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A Simple Toxicokinetic Model Exhibiting Complex Dynamics and Nonlinear Exposure Response

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Abstract

Uncertainty in model predictions of exposure response at low exposures is a problem for risk assessment. A particular interest is the internal concentration of an agent in biological systems as a function of external exposure concentrations. Physiologically based pharmacokinetic (PBPK) models permit estimation of internal exposure concentrations in target tissues but most assume that model parameters are either fixed or instantaneously dose-dependent. Taking into account response times for biological regulatory mechanisms introduces new dynamic behaviors that have implications for low-dose exposure response in chronic exposure. A simple one-compartment simulation model is described in which internal concentrations summed over time exhibit significant nonlinearity and nonmonotonicity in relation to external concentrations due to delayed up- or downregulation of a metabolic pathway. These behaviors could be the mechanistic basis for homeostasis and for some apparent hormetic effects.

Keywords

Dose response; homeostasis; hormesis; PBPK; simulation; upregulation

1. INTRODUCTION

It is rarely possible to measure attributable health effects at environmental or occupational exposure levels corresponding to target risks in human populations. This is because of insufficient statistical power, measurement error, residual confounding, and inadequate specification of the exposure metric or the model itself. Therefore, low-dose (low-exposure) extrapolation from statistical models of exposure response is an important issue. For some end points, linear extrapolation is often the default either from a point-of-departure (POD) in animal studies (with uncertainty factors) or with linear models of exposure response (XR) in human studies. Deviation from linear response behavior at low exposure concentrations could impact risk assessment in either direction.

In traditional physiologically based pharmacokinetic (PBPK) modeling methodology, fixed, experimentally derived parameters are specified governing flow rates among multiple

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compartments and a system of differential equations is solved to describe concentrations within compartments over time in response to external concentrations. In the case of manganese PBPK models, a good prediction of Mn levels in the primate brain required (i) a saturable storage element, i.e., Mn binding, and (ii) asymmetrical diffusion rate constants (energy-dependent transport) for the brain compartment (Nong, Teeguarden, Clewell, Dorman, & Andersen, 2008). All kinetic parameters in this model were constant in time. Dose-dependent transitions as in upregulation add another layer of complexity to PBPK modeling (Slikker et al., 2004). Thus, for adverse effects, if some parameters change with delays reflecting response times for regulatory processes, then those changes would need to be accounted for, and risk assessments would be improved. Analyses of time course in omics data, as in describing regulatory pathways, present many challenges (Grigorov, 2006, 2011). Extending temporal analyses to the organismic level presents further challenge (Liang & Kelemen, 2017).

Zhang and Andersen (2007) performed numeric simulations of generic antistress gene regulatory networks demonstrating superlinear responses to stress agents at low concentrations that, with increasing concentrations, transitioned to linear or sublinear responses and escalating effects as pathways become saturated. Further elaboration by Zhang, Pi, Woods, and Andersen (2009) using dynamic systems control theory focused on phases I, II, and III activities of xenobiotic metabolizing enzyme systems such as those involving P450, glutathione S-transferase and membrane-bound transporters, respectively, but there the primary concern was on reactive metabolites rather than xenobiotics that are themselves reactive. In that context, metabolic gene regulation produced a variety on nonlinear responses including a physiological basis for hormetic effects (Zhang, Bhattacharya, et al., 2014; Zhang, Pi, et al., 2009) but assuming nonzero background levels of the reactive intermediates. They examined several gene-expression motifs in which system stress transitions from low to a high level based on activation kinetics. In one motif —saddle-node bifurcation—a region of instability was described for a toxic effect resulting from metabolic activation (Zhang, Bhattacharya, et al., 2014). Not examined was a motif where a protective pathway is being induced as might occur with reactive xenobiotic exposures.

Much of the research addressing kinetics in transcription regulatory pathways has been motivated by medical interest in predicting, achieving, and sustaining sufficient levels of therapeutic agents in the context of inducible, interfering metabolic pathways (Kirchmair et al., 2012; Lin, 2006; Tanaka, 1998). Steady-state conditions are generally reported for relatively high concentrations rather than transient responses to administered low doses. Some studies have described the activation of metabolic pathways by xenobiotic agents reporting the time course in terms of half-time parameters for induction or recovery. Cytochrome P450 systems have been a major focus (Gonzalez & Kasper, 1980; Hukkanen, 2012; Santostefano et al., 1998; Uchida et al., 2010), but other studies examine, for example, glutathione conjugation (Nakamura et al., 2000) or deoxyribonucleic acid (DNA) repair (Sirover, 1979). The consequences of inducible pathway effects at low exposure concentrations would not usually be observable as measurable population-level adverse health effects, particularly for chronic diseases.

To illustrate the potential importance of time-dependent metabolic regulation involving protective pathways, a pure simulation example is presented here. This is a nonstatistical, mechanistic simulation as is usually the case in PBPK studies. The possibilities when time-delays are introduced in biological regulation include attainment of (i) homeostatic conditions and (ii) apparent hormetic effects when none are actually present.

2. METHODS

Examples of dynamic complexity are presented arising from a deterministic simulation using a simple model. A protective (or toxifying) metabolic pathway is induced as a function of increasing internal dose of an external agent. Model specifications:

- one compartment,
- one pathway into compartment from environment with fixed influx proportional to external concentration,
- one inducible pathway out of compartment (could be transport, degradation, and conjugation) above a fixed first-order pathway out,
- the inducible function depends on internal current concentration, but with a delay, and varies between a normal low value (downregulated, constitutive) and a high value (maximum upregulated), and
- the accumulated upregulated entity (enzyme, transporter, and so on) concentration follows an negative exponential decline in time (described with a time constant).

