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RESEARCH ARTICLES

ANALYSIS OF FAST KINETICS MODELS FOR THE DISTRIBUTION OF POLYCHLORINATED DIBENZO-P-DIOXINS AND DIBENZOFURANS IN HUMANS

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ABSTRACT

*Models of the disposition of polychlorinated dibenzo-*p*-dioxins and dibenzofurans, commonly known as PCDXs, in the human tissues are considered and partially analyzed. Four cases are investigated : a single initial exposure to PCDXs with constant growth response function of the binding proteins, a linear growth response function, a Holling type response function, and the case of a periodic exposure to the dioxins. In the case of a single initial exposure, we are able to determine some important local dynamics. In the case of a periodic exposure to the dioxins, we are able to show that a small periodic exposure to the dioxins induces a periodic behavior in the concentration dynamics.*

INTRODUCTION

Mixtures of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDXs) are reportedly present everywhere in the environment [1,2]. These substances are persistent and bioaccumulate and therefore contaminate air, water, soil, and most living organisms as well as humans. Several attempts [3-5] have been made to model the effects of these toxic substances on contaminating the environment and the ecological communities. Since their potential for adverse health effects is great and their residence time can be lengthy, it is most important that efforts should be devoted to the modelling of their distribution in human tissues.

As attested by Carrier *et al.* [1], the uncertainties inherent to the conventional dose-response assessment make it difficult to ascertain realistic allowable exposure limits for these substances. In the attempt to reduce such uncertainties in the dose response assessment, physiologically based models have been developed [1-3] to describe the mechanisms of disposition and tissue response in a quantitative manner.

Leung *et al.* [6,7] have developed a five-compartment (liver, fat, muscle/skin, viscera, and blood) physiologically based pharmarcokinetic (PB-PK) model to describle the disposition of Tetrachlorodibenzo-*p*-dioxin (TCDD) in rats and mice. Andersen [8] later used the model to successfully simulate the disposition of the dioxin in female Wistar rats.

In a series of work by Carrier *et al.* [1,2], a mathematical model is also developed in order to describe the toxicokinetics of PCDXs in mamalians, including humans. Their modelling approach does not seem to require as many parameters as the classic PB-PK model, although

its motivation is based on the same biological concepts. The modelling by Carrier *et al.* is conveniently separated into two parts with different time scales. Absorbtion and internal distribution of PCDXs are presumed to occur in a matter of hours to a few days and the intertissue concentrations equilibrate quickly, while overall body load and body concentration varies slowly with time.

The validity of the above approach depends crucially on the stability of the steady state values to which the system equilibrates. The objective of the present work is to carry out an analysis of models based on that of Carrier *et al.* [1] in the four different cases. In the case of a single initial exposure, the growth response function of the binding proteins is first assumed to be constant, then it is allowed to vary linearly with the PCDX concentration (C_x), and then to assume the Holling type functional form. Finally, the case of a periodic exposure to the dioxins is investigated where a Holling type functional response is also assumed.

MODEL DESCRIPTION

The inter and intratissue processes can be described by the schematic diagrams in Figs. 1 and 2, where

C_{at} = concentration of PCDXs in adipose tissues,
C_{bl} = concentration of PCDXs in blood,
C_{-} = concentration of PCDX-binding protein complexes,
C_x = concentration of free PCDX molecules,
C_{pr} = concentration of proteins available for binding.

and γ, δ, ν, μ are positive inter-organ diffusion parameters. The liver kinetic parameters k_a and k_d are the association and dissociation rate constants for protein biding, respectively.

