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**EVALUATION AND TESTING OF
DRUGS FOR MUTAGENICITY :
PRINCIPLES AND PROBLEMS**

Report of a WHO Scientific Group

WORLD HEALTH ORGANIZATION

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WHO SCIENTIFIC GROUP ON THE EVALUATION AND TESTING OF DRUGS
FOR MUTAGENICITY: PRINCIPLES AND PROBLEMS

Geneva, 5-10 July 1971

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EVALUATION AND TESTING OF DRUGS FOR MUTAGENICITY : PRINCIPLES AND PROBLEMS

Report of a WHO Scientific Group

A WHO Scientific Group on the Evaluation and Testing of Drugs for Mutagenicity: Principles and Problems met in Geneva from 5 to 10 July 1971. The meeting was opened on behalf of the Director-General by Dr V. Fattorusso, Director, Division of Pharmacology and Toxicology, who outlined the terms of reference for the present meeting in relation to the WHO programme for the promotion of drug efficacy and safety.

1. INTRODUCTION

The Seventeenth World Health Assembly in 1964 adopted a resolution¹ which requests the Director-General "to undertake, with the assistance of the Advisory Committee on Medical Research, the formulation of generally acceptable principles and requirements for the evaluation of the safety and efficacy of drugs."

In compliance with this request four previous WHO Scientific Groups have been convened to deal with Principles for Pre-Clinical Testing of Drug Safety; Principles for the Clinical Evaluation of Drugs; Principles for the Testing of Drugs for Teratogenicity and Principles for the Testing and Evaluation of Drugs for Carcinogenicity.² The present Scientific Group was convened to discuss the evaluation and testing for mutagenic effects of substances that may be of therapeutic interest.

The Group considered that all drugs should be evaluated for possible mutagenic action. Such evaluation may or may not indicate the need for testing. A set of priorities for the selection of drugs for testing was suggested. When reviewing the test methods available, the Group paid particular attention to those experimental procedures that offer a useful starting point for mutagenicity testing in animals and man and drew attention to certain procedures that seem especially likely to be useful in the near future.

¹ Resolution WHA17.39 (*Off. Rec. Wld Hlth Org.*, 1964, No. 135, p. 17).

² *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 341; 1967, No. 364; 1968, No. 403; and 1969, No. 426 respectively.

Because knowledge of mutagenicity is increasing rapidly and new or improved test methods may soon be available, it is difficult to recommend standard procedures and "inadvisable to establish and prescribe rigidly formulated regulations specifying in detail the tests to be performed."¹ However, the Group endeavoured to lay down the basic principles that should be applied to the evaluation and testing of drugs for mutagenic risks.

The interpretation of the results of testing and their value in making benefit/risk assessments were discussed. In this as in some other areas of toxicology, extrapolation of test results in terms of human risk is a difficult matter that requires a careful interdisciplinary approach.

2. GENERAL CONSIDERATIONS

In recent years there has been widespread and increasing concern that drugs as well as other environmental chemicals may present a potential hazard to mankind by causing gene mutations or chromosome aberrations. This report confines itself to the study of drugs, which are defined as "substances or products that are used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."²

It is the responsibility of the scientific community and the health agencies to:

- (1) determine whether a potentially serious mutagenic problem exists;
- (2) define the magnitude and significance of the problem;
- (3) recommend appropriate safeguards to correct or minimize the health hazards to the population and the individual;
- (4) encourage research on mutagenesis and direct education.

Some observations on these tasks are made below.

(1) *Existence of a potentially serious mutagenic problem*

Although it is not known how much mutagenesis in man is due to drugs, concern that a serious problem may exist stems from a number of observations.

(a) Many substances have been shown to cause gene mutations in micro-organisms and in insects.

¹ WHO Regional Office for Europe (1964) *Symposium on the toxicology of drugs*, Copenhagen (mimeographed document). A limited number of copies of this document are available on request to persons officially or professionally concerned with this field of study. Application should be made to the WHO Regional Office for Europe, Copenhagen, Denmark.

² *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 341, p. 7.

