Physiologically Based Pharmacokinetic Modelling of Dioxin: Structural Analysis and Extension to Other Congeners

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In an earlier paper, a physiologically based pharmacokinetic model of 2,3,7,8-TCDD in humans was analyzed using matrix techniques to yield important parameters such as the half-life and bioconcentration factor as well as an approximate first-order bioconcentration equation.[1] The model is extended here to other problems and compounds.

Analysis of the matrix of parameters describing the model's differential equations shows that it must yield negative eigenvalues, as expected.

With certain reasonable approximations, the model is structurally isomorphic to "resistance" type bioconcentration models often applied to fish. A comparison of the equations for fish and mammals applied to semi-volatile lipophilic compounds shows differences in the importance of the respiratory media and diffusion across the gut. Bioconcentration via respiration from water has a strong dependence on the octanol-water partition coefficient. Respiration from air is usually unimportant compared to uptake from the gut. Various bioconcentration and bioaccumulation phenomenon arise out of this unified approach, dependent on media, chemical properties and animal specific parameters.

The model for humans was adapted to account for lactation. The resulting approximate bioconcentration equation is structurally different from the original. As expected, lactation replaces fecal excretion as the dominant determinant of the half-life for poorly metabolized lipophilic compounds.

The model has also been extended to PCDDs and PCDFs other than 2,3,7,8-TCDD. The metabolic rate and gut absorption are key parameters. On this basis, the half-life of OCDD in humans is estimated as being on the order of several decades.

Finally, there has been a great deal of discussion of the relative merits of using body weight or surface area for interspecies scaling of dosage. Application of the current model suggest a scaling factor from rat to human of about an of magnitude.

1. Webster T, Connett, P. Estimating Bioconcentration Factors and Half-Lives in Humans Using Physiologically Based Pharmacokinetic Modelling: 2,3,7,8-TCDD. **Chemosphere** 1991;23:1763-1768.