The elaboration of these binding proteins in the liver is linked to the presence of free PCDX molecules (C_x) in the liver that bind to Ah receptor, which is the specific cytosolic receptor that is involved in the regulation of the expression of several genes and the synthesis of various enzymes. Although the mechanisms of this binding process are not yet fully understood, evidence supports the assumption [1] that the rate of synthesis of induced proteins is a positive growth response to PCDX concentration C_x available to bind to Ah receptors. The higher the C_x, the greater the amount of this receptor complex and consequently the amount of these binding proteins. Moreover, limitation of the capacity of the process requires that there is a maximum rate at which induction of binding proteins can proceed. Thus, it is reasonable to assume that the growth response of the binding proteins has the general form $\tilde{F}(C_x)$ such that

$$\tilde{F}(C_x = 0) = 0 \tag{1}$$

$$\tilde{F}(C_x \to \infty) = \tilde{F}_{\max} \tag{2}$$

and

$$\frac{d\tilde{F}}{dt} \geq 0 \text{ for all } C_x \tag{3}$$

From the diagrams in Figs.1 and 2 and the above discussions, we can write down the following "fast kinetics" model for the system;

$$\frac{dC_{at}}{dt} = -\delta C_{at} + \gamma C_{bl} + f(t) \tag{4}$$

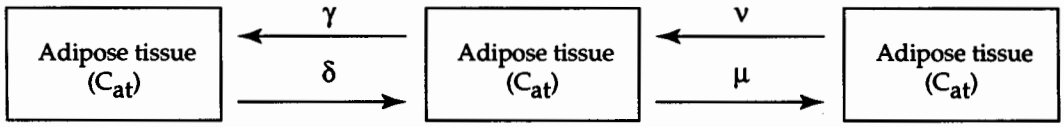

Fig.1 Intertissue exchange of free PCDX molecules amonge 3 compartments; adipose tissue, blood, and liver.

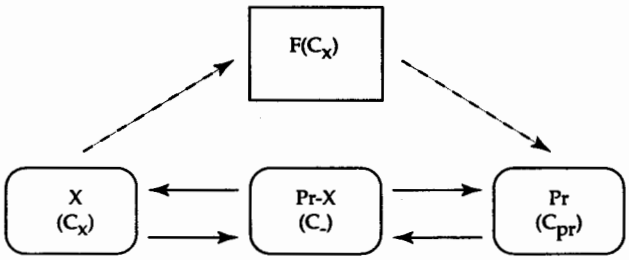

Fig.2 Protien induction and binding process in the liver. Here, X is the free PCDX molecules in liver, Pr the protiens available for binding, Pr-X the PCDX-binding protien complex and $\tilde{F}(C_x)$ is the protien induction response in presense of free PCDXs.

$$\frac{dC_{bl}}{dt} = \delta C_{at} - \gamma C_{bl} - \mu C_{bl} + \nu C_x \tag{5}$$

$$\frac{dC_-}{dt} = k_a C_x C_{pr} - k_d C_- \tag{6}$$

$$\frac{dC_x}{dt} = -k_a C_x C_{pr} + k_d C_- + \mu C_{bl} + \nu C_x \tag{7}$$

$$\frac{dC_{pr}}{dt} = -k_a C_x C_{pr} + k_d C_- + \tilde{F}(C_x) + k' C_{pr} \tag{8}$$

where $\tilde{F}(C_x)$ has the general properties in (1) - (3), and $f(t)$ is the rate at which the substance is introduced into the process at any time t.

MODEL ANALYSIS

We observe that with the above characteristics as set out in (1) - (3) , the most frequently used function to model such behavior is of the Holling type, namely :

$$\tilde{F}(C_x) = \frac{\tilde{F}_{max} C_x}{k + C_x} \tag{9}$$

where $\tilde{F}_{max}$ is the plateau value and k is the half saturation constant.

In the following, we shall first consider the case where $f(t) \equiv 0$ and there is a single initial exposure : $C_{at}(0) = C_{at}^0$, $C_{bl}(0) = C_{bl}^0$, $C_x(0) = C_x^0$, $C_-(0) = C_-^0$, and $C_{pr}(0) = C_{pr}^0$.