(b) The induction of mutations by some drugs has been demonstrated in mammalian systems *in vivo* and in human somatic cells.

(c) In man, significant frequencies of chromosome aberrations have been observed in spontaneous abortions and in newborn infants, although it is not known what part drugs might have played.

(d) The use of drugs that affect nucleic acids is increasing, both in children and in adults with non-malignant disorders, e.g., psoriasis, virus infections, and conditions associated with altered immunological reactivity.

(2) *Magnitude and significance of the problem*

Because of the genetic complexity of man, there are immense possibilities for mutation. There is no valid information regarding recent changes in human mutation rates because no systematic population monitoring has been performed. Genetic diseases are, however, becoming relatively more important owing to the reduction in the incidence and severity of parasitic and bacterial diseases.

Two main types of genetic damage are recognized: chromosome aberrations and gene mutations. These may affect either somatic cells or germinal cells. Although damage to either cell population may have serious consequences, from the public health standpoint mutations in germinal cells are of paramount importance, as they present a hazard to future generations.

While the relation between the ability of a chemical to produce mutations in experimental test systems and its ability to affect humans is not firmly established, the potential hazard to the population is of such magnitude that some action should be taken immediately on the basis of the best currently available knowledge.

(3) *Safeguards to correct or minimize the health hazards to the population and the individual*

The reason for the uncertainty in predicting from animals to man probably lies in our inability to detect damage induced in human cells rather than in any difference between human and animal susceptibility to mutagens. Indeed, virtually all our information concerning the genetics and cytology of man and the higher animals supports their essential similarity. At the present time, no single test or panel of tests is available for making accurate and reliable predictions of mutagenicity in man. Accordingly, attempts to formulate rigid recommendations on the precise nature of routine tests would be detrimental to current and future scientific endeavour in this field. The rest of this report should be interpreted in the light of these statements.

Since there is no unanimity in the scientific community on the best test or tests to use for evaluating the mutagenic effects of drugs, the choice

must be left to the discretion of responsible advisers. Their decisions may be influenced by the expertise and facilities available locally. Variation in the choice of tests may, in fact, be desirable, so that a wider diversity of results and experience can be obtained.

A number of experimental procedures have been developed for detecting and measuring the mutagenic effects of drugs (see section 4). Special importance must be attached to test systems that take into consideration sound pharmacological principles and that lend themselves to the study of such factors as dose response, drug absorption, distribution, receptor-site exposure, metabolism, elimination, interactions between drugs, and interactions of drugs with other chemical or physical agents and with viruses.

(4) Research and education

Since no single test or panel of tests can be expected to fulfil all the necessary requirements for reliable prediction in the foreseeable future, exploration of a variety of techniques and systems should be encouraged, with the aim of developing a relatively accurate panel of tests.

In the field of toxicology, it has seldom been the practice to conduct collaborative studies on routine methods, and little attempt has been made to co-ordinate procedures. Mutagenicity testing offers a real opportunity to initiate such studies prior to the widespread use of these methods. Accordingly, the Group strongly recommends that adequate financial support be given by appropriate agencies to fundamental and applied scientific research in this field. Furthermore, educational and training efforts should be directed towards fostering an interdisciplinary approach to such research, and especially practical collaboration between geneticists and pharmacologists.

3. DRUGS TO BE EVALUATED AND TESTED

3.1 Evaluation and testing

A distinction is drawn between the evaluation and the testing of a drug for mutagenicity. Evaluation may be based on information other than the results of an experimental study in animals, such as the characteristics of the drug, the manner in which it is likely to be used, and epidemiological evidence. Evaluation should also take into account the known structural, biochemical, and pharmacological properties that may cause or be associated with genetic damage. Such evaluation may indicate or discount the need for experimental studies in animals; for example, compounds may not need to be tested if they belong to a well-studied chemical class that has not been found to have mutagenic effects by previous tests or other appropriate evaluation. If, however, a drug has been identified as a

mutagen in animal experiments, a substantial number of chemically and pharmacologically related compounds should also be tested and not merely one or two members of each group. Such comparative testing may identify those agents with the lowest mutagenic risk.