Differential equation describing internal concentration, $X(t)$:

$$d(X(t))/dt = aEXTX(t) - f(X(t, t_0)),$$

where a is a constant, $EXTX(t)$ is external concentration, and f is a function of exposure history from t_0 to t.

Using a finite difference equation, the internal concentration was calculated iteratively over time, i (i = 1,2,3, …, 10,000). (See the Appendix for coding specifications for the model simulation.)

In this calculation, the following variables were defined:

- The time units were 1/25 of a day; 1,000 units ~ 40 days.
- $XD(i) = X(i-D)$, the internal concentration at time $i-D$ for response delay, D (a constant given values: 0.2, 0.5, 1.0, 2.0, 5.0 days)
- $Y(i) = (RV\text{-}XD(i))/500 + Y(i-1) \times e(-0.6931/TH)$, a difference variable comparing internal concentration at earlier time to a reference value, RV, with cumulative effect defined by prior values diminishing with half-life, TH, in time units (a constant derived as: TH = 25 × THD, where THD is given values: 0.2, 0.5, 1.0, 2.0, 5.0 days)

- If $Y < -15.0$ then $Y = -15.0$, to limit extreme values.
- If $Y > 10$ then $Y = 10$, to limit extreme values.
- $R = B + (F-B)/(e^{Y}+1)$, the time-dependent rate constant governing processing of internal concentration, which varies between B (set to 1 per day per unit internal concentration), the downregulated state, and F (set to 50 per day per unit internal concentration), the upregulated state.
- $X(i) = X(i-1) + A \times EXTX - X(i-1) \times R/2.0$, internal concentration at time, i, with external fixed concentration $EXTX$ and constant A.

The construction of this simulation model, particularly choices of constants, was by trial-and-error to produce the illustrative dynamics, a process analogous to biological selection of advantageous traits in organisms. There was minimal application of prior mechanistic design concepts. Different patterns of internal concentration, $X(i)$, over time are displayed corresponding to different choices for the constant external concentration, $EXTX$, and constants D *and* TH. Of special interest, of course, is the average steady-state internal concentration for a fixed external concentration over time. This was calculated by summing $X(i)$ over time following achievement of steady state ($i > 2{,}000$), corresponding to the increment in cumulative exposure over a fixed time interval (2,001–10,000), or 8,000 time units corresponding to 320 days.

Instead of an inducible protective effect for a toxic agent, a toxigenic pathway could be induced if there is a toxifying upregulation, e.g., production of toxic metabolic or conjugation products, or errorprone DNA repair. This behavior was investigated using a model in which the level of toxigenic upregulation depends on internal concentrations of the external agent, with a time delay. In this model, the external agent is transformed to a toxic metabolite that accumulates and is rapidly removed by a simple first-order kinetic process.

3. RESULTS

3.1. Preventive or Detoxifying Pathway

Most choices of model regulatory response times and time constants for downregulation produced nonlinear but monotonically increasing average internal steady-state concentrations of the external agent with increasing, fixed in time, external concentrations. Here, average internal concentration is equal to the increment in cumulative internal concentration (following attainment of steady state) divided by the specified period of accumulation—320 days; it is the time integral of the time-dependent internal concentration over the period 2,000—10,000 time units. For other choices, a nonmonotonic cumulative (average) internal concentration resulted as the fixed external concentration levels were increased (Figs. 1a, 2a, and 3a). For one set of specified parameters (upregulation response time: one day; decay time constant: five days; Fig. 1), the real-time internal concentration with a relatively “low” external exposure level (e.g., 3,000 in this example) exhibited periodicity in time corresponding the cycles of upand downregulation as the system responds to varying internal concentrations (Fig. 1b), while at higher external concentrations (>5,000), the system quickly established essentially full and constant upregulation (Fig. 1c). In this display, the onset of detoxifying upregulation corresponds to the start of the decline in

the internal concentration of the external agent. The relation between increasing external exposure levels and the steady-state average internal concentration changed from a positive slope at low external concentrations to a negative slope and then back to a positive but smaller slope at higher concentrations. Thus, there was a transition to a lower rate of increase with external concentration as the system sustained full upregulation of the detoxifying mechanism (Fig. 1a). Similar patterns resulted from other choices of the time parameters (e.g., Figs. 2 and 3). In Fig. 3(b), the delay from the start of each cycle of increasing internal concentration until the subsequent rapid decline was about 125 time units corresponding to five days, the upregulation response delay time specified for that model.

The ratio of internal to external exposure at low external exposures would have consequences for risk assessment when determining risks at external exposures in or below the transition range, in these examples below 5,000 (Figs. 4 and 5). Thus, in two hypothetical examples, excess risk above a specified acceptable or target level would be predicted at <1,000 or at about 5,000, depending on which linear trend is used (Fig. 4), or at about 1,500 and 25,000, respectively, in another model (Fig. 5).

Another scenario examined was exposures that, like those in an industrial setting, occur typically for eight hours per day followed by 16 hours of no exposure as compared to continuous 24 hours exposure at one-third the concentration. Modeling the internal concentration over time with fixed but periodic external concentrations equivalent to about eight hours per day (9 out of 25 time units were used) produced very similar results but with slightly larger average internal concentrations compared to model with continuous exposure (in 25 contributions per day).

