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**PRINCIPLES FOR THE TESTING  
OF DRUGS  
FOR TERATOGENICITY**

**Report of a WHO Scientific Group**

**WORLD HEALTH ORGANIZATION**

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**WHO SCIENTIFIC GROUP ON PRINCIPLES FOR THE TESTING OF DRUGS  
FOR TERATOGENICITY**

*Geneva, 14-19 November 1966*

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# PRINCIPLES FOR THE TESTING OF DRUGS FOR TERATOGENICITY

## Report of a WHO Scientific Group

A WHO Scientific Group on Principles for the Testing of Drugs for Teratogenicity met in Geneva from 14 to 19 November 1966. The meeting was opened on behalf of the Director-General by Dr P. M. Kaul, Assistant Director-General. He outlined the terms of reference for the present meeting as part of the WHO programme for the promotion of drug safety.

Dr. J. G. Wilson was elected Chairman, Dr H. Tuchmann-Duplessis Vice-Chairman, and Dr. H. M. Peck Rapporteur.

### 1. INTRODUCTION

“Principles for Pre-Clinical Testing of Drug Safety” is the title of a report of a WHO Scientific Group<sup>1</sup> in which the general concept of the evaluation of the safety of drugs<sup>2</sup> in animals and the subsequent extrapolation of animal data to man are discussed.

The principles for the pre-clinical testing of a new drug as presented in that report refer to single and continuous administration by various routes to appropriate species of animals. The need for biochemical studies (including absorption, distribution, transformation and elimination of the drug) is stressed. It is further emphasized that, especially with regard to those factors, due consideration should be given to species and strain differences. The recommendations arising from these considerations may be studied in detail in the report.

Since the above-mentioned Scientific Group had not dealt with the teratogenic effects of drugs, a further Scientific Group was convened to consider this complex problem. The Group reviewed the methods available

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1966, 341.

<sup>2</sup> The WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety defined a drug as a “substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient” (*Wld Hlth Org. techn. Rep. Ser.*, 1966, 341, 7).

for testing drugs for teratogenicity and their scientific basis, attempted an appraisal of their value for predicting teratogenic effects in man and outlined recognized testing procedures and their limitations. The lack of knowledge of developmental processes was found to be a major factor in the difficulties encountered, which, in the view of the Group, could be overcome only by a continuous, concerted research effort of specialists in the various scientific disciplines involved.

## 2. GENERAL CONSIDERATIONS

Drugs have been used in teratological investigations for a number of years, but until very recently such studies have been concerned with the incidence, manifestations and mechanisms of developmental deviations and not with the practical matter of screening for teratogenicity prior to clinical trial. The urgent need for more concern with this aspect was harshly brought to the attention of the world by the clinical experience with thalidomide. This abrupt broadening of interest in teratology has caught the basic researcher unprepared to do what he is now asked to do—namely, recommend reliable and practicable methods for the pre-clinical testing of drugs likely to be taken by women of reproductive age. The necessary background of experience in testing methods does not exist in laboratories that have previously been concerned primarily with fundamental problems. Conversely, laboratories versed in the exacting methods of toxicology lack the essential knowledge of reproductive and embryological processes to perform critical teratological tests. This need to bring together information from two separate and highly specialized fields has found the regulatory agencies, which are expected to provide guidelines for the teratological testing of drugs, in the difficult position of having no fully informed source upon which they can depend for practical measures and advice.

In an effort to meet this urgent need WHO assembled the present Scientific Group, consisting of specialists in embryology, pharmacology, toxicology and human and experimental teratology, to discuss possible recommendations for the teratological testing of drugs, based on the most pertinent information derived from all of the fields represented. It was not expected, nor did it happen, that any specific set of procedures could be authoritatively stated as being necessary to ascertain whether a drug would be absolutely free from teratogenic hazard. Such safeguards are not possible for any drug, regardless of how and by whom it is used. Nevertheless, the Scientific Group set about the difficult assignment of formulating the most reliable recommendations possible, in spite of conflicting opinion, incomplete information and inappropriate current practice. The major handicap was the lack of substantial or, in some cases, any information

on such crucial subjects as teratogenic mechanisms, embryonic as well as maternal metabolism of drugs, and metabolic pathways in animals and man.