3.2 Priorities for testing

Shortages of manpower and of specialized research institutions make it impossible to submit all available drugs to a comprehensive mutagenicity test. For this reason, priorities for mutagenicity testing of existing and new drugs should be established as follows:

3.2.1 *High priority*

- (1) Compounds that are chemically, pharmacologically, and biochemically related to known or suspected mutagens
- (2) Compounds that exhibit certain toxic effects in animals, such as:
 - (a) depression of bone marrow at tolerated doses
 - (b) inhibition of spermatogenesis or oogenesis at tolerated doses
 - (c) inhibition of mitosis (e.g., in intestinal epithelium and other rapidly growing tissues) at maximum tolerated doses
 - (d) teratogenic effects at maximum tolerated doses
 - (e) carcinogenic effects
 - (f) causation of sterility or semi-sterility in reproduction studies
 - (g) stimulation or inhibition of growth or synthetic activity of a specific organ, cell or virus
 - (h) inhibition of immune response at maximum tolerated doses
- (3) Drugs that are often used over a period of years particularly in children and young adults
- (4) Drugs that are prescribed for a large proportion of the population
- (5) Drugs that are used for general prophylaxis
- (6) Drugs subject to widespread abuse
- (7) Drugs that come in contact with sperms in high concentrations, e.g., substances used for sperm preservation and vaginal contraceptives.

3.2.2 *Low priority*

There are many groups of drugs that have been in medical use for years and for which there are no chemical, toxicological, or other indications of

mutagenic action. A few representative compounds of each chemical group should be tested.

3.3 Evaluation and testing of new drugs

New drugs should always be evaluated for mutagenicity.

(1) Compounds chemically, biochemically, or pharmacologically related to known or suspected mutagens should be submitted to screening tests for mutagenic potential prior to the first therapeutic trial.

(2) All compounds showing any of the toxic effects listed in section 3.2.1 and all compounds belonging to a new or little studied chemical class should be tested before formal therapeutic trials.

3.4 Biological substances

Mutagenicity testing of biological substances poses special problems. For example, some live vaccines are known to cause chromosomal damage in man. In setting priorities for these products, agents that contain live micro-organisms or affect DNA should receive special attention.

4. METHODS OF TESTING

Testing for mutagenic activity should be considered as part of the overall toxicological procedure and may be incorporated into the existing testing programme. For example, subacute and chronic toxicity studies may be modified to include dominant lethal tests and cytogenetic studies.

Since no single test or battery of tests can be expected to detect and characterize all mutagenic agents, the use of several tests is desirable. It is, of course, to be expected that the proposed methods will be modified and that new methods will supplant some of those discussed here.

4.1 Specifications of the drug ¹

Adequate specifications should be available before mutagenicity studies are made. These specifications should identify the drug, define its stability, and establish limits for impurities. If the specifications are altered for any reason, for example, as a result of modification in the method of preparation, it is necessary to assess the effect of this in relation to the mutagenicity studies carried out on the original drug preparation.

¹ This section is slightly modified from section 4.2.1 of the report of the WHO Scientific Group on Principles for the Pre-Clinical Testing of Drug Safety (*Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 341, p. 11).

The physical characteristics of the drug—for example, solubility and particle size—have an important influence on biological activity. The nature of the vehicle is also relevant.

4.2 Species for mutagenicity tests

It is recommended that mutagenic tests of drugs should primarily be done in mammals. A number of submammalian test systems using viruses, micro-organisms, drosophila, fishes, birds, and plants are also available for the study of specific questions.

The use of submammalian test systems and *in vitro* cell cultures (even tests with human cells) should be regarded as ancillary procedures. Although results obtained from viruses and micro-organisms are often not directly relevant to mammals, they may help in explaining basic molecular mechanisms.

Mice, rats, and Chinese hamsters are the species most frequently used for mutagenicity tests. For these species substantial background information is available. It is desirable that before a compound is considered non-mutagenic it should be tested in man as well as in a laboratory animal (see sections 5 and 6).

