Chapter IX

Extrapolation of Reproductive Risks From Animal and Human Data

9.1. Introduction

Assessment of human reproductive risk from developmental toxicity data involves three steps: (1) conducting animal and, if possible, human studies; (2) evaluating these data; and (3) using these data in the extrapolation of reproductive risk to humans. The last step is derived from toxicology data and is based on a system of concepts and conservative suppositions. Some of these concepts, such as maternal health and its possible influence on fetal and postnatal development as well as the relative significance of fetal aberrations and malformations, have recently received considerable attention regarding their importance in human risk estimation. Based on these revised concepts and other newer ones that are logically admissible, a framework of risk extrapolation is proposed in this chapter.

Historically, developmental toxicity was ushered in by concerns about malformations in humans. Subsequently, many studies designed to examine the teratogenic potential of chemicals in animals were conducted. As a consequence, the bulk of data dealing with developmental toxicity pertains to teratologic effects, which are considered in greater detail in this chapter. A similar comprehensive evaluation of other endpoints of developmental toxicity is not possible at present because the relevant data are not available. Despite this consideration, it is important to examine the total developmental toxic response of the conceptus to a chemical and not malformation alone.

The judicious extrapolation of human risks from reproductive studies requires a comprehensive database, a broad base of knowledge, and familiarity with the performance of complex studies. In attempting to extrapolate
from data obtained in such studies to the human situation, consideration must be given not only to the differences but also to the similarities of the reproductive process in humans and animal test species. A reproductive study should be interpreted only by an experienced individual with a broad basic knowledge of the toxicology and metabolism of the test material.

Ethical considerations preclude testing new chemicals or suspected hazardous chemicals in humans. Thus, regulatory risk assessment consists of weighing evidence from in vitro and in vivo tests. In addition to the considerable difficulties in evaluating evidence from a number of these tests, there is an additional, and perhaps more questionable, assumption that the results are predictive for the human population. Therefore, data from epidemiological studies are extremely valuable when available to provide confirmation of the degree of correlation between animal and human susceptibility.

The basic toxicity studies that are conducted today have not changed fundamentally in the last 25 years. They are enlarged in scope, use refined measurement and analysis, and cost a great deal more, but they still too often provide a package of conflicting or incomplete evidence that the regulator must use as the basis for a risk-benefit decision. To use an example from teratology, in 1976 Staples reported the figure of 800 chemicals identified as teratogens in laboratory animals, but fewer than 25 are known human teratogens. The situation has not changed since then, except that the ratio of animal to human teratogens has increased (Larsson et al., 1982). When the correlation between known effects in laboratory animals and clinical adverse effects in humans is so low, the value of routine tests in animals for predicting teratogenesis must be questioned. In part, however, this discrepancy may arise from the high loss rates reported in human pregnancies, and such a loss may result in early elimination of aberrant products of conception. Data are not available, however, to confirm or refute this possibility. In addition, dose levels found to be teratogenic in animal studies are often much higher than the human therapeutic doses, and the observed teratogenicity may be associated only with maternotoxic dose levels.

In most cases data from animal studies are insufficient to permit a precise estimate of human risk because of the difficulties of transpecies extrapolation. The test batteries are useful in identifying toxic compounds that cause catastrophic events, such as carcinogenesis, teratogenesis, or fetal death, especially if they do so in a variety of test systems at or near doses actually encountered by humans. However, when only subtle or minimal changes are induced in only some tests or only at high doses or when the mechanism of toxicity is not defined (as is usually the case with the human embryo-fetus, for example), the value of the tests as an indicator or a potential reproductive problem in humans is considerably diminished.

There has been an increasing pressure to include testing for behavioral and organ functions of progeny prenatally exposed to chemicals in the scheme of