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TOXICOKINETICS IN AQUATIC SYSTEMS: MODEL COMPARISONS AND USE IN HAZARD ASSESSMENT

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Abstract—Toxicokinetic models are not constrained by assumptions of equilibrium as are thermodynamic (equilibrium-partitioning) models and are more accurate predictors of toxicant accumulation for non-steady-state exposures and multiple uptake routes. Toxicokinetic models—compartment-based models, physiological-based models, and energetics-based models—are reviewed and the different mathematical formalisms compared. Additionally, the residue-based toxicity approach is reviewed. Coupling toxicokinetic models with tissue concentrations at which toxicity occurs offers a direct link between exposure and hazard. Basing hazard on tissue rather than environmental concentrations avoids the errors associated with accommodating multiple sources, pulsed exposures, and non-steady-state accumulation.

Keywords—Kinetic models Bioaccumulation Tissue residue effects
Sediment contamination Hazard assessment

INTRODUCTION

Assessment and prediction of toxicant effects on aquatic organisms require evaluation of the extent of organism exposure. Exposure assessment establishes the relationship between environmental toxicant concentrations and organism accumulation while accounting for environmental and biological factors that modify exposure. If the relationships between the amount of toxicant accumulated and the resulting effects are known, then the hazard for a particular exposure regime can be established.

Aquatic exposure assessments and predictions have employed mainly steady-state and equilibrium-partitioning models. Early efforts, using simple kinetic models, were designed to provide estimates of steady-state accumulation from water exposures [1,2]. These steady-state estimates were then utilized in hazard assessments based on thermodynamic limits (chemical equilibrium). Such models have been employed with good success for evaluation of general conditions, describing toxicant distribution among ecosystem components and

identifying components dominating toxicant mass balance. This approach has been best refined using the fugacity concept and applied to describe the importance of sediment as a toxicant source [3] and toxicant distributions within ecosystems [4,5].

Although there is a continued focus on equilibrium-partitioning models within regulatory agencies, it is clear that the environment is complex and variable. Therefore, to obtain more accurate predictions and assessments, kinetic models are needed to predict non-steady-state, nonequilibrium accumulation from temporally and spatially varying exposures when the simplifying assumptions of the equilibrium-partitioning models are inappropriate, for example, when multiple sources contribute significantly to accumulation.

Kinetic models have been used successfully in pharmacology for decades. Such models permit prediction of the onset of drug action and allow the monitoring of drug clearance and termination of effects. Further, these kinetic models describe changes in tissue concentrations resulting from absorption, distribution, metabolism, and elimination. In aquatic toxicology, kinetic models have the potential to provide the same level of predictive res-

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olution for toxicant accumulation and distribution and, ultimately, effects. The major difficulty in using such models lies in the number of parameters that must be known for a wide range of species and the difficulty in obtaining some of these values. Yet, when sufficient information is available, kinetic models can predict the accumulation of a toxic dose for either simple short-term exposures [6] or ecosystem exposures with multiple uptake routes [7].

This review provides an overview of the kinetic models available for exposure evaluation, describes their utility and intercomparability, and compares them to steady-state models. The general form of each model for water-only exposures will be presented first, and subsequently the application of these models for invertebrates and sediment-associated toxicants will be described. Finally, we will evaluate the use of these models in hazard assessment, particularly the use of toxicokinetic models to predict effects based on tissue residues.

STEADY-STATE MODELS

Organisms can attain steady state if both the exposure and the environmental/physiological factors affecting the uptake and loss of pollutants remain constant for a sufficiently long time. These steady-state conditions reflect the limit for kinetic models when accumulation from all routes is exactly balanced by the losses. Under these simplifying conditions, steady-state tissue residues classically have been described by a bioconcentration factor for aqueous exposures:

$$\text{BCF} = \frac{C_a}{C_w} \quad (1)$$

where BCF = bioconcentration factor (milliliters per gram), C_a = toxicant concentration in the animal (micrograms per gram), and C_w = toxicant concentration in the water (micrograms per milliliter).

As discussed later, the milliliters and grams of tissue should not be canceled, so the appropriate units are milliliters per gram. The units for this simple model, which are equivalent to those for partition coefficients and correlate with the octanol/water partition coefficient (K_{ow}) for nonpolar compounds, have led to the assumption that the BCF represents the thermodynamic equilibrium between the organism and source compartments. As discussed in Barron [8], the implicit assumption underlying BCFs for neutral organic compounds is that the concentration in the organism is controlled

by the hydrophobicity of the compound and the lipid content of the organism, with solubility in organism tissue dominated by the lipid solubility of the particular toxicant [9-11]. This assumption is the foundation of the simplest fugacity models and has been the premise for development of quantitative structure-activity relationships between BCF and K_{ow} [12].

BCFs can also be used with benthic organisms to predict toxicant uptake from overlying water [13,14] and to estimate accumulation from interstitial water [15,16]. The BCF formalism is impractical when source concentrations are unknown and inappropriate when the solid phases, sediments or food, contribute significantly to uptake. In these cases, steady-state accumulation is usually referenced to sediment or food source rather than water concentration by means of a bioaccumulation factor (BAF). For example, the BAF for sediment is

$$\text{BAF} = \frac{C_a}{C_s} \quad (2)$$

where the BAF is expressed in grams sediment per gram tissue and C_s = sediment concentration (micrograms per gram).

A recently developed steady-state partitioning model for bioaccumulation of sediment-associated neutral organics [17-19] normalizes the tissue residues to the organism lipid content and the environmental concentration to sediment organic carbon content:

$$\text{AF} = \frac{C_a(l)}{C_s(c)} \quad (3)$$

where $C_a(l)$ = organism concentration per gram lipid (micrograms per gram lipid), $C_s(c)$ = sediment concentration per gram organic carbon (micrograms per gram OC), and AF = accumulation factor (grams OC per gram lipid).

This normalization reduces the variability in BAF values among sediments and organisms [18,20-22]. Some authors have used "preference factors," the inverse of AFs [17,20], but AFs are more readily understood as a result of their direct relationship to BAFs.

Although steady-state behavior suggests partitioning behavior, steady state actually represents a balance between toxicant influx and outflux from an organism and is the mathematical limit for toxicokinetic models. Steady state is driven not only by thermodynamics but also by active metabolic

processes. These metabolic processes, such as reductions due to biotransformation [23] and elevations due to active ingestion [24], can result in steady-state accumulations substantially different from those predicted by thermodynamic equilibrium. Additionally, toxicant concentrations in the field can vary manifold over time, violating the assumption of a steady-state exposure. Thus, improved prediction of toxicant accumulation requires application of kinetic models.

KINETIC MODELS

Kinetic approaches for predicting accumulation are not constrained by the assumptions of either constant exposure concentrations or thermodynamic equilibrium. The models to describe toxicant kinetics fall generally into two classes: compartment-based models and models based on organism physiology. Compartment-based models describe toxicant movement between compartments. A compartment represents the amount of a compound that behaves as though it exists in a homogeneously well-mixed container and moves across the compartment boundary with a single uptake or elimination rate coefficient. Compartments may or may not represent a physical entity. The mathematical formalism for the compartment models takes three forms: rate constant or rate coefficient (RC) models [25], clearance volume (CV) models [26], and fugacity models [27]. Each of these forms is mathematically equivalent for exposures with a single uptake route, but differs in the conceptual basis that produces its formalism [27,28].

The physiological and bioenergetic models describe the kinetics and dynamics of toxicant accumulation in relation to physiological processes. Physiological-based pharmacokinetic (PBPK) models describe the accumulation and internal distribution of toxicants among multiple tissues [26,29]. The bioenergetics-based (BE) models describe toxicant accumulation and loss in terms of the organism's energy requirements and usually treat the organism as a single compartment [30].

Compartment models

Each of the compartment models will be defined and its mathematical equivalency demonstrated for a simple two-compartment model containing water and organism compartments. The water represents the source compartment, and the organism represents the toxicant sink. The toxicant is assumed to be well mixed and homogeneous within each compartment. For this specific comparison, we also assume that no compound biotransforma-

tion occurs. The models employ the underlying assumption that the rate constants and clearances remain constant over time. If the organism undergoes physiological change, this assumption can be violated. The models assume that the transfer between compartments is first order. Thus, the flux across a boundary depends on the chemical activity (concentration) in the respective compartment. The net flux is the sum of the uptake and loss fluxes across the compartment boundaries.

The terms used in the models are not standardized throughout the literature, and the reader is cautioned to check units when comparing models. Further, both upper- and lowercase *K* can serve as the symbol for rate constants or coefficients, as well as for partition coefficients. By convention, rate constants or coefficients should be represented by a lowercase *k* and partition coefficients by an uppercase *K*.

First-order rate coefficient models. The rate coefficient (RC) models relate the amount or concentration of a compound in one compartment with that in another. The RCs used in these models take the form of both clearances and rate constants. A clearance is defined as the volume or mass of a compartment scavenged of the contaminant per mass of organism per time and is contrasted to the rate constants that describe the fractional change in a compartment concentration per time. When used in an environmental context, the two compartments are the organism and the environmental compartment containing the toxicant. Thus, the two-compartment model for accumulation from water is

$$\frac{dC_a}{dt} = (k_u \cdot C_w) - (k_e \cdot C_a) \quad (4)$$

where k_u = conditional uptake clearance (milliliters per gram per hour), k_e = conditional elimination rate constant (h^{-1}) and t = time (h). Toxicokinetic RCs are conditional on the experimental conditions (e.g., temperature, physiological condition or feeding regime) under which the measurements are determined.

