

Defining in vivo dose-response curves for kidney DNA adduct formation of aristolochic acid I in rat, mouse and human by an in vitro and physiologically based kinetic modeling approach

ABSTRACT

Aristolochic acid I (AAI) is a well-known genotoxic kidney carcinogen. Metabolic conversion of AAI into the DNA-reactive aristolactam-nitrenium ion is involved in the mode of action of tumor formation. This study aims to predict in vivo AAI-DNA adduct formation in the kidney of rat, mouse and human by translating the in vitro concentration-response curves for AAI-DNA adduct formation to the in vivo situation using physiologically based kinetic (PBK) modeling-based reverse dosimetry. DNA adduct formation in kidney proximal tubular LLC-PK1 cells exposed to AAI was quantified by liquid chromatography-electrospray ionization-tandem mass spectrometry. Subsequently, the in vitro concentration-response curves were converted to predicted in vivo dose-response curves in rat, mouse and human kidney using PBK models. Results obtained revealed a dose-dependent increase in AAI-DNA adduct formation in the rat, mouse and human kidney and the predicted DNA adduct levels were generally within an order of magnitude compared with values reported in the literature. It is concluded that the combined in vitro PBK modeling approach provides a novel way to define in vivo dose-response curves for kidney DNA adduct formation in rat, mouse and human and contributes to the reduction, refinement and replacement of animal testing.

Keyword: DNA adduct formation; Aristolochic acid I (AAI); In vitro-in vivo extrapolation; Physiologically based kinetic (PBK) modeling; Reverse dosimetry