

# A Conceptual Approach to Multiple-Model Integration in Whole Site Risk Assessments

E. P. Albers<sup>a</sup> and K.R. Dixon<sup>a</sup>

<sup>a</sup> The Institute of Environmental and Human Health, Department of Environmental Toxicology, Texas Tech University, Lubbock, Texas ([eric.albers@tiehh.ttu.edu](mailto:eric.albers@tiehh.ttu.edu) [ken.dixon@tiehh.ttu.edu](mailto:ken.dixon@tiehh.ttu.edu))

**Abstract:** In the past, models have focused on one environmental compartment, a single organism, or specific process. All of these topics are limited in scope and often fail to take into account the more complex interactions of the real world. We have endeavored to change this practice by combining environmental transport models with an animal movement model and a physiologically based toxicokinetics (PBTk) model that has an embedded effects model. The example we will depict consists of a hypothetical contaminant plume within a lake and the impacts on the channel catfish (*Ictalurus punctatus*). We compared the PBTk output for the multiple-model approach to that of a single model PBTk using the maximum environmental concentration of 943 ppb as the inhaled dose. The multiple-model approach resulted in organ concentrations two orders of magnitude lower, indicating the maximum-dose approach may be overly conservative due to a simplified characterization of the study system. The greatest problems with multiple model integration are accurate data transfer and processing time. We believe we have arrived at solutions for both through the use of trilinear interpolation, compatible software, and the creation of meshing files.

**Keywords:** Modeling, Perchlorate, PBTk, 3-dimensional visualization, Model integration

## 1. INTRODUCTION

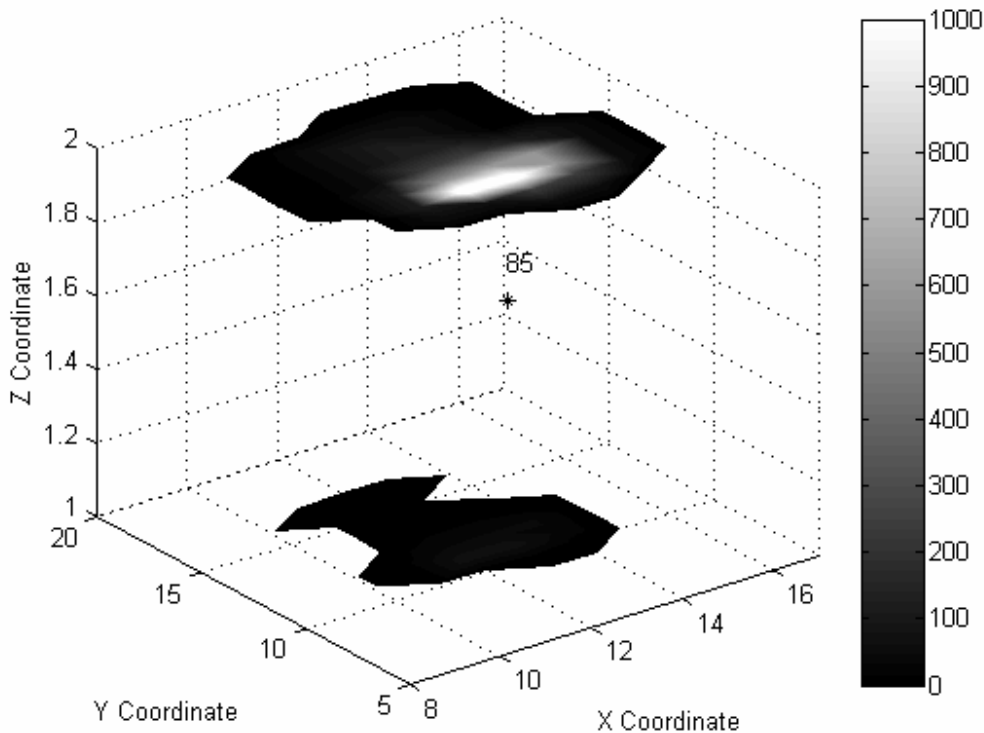
In the past models have focused on one environmental compartment, a single organism, or specific process. While this approach was necessary during the development of modeling within individual fields, we now possess enough knowledge and computing power to create more multi-disciplinary approaches. The use of modeling with contaminants has been largely focused on the area of risk assessments. The major objective of risk assessment was expressed by Whyte and Burton [1980] as “to develop risk management decisions that are more systematic, more comprehensive, more accountable, and more self-aware of what is involved than has been the case in the past.” Utilizing multiple model integration we can greatly improve risk management decision-making by providing more realistic simulations for risk assessments.