The term k_u is equivalent to k_1 [25] where the RC relates C_w to the toxicant flux into the organism. Many researchers have canceled the units of milliliters and grams on the assumption that 1 ml of water equals 1 g of tissue, and have described the coefficient as a rate constant with units of h^{-1} [25]. If this cancellation is performed, the units will not balance between the two sides of Equation 4, and an improper meaning will be imparted to k_u .

Thus, the units should not be canceled [31]. Additionally, leaving in the units reduces the chance of confusing RCs for water and sediment uptake.

The term k_e is equivalent to k_2 [25] and is a rate constant that describes the fractional elimination from the animal. The term k_d has often been used for the elimination rate constant. However, k_d , the depuration rate constant, describes elimination that takes place in the absence of the toxicant and should be reserved for that specific condition; thus, k_e is a better representation of the loss of the toxicant that occurs while the organism is still exposed to the toxicant.

If C_w is held constant, as ideally occurs in flow-through experiments and is often assumed for field exposures, Equation 4 can be exactly integrated to yield

$$C_a = \left(\frac{k_u \cdot C_w}{k_e} \right) (1 - e^{-k_e t}). \quad (5)$$

As time approaches infinity, the organism will approach a constant, steady-state concentration. Under steady-state conditions, we observe that the BCF can be predicted from k_u/k_e , which has led to using relatively short-term kinetics studies to estimate BCFs [1,2].

The above formulations assume no organism growth, which is a reasonable assumption during short-term laboratory experiments but may be violated when the models are applied to predicting field accumulation. When the body size of the organism increases, "growth dilution" occurs as new tissue mass dilutes the toxicant concentration [32]. The apparent elimination rate derived from a growing organism overestimates the actual elimination as it incorporates both k_e and growth. Failure to correct for growth can result in underestimates for the uptake RCs and steady-state tissue residues. Assuming growth is a first-order process, which appears reasonable at least for the early growth phase [33], the RC models can be corrected for growth by adding a first-order growth rate constant to the elimination rate constant:

$$C_a = \frac{k_u \cdot C_w}{k_e + g} (1 - e^{-(k_e + g)t}) \quad (6)$$

where g = first-order growth rate constant (grams per gram per hour or h^{-1}).

Estimation of k_u can be derived experimentally from the slope of the line of tissue residues vs. time. The data used to derive k_u must be from the

linear uptake phase, where elimination is trivial. Elimination rate constants can be derived from depuration studies in which previously exposed organisms are placed in clean water. Estimation of k_u and k_e can also be accomplished through nonlinear curve fits to an uptake curve, if the exposure is sufficiently long so that the curve begins to plateau [31]. Additionally, k_u and k_e may be determined via numerical integration techniques with equations similar to Equation 4 if the temporal variation in the water concentration is known [34]. Although the elimination coefficient can be estimated from an accumulation experiment, it is generally best to perform an independent experiment. Nonlinear fits of data will not permit the experimentalist to determine whether the reason for the plateau in the accumulation curve is due to elimination or contains other contributing factors such as a reduction in uptake from a decrease in bioavailability [35].

k_u and k_e can also be determined through mass-balance static exposures. In addition to their simplicity, static exposure systems allow steady-state tissue concentrations to be obtained more rapidly than flow-through systems, which maintain a constant toxicant concentration. In static systems, C_w declines as the toxicant is accumulated, and the model relies on mass balance of the toxicant (Eqn. 7) to permit the conversion of the differential form to an exact integral (Eqn. 8):

$$A = Q_w + Q_a \quad (7)$$

where A = amount of compound in the system (micrograms, constant), Q_a = quantity of compound in the animal compartment (micrograms), and Q_w = quantity of toxicant in the water compartment (micrograms).

$$Q_a = \frac{(k_{um} \cdot A)(1 - e^{-(k_{um} + k_e)t})}{k_{um} + k_e} \quad (8)$$

where k_{um} = uptake rate constant (h^{-1}).

The uptake rate constant, k_{um} , is not equivalent to k_u and is system dependent. k_{um} describes the fractional change in the total compound mass in the water compartment over time and depends on the relative sizes of the animal and water compartments. To remove the system dependence, the relative size of the compartments must be considered [36]:

$$k_u = k_{um} \left(\frac{V_w}{M_o} \right) \quad (9)$$

where V_w = total water volume in the static system (milliliters) and M_o = total organism mass in the system (grams).

These RC models can be applied to sediments by making sediment the source compartment. To avoid confusion between water and sediment uptake, the sediment uptake coefficient nomenclature was changed to k_s with units of grams sediment per gram organism per hour [35,37]. The k_s value integrates uptake from both interstitial water and ingested solid phases. As with k_u , k_s can be measured either from the slope of the linear uptake phase or from nonlinear fit to long-term uptake data [35,38]. Assuming sediment and not the overlying water is the uptake route, these exposures can be static or flow through without affecting the form of the equation. Because C_s will generally remain constant even under static exposures, the mass balance approach is not usually required. Thus, the model will have a form analogous to the conditions of constant water concentration [35]:

$$\frac{dC_a}{dt} = k_s \cdot C_s - k_e \cdot C_a. \quad (10)$$

BAFs can be calculated from kinetic coefficients (k_s/k_e) [39]. Greater complexity may be required for some compounds as a result of apparent changes in sediment bioavailability that are not reflected as changes in measured chemical concentrations [35] and to incorporate compartments such as additional sources [39].

Fugacity formalism of compartment models. Fugacity (f) is the thermodynamically driven escape tendency of a compound from a particular compartment and is expressed in terms of pressure (Pascals = Pa). A toxicant will always go from the compartment with the higher fugacity to one with lower fugacity, unless there is active transport. Fugacity within a compartment increases linearly with its concentration. The fugacity concept describing the movement and distribution of toxicants in an ecosystem was introduced in terms of equilibrium properties [40,41] and then expanded to include non-steady-state conditions [42]. In the course of these developments, several models have used fugacity concepts for first-order kinetic evaluation of toxicant transfer in fish and invertebrates [24,27, 43–45]. This modeling technique has also been extended to pharmacokinetic-based models for fish [46,47], which will be discussed in the section on PBPK models.

The conversion between the RC models and fugacity models for water-only exposures requires only a few changes in definitions. For Equation 4, the concentrations are given on a microgram-per-gram or microgram-per-milliliter basis, whereas in the fugacity approach all concentrations are on a mole-per-cubic-meter basis. The concentration of any compartment (C_i , moles per cubic meter) is described by the product of the fugacity capacity (Z_i , moles per cubic meter per Pascal) and fugacity (f_i , Pascals) of the compartment (i). A first-order flux, N (moles per hour), is defined in concentration terms as the product of a first-order rate constant (k_i , h^{-1}), the compartment concentration, and the compartment volume (V_i , m^3). Finally, flux in fugacity terms is defined as the product of the transfer coefficient D_i (moles per hour per Pascal) and fugacity. Thus,

$$N = (k_i \cdot C_i \cdot V_i) = (k_i \cdot Z_i \cdot f_i \cdot V_i) = (D_i \cdot f_i), \quad (11)$$

which results in the following definition for a first-order rate constant [41]:

$$k_i = \frac{D_i}{V_i \cdot Z_i}. \quad (12)$$

Subsequently, Equation 4 can be written totally in fugacity terms by multiplying both sides of Equation 4 by the volume of the animal (V_a , cubic meters) to yield Equation 13:

$$(V_a) \left(\frac{dC_a}{dt} \right) = (V_a \cdot k_u \cdot C_w) - (k_e \cdot C_a \cdot V_a). \quad (13)$$

If the above definitions are substituted for the compartment concentrations and RCs, Equation 14 is generated

$$(V_a \cdot Z_a) \left(\frac{df_a}{dt} \right) = (D_u \cdot f_w) - (D_e \cdot f_a) \quad (14)$$

where f_a = fugacity in organism (Pascals), f_w = fugacity in water (Pascals), D_u = transfer coefficient into the organism (moles per hour per Pascal), and D_e = transfer coefficient out of the organism (moles per hour per Pascal). At the limit where the flux equals zero (i.e., steady state) then Equation 15 follows:

$$D_u \cdot f_w = D_e \cdot f_a \quad \text{or} \quad \frac{f_a}{f_w} = \frac{D_u}{D_e} \quad (15)$$

Finally, if both sides of the equation are multiplied by the ratio of Z_a/Z_w , the relationship between the concentrations in the water and organism at steady state is:

$$\frac{C_a}{C_w} = \frac{D_u \cdot Z_a}{D_e \cdot Z_w} = \text{BCF}. \quad (16)$$

In fugacity models, concentrations are on a volume basis; therefore, the units of k_u will be $\text{m}_w^3 \cdot \text{m}_a^{-3} \cdot \text{h}^{-1}$. Thus, both Equation 4 and Equation 14 can be interconverted and will yield equivalent results. In this form, Equation 14 can be manipulated in the same manner as other fugacity equations, and the D values (transfer coefficients) become synonymous with the RCs in the other first-order compartment models. The main difficulty in using this form of the equation is the difficulty in obtaining D values. In many cases, the D values are estimated from RCs obtained by using the RC-based models [46].

Clearance volume model: CV models originated in clinical pharmacology and were used to describe the uptake and elimination of drugs in mammals [48,49]. More recently, researchers have applied CV models to aquatic organisms. CV models have been used to examine the effects of pH on the accumulation of pentachlorophenol in goldfish [50] and the effects of body size [51] and temperature [52] on the uptake of di-2-ethylhexyl phthalate (DEHP) by fish. CV models also have been applied to benthic invertebrates [28]. Although there is essentially no mathematical difference between the CV and RC models, they use different parameter definitions [26]. A comparative review of the two models can be found in Stehly et al. [28].

