

Carcinogenicity Studies

1 INTRODUCTION

In the experimental evaluation of substances for carcinogenesis based on experimental results of studies in a nonhuman species at some relatively high dose or exposure level, an attempt is made to predict the occurrence and level of tumorogenesis in humans at much lower levels. In this chapter we will examine the assumptions involved in this undertaking and review the aspects of design and interpretation of traditional long-term (lifetime) animal carcinogenicity studies as well as some alternative short-term models. It should be noted that these are required of the majority of marketed drugs but are only performed on the minority of drugs which reach a stage of development where a marketing application is likely and to occur within three or so years.

At least in a general way, we now understand what appear to be most of the mechanisms underlying chemical- and radiation-induced carcinogenesis. The most recent regulatory summary on identified carcinogens [National Institutes of Health (NIH), 2000] lists 44 agents classified as known to be human carcinogens. Several hundred other compounds are also described as having lesser degrees of proof. A review of these mechanisms is not germane to this chapter [readers are referred to Miller and Miller (1981) for a good short review], but it is now clear that cancer as seen in humans is the result of a multifocal set of causes.