Chapter 27

Toxicokinetics and Pharmacokinetic Modeling of Arsenic[1]

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Understanding the uptake and distribution of a toxicant is essential to understanding its toxicology. Toxicokinetics describe the rate of uptake of a chemical, how it is distributed within the body and the rate of excretion or metabolic inactivation/activation to less/more toxic forms. The variation of these processes across species and between individuals is an important determinant of the toxicological outcome of exposures. Much research has been devoted to elucidating the toxicokinetics of arsenic in animal models and humans in order to gain a deeper understanding of its toxicology and to provide a quantitative estimate of dose to the target tissues with the goal of providing a sound biological basis for dose-response analysis. This chapter provides an overview of arsenic toxicokinetics and physiologically-based pharmacokinetic (PBPK) modeling with

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particular emphasis on key factors needed for development of a model useful for dose-response analysis, applications of arsenic models, as well research needs.

Overview of Arsenic Toxicokinetics

The metabolism and disposition of inorganic arsenic (iAs) is largely dependent on its valence state and both pentavalent (As^{V}) and trivalent (As^{III}) inorganic arsenic are the arsenicals to which humans are most likely to be exposed in the environment (ATSDR 2007). Based on the rapid excretion of inorganic arsenic and its methylated metabolites in urine in controlled human exposure studies, inorganic arsenic is readily absorbed from the gastrointestinal tract in humans (Buchet et al. 1981; Lee 1999). Studies in mice suggest that As^{III} is more rapidly absorbed and distributed compared to As^{V} following a relatively low single dose (0.4 - 0.5 mg (As)/kg), whereas the reverse appears to be true following a higher single dose (4 - 5 mg (As)/kg) (Hughes et al. 1999; Vahter and Norin 1980).

Inorganic arsenic is rapidly and widely distributed in tissues following acute oral exposure in laboratory animals (IPCS 2001). Limited data available in humans suggest that chronic low level exposure is also characterized by relatively widespread accumulation in tissues with most arsenic present being in the inorganic form, less in the form of dimethyl arsenic (DMA) and monomethyl arsenic (MMA) being generally undetectable except in the liver and kidney (Yamauchi and Yamamura 1983). Studies in rodents indicate that the distribution of arsenic and its methylated metabolites in tissues is both organ-specific and dose-dependent, and not necessarily reflective of overall flux