4.3 Factors influencing testing in mammalian systems

4.3.1 *Absorption, distribution, metabolism, and excretion of the drug*

The pharmacokinetic behaviour and metabolism of a drug may vary from one species to another and this increases the difficulty of predicting its effects in man. When choosing animals for mutagenicity investigations it is therefore necessary to take into account the ways in which the drug is absorbed, distributed, metabolized, and excreted both in the animal species and in man.

Important information will also be gained from studies in which drug concentration at the target organs (e.g., testis, ovary, or bone marrow) or in the cells is measured.

Administration of a drug can stimulate or inhibit the enzymes responsible for its metabolism or for the metabolism of another drug. Therefore enzyme induction and inhibition should be taken into consideration in mutagenicity trials if multiple administrations are used.

4.3.2 *Other factors*

The species, strain, age, sex, and diet of the animals, the nature of their housing, the presence of infectious diseases, and interactions of the

drug with other substances may all influence the results. If these factors are not controlled the results can be misleading.¹

4.4 Experimental procedures²

4.4.1 Drug administration

For initial screening purposes, attempts may be made to maximize the response. This may be done by choosing a route of administration that will assure high tissue and blood levels of the compound. If such studies give positive results, they must always be followed by a definitive experiment in which the drug is administered by the same routes as used clinically.

It is desirable that both single and multiple doses of a drug be tested.

The tests are usually conducted at three different dose levels. The highest dose should be so chosen that it causes clinical, haematological, biochemical, or anatomical changes, that is to say, toxic effects, but it should be consistent with the survival of a majority of the animals. The lowest dose should be close to the pharmacological threshold dose of the substance for the species concerned. The choice will be influenced by the intended therapeutic regimen in man. When choosing doses it is also necessary to take into account possible differences of sensitivity between the animal species and man.

4.4.2 Controls and experimental size

Experiments must be run with adequate controls. Statistical procedures should be used to take account of the variability of the test and determine the size of the test and control groups. Cumulative data from control groups of different experiments may be used to monitor the stability of the test system.

4.4.3 Presentation of results

All information on mutagenicity tests should be recorded in detail and presented in an organized form. The items that should be collected and filed are essentially the same as those recommended for carcinogenicity testing.³ A suitable summary of these data should be published in the scientific literature or otherwise made available to all those interested. For obvious reasons, such publications cannot contain every important detail. They must, however, include sufficient information on the chemical structure and purity of the test compounds; the dose and route of administration; the solvents or suspending media; the experimental test systems and

¹ For further details, see sections 4.1.2 to 4.1.5 in the report of the WHO Scientific Group on Principles for the Testing and Evaluation of Drugs for Carcinogenicity (*Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 426, p. 11-14).

² Further details of these procedures can be found in the references listed on p. 18.

³ See : *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 426, p. 16.

procedures; the number, sex, and strain of the animals; positive and negative controls; and statistical methods. Negative results may be reported in an abbreviated form, but more detailed information should be made available by the investigator on demand. If negative results are at variance with the previous data of another investigator, the information should be presented in detail and possible explanations for the discrepancies should be discussed.

Positive results must be documented in such a way that the experiment can be properly evaluated and can be repeated in every detail by other investigators. Appropriate statistical methods should be used and reported. The biological significance of the results should also be discussed and reference should be made to previously published results obtained with the same or related compounds.

Data should be collected and presented in forms suitable for storage and retrieval.

4.5 Suggested methods of mutagenicity testing

Although there is no unanimity of opinion in the scientific community as to the best procedures for testing drugs for mutagenicity, some scientific committees on related questions have already made recommendations that could reasonably serve as a starting point. These scientific committees have also stressed the need for frequent re-evaluation of procedures and changes in methodologies as new techniques are developed.

The Group believes that it is reasonable to choose provisionally from those tests that are in current use. Representative examples include the dominant lethal test, *in vivo* cytogenetic methods, host-mediated assays, somatic cell genetic systems for detection of gene mutations, scoring of translocations in meiotic preparations of mouse testis, induced chromosome abnormalities in early embryogenesis in mammals, scoring of structural and numerical chromosome aberrations in unfertilized oocytes, gene mutation studies in germ cells, and the detection of translocations by fertility tests of F₁ offspring. In general, the tests are designed to detect gene mutations or somatic or germ cell chromosome abnormalities. Each test has advantages and disadvantages that must be weighed when selecting a panel of tests.