3.2. Homeostasis and Hormesis

At low exposures, some specifications of model parameters, revealing nonmonotonic behavior, display steady-state time-averaged internal concentrations that remain relatively constant over a range of external concentration (e.g., concentrations 3,000–9,000 in Figs. 1a and 2a), thus producing a plateau suggesting a model for homeostasis where an internal concentration is regulated within a narrow range. If a toxic agent is ubiquitous at low levels in the environment, then one consequence of detoxifying upregulation dynamics could be observations that appear to suggest a hormetic effect, sometimes interpreted as a protective effect, at low exposures (Fig. 6): the observed physiological end point would initially exhibit a decline with increasing concentration above background. This could occur in occupational epidemiology when the population has a wide distribution of a hazardous exposure but relatively sparse observation at low exposures, or when there is no comparison population without exposure.

3.3. Toxigenic Pathway

The simple model with a toxigenic effect produces a different picture. In this model, $X(i)$ represents the internal concentration of a toxic metabolite of an agent (nontoxic) arising from an external exposure. The upregulation of the toxifying pathway is driven by the internal concentration of the external agent. In this system, choices of the time constants can

produce a gradual or a rapid transition to upregulation (Figs. 7a and b). This suggests one possible mechanistic basis for a threshold effect.

4. DISCUSSION

4.1. Assumptions and Limitations

This simulation describes plausible behavior in biological systems undergoing time-dependent regulatory changes. The focus here was on chronic, low-level exposures as arising for environmental hazards. The regulatory response time scale, days in this exercise, could be hours or weeks depending on the specific pathways. Overall, long-term cumulative effects would depend not on delayed instantaneous levels but rather on some time integration of internal concentrations. In real biological populations, in contrast to model cellular or animal systems, the transition structure with protective pathways described here would be blunted by normal biological variability of regulatory pathway kinetics (and more complex path structure). This variability could lead to low-dose supralinearity for the exposure response transitioning toward a plateau and then converging to an increasing linear response (with smaller slope) at higher exposures. The superlinear effects at low concentrations are consistent with predictions from the simulations (Zhang & Andersen, 2007). These considerations of system response times would be important in risk assessments for chronic exposures in public health and possibly for some therapeutic regimens.

This proof-of-concept mechanistic model was designed to accommodate delays in regulatory pathway responses. Beyond the examination of ranges of values for the model parameters that were considered, a broader validation of the model could be achieved by different choices in the model structure itself such as alternate monotonic functions in place of the exponential/logistic functions used. However, for those alternatives, it is anticipated that there would be parameter choices that again produce the nonmonotonic exposure responses with chronic exposure predicted in this work. A further validation step would be achieved by identifying biological model systems exhibiting the hypothesized nonlinear behavior.

The conclusion that hormetic phenomena could be observed when there is actually a no underlying hormetic response does not imply that hormesis does not exist. As described by van der Woude, Alink, and Rietjens (2005), for example, the estrogen receptor interacting with quercetin in cell culture can produce a biphasic, hormetic cellular proliferation response. Those authors explore the challenges in deriving *in vivo* human recommendations from *in vitro* findings of hormetic effects using the usual safety factors below the NOAEL. Further, in the presence of multiple xenobiotic toxic agents, it is plausible that the presence of an additional toxic agent that stimulates new protective pathways affecting other agents could result in a net protective effect at low concentrations.

4.2. Empirical Investigation

Many metabolic regulatory systems offer opportunities to examine behavior at low exposure concentrations leading to homeostasis or other detoxification mechanisms, as reviewed by Kong et al. (2001) and Bock (2014). Although adverse effects may not be observable in human studies with low-level concentrations, in animal or *in vitro* models and possibly even

in humans, it may be possible to observe time-series periodicity or plateaus in concentrations of some of the intervening substrates or metabolites with increasing xenobiotic constant exposure levels. That would be mechanistic evidence that exposures are in a range where the transition from unprotective to protective status is occurring and that exposure concentrations below that range may be contributing more to a cumulative effect than would be predicted from exposure responses estimated at higher concentrations. Investigations of estrogen-responsive gene regulation in relation to the endocrine disrupting chemical bisphenol A exposure in rat neuronal cell cultures and rodent myocyte preparations illustrate methods of observing rapid time course regulatory signaling (Belcher, Chen, Yan, & Wang, 2011; Le & Belcher, 2010). Most investigations of regulatory kinetics have not examined short-term low-dose behavior in detail.

Metabolic regulation of metals is an area where homeostasis is Important (Lombo, Posada, Quintanar, Gonsebatt, & Franco, 2018) especially for essential nutrients that become toxic at high concentrations such as zinc or manganese. For ingested manganese, control of blood levels is achieved by regulation in the liver (Andersen, Gearhart, & Clewell, 1999). In workers exposed to manganese in metallurgical work, there was evidence of homeostasis both in observed blood levels (Park, Baldwin, Bouchard, & Mergler, 2014) and in analyses of neurobehavioral adverse effects (Park, Bouchard, Baldwin, Bowler, & Mergler, 2014). For metals that are not essential nutrients, for which one might expect less fine control, wider regulatory fluctuations over time and nonmonotonic exposure response might be observable.

The treatment here assumes that the end point of interest (adverse effect) is well predicted by a cumulative internal concentration that is appropriate when (1) an internal concentration contributes irreversibly to future risk and (2) the contribution of concentration intensity to the cumulative metric is linear, that is, there is no dose-rate effect. This assumption would be appropriate for some chronic diseases including some cancers but would be inappropriate for others. If internal concentrations contribute to the predicting metric more than, or less than, proportionately as with a dose-rate effect, the upregulation dynamics could be modified substantially.