CV models describe the uptake and elimination of a compound by an organism as clearances and use an apparent volume of distribution in order to describe the capacity of the organism to bioconcentrate the chemical. Transfer of a toxicant from water in the CV model is described by

$$C_w \xrightleftharpoons{P} C_a. \quad (17)$$

The movement of compound is represented by a clearance constant, P , the volume of water totally scavenged of compound per gram of organism per hour (milliliters per gram per hour) for our simple two-compartment example. This is the amount of water that would have to be ventilated at 100% assimilation efficiency to account for a particular uptake rate. Clearances are equivalent to k_u in the RC model for water exposure. Clearances are related to rate constants by the following equation:

$$k = \frac{P}{V_d} \quad (18)$$

where k = general rate constant (h^{-1}), P = clearance (milliliters per gram per hour), and V_d = volume of distribution of the compound (milliliters per gram).

The volume of distribution, V_d , describes the capacity of a compartment (e.g., organism or organ) to accumulate a compound. V_d in the aquatic environment is usually referenced to the exposure water and expresses the capacity of the animal to accumulate a particular chemical in terms of the equivalent volume of exposure water holding the same quantity of chemical [28]. These are not true volumes, and if the organism has a greater capacity for the toxicant than the water, V_d will exceed the volume of the organism. In pharmacology, this model employs the blood volume as the reference volume. If blood concentrations can be monitored, this pharmacological approach can also be employed to follow the distribution and elimination within and from aquatic organisms. Note that V_d should not be confused with volume, V_i , in the fugacity model.

The rate of change in the toxicant concentration in the animal (C_a) for an aqueous exposure is

$$\frac{dC_a}{dt} = (P \cdot C_w) - \left(\frac{P \cdot C_a}{V_d} \right). \quad (19)$$

This equation was integrated to give the following expression for C_a :

$$C_a = (C_w \cdot V_d)(1 - e^{(-P/V_d)t}). \quad (20)$$

This integrated equation is mathematically equivalent to Equation 4. As time becomes large, the model yields an estimate of V_d that is equivalent to BCF:

$$V_d = \frac{C_a}{C_w} = \text{BCF}. \quad (21)$$

There are no examples using the CV model in which sediment is the toxicant source. As with all compartment models, following multiple sources (e.g., sediments, water, and food) would require multiple compartments to appropriately model the toxicant accumulation.

Physiological- and energetics-based models

Physiological-based pharmacokinetic models. Physiological-based pharmacokinetic (PBPK) mod-

els were originally developed to describe drug metabolism kinetics in mammals. A comprehensive PBPK model was developed to describe drug distributions in humans [53], and subsequent PBPK models have been successfully used in numerous mammalian studies [54–56]. The use of PBPK models has also been extended to lower vertebrates such as fish [46, 57–60] and invertebrates [61]. The state of the art and the utility for providing a mechanistic approach to aquatic toxicology for fish have recently been reviewed for PBPK models [62].

PBPK models separate an organism into anatomical compartments, each representing a particular organ or group of kinetically related tissues [63]. Data on basic physiological processes such as tissue volumes, blood flow rates, partition coefficients between blood and tissues, and biotransformation rates [26,29,64] are used, and differential mass balance equations are written to describe the accumulation, elimination, and metabolism of the chemical. A representative equation for distribution from the blood to a tissue follows:

$$\frac{dC_x}{dt} = \frac{Q_x \left(C_i - \frac{C_x}{R_x} \right)}{V_x} \quad (22)$$

where C_x is the average toxicant concentration in a selected organ (micrograms per gram tissue), Q_x represents the plasma flow rate through the organ (milliliters per hour), and V_x is the organ volume (milliliters). The concentration of the chemical entering the organ is represented by C_i , and the plasma concentration leaving the organ is represented by C_x/R_x , where R_x is the tissue plasma concentration ratio [58]. The equations for these models can be written in terms of RC [60,65,66] or fugacity [46,67] parameters.

A promising feature of the PBPK approach is the ability to scale the model to other species or body sizes by inserting the appropriate physiological information. This approach has successfully scaled monkey [68] and rodent [69] data to humans, as well as mouse data to various species of sting-rays [57]. Scaling these models to invertebrates will require collection of additional physiological data and may well require adding additional processes, such as accumulation and loss across the integument, that are unimportant for most vertebrates. The ability to scale models has been better investigated with PBPK models than compartment models, but some efforts have been examined with the compartment-based models [27].

PBPK models can appear to better represent re-

ality in the sense that they are focused on the mechanistic nature of the organism and not just rate processes. Further, the compartments in PBPK models have real physiological meaning, compared to those derived from CV models. However, PBPK models are based on the inherent assumption that a particular mechanism(s) is the rate-determining step in the bioaccumulation process. For example, bioaccumulation in invertebrates is assumed, without empirical evidence, to occur via a specific process (e.g., gill ventilation) as the rate-determining step [60]. However, a totally separate process (e.g., ingestion, passive diffusion across the integument, or internal distribution processes) may represent the rate-controlling step. Often there is not enough evidence to justify the formulation of the bioaccumulation processes in terms of a single or combination of physiological processes. Therefore, PBPK models may not represent a more “realistic” picture than the box model approach used by RC models, but instead merely a different approach.

Compared to compartment models, PBPK models require significantly more data and resources for development. Often the required data are not available because analyzing tissue volumes or taking blood samples from small fish or invertebrates is difficult [61,66]. Due to differences in the physiology of invertebrates, such as open circularity systems, compared to large fish, it may be necessary to modify the PBPK model structure for benthic invertebrates.

Bioenergetic-based toxicokinetic models. An organism's contact with the external environment is directly related to the flux of water across its gills to obtain oxygen and the flux of food/sediment through its gut to obtain nutrients. Bioenergetic-based (BE) models predict pollutant uptake as a function of these fluxes, assuming that uptake from each source is proportional to its flux. The general equation for an organism with multiple food types is

$$\frac{dC_a}{dt} = (A_w \cdot C_w \cdot F_w) + \left(\sum_{j=1}^k A_{fj} \cdot C_{fj} \cdot F_{fj} \right) - (k_e \cdot C_a) - (C_a \cdot g) \quad (23)$$

where A_w = toxicant assimilation efficiency from water (unitless), F_w = weight-specific flux of water (milliliters per gram per day), A_{fj} = toxicant assimilation efficiency from food j (unitless), C_{fj} = toxicant concentration in food j (micrograms per gram), F_{fj} = weight-specific flux of food (grams per gram per day), g = first-order growth constant (d^{-1}), and k = total number of food types.

Elimination is not related to the organism's metabolism in this formulation, although a reduction in elimination rate with size may be more appropriate in some cases [70]. The last term, g , accounts for growth dilution as discussed previously.

The metabolic (oxygen) requirements of fish are sufficiently well known [70,71] to allow accurate predictions of the fluxes of water and food over the life cycle or under different environmental conditions for many species. Thus, BE models have successfully predicted tissue residues in freshwater [70,72] and marine [73] fishes and have been used to model toxicant transport through food chains [74].

Application of the BE model to sediment-ingesting invertebrates includes 10 potential uptake routes, even when considering sediment as a single food source [75]. In most cases, however, modeling interstitial and overlying water fluxes and the ingested sediment as the food source should be adequate. Ingested sediment fluxes and concentrations are used instead of bulk sediment to account for any selective consumption. The basic equation for a deposit feeder becomes

$$\begin{aligned} \frac{dC_a}{dt} = & (A_w \cdot F_{wo} \cdot C_{wo}) + (A_w \cdot F_{wi} \cdot C_{wi}) \\ & + (A_{si} \cdot F_{si} \cdot C_{si}) - (k_e \cdot C_a) - (C_a \cdot g) \end{aligned} \quad (24)$$

where C_{wo} = toxicant concentration in overlying water (micrograms per milliliter), C_{wi} = toxicant concentration in interstitial water (micrograms per milliliter), F_{wo} = weight-specific flux of overlying water (milliliters per gram per day), F_{wi} = weight-specific flux of interstitial water (milliliters per gram per day), F_{si} = weight-specific flux of ingested sediment (grams per gram per day), A_{si} = toxicant assimilation efficiency from ingested sediment (unitless), and C_{si} = toxicant concentration of ingested sediment (micrograms per gram).

In addition to these flux-related uptakes, "passive" sorption to exposed body surfaces can be a nontrivial uptake route for metals [76] and organics [77; H. Lee, unpublished data]. In the simplest case, sorption can be incorporated as a constant (i.e., simple partitioning phenomenon) [75]. The tissue residue at time t then becomes

$$C_a(t) = S + \frac{(A_w \cdot F_{wo} \cdot C_{wo}) + (A_w \cdot F_{wi} \cdot C_{wi}) + (A_{si} \cdot F_{si} \cdot C_{si})}{k_e + g} (1 - e^{-(k_e + g) \cdot t}) \quad (25)$$

where S = toxicant sorption onto body surface (micrograms per gram).

Measured, rather than predicted, fluxes of water and sediment have been used for benthic invertebrates [75,78-80]. As we gain a better understanding of benthic invertebrate energetics, it should be possible to predict age (size) and environmental specific fluxes as with fish. However, there are sufficient differences in invertebrate physiology, such as anaerobic metabolism, to warrant caution in the direct application of energetic equations or parameters derived from fish for benthos.

BE models are conceptually related to PBPK models in that the metabolic requirements of an organism are determined by its physiology. In practice, PBPK models have been used primarily to predict the internal distribution of toxicants, whereas BE models have been used to predict uptake by fish under field conditions or the importance of uptake routes for deposit feeders. There is a direct relationship between BE and RC models for water uptake:

$$\frac{dC_a}{dt} = k_u \cdot C_w = A_w \cdot F_w \cdot C_w \quad (26)$$

Here the uptake rate coefficient combines the transfer efficiency and flux of water. However, if dermal uptake is important [61], this simple relationship will not hold. The simple compartment models for accumulation from sediment yielding k_s values are not directly equivalent to the BE models. Because k_s integrates uptake from both interstitial water and ingested sediment, a multi-compartment RC model [39] would be required to compare with the BE model.

