

Reliable Safety Assessment Depends on Species Differences in Epigenetic Mechanisms of Gene Regulation

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Potential carcinogenic hazard of chemical agents to humans is presently based primarily on the results of long-term animal bioassays. The validity of this toxicological approach to human risk assessment depends on two fundamental assumptions. Firstly, the results of an animal bioassay are directly applicable to humans (interspecies extrapolation). Secondly, the doses used in an animal bioassay are relevant for estimating risk at known or expected human exposure levels (dose extrapolation). Although progress has been made the past four decades in understanding the mode of action of chemical carcinogens, it is increasingly important to mechanistically determine the relevance of these modes of action in humans. There is now evidence that the *M6P/IGF2R* functions as a novel tumor suppressor gene in a variety of human cancers. *M6p/Igf2r* is imprinted in rodents and expressed only from the maternal allele after embryonic implantation. In contrast, both alleles are functional in humans. This marked species difference in *M6P/IGF2R* imprinting has important implications for human carcinogen risk assessment since only 1 rather than 2 alleles needs to be mutated in rodents to completely inactivate the function of this tumor suppressor gene. This striking species difference in the imprint status of *M6P/IGF2R* clearly demonstrates that we need to better understand variations in epigenetic mechanisms of gene regulation between rodents and humans in order to accurately perform chemical safety assessment.