If we add equations (4) - (7), we find that

$$\frac{d}{dt}(C_{at} + C_{bl} + C_- + C_x) = 0$$

and hence

$$C_{at} + C_{bl} + C_{-} + C_x \equiv \beta = C_{at}^0 + C_{bl}^0 + C_{-}^0 + C_x^0$$

or

$$C_{at} = \beta - C_{bl} - C_{-} - C_x$$

On substituting the above into equation (5), we find that the equations (4) through (8) may be reduced to

$$\frac{dC_{bl}}{dt} = \delta\beta - (\delta + \gamma + \mu)C_{bl} + (\nu - \delta)C_x - \delta C_{-} \tag{10}$$

$$\frac{dC_{-}}{dt} = k_a C_x C_{pr} - k_d C_{-} \tag{11}$$

$$\frac{dC_x}{dt} = -k_a C_x C_{pr} + k_d C_{-} + \mu C_{bl} - \nu C_x \tag{12}$$

$$\frac{dC_{pr}}{dt} = -k_a C_x C_{pr} + k_d C_{-} + \tilde{F}(C_x) + k' C_{pr} \tag{13}$$

Now, if k is very small then $\tilde{F}(C_x)$ may be approximated by

$$\tilde{F}(C_x) \equiv \tilde{F}_{\max} = \text{constant} \tag{14}$$

On the other hand, if k is very large, then $\tilde{F}(C_x)$ may be approximated by

$$\tilde{F}(C_x) \equiv F_0 C_x \tag{15}$$

where F_0 is a positive constant.

Thus, we investigate each of the above cases separately as follows.

Case 1 : $f(t) \equiv 0, \tilde{F} \equiv \tilde{F}_{\max} > 0$.

Substituting $\tilde{F} = \tilde{F}_{\max}$ in equations (10) - (13), we obtain the following system :

$$\frac{dC_{bl}}{dt} = \delta\beta - (\delta + \gamma + \mu)C_{bl} + (\nu - \delta)C_x - \delta C_{-} \tag{16}$$

$$\frac{dC_{-}}{dt} = k_a C_x C_{pr} - k_d C_{-} \tag{17}$$

$$\frac{dC_x}{dt} = -k_a C_x C_{pr} + k_d C_{-} + \mu C_{bl} - \nu C_x \tag{18}$$

$$\frac{dC_{pr}}{dt} = -k_a C_x C_{pr} + k_d C_{-} + \tilde{F}_{\max} - k' C_{pr} \tag{19}$$

the steady state E_1 of which is

$$(\tilde{C}_{bl}, \tilde{C}_{-}, \tilde{C}_x, \tilde{C}_{pr}) = (a, \frac{k_a \tilde{F}_{\max} \mu a}{k_d k' \nu}, \frac{\mu a}{\nu}, \frac{\tilde{F}_{\max}}{k'}) \tag{20}$$

where

$$a = \frac{\nu\delta\beta k_d k'}{k_d k' (\delta\nu + \gamma\nu + \delta\mu) + \mu\delta k_a \tilde{F}_{\max}} \tag{21}$$

The Jacobian matrix at this steady state is given by

$$J_1 = \begin{bmatrix} -(\delta+\gamma+\mu) & -\delta & -(\delta-\nu) & 0 \\ 0 & -k_d & \frac{k_a\tilde{F}_{max}}{k'} & \frac{k_a\mu a}{\nu} \\ \mu & k_d & -(\frac{k_a\tilde{F}_{max}}{k'}+\nu) & -\frac{k_a\mu a}{\nu} \\ 0 & k_d & \frac{k_a\tilde{F}_{max}}{k'} & -\frac{k_a\mu a}{\nu}+k' \end{bmatrix}$$

With respect to this steady state E_1, we are able to derive sufficiency conditions for its asymptotic stability.

Theorem 1 Let the following inequalities hold.

$$\delta+\nu<\gamma+\mu \tag{22}$$

$$\frac{\tilde{F}_{max}k_a}{k'}+\frac{k_a\mu a}{\nu}<k_d \tag{23}$$

$$k_d+\mu+\frac{k_a\mu a}{\nu}<\nu+\frac{k_a\tilde{F}_{max}}{k'} \tag{24}$$

$$\frac{\tilde{F}_{max}k_a}{k'}+k_d<k'+\frac{k_a\mu a}{\nu} \tag{25}$$

then E_1 is locally asymptotically stable.