It was recognized that drugs may interfere with reproductive processes in other ways than by causing malformation or death of the embryo, for example, by arresting gametogenesis or preventing fertilization. The scope of the present recommendations, however, is limited to the effects of drugs on post-conceptual developmental stages. These cover the fertilized ovum, cleavage, the blastocyst, the embryo, the foetus, and the post-natal animal. The greatest teratological hazard is generally accepted as occurring in the embryonic period, when tissue differentiation and organogenesis occur. Evidence is accumulating, however, to indicate that developmental deviation can also be induced by adverse influences during the entire gestational period. It is also evident that development in the post-natal period may be diverted in both structural and metabolic terms by agents applied during the pre-natal period. The recommendations that follow relate largely to the period of the embryo when, undoubtedly, most malformations begin to develop. It is, however, recognized that developmental deviations of a functional or biochemical nature may also be induced at other stages.

It should, therefore, be understood that the use in this report of the word "malformation" does not necessarily connote only structural maldevelopment but may also include functional and biochemical entities. For the present purpose *teratology* is considered to concern developmental deviations of a structural, functional or biochemical nature that are initiated pre-natally. The functional category includes behavioural parameters and the biochemical category metabolic parameters. "Embryopathy" is synonymous with "developmental deviation".

### 3. TEST ANIMALS

#### 3.1 Species

Mice, rats and rabbits are the test animals most frequently used. They have been selected primarily on the basis of prior experience with teratogenic agents and of the availability of these animals in most laboratories. Otherwise the choice is arbitrary, in the absence of any indication, as yet, of a species with a susceptibility close to that of man.

The chick embryo contributes greatly to basic embryological knowledge. However, for the screening of drugs for teratogenicity its use is not recommended. It is too sensitive to a wide range of agents and affords no parallel with the anatomical and physiological relationship existing between the pregnant mammal and her conceptus.

Although it has been possible in the mouse, rat and rabbit to demonstrate teratogenic activity by all substances that have been shown to be teratogenic in man, there is no absolute assurance that negative results obtained by testing drugs in these species can be used to predict that an agent will lack teratogenic effects in man. Similarly, it cannot be said that agents that are teratogenic in high doses in these species will necessarily produce teratogenic effects in man at therapeutic dose levels.

Other species, such as pigs, dogs, cats, and monkeys, are being used in teratological studies, but much less extensively. The high fertility and good susceptibility of the pig to teratogens commend it for more widespread use. Since the dog and the cat are widely employed in pharmacological studies, much should be known about the pharmacodynamics and metabolism of a specific drug prior to teratological studies in these two species, but their use for this purpose is limited by the relative scarcity of knowledge of their normal developmental processes.

The choice of certain monkeys appears to be logical because of their phylogenetic proximity to man, and it is hoped that the results of the studies now being made in a few centres will indicate that these primates are more useful than the rodents. Preliminary reports suggest that the susceptibility of the monkey embryo to teratological agents resembles that of the human more closely than does the susceptibility of embryos of any other species. Such results make it essential that the greatest possible resources and efforts be directed towards more intensive teratological studies in the monkey. Since such studies in these primates require special technical skills, financial investment, and close co-operation between various disciplines, the best approach would be by means of suitably located co-ordinated research units. It was also felt that the further investigation of certain lower primates (e.g., galagos), with a view to developing teratological screening techniques, might be fruitful, and it should be noted that in some species two pregnancies occur per year and each pregnancy may yield two offspring.

The idea that drugs could be routinely tested on women scheduled to have their pregnancies terminated for therapeutic reasons was rejected by the Group as undesirable and impracticable.

### 3.2 Numbers

When rodents are used the number of animals can be made large enough to satisfy statistical requirements. In the case of species more closely related to man, or possessing features of metabolism closely similar to those of man and having a particular value for certain special investigations, the number of animals should be as large as practicable, in order to obtain reproducible results.

### 3.3 State of health and standard of care

Animals that are to be used for teratological studies of drugs must be healthy and should be housed under the best possible environmental conditions. The best practices of animal care must be maintained; specific-pathogen-free animals would not be required under these conditions. It is advisable that strains with known genetically unstable constitutions be avoided. The animal quarters should provide constant temperature, adequate light and protection from noise or other interference. When temperature and light cannot be controlled, the seasonal variation of the reproductive activity of the animals must be considered. Caging should conform to the best standards available. The use of pesticides must be restricted. It must be remembered, particularly for drugs that act upon the central nervous system, that housing groups of animals in a single cage may increase the noxious effects of certain drugs. All animals should receive an adequate diet; since the administration of a drug may decrease or increase the food consumption of the treated animals, it may be necessary to adjust the food intake of control animals correspondingly.

