Genotoxicity

Genotoxicity encompasses all the potential means by which the genetic material of higher organisms may be damaged, with resulting serious consequences. Most forms of genotoxicity are expressions of mutagenicity—the induction of deoxyribonucleic acid (DNA) damage and other genetic alterations, with changes in one or a few DNA bare pairs (gene mutations). Others are clastogenicity, with gross changes in chromosomal structure (i.e., chromosomal aberrations) or in chromosome numbers. Clearly the potential of any pharmaceutical to cause such damage is a concern.

It has been known for several hundred years that exposure to particular chemicals or complex mixtures can lead to cancer in later life (Doll, 1977), and it has been postulated more recently that chemicals can also induce heritable changes in humans, leading to diseases in the next generation (ICEMC, 1983). There has been accumulating evidence that such changes can arise following damage to DNA and resulting mutations (see, e.g., Bridges, 1976). Therefore, it has become necessary to determine whether widely used drugs or potentially useful new drugs possess the ability to damage DNA. In pharmaceutical development, such information may be used to discard a new candidate drug from further work, to control or eliminate human exposure for a mutagenic industrial compound, or, for a drug, to proceed with development if benefits clearly outweigh risks. Data concerning the genotoxicity of a new drug have become part of the safety package, though the timing of the performance of the tests may vary. They are needed for decision making and to reduce risks that might otherwise be unforeseen.

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