ENVIRONMENTAL AND PHYSIOLOGICAL FACTORS

The conditional nature of the rate coefficients used in all of these models must be understood. Environmental, physiological, and toxicological factors can cause the RCs to change over time. Some of the environmental factors (e.g., temperature) exert their influence by directly modifying the physiology, whereas others modify the toxicant chemistry, which in turn modifies the kinetics.

One of the major biological factors to be considered is the biotransformation capability of the

organism. Biotransformation can alter the toxicant distribution among the various tissues of an organism [81,82] and will alter any estimate of the elimination rate or BCF measured with total radiotracer unless biotransformation losses are considered [23,82–87]. If k_e is derived from measurement of the parent compound, it will include both the elimination of the parent toxicant and its metabolism.

The rates of uptake, elimination, and contaminant distribution within the organism vary with organism size [13,14,51,61,88,89]. Growth often results in alteration of the organism lipid content, which affects the elimination of nonpolar organic compounds. For example, increases in total lipid content decrease the apparent elimination rate for *Diporeia* and *Hexagenia* [13,90], and the turnover of lipids can be the driving force for loss of very hydrophobic contaminants [13]. Additionally, aquatic organisms exhibit changes in kinetic processes as the reproductive condition of the organism varies [91] or due to toxic stress [92–95].

Sorption of a toxicant to organic matter, whether in water [96] or sediment [39,97], reduces the effective concentration driving the accumulation and results in an apparent decrease in uptake RCs. However, if the kinetics for aqueous exposure are based on the freely dissolved pool, the accumulation will be correctly predicted independently of the amount of dissolved organic matter [98,99]. Several researchers have suggested that normalization to organic carbon will essentially eliminate the variability in bioavailability of sediment-associated nonpolar organic compounds [100,101], and a comparison of sediment uptake RCs has shown a relationship with sediment carbon [37,97]. However, simple carbon normalization does not account for the effects of different carbon types on partitioning [102] or the effects of aging on bioavailability [37,103].

Environmental factors such as pH can alter the characteristics of the chemical through ionization of functional groups or hydrolysis of ester and amide linkages, reducing bioavailability and, therefore, the uptake rate [50,104,105]. Temperature generally alters toxicokinetics by changing organism physiology. Effects of temperature can be observed on both the uptake and the elimination of compounds [13,14,90,104–106].

UTILIZING KINETIC MODELS IN EXPOSURE ASSESSMENT

One of the goals of the equilibrium and kinetic models is to predict whole-body burdens from environmental concentrations of toxicants. In gen-

eral, kinetic models require more data and are more complicated to apply than the equilibrium-partitioning models. From a regulatory standpoint, the kinetic models are worth the additional resources only if the equilibrium approaches do not generate “sufficient” accuracy. Sufficient accuracy depends on the user’s goals, but one suggestion for equilibrium models is predictions within twofold of observed values [100]. In the recognition of the multiplicative nature of error, 80% accuracy has been suggested as the desired level for sediment bioaccumulation tests [77]. This value is based on obtaining a final tissue residue within twofold of observed, assuming a three-step food chain and 80% accuracy at each transfer.

Predictions of BCFs from physicochemical parameters can differ substantially among regressions, depending on the relationships chosen to make the predictions [12], and predictions for a compound are often no better than one or two orders of magnitude [8]. Further, fugacities of superlipophilic compounds can be substantially higher in fish than in water [107], suggesting that additional uptake from food permits increased accumulation above the water fugacity limit [24,46,47].

The accuracy of the equilibrium-partitioning model for sediment exposures (Eqn. 3) has been most thoroughly evaluated for polychlorinated biphenyls (PCBs). AFs for total PCB or Aroclors from different studies ranged by more than 20-fold [22], and values for a single hexachlorobiphenyl congener ranged 80-fold [21]. Ranges for mean AFs for total PCBs within a single study were of the same magnitude [21], indicating that the variation was not solely methodological such as might result from using different lipid methods [108]. Additionally, several of the AFs exceeded those predicted from equilibrium partitioning [22].

It is apparent that in many cases simple equilibrium-partitioning models do not predict residues of high K_{ow} neutral organics, the compounds with the greatest bioaccumulation potential, within a twofold, much less an 80%, accuracy for either water or sediment. However, the utility of the partitioning approaches are severalfold. First, they serve as a point of departure. Values deviating from equilibrium indicate additional processes hindering or facilitating uptake and/or elimination of the target compound. Second, equilibrium models predict the overall trends in relation to physicochemical attributes. Third, equilibrium models are well suited as cost-effective screening tools, such as screening of dredge material with the equilibrium-partitioning bioaccumulation model [109].

Kinetic models are more appropriate than simple equilibrium-partitioning models when the exposure concentrations vary over time, passive diffusion is not the only driving force for accumulation, multiple toxicant sources are responsible for accumulation, or the time course of uptake is of direct concern. This implicitly assumes kinetic models are better predictors than equilibrium models, although the data are limited. Perhaps the strongest case for the accuracy of kinetic models is their success in pharmacology. The success of the PBPK models to predict uptake and distribution of pollutants and the BE models to predict uptake in the fish populations demonstrates these models are adaptable to environmental toxicants, at least for fish. There are fewer data to evaluate the accuracy of kinetic models with sediment contaminants. In a short-term laboratory experiment with *Macoma* exposed to sediment-associated hexachlorobenzene, the mass balance derived from a BE model was very close to the observed tissue residues (92–114%) [75]. When using independently derived values for k_s and k_e , an RC model predicted BAFs by *Macoma* within 90% (range 69–165%) of observed BAF for a range of PCB congeners, although the kinetics were less successful in predicting the time to steady state [110]. In the only apparent field validation for benthic organisms, the RC model faithfully predicted seasonal changes in benzo[*a*]pyrene in amphipods when environmental and physiological factors were considered [111]. The concentrations of more water-soluble polycyclic aromatic hydrocarbons (PAHs), however, were not as successfully modeled.

Based on the available data, the kinetic models are more appropriate than simple equilibrium-partitioning models for other than steady-state, water-only exposures. The present models may not always

obtain 80% or even twofold accuracy, either due to incomplete or incorrect description of key processes or due to errors associated with measurements of parameters. However, both of these sources of error are potentially correctable.

This conclusion raises the question of which of the kinetic models to use. There is no simple answer, as the choice depends on the question being addressed, the experimentalist's experience, and the ease of data collection. In general, the use of the simplest model that will adequately address the question should minimize the errors associated with parameter estimation and, thus, result in the most precise estimates. The rest of this section will present some general guidelines, which are summarized in Table 1.

When describing a steady-state, two-compartment system with water as the exposure compartment, all the compartment models are mathematically interconvertible and will lead to the same general conclusions about the kinetics. They will all give similar estimates of accumulation, although the actual values may vary somewhat as a result of the different error sources associated with the methods of deriving the values. The models may not be equivalent with more complex exposure scenarios. For example, fugacity does not account for the active transport of compounds, such as phagocytosis in the gut. If this process were important in a deposit feeder, prediction of steady-state accumulation would differ between an RC model (Eqn. 14) using an empirically measured sediment uptake RC and a prediction based on fugacity differences in the sediment and organism.

All the kinetic approaches except the BE models can be used to describe or predict the internal distribution of toxicants among compartments within an organism. Because CV models reference

Table 1. Comparison of the equilibrium and kinetic models

Model/attribute	Model					
	Equilibrium	RC ^a	Fugacity	CV ^b	PBPK ^c	BE ^d
Requires assumption of equilibrium	Yes	No	No	No	No	No
Models multiple compartments	No	Yes	Yes	Yes	Yes	Yes
Models multiple uptake routes	No	Yes	Yes	No	Yes	Yes
Can be used to model internal distribution of toxicants	No	Yes	Yes	Yes	Yes	No
Potential to scale to other species (by lipid content)	Yes	Some	Some	No	Yes	Yes
Data requirements	Low	Moderate	Moderate-High	Moderate	High	High

^aRC = rate coefficient.

^bCV = clearance volume.

^cPBPK = physiological-based pharmacokinetic.

^dBE = bioenergetic.

all compartments to a single reference compartment (e.g., plasma), it is a relatively simple matter to incorporate a second compartment within the organism to help describe the distribution resistance or multiple storage sites that can affect the observed kinetics [26]. However, as has been pointed out by Barron et al. [26], the RCs in CV models may have little physiological meaning, making it difficult to extrapolate to other species or toxicants. However, compartment-based models have had limited success in scaling data to different size organisms that are closely related [27]. Multiple compartments within an organism can also be accommodated in the RC- [59] and fugacity-based formats [67]. The PBPK models focus more on the physiological and mechanistic parameters, and the use of allometric relationships permits the models to be successfully scaled from one species to another, as discussed previously.

Contaminant sources, in addition to overlying water, must be accommodated for proper evaluation of the accumulation of many toxicants. These potential sources are readily accommodated in kinetic models, except there are no references for multiple sources using the CV model in aquatic studies. These additional sources generally involve the diet of the organism, whether it is sediment detrital material [31,39,44,75,78,79,112,113] or prey for fish [24,46,47,66,106,114-116]. The extent of the dietary route depends on the feeding rate [79,113]; assimilation efficiency, which can vary with feeding rate [78]; and concentration in the food [66]. Additionally, food quality, such as lipid content, may alter contaminant transport into the organism [117]. If the question is specifically to determine the importance of various routes, the BE model may be the best choice, as it directly focuses on uptake from each route.

