ABSTRACT

The existence of thresholds for toxicants is a matter of debate in chemical risk assessment and regulation. Current risk assessment methods are based on the assumption that, in the absence of sufficient data, carcinogenesis does not have a threshold, while non-carcinogenic endpoints are assumed to be thresholded. Advances in our fundamental understanding of the events that underlie toxicity are providing opportunities to address these assumptions about thresholds. A key events dose-response analytic framework was used to evaluate three aspects of toxicity. The first section illustrates how a fundamental understanding of mode of action for the hepatic toxicity and the hepatocarcinogenicity of chloroform in rodents can replace the assumption of low-dose linearity. The second section describes how advances in our understanding of the molecular aspects of carcinogenesis allow us to consider the critical steps in genotoxic carcinogenesis in a key events framework. The third section deals with the case of endocrine disrupters, where the most significant question regarding thresholds is the possible additivity to an endogenous background of hormonal activity. Each of the examples suggests that current assumptions about thresholds can be refined. Understanding inter-individual variability in the events involved in toxicological effects may enable a true population threshold(s) to be identified.