In addition, there are a number of research areas that are promising and may provide useful test methods in the future. These include pachytene mapping, fluorescent chromosome analysis, denaturation-renaturation analysis of chromosomes, differential susceptibility of various somatic and germinal cell types to mutation induction, automated chromosome analysis, assay of body fluids for mutagenic substances on micro-organisms or other indicator systems and use of sequestered cell indicator systems in human hosts.

The above lists are not exhaustive and they are not intended to exclude from consideration any tests that have been omitted.

It should be emphasized that, in certain special cases, after screening procedures have left doubts on interpretation, other currently available tests may be needed to assist in the evaluation of the problem. An example is the use of the specific-locus test to evaluate gene mutations directly in germ cells of mammals after chromosomal or gene mutations have been detected by other techniques.

5. IN VIVO STUDIES IN MAN

Studies in man can be considered in two categories.¹ The first is examination of individuals and the second is epidemiological. These may be limited by medical, ethical, and legal considerations. The design is often complicated by uncontrollable variables.

5.1 Studies of individuals

- (a) chromosome examination in somatic cells
- (b) studies of chromosome aberrations in germ cells (spermatogenesis, oogenesis), which should be made only in special circumstances
- (c) human host-mediated assay

5.2 Epidemiological studies (population monitoring)

Epidemiological studies can be used to detect the mutagenicity of an agent missed in the initial screening, although the many uncontrolled variables are a disadvantage.

(a) Chromosome examination of a fetus delivered by spontaneous abortion: the time from conception to detection of abortion alters the results materially and, as in any epidemiological study, it is difficult, if not impossible, to determine the etiology.

(b) Chromosome aberrations among newborn infants.

(c) Sex ratio shift: the human sex ratio is influenced by many factors, so that any shift is difficult to interpret and this method will only detect gross effects.

(d) Marker phenotypes: an expensive procedure that can be expected to detect only gross changes and that suffers from the disadvantage that it is difficult to reach an exact diagnosis, particularly as phenocopies are possible.

¹ Further details of these studies will be found in the references listed on p. 18.

(e) Somatic cell markers: a variety of somatic cell markers including enzyme activity and chromosome and protein markers, such as haemoglobins, are being developed to detect changes in cells from individuals and from populations; these methods are promising, but are in an early stage of development.

6. INTERPRETATION OF RESULTS

The decision that mutagenic activity in animals is relevant to man presents problems similar to those in some other fields of toxicology. The confirmation in man of a positive mutagenic finding in experimental animals may, however, be more difficult to establish than non-mutagenic toxic effects. A positive finding in a species should be considered as an indication of potential mutagenic activity in man unless relevant differences in metabolism, pharmacokinetic behaviour and/or pharmacological effects can be demonstrated between the species used and man. If, however, such differences are observed then the relevance to man of the positive mutagenic findings should be questioned.

6.1 Dose-response relationship

As in other areas of toxicological testing, the dose-response relationship is important and should be established whenever feasible.

The interpretation of the dose-response relationship should also take into account the possibility that the mutagenic effect of a compound may be due to two or more different mechanisms, acting, for example, during different phases of the cell cycle, and separate dose-response curves should be established.

It is also important to correlate mutagenic dose-response curves with those of other important biological effects. This is particularly true for the processes involved in absorption, biotransformation, and excretion of the drugs, as well as for their penetration through biological barriers. Efforts should be made to correlate the mutagenic dose-response curves with those of drug concentrations in the target organs (testis, ovary, bone marrow, etc.) and in the cells. Changes in metabolism and excretion due to overloading with drugs, stimulation or inhibition of drug-metabolizing enzymes, and interaction with concomitant drug therapy should be taken into consideration.

6.2 Interpretation

The interpretation of results can be meaningful only if the experiments are well conducted. Judgment as to the use of the drug under investigation can be made only by informed experts who have taken into consideration

all the factors in the investigations, including the reconciliation of conflicting test results, other biological information on the compound under consideration, as well as its intended use. Periodic reappraisal of decisions will be necessary in the light of expanding knowledge and improvement of techniques.