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Lynne Haber and Dale Hattis provided helpful insights and improvements reviewing an earlier draft of this work. The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

APPENDIX

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C   UPR19XRA.for  TO SIMULATE DYNAMIC PROPERTIES OF UPREGULATION IN DETOX SYSTEM
C                   INCLUDING TOXIFICATION PATHWAY
C   SPECIFICATIONS:
C
C         S - TIME RESOLUTION (TIME UNITS/DAY)
C      EXTX - EXTERNAL DOSE (CONCENTRATION)
C         X - INTERNAL CONCENTRATION
C        XD - INTERNAL CONCENTRATION WITH DELAY
C         A - ABSORBED DOSE PER DAY
C         D - UPREG RESPONSE TIME IN DAYS
C        BD - CONSTITUTIVE RATE OF TOXIFICATION
C        FD - MAXIMUM RATE OF TOXIFICATION (SATURATION) LEVEL PER DAY
C       THD - HALF-LIFE OF UPREG ACTIVITY
C         B - CLEARANCE RATE @ CONSTITUTIVE LEVEL PER UNIT TIME
C         T - UPREG RESPONSE TIME (DELAY) PER UNIT TIME
C         F - CLEARANCE RATE AT MAXIMUM (SATURATION) LEVEL PER UNIT TIME
C        UT - INT CONCENTRATION AT HALF-MAX UPREGULATION
C         Y - PARAMETER DRIVING TRANSITION
C         R - DEGREE OF UPREGULATION, BETWEEN B AND F
C      cumX - CUMULATIVE INTERNAL CONCENTRATION,
C      cumT - CUMULATIVE INTERNAL CONCENTRATION, TOXIGENIC
C        AR - ARRAY OF cumX ACROSS TIME CONSTANTS
C       ART - ARRAY OF cumT ACROSS TIME CONSTANTS
C      cumX - CUMULATIVE INTERNAL CONCENTRATION OF TOXIC EXTERNAL EXPOSURE
C      cumT - CUMULATIVE INTERNAL CONCENTRATION OF TOXIC METABOLITE OF NONTOXIC EXPOSURE
C
      REAL X(10000),EXTX(20),CUMX(20),CUMT(20),AR(26,20),ART(26,20),D(5),THD(5)
      OPEN(1,FILE='C:\TOUT\XR1SER0i.DAT')
      OPEN(2,FILE='C:\TOUT\XR1TDX0i.DAT')
      OPEN(3,FILE='C:\TOUT\XR1ARR0i.DAT')

      DATA CUMX/20*0.0/,CUMT/20*0.0/,BD,FD,S/1.0,50.0,25/,
     1 AR/520*0.0/,ART/520*0.0/
      DATA D/0.2,0.5,1,2,5/,THD/0.2,0.5,1,2,5/

C  DATA FOR DETOX
C     DATA EXTX/100,500,1000,2000,3000,4000,5000,6000,7000,8000,
C    1  10000,12000,14000,16000,18000,20000,25000,30000,40000,50000/

C  DATA FOR TOXIFY
      DATA EXTX/1,5,10,20,30,40,50,60,70,80,
     1  100,120,140,160,180,200,250,300,400,500/

      DO 6 IX=1,20
        AR(1,IX)=EXTX(IX)
        ART(1,IX)=EXTX(IX)
    6 CONTINUE

      B=BD/S
      F=FD/S
C     set regulation reference value
      UT=(500/(2*S))*(1/F + 1/B)/2.0

C     cycle through half-life values
      DO 52 N=1,5

      THP=THD(N)
      TH=THP*S

C     cycle through time delay values

      DO 5 K=1,5

      T=D(K)*S


      IT=INT(T)
      TP=D(K)

C     cycle through levels of fixed external concentration
      DO 1 J=1,20

      A1=EXTX(J)/(2*S)
      X(1)=0.0
      Y=0.0
      CUMX=0.0
      CUMT=0.0
      NC=0

C     advance through time
      DO 2 I=2,10000

      IF(IT.LT.I)GOTO 3
      XD=X(1)
      GOTO 4
    3 XD=X(I-IT)
    4 Y=(UT-XD)/500+Y*EXP(-0.6931/TH)
      IF(Y.LT.-15.0) Y=-15.0
      IF(Y.GT.10) Y=10
      R=B+(F-B)/(EXP(Y)+1)
      X(I)=X(I-1)+A1-X(I-1)*R/2.0
      IF(I.LE.2000)GOTO 2
      CUMX(J)=CUMX(J)+X(I)/S
      CUMT(J)=CUMT(J)+X(I)*(R/40.0-0.001)/S
C SELECT SUBSET OF TIME CONSTANTS FOR DISPLAYING ACTUAL TIME COURSE OF X
      IF((K.EQ.4.AND.N.EQ.2).OR.(K.EQ.3.AND.N.EQ.5).OR.(K.EQ.5.AND.N.EQ.4))
     1WRITE(2,204) K,N,J,I,EXTX(J),X(I),CUMX(J),CUMT(J)
  204 FORMAT(2I2,I3,I6,4F10.2)
    2 CONTINUE

C     WRITE(2,201) EXTX(J),CUMX(J),N,K
  201 FORMAT(F7.0,F12.0,2I2)

        L=K+5*(N-1)
        AR(L+1,J)=CUMX(J)
        ART(L+1,J)=CUMT(J)

