ESTIMATING BIOCONCENTRATION FACTORS AND HALF-LIVES IN HUMANS USING PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING, PART I: 2,3,7,8-TCDD

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ABSTRACT

A bioconcentration factor and a halflife of 2,3,7,8-TCDD in 70 kg reference humans is estimated from a physiologically based pharmacokinetic model. The system of differential equations is solved using eigenvalue methods. The results can be approximated using a standard first-order bioconcentration equation.

KEYWORDS

Bioconcentration; halflife; humans; 2,3,7,8-TCDD ; pharmacokinetic modelling

INTRODUCTION

Despite their growing use in environmental fate models, bioconcentration factors (BCFs) and biotransfer factors (BTFs) for terrestial animals remain largely empirical. Several important questions remain open. Do BCFs/BTFs increase linearly with lipophilicity (Kow), as has been suggested in analogy to fish (Travis et al., 1988), or do they reach some upper limit? Do compounds bioconcentrate to levels greater than that found in their food and why? Under what conditions are first order models appropriate simplifications? Can BCFs and half-lives be predicted?

Physiologically based pharmacokinetic (PBPK) models show great promise for elucidating these questions. Patterson and MacKay (1986) developed a PBPK model based on fugacity (a thermodynamic variable related to chemical potential), a concept particularly useful in analyzing partitioning between blood, other fluids and tissues. Patterson and MacKay (1987) provided an algebraic expression for the relationship at steady-state of the fugacity of various organs, air and food. The solution is, however, difficult to interpret because of its complexity. Kissel and Robarge (1988) used a similar model to numerically simulate the half-life of 2,3,7,8-TCDD in humans with good results.

We present an algorithm for a complete numerical solution of this problem as well as an approximate first order rate equation. This conceptually simpler solution is useful for answering some of the questions posed above. The model will be applied here to 2,3,7,8-TCDD and to other compounds in a second paper.

Solution of the Pharmacokinetic Model with Matrix Techniques

Kissel and Robarge's model (1988) consists of eleven simultaneous first order differential equations for fugacities in the lung, venous and arterial blood, liver, muscle, skin, fat, kidneys, richly perfused tissue, gut tissue and gut

lumen. The two exogenous variables are the fugacities of air and food. For lipophilic compounds with small Henry's Law constants, the lung can be ignored and venous and arterial blood collapsed into one compartment. The resulting model consists of nine simultaneous first order linear differential equations with constant coefficients. In vector notation:

$$df/dt = A*f + b$$

where f is the vector describing the fugacity of each compartment and A is the matrix of coefficients. The vector b contains the non-homogenous (exogenous) terms; the only non-zero term is a constant proportional to the fugacity of food in the equation for gut lumen .

The steady-state solution (fss) is easily obtained by inverting the matrix:

$$fss = -A^{-1}*b$$

The time varying solution (f(t)) can be derived using standard mathematical techniques for eigensystems (Press et al., 1986). The fugacity of each compartment as a function of time can be expressed as the sum of nine exponential terms with exponents equal to the eigenvalues (m_i), plus a particular solution consisting, in this case, of the steady-state solution:

$$f(t) = B*e + fss$$

$$e_i = C_i*\exp(m_i)$$

B is the matrix of eigenvectors, and e is a vector of constants (C_i, dependent on initial conditions) multiplied by the exponential terms. For example, when the fugacities of all body fluids and tissues are initally zero (and all exponentials equal one), the vector of constants can be easily solved as:

$$C = -B^{-1}*fss$$

Application to 2,3,7,8-TCDD

We applied this technique to 2,3,7,8-TCDD using Kissel and Robarge's (1988) parameters for a 70 kg non-lactating "reference" human. This includes the important assumption that metabolism is negligible. All nine eigenvalues were real negative numbers. Hence, with a constant fugacity of the chemical in food, the system converges on the steady state values. The smallest eigenvalue, $-1.87*10^{-5}$ hr^{-1}, corresponds to a halflife of 4.2 years. The term containing this exponent has the largest coefficient for all compartments when fugacities are initially zero. Similar results are obtained when the fugacity in food is zero and the system is allowed to decay from steady state. Hence, this term dominates long-run bioaccumulation and decay kinetics.

The computed ratio of the fugacities of 2,3,7,8-TCDD in adipose tissue and food steady-state is about 9.37. This can be converted to a BCF (w/w) of about 400:

$$BCF = (f_{fat,ss}/f_{food}) * (Z_{fat}/d_{fat})/(Z_{food}/d_{food})$$

where f, Z and d describe the steady-state fugacities, fugacity capacities and densities of adipose tissue and food. This value is based on food and water consumption of 2.68 kg/day. When adjusted to the food consumption rate of 0.63 kg/d used by Geyer et al. (1986, 1987), the result (95) is reasonably close to their range of 115-229 estimated using an adipose tissue concentration of 11.9 pg/g lipid (perhaps high) and a daily intake of 44 pg/d. Note that the contribution of water to the 2,3,7,8-TCDD in the diet is negligible because of its small fugacity capacity relative to food.