## 4. DRUG DOSAGE AND ADMINISTRATION

### 4.1 Dosage

The choice of doses with which to initiate teratological studies should be made against the carefully considered background of the pharmacological and toxicological activity of the drug. There is a complex inter-relationship between lethal action upon the embryo, toxicity for the mother and teratogenic effect. The observer, therefore, should be aware that the action of the drug on the mother may affect the results of teratological studies and thus make their interpretation more difficult. In most instances dosage should be based on body-weight.

#### 4.1.1 *Range of doses*

The experimental doses should be selected with reference to the dose-response curves in the adult animal (e.g., in relation to the maximum tolerated dose, the  $LD_{50}$ , or the  $ED_{50}$ ). Thus, the highest dose may be toxic but not lethal to the mother, while the lowest dose should, if possible, produce clinically significant effects.

It is recommended that at least one intermediate dose be employed. Should these doses be without teratogenic or lethal effect on the foetus, additional tests using higher doses may be performed until a level is reached that is lethal to the foetus or the mother.

#### 4.1.2 *Timing and duration of treatment*

Continuous dosage can determine whether the drug will have an effect on the conceptus. However, by giving single doses it is possible to establish when the drug produces its effect and the period of greatest sensitivity to it. Although it might seem logical to give a drug continuously throughout pregnancy, such a regimen may seriously alter the mother's metabolism of the drug and so mask a teratogenic action. Therefore, such tests should be supplemented by others in which doses are given only at specific times, since these may correspond to periods of special sensitivity to the drug under test, in general thought to coincide with the period of organogenesis.

#### 4.2 **Route of administration**

Special emphasis should be laid on those experiments in which the drug is given by the route to be used clinically, but in the intensive search for teratogenic activity other routes are important. It must be borne in mind that when the drug is given in the diet it is difficult to estimate the amount of drug consumed. Therefore, when the oral route is chosen it is recommended that administration by stomach tube or capsule be employed. It is important to determine the rate at which the drug is absorbed, whatever the route of administration. If different routes produce differences in metabolism, teratological tests should be done using each route.

#### 4.3 **Controls**

The control animals used in each experiment must be subjected to the same procedures as the test groups. Therefore they should be given the appropriate placebo (e.g., capsule or vehicle) by the same treatment regimen.

### 5. TYPES OF OBSERVATION

#### 5.1 **Personnel**

The observations must be supervised by a qualified scientist with knowledge of, and practical experience in, the reproductive physiology, embryology and anatomy of the test animal. If such a person is not available in the laboratory, testing should not be undertaken until arrangements have been made for supervision, or at least consultation, by a qualified scientist. When suitable supervision is available, technicians can be trained and entrusted to undertake routine breeding and examination of offspring. All questionable situations or specimens that the technician encounters should be referred to the supervisory scientist for final decisions. It is the responsibility of the supervising scientist to establish or adopt suitable methods

and techniques, where necessary utilizing published accounts in current scientific literature.

## 5.2 Breeding

The time of mating should be limited as much as possible in order to determine accurately the onset of pregnancy. At the end of the mating period successful copulation should be verified by a vaginal smear or other suitable technique. An effort should be made to estimate the time of fertilization. If this is not possible, pregnancy should be dated from the time of copulation. The rabbit offers an advantage in that the time of ovulation can be accurately determined. It is advisable to use females of comparable weight and age ranges in each test.

The parity of test females varies in practice; virgin females will be preferred if corpora lutea are to be counted to determine early wastage and failure to implant, but for other purposes proof of fertility may be desirable. Each female should be weighed when insemination has been verified and at regular intervals thereafter to determine her nutritional state and general health. Single caging of females is advisable to rule out possible effects due to crowding and group toxicity.