7. BENEFIT/RISK ASSESSMENT

Although a precise benefit/risk assessment applicable to clinical practice is impossible owing to lack of information, the physician is still faced with the problem of having to decide when to use drugs of known and unknown mutagenic potency. Plainly there is no difficulty in deciding to use a known mutagen in serious or life-threatening disease, but mutagens are increasingly being used in diseases that may run a prolonged course, during which the patient may reproduce. Such diseases include psoriasis, rheumatoid arthritis, and other conditions associated with altered immune reactivity. The use of some antiviral and antimicrobial agents may present similar problems.

It is hard to estimate the absolute amounts of expressed damage resulting from mutations, but the hazard can be reduced by various procedures. For example, where known mutagenic drugs are used in either sex, measures to prevent procreation during and for a few months after treatment are desirable. This practice is already being followed for patients receiving ionizing radiation. Again, where there is a choice of several drugs of known mutagenic potential, the drug with the smallest mutagenic risk for the individual and the population should be chosen.

Finally, it is necessary to take into account the strength of the evidence for mutagenicity, the availability of alternative treatments, the nature of the disease, and the status of the patient.

8. RESEARCH NEEDS

In estimating the amount and kind of research that will be needed for an adequate understanding of chemical mutagenesis, it is instructive to compare the many complexities of this field with the fewer, but still difficult, problems of radiation-induced mutagenesis. For example, in contrast to the small number of qualitatively different types of ionizing radiation, there is a vast and increasing number of chemically different classes of drugs. Whereas the penetration of radiation to the germ cells in animals can be determined with precision and dosimetry is easy, with chemical mutagenesis the pharmacokinetics of each drug have to be considered, including the determination of how much of the compound (or its metabolites) reaches the target cells, how long it remains there, and how these parameters vary

under different conditions of route of entry and administered dose. All these factors increase the uncertainty of extrapolations from one organism to another and even from one germ-cell stage to another.

In addition to the above complexities, others that were not foreseen have already been revealed by the results obtained from the limited number of studies so far made on chemical mutagenesis in mammals. For example, it has been found that, for several alkylating agents tested, the ratio of gene mutations to chromosome rearrangements in the mouse is much lower than with ionizing radiation. This is surprising since for micro-organisms, *drosophila* and higher plants, the ratio of gene mutations to chromosome rearrangements has long been known to be higher for chemicals than for ionizing radiation.

It is apparent that, although the genetic hazard of individual drugs can be tested to some extent, our best hope of being able to cope effectively with the problem presented by the bewildering array and steadily increasing number of drugs lies in the possibility that basic research will be able to elucidate some useful general principles. It is also abundantly clear that much more research will be required to unravel the complexities of chemical mutagenesis than was necessary for progress in the understanding of radiation mutagenesis.

Among the general principles that require elucidation are the basic mechanisms of chemical mutagenesis at the molecular level. Substantial progress has already been made in this field. Although protection against genetic hazards is not dependent on a complete understanding of molecular mechanisms, support of research in this field should be continued and expanded, for it will undoubtedly contribute significantly to the development of testing procedures.

9. CONCLUSIONS AND RECOMMENDATIONS

- (1) All drugs should be evaluated for mutagenic potential. Such evaluation may or may not include specific testing.
- (2) If mutagenicity testing is deemed necessary, priorities may have to be established, and the report offers guidelines for this purpose.
- (3) No specific test or panel of tests is recommended, but methods suitable for initiating a test programme are listed.
- (4) In addition to those tests in current use there are a number of research areas that are promising and may provide useful test methods in the future.
- (5) Mutagenic testing requires special attention to both genetic and pharmacological principles.

(6) The importance of co-ordination of test procedures, data recording and information services is stressed.

(7) Increased support of fundamental and applied scientific research in mutagenesis is strongly recommended.

(8) Educational and training efforts should be directed to fostering an interdisciplinary approach by geneticists and pharmacologists.

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