Chapter III

Teratogenicity (Embryotoxicity) Studies: Design, Conduct, and Evaluation

3.1. Introduction

The principal source of evidence for adverse effects on fetal development that are recognized at term is teratogenicity studies in experimental animals. The design of these studies should be appropriate for the intended purpose, and their conduct should conform to high standards. This is necessary to provide assurance that the data used in risk estimation are sound. In this chapter only basic principles related to these elements are discussed. References cited in the text should be consulted for details regarding the design and conduct of such studies.

The aim of a teratogenicity, or prenatal, study is to investigate the potential of a test agent to cause fetal malformations, embryo-fetal death, fetal weight (or length) reduction, or adverse effects on maternal health. A number of guidelines are available for the design and conduct of studies appropriate for subsequent risk assessment (FDA, 1970; NHW, 1973; NAS, 1977; EPA, 1981, 1984a; OECD, 1981; CMEA, 1982; WHO, 1984). A teratogenicity study is usually conducted in at least two stages—primary and/or secondary. At the primary stage, the lowest doses that cause embryo-fetal effects and/or overt maternal toxicity as well as the type of embryo-fetal effects and toxicity produced are determined. Secondary, or special, studies are designed to determine the specificity of malformations, mechanisms of action, target cells, distribution and metabolism, and fetal levels of the test chemical or its metabolites. These studies are helpful in defining specific human risks from animal data.
The reliability of estimated teratogenic risk depends upon well-conducted experiments with adequate numbers of test animals, good animal husbandry practices, adequate maternal and fetal appraisals, and the availability of accurate experimental data. Information of questionable quality obtained from inadequately conducted experiments should not be used for risk analysis. The design of animal studies is appropriate for consideration of human-risk estimation when the following are clearly demonstrated: (1) presence or absence of maternal toxicity at each dose tested, (2) dose regimen and route of exposure similar to the major human exposure condition, (3) types of adverse fetal effects, and (4) doses showing positive and no observable effects on fetal development or maternal health together with the shape of dose-response curves.

### 3.2. Protocol

The protocol clearly states the objective of the study and provides details on the test chemical (code number, purity, composition, vehicle for suspension, and solubility), test species (descriptions of strain, body-weight range, age, source of supply, and method of animal identification), and experimental design (doses, route and duration of treatment, identification of and methods for measuring fetal and maternal endpoints, and intended methods of statistical analysis). Any deviations from the protocol during the conduct of the study must be justified and recorded as amendments.

### 3.3. Conduct of the Study

The test chemical is of defined purity; its stability, homogeneity, and concentration in the defined vehicle or diet for the duration of the dosing period is supported by analyses of an adequate number of samples. Exposure conditions simulate the major human-exposure conditions with respect to the route and duration. A suitable selection is made of dose levels—high (maximum maternally or fetally tolerated), low (no adverse fetal effects), and medium (some effects on fetuses or maternal animals). The mated females are dosed daily during the period of organogenesis, from days 6–16 of pregnancy in rats, days 6–15 in mice, and days 6–19 in rabbits, with the day of insemination considered as day 0 of pregnancy. Experimental animals are preferably from an outbred, healthy stock that is sensitive to known teratogenic agents. Animal husbandry in the animal colony includes efficient quarantine facilities, effective disease control, and stringent restrictions on intercurrent contagious