Methods for Assessing the Effects of Chemicals on Reproductive Functions
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Experimental Methods in Embryotoxicity Risk Assessment

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1 SUMMARY*

Embryotoxicity is a hazard to the fetus arising from environmental, infectious, genetic and other agents. The manifestations of embryotoxicity include prenatal death, structural and functional defects and, in their mildest form, growth retardation of the conceptus. The embryotoxic outcomes have a 'normal' or 'spontaneous' occurrence in human populations upon which are superimposed any additional cases possibly arising from exposures to drugs, food additives, cosmetics and other chemicals from environmental sources.

Although it would be most desirable to have integrated screening systems capable of predicting a broad range of effects from mutagenesis to behavioural defects and, perhaps, carcinogenesis, such comprehensive test systems are not yet available. The development of such systems is dependent upon future research, and must be based on an understanding of the basic biological relationships between mutagenesis, teratogenesis and carcinogenesis.

Direct evidence for the embryotoxic potential of a substance can usually be secured only from animal experiments. However, animal tests are considered by some experts to be of low predictive value for man; only a few chemicals have been proven as teratogens in man compared to the hundreds exhibiting the embryotoxic potential in laboratory animals.

Screening for reproductive toxicity became a matter of legislation as long as 15 years ago in many countries. The currently used official procedures, especially those that are believed to mimic features of human teratogenesis, are considered by many to afford satisfactory safeguards. Alternative methods adapted from basic teratological research employ simple experimental systems ranging from individual cells and more or less isolated parts of mammalian fetoplacental units to embryos of non-mammalian species. According to a widespread opinion, these techniques represent an important complement to teratological research, but generally cannot replace the official procedures for regulatory purposes.

* Only the summary is included here because of space limitations. The full report can be requested from the authors.

More fundamentally, however, it must be recognized that a reliable test system should not only examine various features of embryotoxicity but must also be capable of screening for human embryotoxic metabolites if the *in vitro* techniques (including the avian embryo) are to be valid.

Probably the specificity of embryotoxic action of chemicals in humans resides neither in the basic morphogenetic processes nor in the unusual properties of placental transfer of xenobiotics alone, but also often in metabolic transformation within the maternal organism which frequently differs between species. Thus, any procedure using a non-human pregnant animal suffers from the possible introduction of an additional unknown variable. For this reason it is desirable to test not only the parent substance but also metabolites occurring in man. Blood sera of the exposed human individuals can in some cases be employed as their source.

In basic teratological research it is recommended to cease the search for an animal similar to man and turn to the more useful activity of investigating the possibility of using *in vitro* techniques for more exact estimation of the embryotoxicity dose range for a pregnant mammal. The major task of basic research, however, remains the investigation of the functional properties of embryonic, fetal, perinatal and postnatal morphogenetic systems and the factors underlying the sensitivity of their constituent cell populations to toxic agents coming from the environment. As to testing needs, an approach involving multilevel screening procedures starting with *in vitro* techniques is suggested as a priority selection system.

In the area of applied research, practical tests need to be devised starting from the most promising developments in basic teratological research. Such tests would then be eligible for trial and for standardization.

The regulatory agencies will need to collect and evaluate critically the information necessary for proposing new guidelines for embryotoxicity testing that will cover the range of chemicals to which man may be exposed in the present society. Meanwhile, basic research must aim towards a better understanding of the biological inter-relationships of the various possible effects on the fetus such as mutagenesis, teratogenesis and carcinogenesis arising from exposure to toxic chemicals.

More detailed discussion of methods and procedures for teratogenicity testing developed in Czechoslovak laboratories may be found in the papers published by the authors and their collaborators listed below.

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