Abstract

A public workshop, organized by a Steering Committee of scientists from government, industry, universities, and research organizations, was held at the National Institute of Environmental Health Sciences (NIEHS) in September, 2010. The workshop explored the dose-response implications of toxicant modes of action (MOA) mediated by nuclear receptors. The dominant paradigm in human health risk assessment has been linear extrapolation without a threshold for cancer, and estimation of sub-threshold doses for non-cancer and (in appropriate cases) cancer endpoints. However, recent publications question the application of dose-response modeling approaches with a threshold. The growing body of molecular toxicology information and computational toxicology tools has allowed for exploration of the presence or absence of sub-threshold doses for a number of receptor-mediated MOAs. The workshop explored the development of dose-response approaches for nuclear receptor-mediated liver cancer, within a MOA Human Relevance Framework (HRF). Case studies addressed activation of the AHR; the CAR/PXR, and the PPARα. This paper describes the workshop process, key issues discussed, and conclusions. The value of an interactive workshop approach to apply current MOA/HRF frameworks was demonstrated. The results may help direct research on the MOA and dose-response of receptor-based toxicity, since there are commonalities for many receptors in the basic pathways involved for late steps in the MOA and similar data gaps in early steps. Three additional papers in this series describe the results and conclusions for each case-study receptor regarding its MOA, relevance of the MOA to humans, and the resulting dose-response implications.