One important application of these models is to predict accumulation in the field over long-term exposures. Such a scenario will usually require the ability to incorporate growth and various other physiological and environmental changes. All models that represent the organism as a single compartment will be insufficient to describe multicompartment kinetics that are important when modeling depletion of a fast compartment, as may occur during fluctuating exposures. The PBPK models include the physiological changes in greater detail and can account for differential rates of elimination from various tissues, allowing a description of biphasic elimination. However, PBPK models may incorporate more detail than necessary, or at least feasible, to incorporate in many cases. The BE

models integrate most of the key physiological process in the energetic terms and can directly incorporate season effects on most of the parameters and, thus, are a good choice. Although able to incorporate multiple-compartment kinetics, the CV model has been demonstrated only for simple water exposures with aquatic species. The RC and non-steady-state fugacity models would also be appropriate if temperature and age-specific uptake coefficients were used. At a broader level, if the question is to determine the movement of toxicants among ecosystem components, the fugacity models are the best choice, as they offer a mechanism to predict concentrations in abiotic components.

COUPLING EXPOSURE ASSESSMENT TO HAZARD ASSESSMENT

The foundation of toxicology is based on the toxicant concentration that produces an effect at a target site. Therefore, establishing the relationship between an organism's exposure, which toxicokinetics models attempt to describe, and the toxicant concentration at the target site(s) is the link between exposure assessment and dose response for hazard assessment. Standard regulatory paradigms such as water quality criteria use the environmental concentration as a surrogate for the concentration at the receptor site. These paradigms are based on the premise that the toxicant concentration at the receptor is proportional to the organism concentration, which is in turn proportional to the exposure concentration. Some of the limitations of this approach include the difficulties in determining the bioavailable fraction of the environmental concentration, multiple uptake routes, pulsed doses, non-steady-state situations (e.g., short exposure times), and toxicant biotransformations.

If effects were based on the body burden required to produce the effect, complications arising from the uncertainty regarding bioavailability and accumulation would essentially be eliminated. It is not necessary to identify the target site or the toxicant concentration at the target site, as long as the concentration at the target site is proportional to the concentration in any tissue or the whole body—a common assumption when dealing with drug effects in pharmacology. This approach for establishing a residue basis for toxicity has been discussed in McCarty et al. [118-121], and Landrum and Dupuis [6], and reviewed by McCarty [122].

The tissue residue for a wide range of neutral narcotics ranges from 2 to 6 mmol kg⁻¹ for small fish and invertebrates to yield 50% mortality for acute exposures [6,86,95,118,120,122,123]. Neutral

organics seem to act as additive toxins when combined on a molar basis [95], greatly simplifying prediction of toxic effects for this group of compounds. When the tissue concentration required to produce 50% acute mortality is below 0.5 mmol kg^{-1} [6,86,94], the toxicant acts by a specific mechanism of action, which is indeterminate between about 0.5 and 2 mmol kg^{-1} [122].

The residue concentrations required to produce chronic effects are much lower than those needed for acute mortality. For 50% mortality, the residue concentration for chronic exposure to non-polar narcotics is about 10% of that required to produce the acute response [118,122]. If instead of mortality, scope for growth is used as the effect end point, a residue concentration of approximately $4 \mu\text{mol kg}^{-1}$ is required for 50% reduction in the scope for growth with toxins having a nonpolar mechanism of action [124].

Coupling of kinetic models with the tissue residue approach allows the prediction of toxic effects resulting from complex exposure scenarios. Recently, the residue concentration approach was applied to multiple compartments with multiple source exposures, including a relatively complex food chain, using fugacity nomenclature to predict steady-state body burdens that would result in effects [125]. Kinetic models can also predict the dynamics of toxicant concentrations. For example, the kinetics were able to predict the measured residue required to elicit 50% mortality for both carbaryl and pentachlorophenol in *Diporeia* spp. and *Mysis relicta* over several lengths of exposure [6].

This approach permits interpretation of pulsed exposures [122], which are common in the environment and produce effects that can be interpreted in terms of the body residue but not directly using the average environmental exposure concentrations for the organism [126]. Tissue thresholds generate an integrated measure of exposure resulting from these pulsed exposures, compared to the instantaneous "snapshot" from the measurement of an environmental concentration. Tissue residues also integrate spatial variations in exposure in mobile organisms.

Coupling kinetic models with a tissue threshold will allow a prediction of how close an organism would be to a chronic or acute toxic response under various exposure scenarios. Kinetic models also will predict the time course for approaching the toxic threshold. Besides these predictions, monitoring tissue residues in field-collected organisms would generate a relatively straightforward assessment of an organism's or population's health. The difference between the measured or predicted tis-

sue residue and the threshold could be used to set discharge limits or cleanup levels.

The use of tissue thresholds predicts a chronic or acute response on an individual level. This single value is analogous to other single estimates of toxicity (e.g., LC50). The predicted effects on individuals could be incorporated into population models to predict population effects. The structure of the population model would vary with the threshold (e.g., chronic effect on reproduction or acute mortality). Ideally, these population effects could be incorporated into ecosystem models to estimate effects on community structure [7].

There are, of course, a number of limitations to tissue thresholds. For the residue approach to work, the toxicodynamics of the compound must be considered. The compound distribution among the tissues must be at steady state, or at least proportional to the distribution that would occur at steady state. If not, then the concentration at the receptor site may not be in proportion to the whole-body residue concentration. Therefore, the tissue residue approach may not work for very short exposures. Such disproportionality of distribution between tissues has been observed for short-term exposures for fish [122] and even in small invertebrates such as *Mysis relicta* [81]. To predict effects from short-term exposures or for larger animals, a PBPK model would be useful to predict the concentrations in specific target tissues.

Considerable research is needed to determine the minimum data sets required to establish threshold tissue concentrations for the major environmental toxicants. Although more research is also needed with lower- K_{ow} organics to establish that the narcotizing effect is a general response, including benthic invertebrates, the real challenge is the higher- K_{ow} compounds. The high- K_{ow} compounds have more bioavailability limitations and will be more difficult to predict. Additionally, development of residue-based concentrations for compounds that exhibit specific mechanisms of action will require exposure to a range of taxa to ensure that sensitivity species are included. This approach is not fundamentally different from establishing water quality criteria, although the tissue residue thresholds are not specific to a particular route of exposure.

Acceptance of the residue approach, in combination with the application of kinetic models, will allow the development of much better hazard assessments for aquatic organisms. Although the state of the art for these assessments has made considerable progress, as reviewed by Bartell et al. [7],

the focus of hazard assessments remains on individual compounds. However, the needed hazard assessment requires evaluation of exposures to multiple compounds of multiple mechanisms of action. Thus, the future for this field will be the continued development of the connection between bioaccumulation and toxic effects and the incorporation of mixtures in the assessment arena.

