND IARC CARCINOGENS WITH THEIR MUTAGENICITY IN SALMONELLA


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SUMMARY

Carcinogens identified by the NCI Bioassay Program and by recent IARC monographs were reviewed for mutagenicity in the Salmonella/microsome assay. Out of 124 NCI carcinogens, 33 were mutagenic in Salmonella, 24 were non-mutagenic, 19 were incompletely tested in Salmonella, and 48 were not tested. Out of 60 IARC carcinogens, 30 were mutagenic, 15 were non-mutagenic and 15 incompletely or not tested. Of the 102 adequately-tested carcinogens, 63 were mutagenic, giving an overall "success rate" of 62% (i.e. 62% of carcinogens were also mutagenic). If incompletely-tested carcinogens are eventually proven to be non-mutagenic, the success rate would be far lower. The large number of carcinogens which have either been incompletely tested in the Salmonella/microsome assay or not tested at all clearly deserve priority for in vitro testing.

Many of the non-mutagenic carcinogens fall into predictable chemical classes, especially chlorinated aliphatics and mono-substituted or complex aromatic amines. Other instances of non-mutagenic carcinogens can be explained by the inability of in vitro bioactivation to mimic host metabolism, especially with...
reference to complex metabolic activation and to short-lived electrophiles.

The usefulness of mutagen–carcinogen correlations also depends on the quality of carcinogenicity data, and the statistical power to eliminate both false positives and false negatives. The quality of the Bioassay data was quite variable, often due to inconsistencies between experimental protocol and the established NCI guidelines. In several instances the maximum tolerated dose was not adequately determined, or was not used in lifetime studies. In other instances length of exposure was half-lifetime or three-quarter lifetime. Some reports utilized only one rodent species, and others used fewer than 50 animals per group. Finally, many chemicals contained varying amounts of impurities; although this may more accurately mimic human exposure and may provide some indication that an impurity has a biological effect, these impurities might also contribute to toxicity, or other effects (tumor promotion, induction of metabolizing enzymes and so on). In at least two instances, impurities were responsible for mutagenicity.

The statistical design of the Bioassays reflects a desire to detect only the most potent carcinogens, namely those which cause a 5-fold or greater increase in incidence over a very narrow range of spontaneous incidence. Only a few sites have the statistical sensitivity to detect significant increases in incidence, the most prominent of which is the liver. Historical controls are of little use for any purpose other than suggesting a causal appearance of rare tumors, primarily because of the extremely wide range of reported incidences at several sites. Even with these drawbacks, a comparison of relative carcinogenic potency can be made on the basis of the degree of response per dose of chemical.

INTRODUCTION

The final purpose of doing any biological test for mutagenicity or carcinogenicity is to provide data that can be used to calculate risks to humans. Extrapolation from animal cancer to human cancer based on some indication of carcinogenic potency in animals should be fairly straight-forward, although attempts to do so have been beset by arguments over details which are more important for regulation than for theories of chemical carcinogenesis. Since it is impractical to perform lifetime bioassays for any but the most highly suspect or widely used chemicals, we naturally rely on short-term tests to provide additional information. These short-term tests are designed to detect different parts of the carcinogenic process such as point mutation, transformation, structural chromosome damage, DNA synthesis and repair, and so on.