    1 CONTINUE
    5 CONTINUE
   52 CONTINUE

      WRITE(3,301) AR
  301 FORMAT(26F10.1)
      WRITE(3,301) ART

      STOP
      END
```

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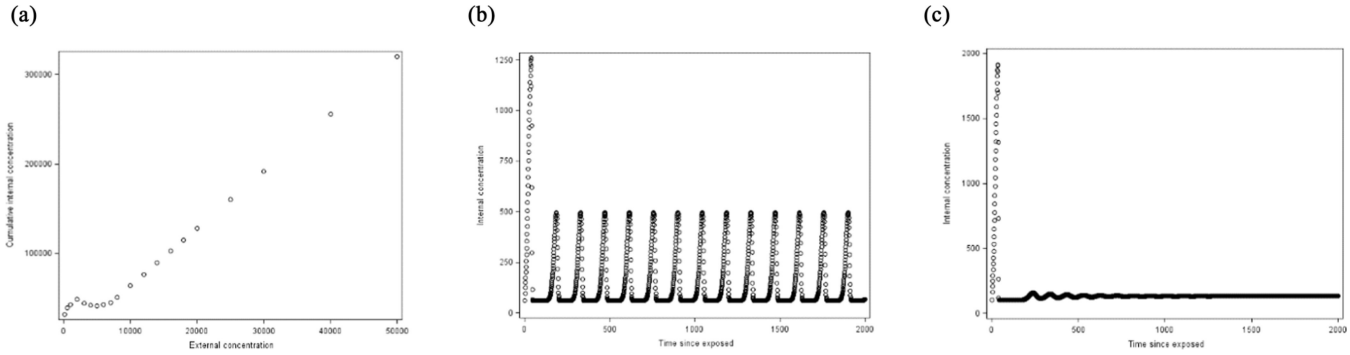

Fig 1.

Internal versus external concentrations of an exposure agent (detoxification upregulation response time: one day; decay time: five days): (a) cumulative internal concentrations (time-averaged over days 81–400) as a function of fixed external concentrations, (b) real-time internal concentration since start of exposure in time units of 1/25 of a day, for external exposure = 3,000, and (c) internal concentration for external exposure = 5,000.