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REFERENCES

1. Branson, D.R., G.E. Blau, H.C. Alexander and W.B. Neely. 1975. Bioconcentration of 2,2',4,4'-tetrachlorobiphenyl in rainbow trout as measured by an accelerated test. *Trans. Am. Fish. Soc.* 4:785-792.
2. Neely, W.B. 1979. Estimating rate constants for the uptake and clearance of chemicals by fish. *Environ. Sci. Technol.* 13:1506-1510.
3. Mackay, D., M. Diamond and W. Stiver. 1991. The case for modeling sediment-water interactions in aquatic and marine systems. In R.A. Baker, ed., *Organic Substances and Sediments in Water*, Vol. 3—Biological. Lewis Publishers, Chelsea, MI, pp. 43-63.
4. Mackay, D. and M. Diamond. 1989. Application of the QWASI (quantitative water air sediment interaction) fugacity model to the dynamics of organic and inorganic chemicals in lakes. *Chemosphere* 18:1343-1365.
5. Clark, T., K. Clark, S. Paterson, D. Mackay and R.J. Norstrom. 1988. Wildlife monitoring, modeling, and fugacity. *Environ. Sci. Technol.* 22:120-127.
6. Landrum, P.F. and W.S. Dupuis. 1990. Toxicity and toxicokinetics of pentachlorophenol and carbaryl to *Pontoporeia hoyi* and *Mysis relicta*. In W.G. Landis and W.H. van der Schalie, eds., *Aquatic Toxicology and Risk Assessment: Thirteenth Volume*. STP 1096. American Society for Testing and Materials, Philadelphia, PA, pp. 278-289.
7. Bartell, S.M., R.H. Gardner and R.V. O'Neill. 1992. *Ecological Risk Estimation*. Lewis Publishers, Chelsea, MI.
8. Barron, M.G. 1990. Bioconcentration. *Environ. Sci. Technol.* 24:1612-1618.
9. Dobbs, A.J. and N. Williams. 1983. Fat solubility—a property of environmental relevance? *Chemosphere* 12:97-104.
10. Roberts, J.R., A.S.W. deFries and M.A.J. Gidney. 1977. Influence of lipid pool size on bioaccumulation of the insecticide chlordane by northern redbreast suckers (*Moxostoma macrolepidotum*). *J. Fish. Res. Board Can.* 34:89-97.
11. Connell, D.W. 1988. Bioaccumulation behavior of persistent organic chemicals with aquatic organisms. *Rev. Environ. Contam. Toxicol.* 101:117-154.
12. Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1990. *Handbook of Chemical Estimation Methods*. American Chemical Society, Washington, DC.
13. Landrum, P.F. 1988. Toxicokinetics of organic xenobiotics in the amphipod, *Pontoporeia hoyi*: Role of physiological and environmental variables. *Aquat. Toxicol.* 12:245-271.
14. Fisher, S.W., D.C. Gossiaux, K.A. Bruner and P.F. Landrum. 1992. Preliminary investigations of the toxicokinetics of hydrophobic contaminants in the zebra mussel, *Dreissena polymorpha* Pallas. In T.F. Nalepa and D.W. Schloesser, eds., *Zebra Mussels: Biology, Impacts, and Control*. Lewis Publishers, Chelsea, MI, pp. 466-490.
15. Adams, W.J., R.A. Kimerle and R.G. Mosher. 1985. Aquatic safety assessment of chemicals sorbed to sediments. In R.D. Cardwell, R. Purdy and R.C. Bahner, eds., *Aquatic Toxicology and Hazard Assessment: Seventh Symposium*. STP 854. American Society for Testing and Materials, Philadelphia, PA, pp. 429-453.
16. Adams, W.J. 1987. Bioavailability of neutral lipophilic organic chemical contaminants on sediments: A review. In K.L. Dickson, A.W. Maki and W.A. Brungs, eds., *Fate and Effects of Sediment-Bound Chemicals in Aquatic Systems*. Pergamon Press, Elmsford, NY, pp. 219-244.
17. Lake, J.L., N.I. Rubinstein and S. Pavignano. 1987. Predicting bioaccumulation: Development of a partitioning model for use as a screening tool in regulating ocean disposal of wastes. In K.L. Dickson, A.W. Maki and W.A. Brungs, eds., *Fate and Effects of Sediment-Bound Chemicals in Aquatic Systems*. Pergamon Press, Elmsford, NY, pp. 151-166.
18. Ferraro, S.P., H. Lee II, R. Ozretich and D. Specht. 1990. Predicting bioaccumulation potential: A test of a fugacity-based model. *Arch. Environ. Contam. Toxicol.* 19:386-394.
19. Ferraro, S.P., H. Lee II, L. Smith, R. Ozretich and D. Specht. 1991. Accumulation factors for eleven polychlorinated biphenyl congeners. *Bull. Environ. Contam. Toxicol.* 46:276-372.
20. McElroy, A.E. and J.C. Means. 1988. Factors affecting the bioavailability of hexachlorobiphenyls to benthic organisms. In W.J. Adams, G.A. Chapman and W.G. Landis, eds., *Aquatic Toxicology and Hazard Assessment: 10th Volume*. STP 971. American Society for Testing and Materials, Philadelphia, PA, pp. 149-158.
21. Lake, J.L., N.I. Rubinstein, H. Lee, C.A. Lake, J. Heltshe and S. Pavignano. 1990. Equilibrium partitioning and bioaccumulation of sediment-associated contaminants by infaunal organisms. *Environ. Toxicol. Chem.* 9:1095-1106.
22. Lee, H. II. 1992. Models, muddles and mud: Predicting bioaccumulation of sediment-associated pollutants. In A. Burton, ed., *Sediment Toxicity Assessment*. Lewis Publishers, Chelsea, MI, pp. 267-294.
23. Leversee, G.J., J.P. Giesy, P.F. Landrum, S. Gerould, J.W. Bowling, T.E. Fannin, J.D. Haddock and S.M. Bartell. 1982. Kinetics and biotransformation of benzo(a)pyrene in *Chironomus riparius*. *Arch. Environ. Contam. Toxicol.* 11:25-31.
24. Gobas, F.A.P.C., D.C.G. Muir and D. Mackay. 1988. Dynamics of dietary bioaccumulation and fecal elimination of hydrophobic organic chemicals in fish. *Chemosphere* 17:943-962.

25. Spacie, A. and J.L. Hamelink. 1982. Alternative models for describing the bioconcentration of organics in fish. *Environ. Toxicol. Chem.* 1:309-320.
26. Barron, M.G., G.R. Stehly and W.L. Hayton. 1990. Pharmacokinetic modeling in aquatic animals. I. Models and concepts. *Aquat. Toxicol.* 17:187-212.
27. Gobas, F.A.P.C. and D. Mackay. 1987. Dynamics of hydrophobic organic bioconcentration in fish. *Environ. Toxicol. Chem.* 6:495-504.
28. Stehly, G.R., P.F. Landrum, M.G. Henry and C. Klemm. 1990. Toxicokinetics of PAHs in *Hexagenia*. *Environ. Toxicol. Chem.* 9:167-174.
29. Himmelman, K.J. and R.J. Lutz. 1979. A review of the application of physiologically based pharmacokinetic modeling. *J. Pharmacokinet. Biopharm.* 7:127-137.
30. Breck, J.E. and S.M. Bartell. 1988. Approaches to modeling the fate and effects of toxicants in pelagic systems. In M.S. Evans, ed., *Toxic Contaminants and Ecosystem Health: A Great Lakes Focus*. John Wiley & Sons, New York, NY, pp. 427-446.
31. Landrum, P.F. and D. Scavia. 1983. Influence of sediment on anthracene uptake, depuration and biotransformation by the amphipod *Hyaella azteca*. *Can. J. Fish. Aquat. Sci.* 40:427-437.
32. Niimi, A.J. and C.Y. Cho. 1981. Elimination of hexachlorobenzene (HCB) by rainbow trout (*Salmo gairdneri*), and an examination of its kinetics in Lake Ontario salmonids. *Can. J. Fish. Aquat. Sci.* 38:1350-1356.
33. Muir, D.C.G., A.L. Yarechewski, D.A. Metner, W.L. Lockhart, G.R.B. Webster and K.J. Friesen. 1990. Dietary accumulation and sustained hepatic mixed function oxidase enzyme induction by 2,3,4,7,8-pentachlorodibenzofuran in rainbow trout. *Environ. Toxicol. Chem.* 9:1463-1472.
34. Gobas, F.A.P.C., E.J. McNeil, L. Lovett-Doust and G.D. Haffner. 1991. Bioconcentration of chlorinated hydrocarbons in aquatic macrophytes. *Environ. Sci. Technol.* 25:924-929.
35. Landrum, P.F. 1989. Bioavailability and toxicokinetics of polycyclic aromatic hydrocarbons sorbed to sediments for the amphipod, *Pontoporeia hoyi*. *Environ. Sci. Technol.* 23:588-595.
36. Landrum, P.F. 1983. The effect of co-contaminants on the bioavailability of polycyclic aromatic hydrocarbons to *Pontoporeia hoyi*. In M.W. Cooke and A.J. Dennis, eds., *Polynuclear Aromatic Hydrocarbons: Seventh International Symposium on Formation, Metabolism and Measurement*. Battelle Press, Columbus, OH, pp. 731-743.
37. Lee, H. II. 1991. A clam's eye view of the bioavailability of sediment-associated pollutants. In R.A. Baker, ed., *Organic Substances and Sediments in Water*, Vol. 3. Lewis Publishers, Chelsea, MI, pp. 73-1099.
38. Foster, G.D., S.M. Baski and J.C. Means. 1987. Bioaccumulation of trace organic contaminants from sediment by baltic clams (*Macoma balthica*) and soft-shell clams (*Mya arenaria*). *Environ. Toxicol. Chem.* 6:969-976.
39. Landrum, P.F. and J.A. Robbins. 1990. Bioavailability of sediment-associated contaminants to benthic invertebrates. In R. Baudo, J.P. Giesy and H. Muntau, eds., *Sediments: Chemistry and Toxicity of In-Place Pollutants*. Lewis Publishers, Chelsea, MI, pp. 237-263.
40. Mackay, D. 1979. Finding fugacity feasible. *Environ. Sci. Technol.* 13:1218-1223.
41. Mackay, D. and S. Paterson. 1981. Calculating fugacity. *Environ. Sci. Technol.* 15:1006-1014.
42. Mackay, D. and S. Paterson. 1991. Evaluating the multimedia fate of organic chemicals: A level III fugacity model. *Environ. Sci. Technol.* 25:427-436.
43. Mackay, D. and S. Paterson. 1982. Fugacity revisited. *Environ. Sci. Technol.* 16:654A-660A.
44. Gobas, F.A.P.C., D.C. Bedard, J.J.H. Ciborowski and G.D. Haffner. 1989. Bioaccumulation of chlorinated hydrocarbons by the mayfly (*Hexagenia limbata*) in Lake St. Clair. *J. Great Lakes Res.* 15:581-588.
45. Gobas, F.A.P.C., K.E. Clark, W.Y. Shiu and D. Mackay. 1989. Bioconcentration of polybrominated benzenes and biphenyls and related superhydrophobic chemicals in fish: Role of bioavailability and elimination into the feces. *Environ. Toxicol. Chem.* 8:231-245.
46. Clark, K.E., F.A.P.C. Gobas and D. Mackay. 1990. Model of organic chemical uptake and clearance by fish from food and water. *Environ. Sci. Technol.* 24:1203-1213.
47. Clark, K.E. and D. Mackay. 1991. Dietary uptake and biomagnification of four chlorinated hydrocarbons by guppies. *Environ. Toxicol. Chem.* 10:1205-1217.
48. Rowland, M., L.Z. Benet and G.G. Graham. 1973. Clearance concept in pharmacokinetics. *J. Pharmacokinet. Biopharm.* 1:123-126.
49. Wilkinson, G.R. and D.G. Shand. 1975. A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.* 18:377-390.
50. Stehly, G.R. and W.L. Hayton. 1990. Effect of pH on the accumulation kinetics of pentachlorophenol in goldfish. *Arch. Environ. Contam. Toxicol.* 19:464-470.
51. Tarr, B.D., M.G. Barron and W.L. Hayton. 1990. Effect of body size on the uptake and bioconcentration of di-2-ethylhexylphthalate in rainbow trout. *Environ. Toxicol. Chem.* 9:989-995.
52. Karara, A.H. and W.L. Hayton. 1989. A pharmacokinetic analysis of the effect of temperature on the accumulation of di-2-ethylhexyl phthalate (DEHP) in sheepshead minnow. *Aquat. Toxicol.* 15:27-36.
53. Bischoff, K.B. and R.G. Brown. 1966. Drug distribution in mammals. *Chem. Eng. Prog. Symp. Ser.* 62:32-45.
54. Anderson, M.E. 1981. A physiologically based toxicokinetic description of the metabolism of inhaled gases and vapors. Analysis at steady state. *Toxicol. Appl. Pharmacol.* 60:509-526.
55. Gabrielson, J.L. and L.K. Paalzow. 1983. A physiological pharmacokinetic model for morphine disposition in the pregnant rat. *J. Pharmacokinet. Biopharm.* 11:147-163.
56. Igari, Y., Y. Sugiyama, S. Awazu and M. Hanano. 1982. Comparative physiology based pharmacokinetics of hexobarbital, phenobarbital and thiopental in the rat. *J. Pharmacokinet. Biopharm.* 10:53-75.
57. Zaharko, D.S., R.L. Dedrick and V.T. Oliverio. 1972. Prediction of the distribution of methotrexate

