EVALUATION OF CHRONIC RODENT BIOASSAYS AND AMES ASSAY TESTS AS ACCURATE MODELS FOR PREDICTING HUMAN CARCINOGENS

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INTRODUCTION

The question "What percentages of mammalian carcinogens and noncancerous substances can be predicted by bacterial mutation tests?" probably cannot be answered for the following reasons:

1.) There seems to be no universal agreement upon what criteria are absolutely necessary to unequivocally establish a carcinogen for mammals. Consequently, the bull's eye of the target for which the bacterial tests must aim continually shifts, causing the results of comparisons conducted at one point in time to be adjusted at a different point in time.

2.) Carcinogen results are not obtained for "mammals", they are obtained in unique mammalian species which often differ among themselves as to whether a particular chemical is a carcinogen or not. Bacterial tests might hopefully match the results in a single mammalian model but cannot be expected to match the combined results from several mammalian species which fail to agree among themselves as to the correct answer.

The dilemma identified in the previous two points is best shown via an analysis of the correlation between mutation data from the "standard" Ames test and the "standard" rodent lifetime cancer bioassay. The data used in this analysis is derived from 200 studies supported by the National Cancer Institute (NCI) (3). The comparison includes a sample of approximately 25% of the total data base and is probably representative of the complete set of responses.
The Bacterial Mutagenesis Study

This portion of the data base was developed from the results of a detailed collaborative study of the Ames test coordinated by Dr. V.C. Dunkel. A portion of this study, conducted in four laboratories, involved a set of chemicals not among the 200 reported by NCI and preliminary results have been reported by Dunkel in 1979 (4). The initial group of chemicals were tested to provide a summary of data from studies conducted to standardize test methods, the evaluation of factors involved in inter-laboratory variability, and the criteria involved in data evaluation. The set of chemicals reported here were chosen on compound availability and stability since many of the cancer bioassays had been conducted several years earlier.

The investigation was designed to be a study of how the results from the Ames test compared with those in the NCI animal data base. All four laboratories tested the same compounds under code, and the data were evaluated and reported by code numbers. Only after all four laboratories had completed a set of chemicals and submitted their evaluations to the study coordinator were the chemicals identified. The test materials used in the Ames test were from the same lots used in the rodent carcinogenicity studies, and the rat and mouse S9 preparations were made from the two rodent strains used in the NCI bioassay (Fischer 344 rats and B6C3F1 mice).

The protocol employed was extensive with redundancies designed into the procedures. Table 1 summarizes the basic parameters of the test methods used in each of the four laboratories for each compound. A single chemical, for example, would have a total of 84 plates per dose level per strain tested (3 plates x 1 nonactivation group x 6 activation groups x 4 laboratories), therefore, the minimal composite data from the Ames assay for each chemical consisted of a minimum of 3,360 plates (84 plates per dose group x a minimum of 6 dose levels and 2 control groups x 5 strains). Consequently, the resolving power of this protocol was extremely high and a composite positive or negative response carried substantial reliability.

The criteria used to decide whether the data for a chemical were positive consisted of the demonstration of a dose response effect with a concomitant two-fold increase over the solvent control value in at least one Salmonella tester strain for at least one treatment condition. Uniformity among laboratories with respect to strain and activation system specificity was very high (approximately 95% concordance in all four laboratories). For most compounds, the dose range showing activity was also similar among the four laboratories.

Thus, the Ames test data base represented a relatively good indication of the type of data which can be expected from multiple