## 5.3 Treatment

Care should be exercised at the time of treatment so that the animals do not suffer excessive handling or undue excitement or trauma. Anaesthesia to avoid struggling by the animal is to be used with caution and in any case controls must be similarly handled. After treatment, daily weighing is useful in determining the progress of pregnancy, food consumption and the general well-being of the test animal. Spontaneous death of a treated animal should be followed by autopsy to determine the existence of pregnancy and the possible cause of death. Vaginal bleeding at times other than that of the usual "placental sign" should be recorded because it may be associated with resorption or abortion.

## 5.4 Removal of offspring

When near-term foetuses are to be studied, pregnancy should be interrupted a few hours or a full day prior to expected delivery to permit (a) counting of resorption sites and macerated or dead foetuses *in situ* and (b) salvage of all surviving foetuses from possible destruction by the mother (in several species of laboratory mammals the mother is said to devour some or all defective or moribund offspring). The mother may be killed or operated on by any method that does not result in unnecessary trauma to the foetuses. The uterus should be examined for the number and position of implantations. A difference between total implantations and

total corpora lutea is indicative of either pre-implantation loss or, possibly, early resorption. Most, if not all, established implantations leave a "metrial gland"<sup>1</sup> as an indicator, even if death and resorption of the conceptus does occur early. The number of resorptions is the difference between the total implantations and the total near-term offspring. Resorption sites vary from metrial glands to large sites containing more or less macerated foetuses and more or less involuted placentae.

### 5.5 Examination of foetuses

All foetuses, live or dead, are counted, weighed, sexed, examined for external malformations and either fixed for subsequent study of internal structures or autopsied in the fresh state. Variations in the quantity or colour of amniotic fluid should be noted. The placenta should be inspected and if there is any indication of deviation from the normal range, it should be weighed and, possibly, examined histologically. *All* fixed foetuses should be examined for internal abnormality—some by clearing methods for skeletal structure, others by fresh autopsy or sectioning of fixed specimens by methods that reveal internal organ structure. The freehand razor-blade method of preparing sections of rodent and rabbit foetuses has been found to be fast and sufficiently accurate for survey purposes. Abnormalities affecting tissue organization or differentiation will require viewing of conventional histological sections under the microscope. The number of animals to be studied by these various methods depends on the types of malformations and other considerations, but a significant proportion of foetuses in each test group should be studied for skeletal structure and the remainder for organ structures.

In the case of total resorption at term, it may be of interest to interrupt pregnancy at earlier stages to examine embryos before death, although in most cases it would be advisable to adjust the dose so as to obtain surviving foetuses at term. All of the foregoing observations should be recorded in detail on standardized forms.

### 5.6 Examination of post-natal animals

Because of increasing awareness of the possibility that developmental derangements may affect biochemical or functional (including behavioural) parameters, it is advisable to allow some offspring from appropriate test groups to be delivered and to survive until sexual maturity. Prior experience in the study of such animals is too meagre to warrant recommendations as to the types of biochemical or functional tests that can or should be done. The pharmacological action of the drug being tested may suggest

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<sup>1</sup> Metrial glands are conspicuous, highly vascularized nodules at the utero-mesometrial attachment.

that certain tests are appropriate, e.g., behavioural tests when drugs that act on the central nervous system have been used.

### 5.7 Criteria of a malformation

The problem of distinguishing between a minor variation and a malformation is a difficult one. The range of normal variations in each strain of each species must be determined in each laboratory, using the same study procedure as in the testing situation. This is best done not only by the routine study of control animals in each test but also by keeping cumulative records of variations observed in all untreated and treated control animals studied by the standardized methods. The rate of spontaneous malformation should also be determined from cumulative studies of untreated and treated control animals. After treatment with a test agent, not only defects that are traditionally recognized as malformations (cleft palate, renal agenesis, club foot, etc.), but also any exceptional, less frequent variations, if they occur in a percentage exceeding that arbitrarily set in a group of control animals, should usually be regarded as induced malformations.

There is a continuum of variation from the hypothetical norm to the extreme deviant, and there is no logical place at which to draw a line of separation. The distinction between minor variation and frank malformation, therefore, is an arbitrary one and each investigator must establish his own criteria and apply them to spontaneous and induced malformations alike.

A treatment that causes any demonstrable rise in the incidence of malformation above the spontaneous rate can be suspected of having a teratogenic effect. Statistical significance can be estimated by appropriate methods. When an increase in the incidence of malformations is so small as to require elaborate statistical methods to show it, the safest procedure is to increase the size of the test group. Some investigators adopt an arbitrary but sizable number of foetuses as the minimum to be used at each dose level, time of treatment, and drug under test. For example, 10 pregnant female rats will usually yield somewhat more than 100 implantations, which might be taken as the smallest number acceptable for each test group. If equivocal results are obtained, more animals should be added to each group.