Proof If inequalities (22)-(25) hold, then by Gerschgorin's theorem [8], all eigenvalues of J_1 have negative real parts, and the theorem follows.

Case 2 : $f(t)\equiv 0,\ \tilde{F}\equiv F_0C_x$

On substituting $\tilde{F}\equiv F_0C_x$ in equations (10)-(13), we obtain the following steady state E_2 :

$$(\tilde{C}_{bl},\tilde{C}_{-},\tilde{C}_x,\tilde{C}_{pr})=(b,\frac{k_a\mu^2b^2}{k_dk'\nu^2},\frac{\mu b}{\nu},\frac{\mu F_0b}{k'\nu}) \tag{26}$$

where

$$b=\frac{-(\delta+\frac{\delta\mu}{\nu}+\gamma)+\sqrt{(\delta+\frac{\delta\mu}{\nu}+\gamma)^2\frac{4\beta k_a\mu^2\delta^2}{k_dk'\nu^2}}}{\frac{2\mu^2\delta k_a}{k'\nu^2k_d}} \tag{27}$$

and the corresponding Jacobian matrix is

$$J_2 = \begin{bmatrix} -(\delta+\gamma+\mu) & -\delta & -(\delta-\nu) & 0 \\ 0 & -k_d & \frac{k_a\mu F_0b}{k'\nu} & \frac{k_a\mu b}{\nu} \\ \mu & k_d & -(\frac{k_a\mu F_0b}{k'\nu}+\nu) & -\frac{k_a\mu b}{\nu} \\ 0 & k_d & -\frac{k_a\mu F_0b}{k'\nu}+F_0 & -\left(\frac{k_a\mu b}{\nu}+k'\right) \end{bmatrix} \tag{28}$$

For E_2, we are also able to prove the following theorem.

Theorem 2 Let the following inequalities hold.

$$\delta + \nu < \gamma + \mu \tag{29}$$

$$\frac{F_0 k_a b\mu}{k'\nu} + \frac{k_a \mu b}{\nu} < k_d \tag{30}$$

$$k_d + \mu + \frac{k_a \mu b}{\nu} < \nu + \frac{\mu k_a F_0 b}{k'\nu} \tag{31}$$

$$\frac{\mu F_0 k_a b}{k'\nu} + k_d + F_0 < k' + \frac{k_a \mu b}{\nu} \tag{32}$$

Then E_2 is locally asymptotically stable.

Proof When the Gerschgorin's theorem is applied to the matrix J_2 then the theorem again follows.

Case 3 : $f(t) \equiv 0$, $\tilde{F} \equiv \dfrac{\tilde{F}_{max} C_x}{k + C_x}$

In this case, we simplify the analysis by considering only two compartments, lumping the adipose tissues with the blood. The intertissue exchange described schematically in Fig. 3 together with the binding process in the liver described in Fig. 2 can be modelled by the following system of differential equations :

$$\frac{d}{dt} C_{a-b} = -\mu C_{a-b} + \nu C_x + f(t) \tag{33}$$

$$\frac{dC_-}{dt} = k_a C_x C_{pr} - k_d C_- \tag{34}$$

$$\frac{dC_x}{dt} = -k_a C_x C_{pr} + k_d C_- + \mu C_{a-b} - \nu C_x \tag{35}$$

$$\frac{dC_{pr}}{dt} = -k_a C_x C_{pr} + k_d C_- + \tilde{F}(C_x) - k' C_{pr} \tag{36}$$

where C_{a-b} respresents the concentration of PCDXs in the adipose tissue and blood.