- in the sting rays *Dasyatidae sabrina* and *D. Sayi* by use of a model developed in mice. *Comp. Biochem. Physiol.* **42A**:183-194.
58. **Bungay, P.M., R.L. Dedrick and A.M. Guarino.** 1976. Pharmacokinetic modeling of the dogfish shark (*Squalus acanthias*): Distribution and urinary and biliary excretion of phenol red and its glucuronide. *J. Pharmacol. Biopharm.* **4**:377-388.
59. **McKim, J.M., P.K. Schmieder and R.J. Erickson.** 1986. Toxicokinetic modeling of [¹⁴C]pentachlorophenol in the rainbow trout (*Salmo gairdneri*). *Aquat. Toxicol.* **9**:59-80.
60. **Barber, M.C., L.A. Suarez and R.R. Lassiter.** 1988. Modeling bioconcentration of nonpolar organic pollutants in fish. *Environ. Toxicol. Chem.* **7**:545-558.
61. **Landrum, P.F. and C.R. Stubblefield.** 1991. Role of respiration in the accumulation of organic xenobiotics by the amphipod *Diporeia* sp. *Environ. Toxicol. Chem.* **10**:1019-1028.
62. **McKim, J.M. and J.W. Nichols.** 1992. Use of physiologically-based toxicokinetic models in a mechanistic approach to aquatic toxicology. In G.K. Ostrander and D.C. Malins, eds., *Molecular Biological and Biochemical Approaches to Aquatic Toxicology*. Lewis Publishers, Chelsea, MI (in press).
63. **Roland, M.** 1985. Physiological pharmacokinetic models and interanimal species scaling. *Pharmacol. Ther.* **29**:49-68.
64. **Lutz, R.J. and R.L. Dedrick.** 1985. Physiological pharmacokinetics: Relevance to human risk assessment. In A.P. Li, ed., *New Approaches in Toxicity Testing and Their Application in Human Risk Assessment*. Raven Press, New York, NY, pp. 129-149.
65. **McKim, J.M., P.K. Schmieder, R.W. Carlson, E.P. Hunt and G.J. Niimi.** 1987. Use of respiratory-cardiovascular responses of rainbow trout (*Salmo gairdneri*) in identifying acute toxicity syndromes in fish. Part 1. Pentachlorophenol, 2,4-dinitrophenol, tris(1-cyanoethyl)phosphorothionate and 1-octanol. *Environ. Toxicol. Chem.* **6**:295-312.
66. **Opperhuizen, A. and S.M. Schrap.** 1987. Relationship between aqueous oxygen concentration and uptake and elimination rates during bioconcentration of hydrophobic chemicals in fish. *Environ. Toxicol. Chem.* **6**:335-342.
67. **Paterson, S. and D. Mackay.** 1987. A steady-state fugacity-based pharmacokinetic model with simultaneous multiple exposure routes. *Environ. Toxicol. Chem.* **6**:395-408.
68. **Benowitz, N., R.P. Foysyth, K.L. Melmon and M. Rowland.** 1974. Lidocaine disposition kinetics in monkey and man. I. Prediction of a perfusion model. *Clin. Pharmacol. Ther.* **16**:87-109.
69. **Ramsey, J.C. and M.E. Anderson.** 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* **73**:159-175.
70. **Norstrom, R.J., A.E. McKinnon and A.S. deFreitas.** 1976. A bioenergetic based model for pollutant accumulation by fish. Simulation of PCB and methylmercury residue levels in Ottawa River. *J. Fish. Res. Board Can.* **33**:248-267.
71. **Ricker, W.E., ed.** 1968. *Methods for Assessment of Fish Production in Fresh Water*. IBP Handbook No. 3. Blackwell Scientific, Oxford, UK.
72. **Jensen, A.L., S.A. Spigarelli and M.M. Thommes.** 1982. PCB uptake by species of fish in Lake Michigan, Green Bay of Lake Michigan, and Cayuga, New York, NY. *Can. J. Fish. Aquat. Sci.* **39**:700-709.
73. **Connolly, J.P. and R. Tonelli.** 1985. Modeling kepone in striped bass food chain of the James River estuary. *Estuarine Coastal Shelf Sci.* **20**:349-366.
74. **Thomann, R.V.** 1989. Bioaccumulation model of organic chemical distribution in aquatic food chains. *Environ. Sci. Technol.* **23**:699-707.
75. **Boese, B.L., H. Lee, D.T. Specht, R.C. Randall and M. Winsor.** 1990. Comparison of aqueous and solid-phase uptake for hexachlorobenzene in the tellinid clam, *Macoma nasuta* (Conrad): A mass balance approach. *Environ. Toxicol. Chem.* **9**:221-231.
76. **Flemming, T.P. and K. Richards.** 1981. A technique to quantify surface adsorption of heavy metals by soft-bodied invertebrates. *Comp. Biochem. Physiol.* **69C**:391-394.
77. **Lee, H. II, B.L. Boese, J. Pelletier, M. Winsor, D.T. Specht and R.C. Randall.** 1989. Guidance manual: Bedded sediment bioaccumulation tests. EPA 600/x-89-302 (ERLN-N111). U.S. Environmental Protection Agency, Narragansett, RI.
78. **Klump, J.V., J.R. Krezoski, M.E. Smith and J.L. Kaster.** 1987. Dual tracer study of the assimilation of an organic contaminant from sediments by deposit feeding oligochaetes. *Can. J. Fish. Aquat. Sci.* **44**:1574-1583.
79. **Weston, D.P.** 1990. Hydrocarbon bioaccumulation from contaminated sediment by the deposit-feeding polychaete *Abarenicola pacifica*. *Mar. Biol.* **107**:159-170.
80. **Winsor, M.H., B.L. Boese, H. Lee II, R.C. Randall and D.T. Specht.** 1990. Determination of the ventilation rates of interstitial and overlying water by the clam *Macoma nasuta*. *Environ. Toxicol. Chem.* **9**:209-213.
81. **Gardner, W.S., P.F. Landrum and J.F. Cavaletto.** 1990. Lipid-partitioning and disposition of benzo(a)pyrene and hexachlorobiphenyl in Lake Michigan *Pontoporeia hoyi* and *Mysis relicta*. *Environ. Toxicol. Chem.* **9**:1269-1278.
82. **Stehly, G.R. and W.L. Hayton.** 1989. Disposition of pentachlorophenol in rainbow trout (*Salmo gairdneri*): Effect of inhibition of metabolism. *Aquat. Toxicol.* **14**:131-148.
83. **Opperhuizen, A. and P.I. Voors.** 1987. Uptake and elimination of polychlorinated aromatic ethers by fish: Chloroanisols. *Chemosphere* **16**:953-962.
84. **Kennedy, C.J. and F.C.P. Law.** 1990. Toxicokinetics of selected polycyclic aromatic hydrocarbons in rainbow trout following different routes of exposure. *Environ. Toxicol. Chem.* **9**:133-139.
85. **Reichert, W.L., B.L. Eberhart and U. Varanasi.** 1985. Exposure of two species of deposit-feeding amphipods to sediment-associated [³H]benzo[a]pyrene: Uptake, metabolism and covalent binding to tissue macromolecules. *Aquat. Toxicol.* **6**:45-56.
86. **De Bruijn, J. and J. Mermens.** 1991. Uptake and elimination kinetics of organophosphorus pesticides in the guppy (*Poecilia reticulata*): Correlations with the octano/water partition coefficient. *Environ. Toxicol. Chem.* **10**:791-804.
87. **Goerke, H. and K. Weber.** 1990. Population-depen-

