Development of a Physiologically Based Pharmacokinetic Model for Multiday Inhalation of Carbon Tetrachloride

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INTRODUCTION

The extrapolation of animal data to humans has generally been considered a nonquantitative exercise that is affected by numerous unknown biological factors. It has been recognized that this process, often called scaleup or extrapolation, should be influenced by differences in metabolism, body size, and pharmacokinetics between the test species and man. In the past, because a mathematical method for describing these differences was not clearly defined, safety factors were used in an attempt to account for these differences between species (Calabrese, 1983; Dourson and Stara, 1983; Gaylor, 1983; Krewski et al., 1984; National Research Council, 1975; Weil, 1972; Zielhuis and van der Kreek, 1979 a,b).

Physiologically based pharmacokinetic (PB-PK) modeling offers a promising approach for scaling up animal data to predict kinetic behavior in humans (Andersen, 1981a,b; Dedrick and Bischoff, 1980; Himmelstein and Lutz, 1979). These models have been developed for styrene (Ramsey and Andersen, 1984), polybrominated biphenyls (Dedrick, 1973), tetrachlorinated dibenzofurans (King et al., 1983), hepatic glutathione depletion (D'Souza et al., 1987), and methylene chloride (Andersen et al., 1987a). In general, these models quantitatively describe the kinetic behavior of the parent molecule and its metabolites in the test species, and ideally, they successfully predict the metabolism and elimination of that molecule in humans (Clewell and Andersen, 1985). The underpinnings