In this case $f(t) = 0$, and if we add equations (33)-(35) together, then we find

$$\frac{d}{dt}(C_{a-b} + C_- + C_x) = 0 \tag{37}$$

which means

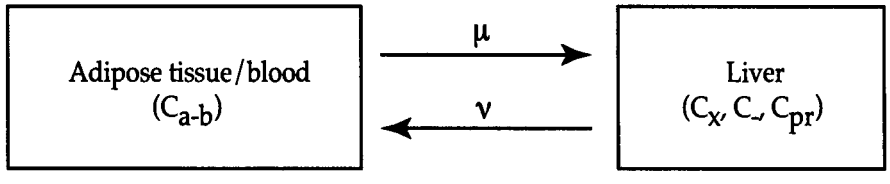

Fig.3 Intertissue exchange of free PCDX molecules amonge 2 compartments, adipose tissue/blood and liver, investigated in Case 3 of the text.

$$C_{a-b} + C_- + C_x \equiv \alpha = C^0_{a-b} + C^0_- + C^0_x \tag{38}$$

or

$$C_{a-b} = \alpha - C_- - C_x \tag{39}$$

Thus, using (39), equations (33) through (36) can be reduced to the following system of 3 differential equations.

$$\frac{dC}{dt} = k_a C_x C_{pr} - k_d C_- \tag{40}$$

$$\frac{dC_x}{dt} = -k_a C_x C_{pr} + k_d C_- - (\mu + \nu) C_x - \mu C_- + \alpha\mu \tag{41}$$

$$\frac{dC_{pr}}{dt} = -k_a C_x C_{pr} + k_d C_- + \frac{\tilde{F}_{\max} C_x}{k + C_x} - k' C_{pr} \tag{42}$$

The steady state E_3 of the system in this case is

$$(\tilde{C}_-, \tilde{C}_x, \tilde{C}_{pr}) = (\alpha - (\mu + \nu)\sigma, \mu\sigma, d) \tag{43}$$

where

$$d = \frac{-\theta + \sqrt{\theta^2 4k' k_a k \alpha \mu^2 \tilde{F}_{\max}}}{2k' k_a k \mu} \tag{44}$$

with

$$\theta = k' k_d (k\mu + k\nu + \alpha\mu) \tag{45}$$

and

$$\sigma = \frac{k_d \alpha}{\mu k_a d + \mu k_d + k_d \nu}$$

while the corresponding Jacobian matrix is

$$J_3 = \begin{bmatrix} -k_d & k_a d & \mu\sigma k_a \\ k_d - \mu & -k_a d - \mu - \nu & -\mu\sigma k_a \\ k_d & -k_a d + \dfrac{\tilde{F}_{\max} k}{(k + \mu\sigma)^2} & -\mu\sigma k_a - k' \end{bmatrix}$$

We are then able to write down the following theorem for the stability of E_3.

Theorem 3 Let the following inequalities hold.

$$k_a d + \mu\sigma k_a < k_d \tag{46}$$

$$k_a d + \mu\sigma k_a < k_d d + \nu \tag{47}$$

$$k_d + k_a d + \frac{k\tilde{F}_{\max}}{(k + \mu\sigma)^2} < \mu\sigma k_a + k' \tag{48}$$

Then E_3 is locally asymptotically stable.

Proof Again we invoke the Gerschgorin's theorem and we find that all eigenvalues of J_3 have negative real parts when conditions (46)-(48) hold and therefore E_3 will be locally asymptotically stable.

Case 4 : $f(t) \equiv \varepsilon\varphi(t) \equiv \varepsilon\varphi(t+\omega),\ \tilde{F} \equiv \dfrac{\tilde{F}_{\max} C_x}{k + C_x}$

On substituting $f(t) \equiv \varepsilon\varphi(t)$ and $\tilde{F} \equiv \dfrac{\tilde{F}_{\max} C_x}{k + C_x}$ into (33)-(36) we obtain the following system.

$$\frac{dC_{a-b}}{dt} = -\mu C_{a-b} + \nu C_x + \varepsilon\varphi(t) \tag{49}$$

$$\frac{dC_-}{dt} = k_a C_x C_{pr} - k_d C_- \tag{50}$$

$$\frac{dC_x}{dt} = -k_a C_x C_{pr} + k_d C_- + \mu C_{a-b} - \nu C_x \tag{51}$$

$$\frac{dC_{pr}}{dt} = -k_a C_x C_{pr} + k_d C_- + \frac{\tilde{F}_{\max} C_x}{k + C_x} - k' C_{pr} \tag{52}$$