- dent elimination of various polychlorinated biphenyls in *Nereis diversicolor* (Polychaeta). *Mar. Environ. Res.* **29**:205-226.
88. **Connell, D.W.** 1987. Age to PCB concentration relationship with the striped bass (*Morone saxatilis*) in the Hudson River and Long Island Sound. *Chemosphere* **16**:1469-1474.
 89. **Gorge, G. and R. Nagel.** 1990. Kinetics and metabolism of ¹⁴C-lindane and ¹⁴C-atrazine in early life stages of zebra fish. *Chemosphere* **21**:1125-1137.
 90. **Landrum, P.F. and R. Poore.** 1988. Toxicokinetics of selected xenobiotics in *Hexagenia limbata*. *J. Great Lakes Res.* **14**:427-437.
 91. **Jovanovich, M.C. and K.R. Marion.** 1987. Seasonal variation in uptake and depuration of anthracene by the brackish water clam *Rangia cuneata*. *Mar. Biol.* **95**:395-403.
 92. **Carr, R.S. and J.M. Neff.** 1988. Influence of prior exposure to xenobiotics on the metabolism and disposition of polychlorinated biphenyls and phenanthrene in winter flounder, *Pseudopleuronectes americanus*. *Mar. Environ. Res.* **24**:73-77.
 93. **Black, M.C. and J.F. McCarthy.** 1990. Effects of sublethal exposure to chlorine on the uptake of polychlorinated biphenyl congeners by rainbow trout. *Salmo gairdneri* (Richardson). *Aquat. Toxicol.* **17**:275-290.
 94. **Landrum, P.F., W.R. Faust and B.J. Eadie.** 1989. Bioavailability and toxicity of a mixture of sediment-associated chlorinated hydrocarbons to the amphipod *Pontoporeia hoyi*. In U.M. Cowgill and L.R. Williams, eds., *Aquatic Toxicology and Hazard Assessment: Twelfth Volume*. STP 1027. American Society for Testing and Materials, Philadelphia, PA, pp. 315-329.
 95. **Landrum, P.F., B.J. Eadie and W.R. Faust.** 1991. Toxicokinetics and toxicity of a mixture of sediment-associated polycyclic aromatic hydrocarbons to the amphipod *Diporeia* sp. *Environ. Toxicol. Chem.* **10**:35-46.
 96. **Kukkonen, J. and A. Oikari.** 1991. Bioavailability of organic pollutants in boreal waters with varying levels of dissolved organic material. *Water Res.* **25**:455-463.
 97. **Landrum, P.F. and W.R. Faust.** 1991. Effect of variation in sediment composition on the uptake rate coefficient for selected PCB and PAH congeners by the amphipod, *Diporeia* sp. In M.A. Mayes and M.G. Barron, eds., *Aquatic Toxicology and Risk Assessment: Fourteenth Volume*. STP 1124. American Society for Testing and Materials, Philadelphia, PA, pp. 263-279.
 98. **Landrum, P.F., M.D. Reinhold, S.R. Nihart and B.J. Eadie.** 1985. Predicting the bioavailability of organic xenobiotics to *Pontoporeia hoyi* in the presence of humic and fulvic materials and natural dissolved organic matter. *Environ. Toxicol. Chem.* **4**:459-467.
 99. **Landrum, P.F., S.R. Nihart, B.J. Eadie and L.R. Herche.** 1987. Reduction in bioavailability of organic contaminants to the amphipod *Pontoporeia hoyi* by dissolved organic matter of sediment interstitial waters. *Environ. Toxicol. Chem.* **6**:11-20.
 100. **Di Toro, D.M., C.S. Zarba, D.J. Hansen, W.J. Berry, R.C. Swartz, C.E. Cowan, S.P. Pavlou, H.E. Allen, N.A. Thomas and P.R. Paquin.** 1991. Technical basis for establishing sediment quality criteria for non-ionic organic chemicals by using equilibrium partitioning. *Environ. Toxicol. Chem.* **10**:1541-1583.
 101. **Gabric, A.J., D.W. Connell and P.R.E. Bell.** 1990. A kinetic model for bioconcentration of lipophilic compounds by oligochaetes. *Water Res.* **24**:1225-1231.
 102. **Grathwohl, P.** 1991. Influence of organic matter from soils and sediments from various origins on the sorption of some chlorinated aliphatic hydrocarbons: Implications on K_{oc} correlations. *Environ. Sci. Technol.* **24**:1687-1692.
 103. **Landrum, P.F., B.J. Eadie and W.R. Faust.** 1992. Variation in the bioavailability of polycyclic aromatic hydrocarbons to the amphipod, *Diporeia* spp., with sediment aging. *Environ. Toxicol. Chem.* **11**:1197-1208.
 104. **Lydy, M.J., T.W. Lohner and S.W. Fisher.** 1990. Influence of pH, temperature and sediment type on the toxicity, accumulation and degradation of parathion in aquatic systems. *Aquat. Toxicol.* **17**:27-44.
 105. **Lohner, T.W. and S.W. Fisher.** 1990. Effects of pH and temperature on the acute toxicity and uptake of carbaryl in the midge, *Chironomus riparius*. *Aquat. Toxicol.* **16**:335-354.
 106. **Jimenez, B.D., C.P. Cirimo and J.F. McCarthy.** 1987. Effects of feeding and temperature on uptake, elimination and metabolism of benzo(a)pyrene in bluegill sunfish (*Lepomis macrochirus*). *Aquat. Toxicol.* **10**:41-57.
 107. **Connolly, J.P. and C.J. Pedersen.** 1988. A thermodynamic-based evaluation of organic chemical accumulation in aquatic organisms. *Environ. Sci. Technol.* **22**:99-103.
 108. **Randall, R., H. Lee, R. Ozretich, J. Lake and R. Pruell.** 1991. Evaluation of selected lipid methods for normalizing pollutant bioaccumulation. *Environ. Toxicol. Chem.* **10**:1431-1436.
 109. **U.S. Environmental Protection Agency/U.S. Army Corps of Engineers.** 1991. Ecological evaluation of proposed discharge of dredged material into ocean waters. Implementation manual. EPA 503/8-91-001. Office of Marine and Estuarine Protection, Washington, DC.
 110. **Boese, B.L., M. Winsor, H. Lee II and S. Echols.** 1991. Comparison of bioaccumulation factors estimated from a kinetic model with observed values. *Abstracts*, 12th Annual Meeting of the Society of Environmental Toxicology and Chemistry, Seattle, WA, November 3-7, Abstract P270.
 111. **Landrum, P.F., T.D. Fontaine, W.R. Faust, B.J. Eadie and G.A. Lang.** 1992. Modeling the accumulation of polycyclic aromatic hydrocarbons by the amphipod *Diporeia* spp. In F.A.P.C. Gobas and A. McCorquodale, eds., *Chemical Dynamics in Freshwater Ecosystem*. Lewis Publishers, Chelsea, MI, pp. 111-128.
 112. **Klump, J.V., J.L. Kaster and M.E. Sierszen.** 1991. *Mysis relicta* assimilation of hexachlorobiphenyl from sediments. *Can. J. Fish. Aquat. Sci.* **48**:284-289.
 113. **Fisher, D.J. and J.R. Clark.** 1990. Bioaccumulation of kepone by grass shrimp (*Palaemonetes pugio*): Importance of dietary accumulation and food ration. *Aquat. Toxicol.* **17**:167-186.
 114. **Opperhuizen, A.** 1991. Bioaccumulation kinetics:

- Experimental data and modeling. In G. Angeletti and A. Bjørseth, eds., *Organic Micropollutants in the Aquatic Environment, Proceedings*, Sixth European Symposium. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 61–70.
115. Niimi, A.J. and G.P. Dookhran. 1989. Dietary absorption efficiencies and elimination rates of polycyclic aromatic hydrocarbons (PAHS) in rainbow trout (*Salmo gairdneri*). *Environ. Toxicol. Chem.* **8**:719–722.
 116. Rhead, M.M. and J.M. Perkins. 1984. An evaluation of the relative importance of food and water as sources of *p,p'*-DDT to the goldfish, *Carassius auratus* (L.). *Water Res.* **18**:719–725.
 117. Gobas, F.A.P.C., J.R. McCorquodale and G.D. Haffner. 1993. Intestinal absorption and biomagnification of organochlorines. *Environ. Toxicol. Chem.* (in press).
 118. McCarty, L.S. 1986. The relationship between aquatic toxicology QSARS and bioconcentration for some organic chemicals. *Environ. Toxicol. Chem.* **5**:1071–1080.
 119. McCarty, L.S., G.W. Ozburn, A.D. Smith, A. Bharath, D. Orr and D.G. Dixon. 1989. Hypothesis formulation and testing in aquatic bioassays: A deterministic model approach. *Hydrobiologia* **188/189**:533–542.
 120. McCarty, L.S. 1991. Toxicant body residues: Implications for aquatic bioassays with some organic chemicals. In M.A. Mayes and M.G. Barron, eds., *Aquatic Toxicology and Risk Assessment: Fourteenth Volume*. STP 1124. American Society for Testing and Materials, Philadelphia, PA, pp. 183–192.
 121. McCarty, L.S., D. Mackay, A.D. Smith, G.W. Ozburn and D.G. Dixon. 1993. Residue-based interpretation of toxicity and bioaccumulation QSARs from aquatic bioassays: Neutral narcotic organics. *Environ. Toxicol. Chem.* **11**:917–930.
 122. McCarty, L.S. 1990. A kinetics-based analysis of quantitative structure–activity relationships in aquatic toxicology and bioconcentration bioassays with organic chemicals. Ph.D. thesis. University of Waterloo, Ontario, Canada.
 123. Van Hoogen, G. and A. Opperhuizen. 1988. Toxicokinetics of chlorobenzenes in fish. *Environ. Toxicol. Chem.* **7**:213–219.
 124. Widdows, J. and P. Donkin. 1989. The application of combined tissue residue chemistry and physiological measurements of mussels (*Mytilus edulis*) for the assessment of environmental pollution. *Hydrobiologia* **188/189**:455–461.
 125. Gobas, F.A.P.C. 1992. A model for predicting the dynamics and toxic effects of organic chemicals in aquatic food webs: An application to Lake Ontario. *Ecol. Modell.* (in press).
 126. Ellis, J.B., R.B. Shutes and D. Revitt. 1993. Ecotoxicological approaches and criteria for the assessment of urban runoff impacts on receiving waters. In E.E. Herricks, J.E. Jones and B. Urbonas, eds., *Proceedings, Effects of Urban and Receiving Systems Symposium*, American Society of Civil Engineers, Mt. Crestal Butte, CO, August 9–11, 1991 (in press).