Abstract

The ability of a chemical to induce mutations has long been a driver in the cancer risk assessment process. The default strategy has been that mutagenic chemicals demonstrate linear cancer dose responses, especially at low exposure levels. In the absence of additional confounding information, this is a reasonable approach, because risk assessment is appropriately considered as being protective of human health. The concept of mode of action has allowed for an opportunity to move off this default position; mutagenicity is now not considered as the driver but rather the mode of action is. In a more precise way, it is the set of key events that define a mode of action that is fundamental in defining the shape of a cancer dose response. A key event is an informative bioindicator of the cancer response and as such should be predictive of the tumor response, at least in a qualitative way. A clear example of the use of key events in cancer risk assessment is for DNA reactive chemicals. A series of such key events is initiated by the production of DNA damage in target cells through direct interaction of the chemical with DNA through the production of mutations by misreplication leading to enhanced cell replication, eventually leading to the development of preneoplastic cells and ultimately overt neoplasms. The response of each of these key events to dose of the chemical can inform the cancer dose-response curve shape. Thus, the dose-response curve for any DNA-reactive chemical can be predicted from knowledge of its mode of action and the behavior of the induced key events.