Following the example of Freedman and Shukla [9] we write the above system as

$$\dot{z} = F(z) + \varepsilon G(t),\ z(0) = z_0 \tag{53}$$

where

$$z = \begin{bmatrix} z_1 \\ z_2 \\ z_3 \\ z_4 \end{bmatrix} = \begin{bmatrix} C_{a-b} \\ C_- \\ C_x \\ C_{pr} \end{bmatrix},$$

$$F(z) = \begin{bmatrix} -\mu C_{a-b} + \nu C_x \\ k_a C_x C_{pr} - k_d C_- \\ -k_a C_x C_{pr} + k_d C_- + \mu C_{a-b} - \nu C_x \\ -k_a C_x C_{pr} + k_d C_- + \dfrac{\tilde{F}_{\max} C_x}{k + C_x} k' C_{pr} \end{bmatrix}$$

and

$$G(t) = \begin{bmatrix} \varphi(t) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \qquad z_0 = \begin{bmatrix} C_{a-b} \\ C_- \\ C_x \\ C_{pr} \end{bmatrix}_{t=0}$$

Let $z(t, \xi, \varepsilon)$ be the solution of equations (49)-(52) such that

$$z(0, \xi, \varepsilon) = \tilde{z} + \xi$$

where $\tilde{z}$ is the steady state of the system of equations (49)-(52) when $\varepsilon = 0$. We then note that

$$z(t, 0, 0) \equiv \tilde{z}$$

In order now to establish the existence of a periodic solution of period ω of the system of equations (49)-(52) for sufficiently small ε, which tends to $\tilde{z}$ as $\varepsilon \to 0$, we need only to show that ξ can be chosen as a function of ε for ε small, $\xi \to 0$ as $\varepsilon \to 0$, such that

$$z(\omega, \xi, \varepsilon) = \tilde{z} + \xi$$

With this in mind, we define

$$J(\xi,\varepsilon) = z(\omega,\xi,\varepsilon) - \tilde{z} - \xi \tag{54}$$

then show that $J(\xi,\varepsilon) = 0$ has a solution $\xi(\varepsilon)$ of ε, such that $\xi(0) = 0$.
Now, we observe that

$$J(0,0) = z(\omega,0,0) - \tilde{z} = 0$$

while

$$J_{\xi}(0,0) = z_{\xi}(\omega,0,0) - I$$

where I is the identity matrix. However,

$$z_{\xi} = (t,\xi,\varepsilon) = F_{z}(z(t,\xi,\varepsilon))z_{\xi}(t,\xi,\varepsilon) \tag{55}$$

and

$$z_{\xi}(0,\xi,\varepsilon) = I \tag{56}$$

Hence, setting $\xi = 0$ and $\varepsilon = 0$ into (55) and (56), we have that $z_{\xi}(t,0,0)$ is the matrix solution of

$$\dot{z}_{\xi} = (t,0,0) = F_{z}(z(t,0,0))z_{\xi}(t,0,0), z_{\xi}(0,0,0) = I \tag{57}$$

But $z(t,0,0) = \tilde{z}$ and $F_{z}(\tilde{z})$ is the Jacobian matrix of the model system (49)-(52) evaluated at $\tilde{z}$. Hence,

$$\dot{z}_{\xi} = (t,0,0) = Jz_{\xi}(t,0,0), z_{\xi}(0,0,0) = I \tag{58}$$

The solution of (58) is

$$z_{\xi}(t,0,0) = e^{Jt} \tag{59}$$

and hence

$$J_{\xi}(0,0) = e^{J\omega} - I \tag{60}$$

This leads to the following theorem.

Theorem 4 If J has no eigenvalues with zero real parts, then the system of equations (49)-(52) has a periodic solution of period ω which tends to $\tilde{z}$ as $\varepsilon \to 0$.

