CHAPTER 22

MUTAGENICITY OF SELECTED CHEMICALS IN THE MAMMALIAN
MICRONUCLEUS TEST

B. E. Matter

Biological and Medical Research Division
Sandoz Ltd., Basle, Switzerland

and

D. Wild

Zentrallabor für Mutagenitätsprüfung der Deutschen
Forschungsgemeinschaft, Freiburg, F.R.G.

INTRODUCTION

The production of micronuclei as a result of chromosome aberration has been known for many years. Only recently, however, has there been interest in micronuclei for the purpose of rapid screening of mutagens in the environment, as a result of pioneer work by Schmid et al. (1-4). In recent years, a substantial number of different classes of chemical compounds has been tested with the micronucleus test in various laboratories.

Experiments have revealed that the micronucleus test is a simple and practical in vivo cytogenetic procedure for detecting both chromosome breaking agents (clastogens) and agents causing chromosome loss due to partial impairment of the mitotic apparatus (3-5).

Although micronuclei are known to occur in different cells and tissues of various organisms, the term "micronucleus-test" (mt) refers to a procedure in which the bone marrow of in vivo-treated mammals is analyzed for the presence of micronuclei in the anucleated young erythrocytes. For a detailed description
of the nature of micronuclei, methodological aspects, advantages, limitations and other features of the method, the reader is referred to the review articles by Schmid (3-5).

The aim of this paper is to review and tabulate the results obtained so far with the mt. If not otherwise stated, the tables contain only results obtained in anucleated young erythrocytes. It should be mentioned, however, that several authors have reported findings in other bone marrow cells in addition to those obtained in erythrocytes, for example by means of the "nucleus anomaly test" or other modifications of the mt (1,6-8). These additional findings are not included in the tables, as the great majority of induced micronuclei present themselves in the anucleated young erythrocyte (3,5,6) and the nearly unlimited supply of scoreable young erythrocytes as well as the ease of scoring them for the presence of micronuclei are important features rendering the mt practicable for screening purposes (5).

The mean spontaneous incidence of micronucleated erythrocytes (MNE) are very low, and their range in individual animals quite narrow. For mice and Chinese hamsters, for example, the mean incidences of MNE among the total erythrocytes scored amount to 0-0.7% for individual animals (9). Similar results have been obtained in other laboratories as well as with other species (10-12).

It is well known that—as in other cytogenetic methods—various factors can influence the outcome of an experiment. These relate either to specificities of the compound and test material in question (e.g., relative toxicity and cytotoxicity, mechanisms of action), or to the test protocol (e.g., treatment and preparation of bone marrow, mode of scoring erythrocytes). Such factors have been described in detail elsewhere (4-6,8,13).

These factors must be considered when comparing results from different laboratories. A survey of the literature has revealed that such factors influence results mainly in quantitative terms (e.g., shapes of dose-response curves), whereas the reproducibility of findings in qualitative terms is very satisfactory. For the evaluation of the mt data, therefore, the "yes-or-no-approach" has been used as follows.

Any compound revealing a statistically significant increase in MNE over the spontaneous level of concurrent controls in one or more dose groups was considered by us to be a mutagen in this test system, and marked with a plus sign (+). Such signs were also used in the absence of a statistical evaluation, as long as the treated group(s) showed an increase over the spontaneous level by a factor of 3 or more. Compounds showing no effects