## 2. ENVIRONMENTAL MODELING

Contaminant transport models have been developed over the last few decades for every major environmental compartment. Unfortunately very

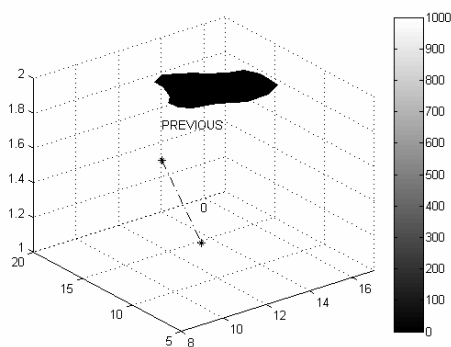
few of these have been designed to work in conjunction with other environmental models, i.e. an atmospheric model linking to a watershed model to account for contaminant deposition. One example of a modeling package that does allow for easy data transfer is the Department of Defense Groundwater Modeling System (GMS) (BYU 2001), Watershed Modeling System (WMS) (BYU 2001), and Surfacewater Modeling System (SMS) (BYU 2001), which are used in our example. If compatible models are not available a “linking file” must be programmed to appropriately transfer data from one software package to another.

To keep our example simple we will take a hypothetical perchlorate (ClO<sub>4</sub><sup>-</sup>) plume that is defined by a single column of numbers as is exported by the SMS package. The numbers represent a given concentration in parts per billion (ppb) with their position within the column defining their coordinates on the xyz plane. For example if the fifth number in the column is 25 then the concentration is 25 ppb at x=5, y=1, and z=1. The coordinates represent the concentration at the center point of a 10m<sup>3</sup> cube. A 30x30x2 grid (180,000m<sup>3</sup>) encompasses the lake and surrounding land. The entire extent of the lake was initially contaminated with concentrations ranging from 5 ppb



**Figure 1.** Lake perchlorate concentrations and dose (ppb) received at t=1 hour.

to 943 ppb and visualized with the MATLAB® software package (Figure 1). The plume followed first order degradation at a rate of 5% per hour representing hypothetical remediation or offsite movement (Figure 2).



**Figure 2.** Plume concentration, previous animal location (\* Previous), movement path (dashed line), and dose received at current location (\* 'numeric value') at t = 96 hours.

This could easily be replaced with real plume time course data with the same end result. Graphically the plume was displayed as two slices on a 3-dimensional axis. Obviously greater contrast could be achieved through the use of color instead of black-and-white. As we created each graph we took a screen capture (photo of the image on the screen) that allowed us to generate a movie of the plume degradation and animal movement by viewing them sequentially.

### 3. DOSE AND EFFECTS CALCULATIONS

#### 3.1 Dose Interpolation

Even though we only have concentration data for the two slices, it is possible to compute the value at any location within the extent of the lake. This was done by generating a trilinear interpolation subroutine to calculate only the concentration at the coordinates that represent an individual's location, instead of increasing the number of data points

within the matrix as a whole. This allowed us to use locations as precise as  $1\text{mm}^3$ , instead of the initial  $10\text{m}^3$  cell size. To increase the entire matrix precision to the same level for each hour of the 96-hour simulation time would require a total of 1,728,000,000 data points (30 cells x 30 cells x 2 cells x  $10\text{ m}^3/\text{cell}$  x 1000 mm/1m x 96 hours) instead of 96 (1 location/hour x 96 hours). This computational reduction equates to significantly decreased processing time. Interpolating over smaller distances, i.e. decreasing the cell size used in the SMS package, and including additional real-world data, could increase the accuracy of the interpolated results. In the instance of having additional data being spread out in a non-uniform manner, one can utilize 3-dimensional cubic interpolation to interpolate to the nearest 64 points instead of the nearest 8 as is done with a trilinear approach. Obviously, this will result in additional processing time and, for large data sets, might require a supercomputer.

### 3.2 Movement Modeling

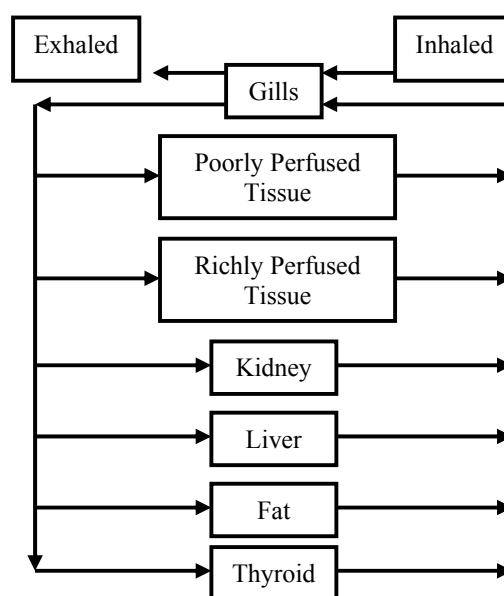
To determine the locations at which the dose will be received by the channel catfish (*Ictalurus punctatus*), an animal movement model can be utilized to describe likely movement paths for an individual. This is important because it allows us to calculate only the concentration of the lake at the point the individual is as described in section 3.1. These paths could be based on real-time tracking data [White and Garrot 1990], behavioral studies [Marsh and Jones, 1988], or topographical constraints. Keeping with the simplistic approach in this project, we utilized a random movement model with three constraints. The catfish:

1. could not move beyond the lake boundaries – topographical constraint.
2. move no faster than 30 meters/hour – hypothetical tracking data constraint.
3. would stay in the bottom  $\frac{1}{2}$  of the lake – behavioral constraint.