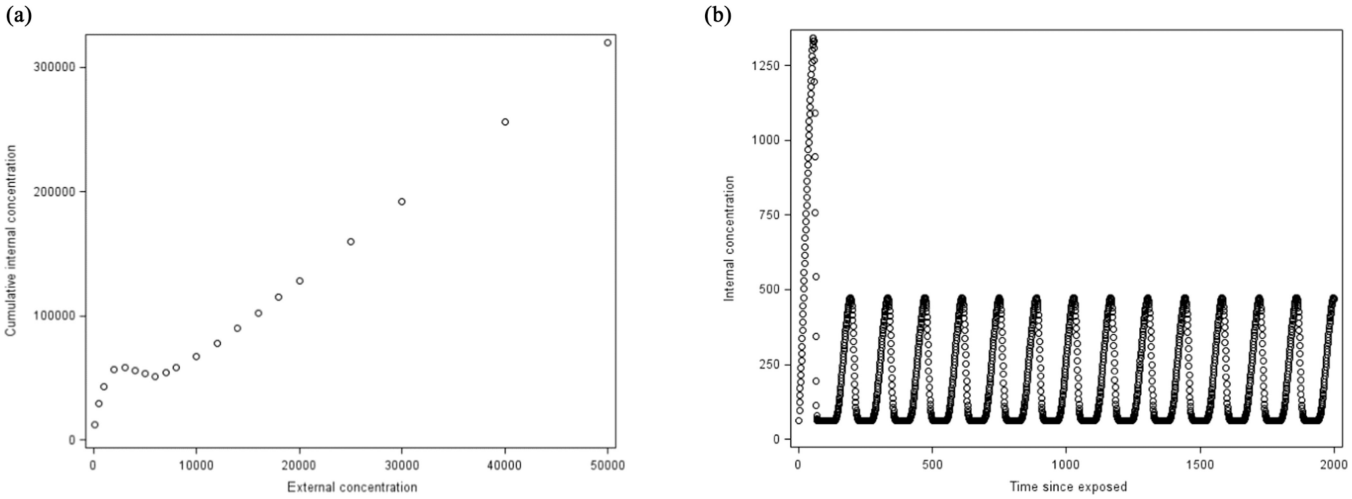

Fig 2.

Internal versus external concentrations (upregulation response time: 2 days; decay time: 0.5 days) (a) cumulative internal concentration (time-averaged over days 81–400) as a function of fixed external concentrations, and (b) real-time internal concentration since start of exposure in time units of 1/25 of a day, for external exposure = 3,000.

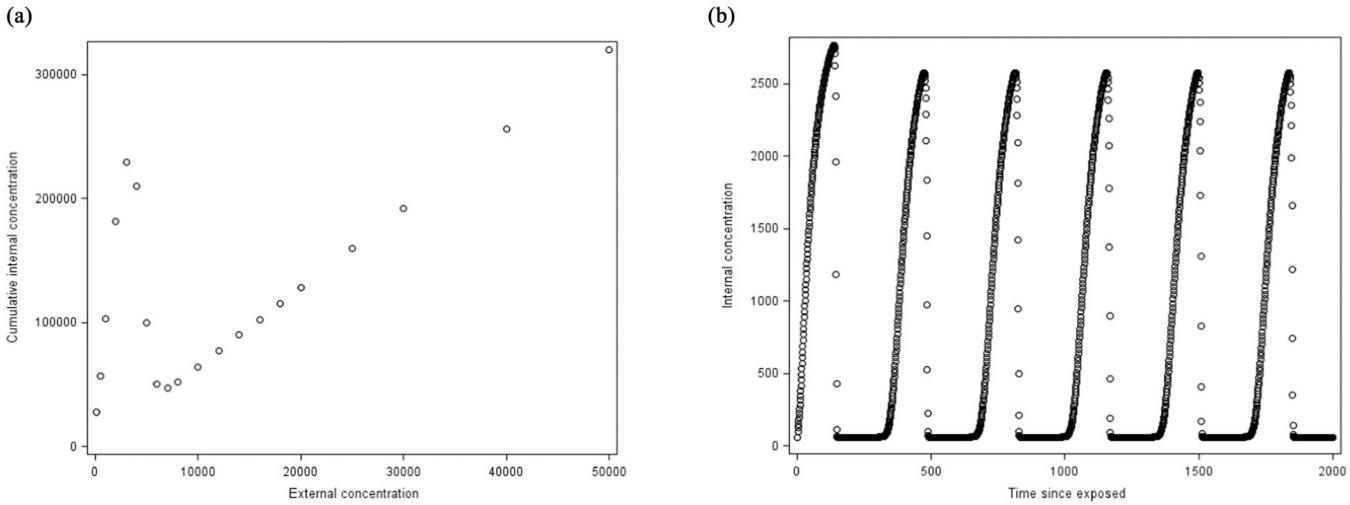

Fig 3.

Internal versus external concentrations (upregulation response time: five days; decay time: two days): (a) cumulative internal concentration (time-averaged over