The foregoing discussion is primarily applicable to small laboratory rodents and rabbits. The use of dogs, pigs or primates as one of the test species is recommended whenever feasible. Foetuses of these larger animals can be studied adequately by routine post-mortem and X-ray examinations. The number of animals in each test group will necessarily be smaller than when mice, rats or rabbits are used, but tests in the larger animals will usually be conducted after initial trials on smaller animals and will, therefore, often be confirmatory in nature. The need for animal tests intermediate between tests performed on the conventional laboratory animals and

clinical trials has been emphasized elsewhere in this report ; this is all the more important where the drug in question is likely to be used by pregnant women.

## 6. EVALUATION

### 6.1 Sources of error

In the performance of teratological studies, as in other biological tests, errors can arise if procedures are not followed accurately, and can lead to false conclusions.

Errors may arise from the faulty maintenance of the animal in the laboratory and from the selection of animals in an unsatisfactory state of health. Other factors include poor animal husbandry before the initiation of the experiment, during the period of treatment, and until the termination of the study. Mishandling of the animal, e.g., inconsiderate treatment, may also lead to false results.

The actual treatment of the animal with a drug may result in differences in food intake between the treated and the control animals, thus leading to a greater or a slower growth rate of both the mother and the foetuses.

Selection of unsuitable strains and species of animals, such as those that show a high incidence of spontaneous malformations or those known to be resistant to teratogenic procedures, may lead to unfair condemnation of a drug or to the approval of a drug that has unrevealed teratogenic properties. In such cases the use of a reference teratogenic substance would be helpful.

The use of an inadequate number of control and treated animals can lead to misinterpretations, owing to the occurrence of spontaneous malformations in certain strains and species. The selection of animals for the test and control groups must be randomized to prevent a statistical bias.

The faulty selection of drug doses can lead to error, since they may be too low to permit an adequate evaluation of teratogenicity or so high as to produce other adverse effects. If the doses are too high, foetal death may result, with no opportunity for teratogenic effects to be demonstrated. Apart from the matter of dosage, faulty timing and failure to recognize the sensitive stages of development can result in administration of the drug at a time at which no effect could be expected with a known teratogenic agent.

If the observations are not directed to the proper parameters, certain effects of the test drug may be missed. Thus it is necessary to examine the foetuses in each test group for external and internal malformations, including skeletal defects. Another source of error is the failure to allow enough animals to go beyond term to permit the recognition of delayed

post-natal developmental deviations. In studies in which post-natal observation is desired, a foster mother must be provided when the natural mother neglects her young or when the milk supply is inadequate.

One of the basic errors in the performance of teratological studies is failure to consider available knowledge about the drug's metabolism and pharmacological activity.

## **6.2 Significance of findings in animals**

The predictive value of teratogenic tests is still open to question. One of the difficulties of interpretation is due to the constant interaction between the two different biological systems, the mother and the conceptus. Theoretically, the significance of any teratogenic activity that may be observed can be assessed by taking into account the percentage of malformations obtained, the constancy of the results in several subsequent experiments, and the dose at which the teratogenic effect has been observed. If teratogenic effects are obtained in only one of three species of animals, the probability of their occurring in man may be low.

The value of animal screening is borne out by the fact that all drugs that have been established as teratogens in man can be shown to be teratogenic in animals. Likewise, drugs shown to be teratogenic in animals may be teratogenic in man under appropriate conditions of dosage and timing. However, generally the doses required to demonstrate teratogenicity in animals are relatively large.

It has been shown that the reaction of the embryo to exogenous agents depends to a large extent upon its genetic constitution. Furthermore, such reaction varies not only between different species but also within a given species from strain to strain and even between individuals of the same strain. The immediate causes of species differences in reaction to teratogenic agents are still largely unknown, but it has been suggested that they could be related to different metabolic pathways or possibly to the formation of noxious metabolites in some species but not in others.