Proof If J has no eigenvalues with zero real parts, then 1 is not an eigenvalue of $e^{J\omega}$. Therefore,

$$\det J_{\xi}(0,0) = \det (e^{J\omega} - I) \neq 0$$

and, by the implicit function theorem [10], equation $J(\xi,\varepsilon) = 0$ can be solved for $\xi(\varepsilon)$ such that $\xi(0) = 0$.

This means that we have found a solution $z = (t,\xi,\varepsilon)$ of the system of equations (49)-(52) such that

$$z = (\omega, \xi, \varepsilon) = \tilde{z} + \xi = z(0, \xi, \varepsilon)$$

This establishes the existence of a periodic solution of period ω.

CONCLUSION

In this paper, we have considered compartmental models of the absorption and disposition of PCDXs in the human body tissues. Four cases have been investigated, in the first three of which we have been able to obtain criteria for the asymptotic stability for the steady state. The third case in fact includes the first two limiting cases in the limit as $k \to 0$ or $k \to$.

In the periodic case, we have shown that a small periodic exposure of the dioxins induces a periodic behavior in the intra-tissue concentrations. In such a situation, therefore, it would not be possible to take all concentrations at their "internal" equilibrium values $\tilde{C}_{a-b}, \tilde{C}_{-}, \tilde{C}_{x}$, and $\tilde{C}_{pr}$ in order to establish the overall body concentration $\tilde{C}_{b}(t)$ in the manner suggested by Carrier *et al.* in [1] and [2]. The validity of the steady state approximation of enzyme kinetics is then in question. Yet, these toxic compounds have been shown to cause immunological, neurological, and heptic effects, as well as reproductive disorders at relatively low daily doses. As humans are exposed to low levels of PCDXs over the lifetime, the possible toxicological consequences are of grave concern. Thus, this question of longterm disposition of the dioxins in the body tissues subject to repeated exposure is of great interest, and needs to be more extensively explored in future research.

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REFERENCES

1. Carrier, G., Brunet, R., Brodeur, J. Modeling of the Toxicokinetics of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans in Mammalians, Including Humans I. Nonlinear Distribution of PCDD/PCDF Body Burden Between Liver and Adipose Tissues. *Toxicol. Appl. Pharmacol.* **131**(1995) 253-266.
2. Carrier, G., Brunet, R., Brodeur, J. Modeling of the Toxicokinetics of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans in Mammalians, Including Humans II. Kinetics of Absorption and Disposition of PCDDs/PCDFs. *Toxicol. Appl. Pharmacol.* **131**(1995) 267-276.
3. Hallam, T. G., Clark, C. E., Lassiter, R. R. Effects of Toxicants on Populations: a Qualitative Approach I. Equilibrium Environmental Exposure. *Ecolog. Model.* **18**(1983) 291-304.
4. Shukla, J. B., Freedman, H. I., Pal, V. N., Misra, O. P., Agrawal, M., Shula, A.: Degradation and Subsequent Regeneration of a Forestry Resource: a Mathematical Model. *Ecolog. Model.* **44**(1989) 219-229.
5. Lenbury, Y., Tumrasvin, N. Singular Perturbation Analysis of a Model for the Effect of Toxicant in Single-species Systems. *Mathl. Comput. Modelling.* In press.
6. Leung, H. W., Ku, R. H., Paustenbach, D. J., Andersen, M. E. A physiologically-based phamacokinetic model for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in C57Bl/2J mice. *Toxicol. Lett.* **42**(1988)15-28.
7. Leung, H. W., Paustenbach, D. J., Murray, F. J., Andersen, M. E. A physiologically-based phamacokinetic description of the tissue distribution and enzyme-inducing properties of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the rat. *Toxicol. Appl. Pharmacol.* **103**(1990) 399-410.
8. Lancaster, P. L., Tismenetsky, M.(1985) The Theory of Matrices, Second Edition. New York: Academic Press.
9. Freedman, H. I., Shukla J. B. Models for the effect of toxicant in single-species and predator-prey systems. *J. Math. Biol.* **30**(1991) 15-30.
10. Freedman, H. I. The implicit function theorem in the scalar case. *Can. Math. Bull.* **12**(1969) 721-732.