Pirkle et al. (1989) estimated a median halflife of 2,3,7,8-TCDD in Ranch Handers of 7.1 years, while Poiger et al. (1986) initially estimated 5.8 years. The latter experiment involved a larger person that the "reference"

human. When this is taken into account, the estimated half-life increases to about 6-7 years (see also Kissel and Robarge, 1988). Nevertheless, our model is, after initial transients, essentially monophasic (the second smallest eigenvalue is 0.0616 hr^{-1}). In contrast, Poiger et al (1988) report a decrease of elimination rate over a much longer period of time. This might be explained by a change in adipose tissue content over the course of the experiment or by an effective partitioning of adipose tissue into two compartments, one with less blood supply and thus having slower elimination. More work is needed to explain this phenomenon.

Simplified Analytical Solution

With the exception of initial transients, the solution we have derived for 2,3,7,8-TCDD behaves much like a first order system. This is not surprising given two facts. First, the volume of distribution is dominated by fat; in fugacity terms, the product of volume and fugacity capacity (Z) is by far the largest for fat. Secondly, the characteristic time--the halflife for equilibration for a given compartment when all others are held constant--is much longer for fat than others. Hence, one can approximate the behavior of the system by simultaneously solving for the fugacity of the other compartments, treating the fugacity of the fat as an exogenous variable. The result is then substituted into the equation for fat, resulting in a classic first order bioaccumulation equation expressed in terms of fugacity:

$$df_{fat}/dt = k_1 * f_{food} - k_2 * f_{fat}$$

$$R = f_{fat,ss}/f_{food} = k_1 / k_2$$

where R is the ratio of the steady-state fugacity of fat relative to food. The value of R and k_2 derived in this way, 9.37 and $1.99*10^{-5}$ hr^{-1} are close to the values obtained with full analytical methods outlined above.

The behavior of the model can be understood by analyzing the parameters k_1, k_2 and R. The intake rate constant (k_1) is proportional to the rate of intake of food (Q_{food}) divided by the volume of the fat compartment (V_{fat}). The value (a) is the fraction of the dose absorbed into fat when the initial fat concentration is zero (no "back-pressure" across the gut). In this case, it is closely approximated by the initial absorption across the gut:

$$k_1 = a*(Q_{food}*Z_{food}) / (V_{fat}*Z_{fat})$$

$$a = (g+1)/g; \qquad g = D23/Q_{feces}*Z_{feces}$$

where D23 is the gut lumen:gut tissue transfer coefficient (Kissel and Robarge, 1988). 2,3,7,8-TCDD is metabolized very slowly (if at all) in humans, so the major route of excretion is via feces:

$$k_2 = (a*Q_{feces}*Z_{feces} + (1-a)*Q_{bile}*Z_{bile}) / (V_{fat}*Z_{fat})$$

$$\text{half-life} = 0.693/k_2$$

Since absorption (a) is close to one (Kissel and Robarge, 1988), k_2 is approximately proportional to the rate of fecal excretion from the body divided by the volume of the fat compartment. Thus, the long half-life of 2,3,7,8-TCDD in humans is, according to this model, due to a combination of low metabolism and low fecal excretion relative to the large capacity of adipose tissue.

The ratio of the fugacity in fat divided by the fugacity of food is, at steady state:

$$R = (a*Q_{food}*Z_{food}) / (a*Q_{feces}*Z_{feces} + (1-a)*Q_{bile}*Z_{bile})$$

The capability of the gut to transport the compound--as measured by the product of flow (Q) and fugacity capacity (Z)--decreases in this model from food to feces. This causes concentrations in body fat to exceed those in food. With absorption close to one, R for 2,3,7,8-TCDD is approximately

equal to food intake divided by fecal excretion, with a small correction for transport via bile.

If we assume that the relative distribution between organs and fluids is determined primarily by fugacity capacity (Z), these equations predict that the bioconcentration factors and halflifes of highly lipophilic, poorly metabolized compounds do not continue to increase with octanol/water partition coefficient, but reach a plateau, a phenomenon hypothesized by Geyer et al (1987). However, if gut absorption decreases for slowly metabolized higher chlorinated dioxins, as indicated by MacLachlan et al. (1989) for cattle, BCFs will decrease relative to 2,3,7,8-TCDD while halflifes increase.

CONCLUSIONS

The bioconcentration factor and halflife of 2,3,7,8-TCDD in humans was predicted using a physiologically based pharmacokinetic model and eigenvalue techniques. The solution can be approximated by a single first order equation, clarifying a possible cause for the long halflife of this compound in humans: negligible metabolism and low excretion via feces relative to the large storage ability of adipose tissue. The results agree roughly with values in the literature, but biphasic results observed in one experiment cannot be explained by the model as it is currently formulated. Application to other compounds will be performed in a following paper. Preliminary results indicate that the BCF does not continue to increase with lipophilicity for poorly metabolized compounds, but stabilize or even decreases.

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