Barbara D. Beck, Ph.D., DABT, ERT, ATS

2019 SOT Conference
Roundtable: The Delaney Clause, from 1958 to 2019: Making the Model Relevant
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11:00AM-12:20PM

Updating the Delaney Clause: Mode of Action Considerations for Carcinogens.

The institution of the Delaney Clause (Delaney),more than a half century ago, occurred a time when understanding of chemical carcinogenesis was limited. The recognition that certain carcinogens could interact with DNA, causing mutation, and also that tumors are clonal in origin led to a proposed mechanism for chemical carcinogenesis, whereby a single molecular event could initiate the carcinogenic process, thus increasing risk of cancer. This proposed mechanism resulted in the development of the linear no-threshold (LNT) doseresponse for calculating cancer risks, although, due to the lack of empirical data at dose levels of typical regulatory interest, such risks represent hypothetical risks. Understanding of chemical carcinogenesis has evolved since Delaney, with the recognition of two basic modes of action (MOAs) for chemical carcinogenesis. The first MoA invovles direct genotoxicity whereby DNA damage occurs in multiple oncogenes or tumor suppressor genes in a single progenitor or stem cell in a particular tissue, the damage is unrepaired and leads to cellular growth advantage of the mutated cells over undamaged cells. The second MOA involves indirect enhancement of cell proliferation due to several potential mechanisms, including increased mitogenicity from hormonal or growth factor stimulation, prolonged cytotoxicity leading to regenerative hyperplasia, and reduced apoptosis. However, the enhanced cell proliferation occurs, it increases the potential for DNA damage to occur in multiple oncogenes or tumor suppressor genes, leading to cancer. While there is evidence that even direct genotoxic mechanisms may not necessarily result in a LNT dose-response for all such carcinogens, MOAs that involve enhanced cell proliferation can be presumed to operate via a threshold dose-response. A revised Delaney should consider the use of a threshold dose-response in setting permissible limits for animal carcinogens that operate via enhancement of cell proliferation. Consideration should also be given to setting riskbased limits for genotoxic carcinogens, for which a threshold dose-response relationship has not been confirmed. The relevance of MOA considerations will be demonstrated by using an example of a chemical whose presence in food is banned under Delaney, but which, using MOA considerations would be permissible.