days 81–400) as a function of fixed external concentrations and (b) real-time internal concentration since start of exposure in time units of 1/25 of a day for external exposure = 3,000.

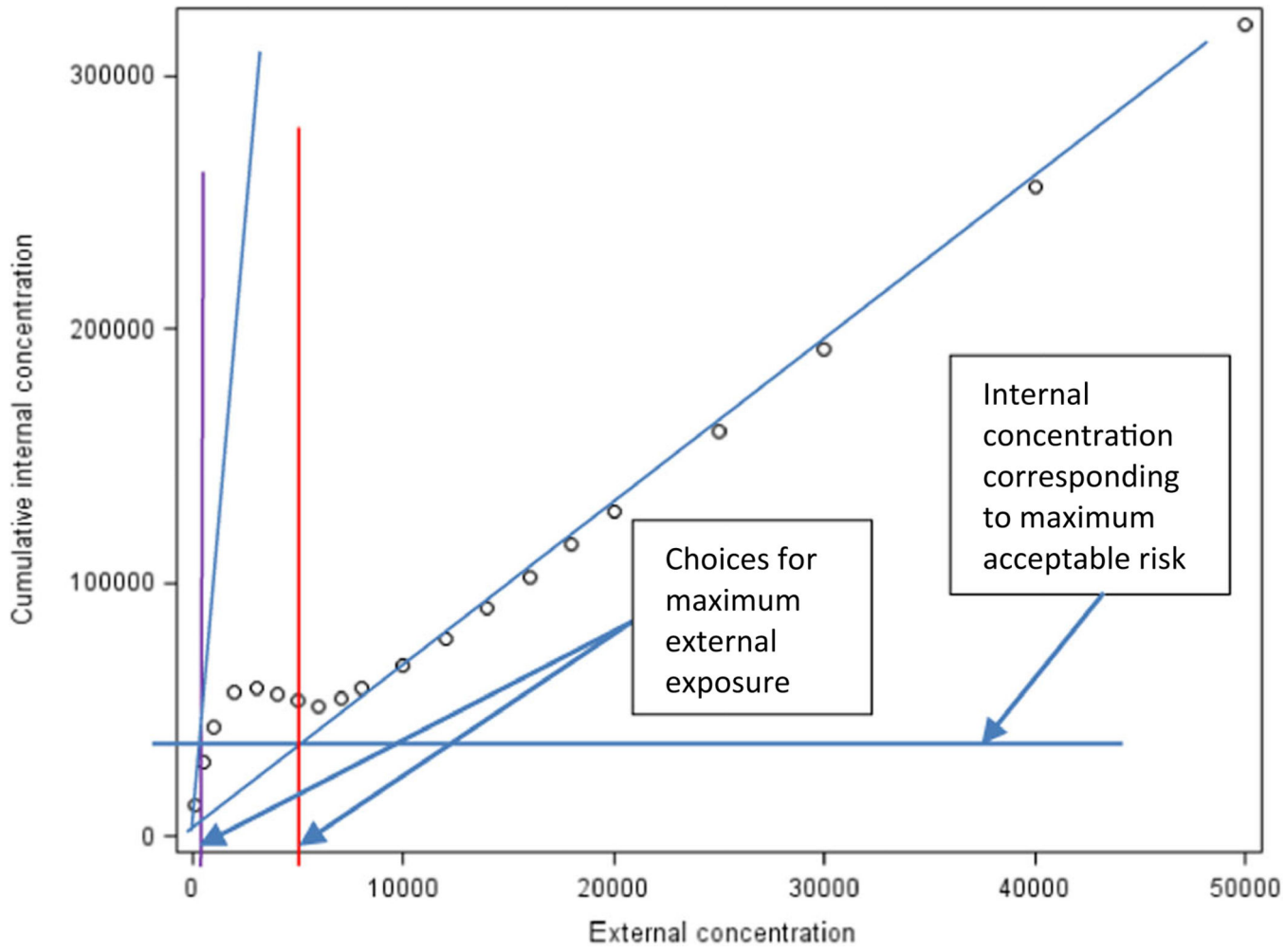

Fig 4.

Risk assessment consequences for an upregulated detoxification effect: choices for recommended exposure limit (example: upresponse time: two days; decay time: 0.5 days).

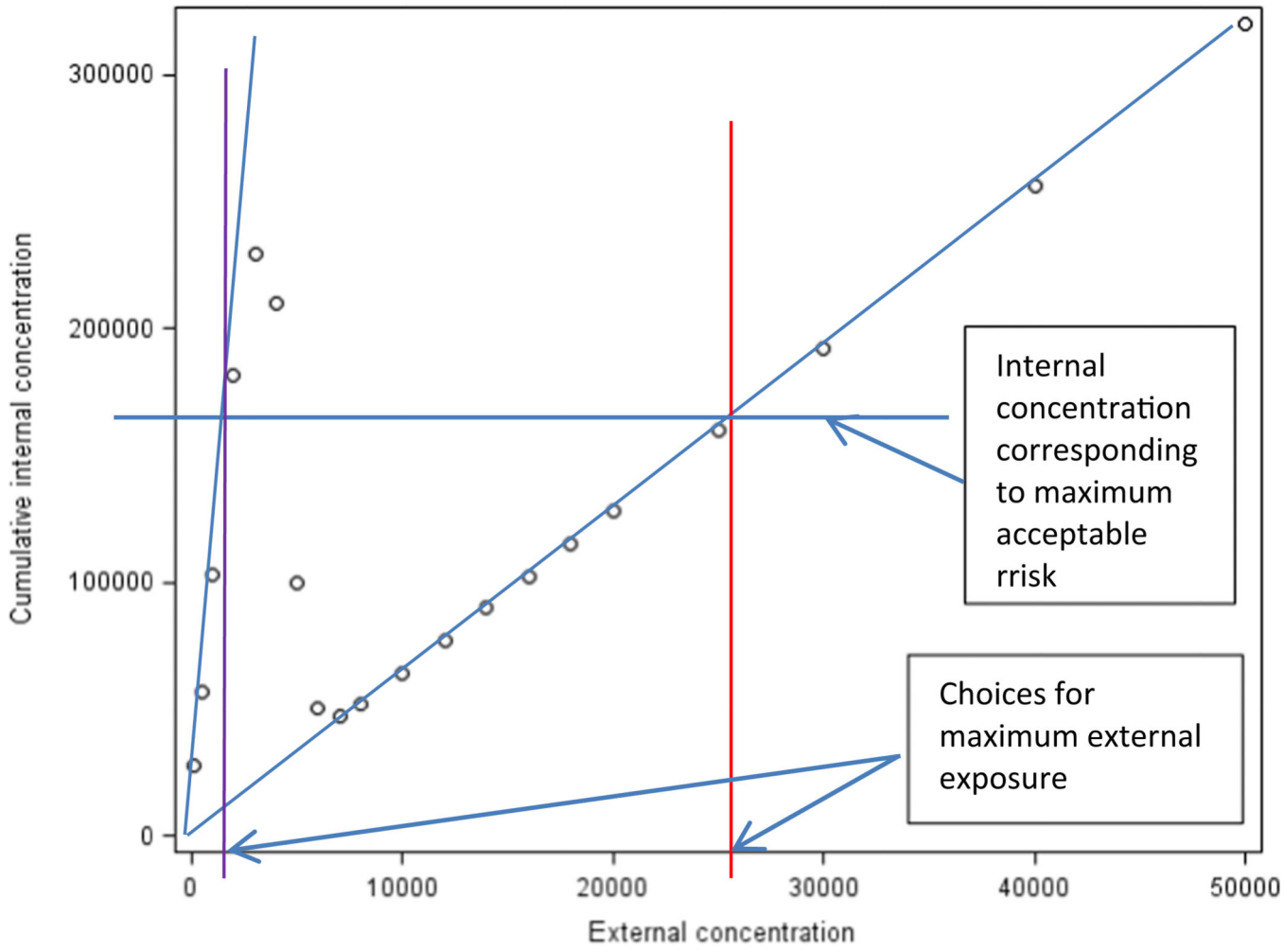

Fig 5.
Risk assessment consequences for an upregulated detoxification effect: choices for recommended exposure limit (example: upresponse time: five days; decay time: two days).

