Biomarkers of Exposure and Effect: Implications for Risk Assessment

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Tremendous advances have been made in the study of biomarkers related to carcinogenesis during the past 20 years. This perspective will briefly review improvements in methodology and instrumentation that have increased our abilities to measure the formation, repair and consequences of DNA adducts. These biomarkers of exposure, along with surrogates such as protein adducts, have greatly improved our understanding of species differences in metabolism and effects of chemical stability and DNA repair on tissue differences in molecular dose. During this same time frame, improvements in assays for biomarkers of effect have provided better data and an improved understanding of the dose responses for both gene and chromosomal mutations. A Framework Analysis approach was used to examine the Mode of Action of genotoxic chemicals and the default assumption that cancer can be expected to be linear at very low doses. This analysis showed that biomarkers of exposure are usually linear at low doses, with the exception being when identical adducts are formed endogenously. Whereas biomarkers of exposure extrapolate down to zero, biomarkers of effect can only be interpolated back to a clear spontaneous or background number of mutations. The likely explanation for this major difference is that at high exposures, the biology that results in mutagenesis is driven by DNA damage resulting from the chemical exposure. In contrast, at very low exposures, the biology that results in mutagenesis is driven by endogenous DNA damage. The shapes of the dose response curves can be very different and should better inform quantitative estimates of risk for cancer. It is also clear, however, that low dose data on mutagenesis is needed for many more chemicals.

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