## **7. PERSPECTIVES**

### **7.1 Interchange of information**

Until the basic biochemical and physiological processes of development are better understood, the interpretation of drug tests on animals will continue to be difficult. Although drug screening in animals is at present the best available approach to the problem of drug-induced teratogenicity in man, it must be accepted that tests in animals cannot guarantee complete safety. They may suggest, but cannot prove, that drugs act similarly on the embryos of laboratory animals and those of man. It is therefore neces-

sary that a new drug, however carefully tested in animals, be kept under close surveillance for several years after its introduction into clinical use.

It has been suggested that national agencies and drug-safety committees should establish a rapid, reciprocal exchange of information on adverse reactions to drugs. In this connexion special attention should be given to proven or suspected teratogenic effects pending the organization of an international programme for this purpose.

It is essential that further efforts be made to keep the medical profession informed of the continuing teratogenic risk of new drugs, even when these have been screened by approved methods.

The continuation and improvement of epidemiological studies of congenital malformations is badly needed to provide the base-lines necessary for a realistic appraisal of the cause-effect relationship that could be derived from drug-monitoring activities.

Contacts between administrative and professional groups within and between countries would be improved through national and international conferences, symposia, seminars, and appropriate communications media. It is also hoped that such meetings would facilitate international agreement on the testing and epidemiological procedures that could best be used to reduce the teratogenic hazard of drugs.

## 7.2 Co-operative research efforts

The international nature of the problem of drug safety testing is now fully recognized. Drugs manufactured in one country are often distributed to others. The need for internationally acceptable criteria and methods for testing justifies, and even requires, internationally organized and supported research.

Areas in which such research is needed include :

Embryonic metabolism in general and especially of drugs and biochemical substances that simulate commonly used drugs ;

Immunological processes that might affect the embryo and its relationship to the maternal system ;

Interference of drugs and their metabolites with the normal functions of the early placenta, i.e., the mammalian placenta during the period of teratogenic susceptibility of the embryo ;

Comparative biochemical and metabolic studies of the early embryos of relevant mammalian species, to ascertain whether embryos of different species might be more alike than their post-natal counterparts ;

Validity in teratological screening of tests done on cell, tissue, and organ cultures and on lower animals, using teratogenic and potentially teratogenic drugs ;

Basic teratogenic mechanisms at the organismic, cellular and subcellular levels.

A large-scale effort covering long-range research projects in a variety of fields would require well-planned laboratory work in a single centre, co-ordinated with the various national research activities.

The disciplines represented in a central institution might include :

*Embryology*, with emphasis on biochemistry, immunology, pharmacology and electron-microscopy ;

*Cytogenetics* ;

*Animal breeding* on a large scale, including breeding of primates.

It is unlikely that any national programme could cover effectively all of the subject areas in which studies are now urgently needed. Nevertheless, national efforts are to be encouraged in every way possible.

## 8. CONCLUSIONS

(1) At present no method of preliminary screening in animals can provide absolute assurance against the occurrence of a teratological reaction in human pregnancy. Nevertheless, it is believed that it should be possible greatly to reduce the risk by improved pre-clinical screening for teratogenic effects, especially with the exercise of sufficient care in the choice of appropriate species, time of testing and effective dosage levels.

(2) The predictive value of teratological screening can be enhanced by observing the procedures recommended in this report and by avoiding the sources of error described. Further improvement of the predictive reliability of tests can be expected when research provides the necessary information on basic mechanisms of teratogenesis. Because of the lack of key information in several areas related to teratology, extensive programmes of research must be undertaken if teratogenic risk to man is to be reduced to the lowest possible level.

(3) The limited knowledge of the fundamental developmental processes and the mechanisms of teratogenic drug action on the one hand, and the need for internationally acceptable criteria and methods for testing on the other, necessitate internationally organized, multi-disciplinary research efforts of long-range character.

(4) Teratological studies in primates should occupy a prominent place in research efforts.

(5) Since animal tests cannot with certainty predict teratogenic drug effects in man, it is essential that drugs be kept under close surveillance for several years after their introduction.

(6) Epidemiological studies of congenital malformations are an indispensable supplement to drug-monitoring activities.

(7) Further efforts must be made to inform the medical profession of the teratogenic risks presented by drugs in spite of their clearance through approved screening methods.

(8) In women, the balance between the therapeutic benefit and the teratogenic risk of a drug should be carefully assessed at all times during the reproductive span, especially when the possibility of pregnancy cannot be excluded.

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