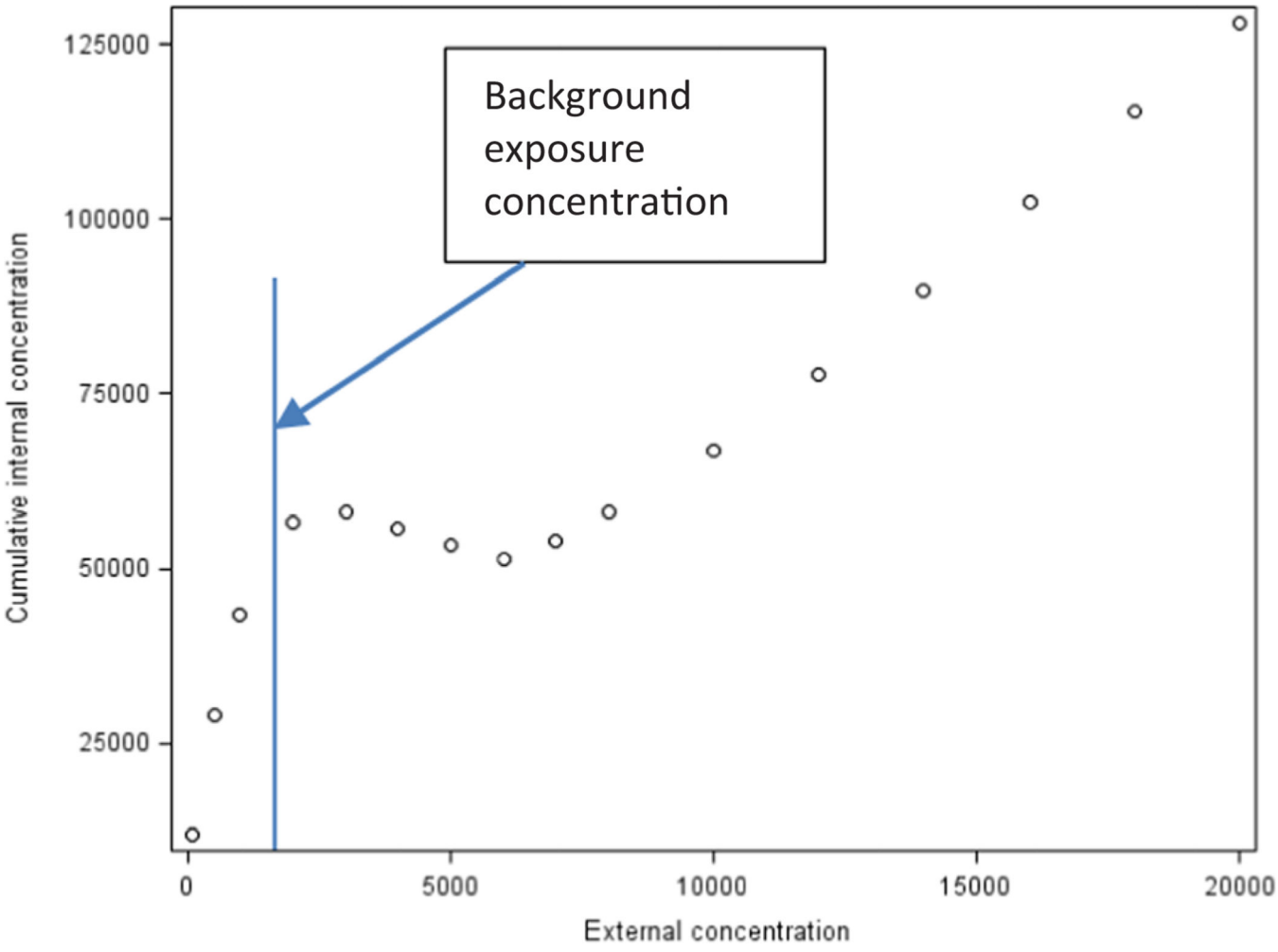

Fig 6.

Internal concentration over time with fixed external concentrations (upregulation response time: two days; decay time: 0.5 days) cumulative internal concentration (over 81–400 days): possible hormesis interpretation in the absence of unexposed comparison or with significant background exposure.

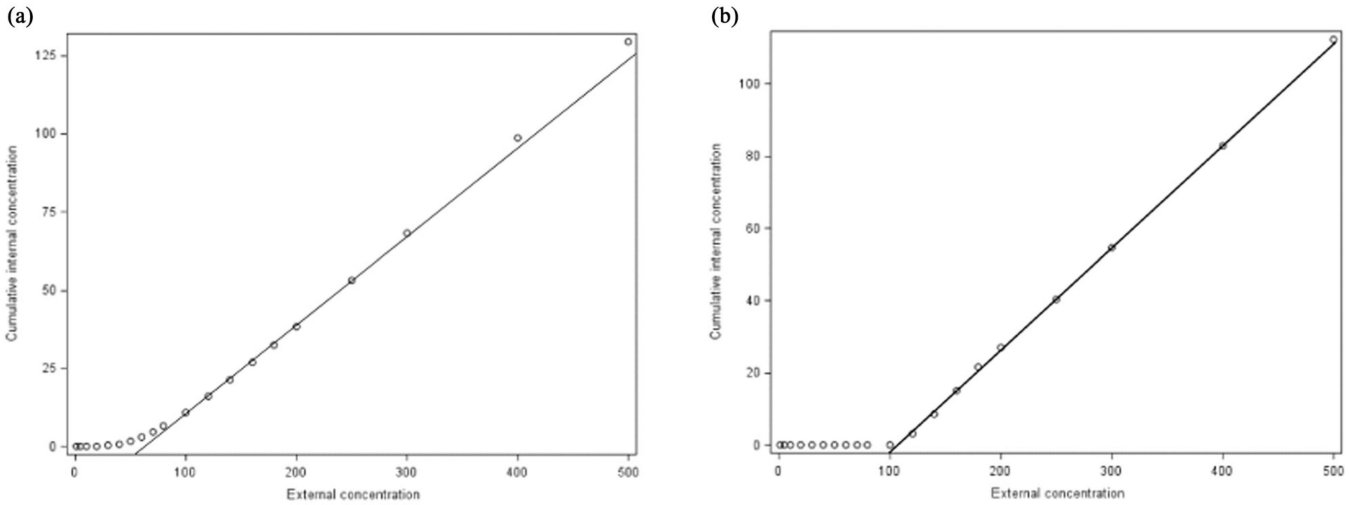

Fig 7.

Toxigenic example: cumulative concentration for a toxic product derived from a fixed external exposure through upregulation: (a) smooth transition (response time: 0.2 days; decay time: one day) and (b) sharp transition (response time: one day; decay time: five days).