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A physiologically based pharmacokinetic model for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in C57BL/6J and DBA/2J mice

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SUMMARY

A five-compartment physiologically based pharmacokinetic (PB-PK) model was developed to describe the time course of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the tissues of both C57BL/6J and DBA/2J mice. The PB-PK model included binding in blood and two hepatic binding sites, one in the cytosol and the other in the microsomes. First-order metabolism occurred in the liver. Model simulations were compared to literature results for the disposition of a single intraperitoneal dose of 10 µg/kg of [³H]TCDD, reported by Gasiewicz et al. [Drug Metab. Dispos. 11 (1983) 397–403]. In contrast to previous speculation, the greater accumulation of TCDD in the liver of the C57BL/6J mouse, as compared to the DBA/2J mouse, was not attributable to the higher fat content in the DBA/2J mouse. Instead, the disposition of TCDD in these mice was more dependent on the affinity of the microsomal binding proteins than on fat content. The microsomal dissociation constant in the C57BL/6J mouse estimated by the PB-PK model was about one-third its value in the DBA/2J mouse (20 versus 75 nM), i.e. there is more avid microsomal binding in the liver of the C57BL/6J mouse. In the concentration range covered in these time-course studies, the cytosolic receptor, with its low capacity and very high affinity binding characteristics, does not play a major role in determining the overall tissue distribution pattern. The concentration and affinity of the microsomal binding protein in the liver appear to be primarily responsible for explaining the differences in the liver/fat concentration ratios between various strains and species of laboratory animals.