At each hour during the 96 hour simulation time we randomly determined a point location for the catfish with the above three constraints and used the concentration derived from the trilinear interpolation as the inhaled dose for the physiologically based toxicokinetic (PBTk) model.

### 3.3 Physiologically Based Toxicokinetic (PBTk) Model

A 7-compartment individually-based stochastic PBTk model was developed for perchlorate movement in the channel catfish, using the MATLAB® software. The model is stochastic in that it contains partitioning coefficients randomized within the range determined from lab data. These random variables provide the additional capability to conduct Monte Carlo simulations. The PBTk model included compartments for gills, poorly perfused tissue (primarily white muscle and skin), richly perfused tissue (gut, GI tract, spleen, and gonads), kidney, liver, fat, and thyroid, (Figure 3).



**Figure 3** Flow Diagram of the PBTk model for perchlorate inhalation in fish.

Additional compartments could be added as the need is identified. The general equations used in the model were taken from a PBTk for fish (Nichols et al., 1990, 1991) using a countercurrent chemical exchange surface at the gill (eq. 1) and an assumed blood flow limitation to chemical flux at the tissue (eq. 2.). Physiological parameters, including organ volumes and partitioning coefficients, were derived from lab data for a 5-day 100ppb dosing study of channel catfish. Subsets of the data were used to calibrate the model.

### 3.3.1 Major Governing Equations

Water intake (dose) was governed by the gill flux equation below:

Eq. 1)

$$F^G = k_X^G (f_W C_W^{aff,G} - f_B C_B^{aff,G})$$

where

$F^G$  = flux of perchlorate across the gills,  $\text{mg}\cong\text{kg}^{-1}\cong\text{h}^{-1}$

$k_X^G$  = exchange coefficient  $\text{h}^{-1}$

$f_W$  = ratio of free chemical in exposure water to total concentration

$C_W^{aff,G}$  = total concentration of perchlorate in exposure water,  $\text{mg}\cong\text{l}^{-1}$

$f_B$  = ratio of free to total perchlorate in blood

$C_B^{aff,G}$  = concentration of perchlorate in the blood afferent (coming into) the gills,  $\text{mg}\cong\text{l}^{-1}$

The rate of change in perchlorate concentration for each tissue compartment was defined by the differential equation:

$$\text{Eq. 2) } \frac{dA^i}{dt} = Q_B^i (C_B^{eff,G} - C_B^{eff,i})$$

$\frac{dA^i}{dt}$  = rate of change in perchlorate concentration

in the tissue compartment,  $\text{mg}\cong\text{l}^{-1}\cong\text{h}^{-1}$

$Q_B^i$  = blood flow rate from the tissue,  $\text{l}\cdot\text{h}^{-1}$

$C_B^{eff,G}$  = concentration of perchlorate in the blood efferent (exiting from) the gills,  $\text{mg}\cong\text{l}^{-1}$

$C_B^{eff,i}$  = concentration of perchlorate in the blood efferent to the tissue compartment,  $\text{mg}\cong\text{l}^{-1}$

### 3.3.2 PBTK Calibration

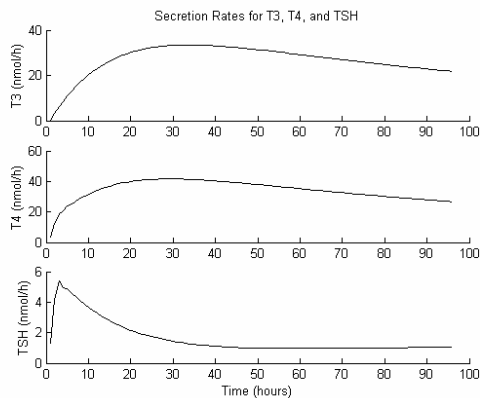
To ensure that the PBTK model accurately simulated the transport and fate of perchlorate in the channel catfish, it was necessary to calibrate the model using laboratory data (Table 1). This was done by initially deriving the tissue/blood partitioning coefficients from measured perchlorate concentrations and organ weights from channel catfish exposed to 100 ppb for 5 days in the lab. Since fish do not possess a thyroid gland, just thyroid tissue, the concentration in the head was used. The model was then calibrated by adjusting the gill exchange coefficient,  $k_X^G$ , until a reasonable fit was achieved based on the measured means and standard deviations.

### 3.4 Effects Model

To further enhance the risk assessment capabilities of the PBTK model we developed an effects model to simulate the impact of perchlorate on the endocrine system. The thyroid hormone submodel was adapted from a model developed for the human thyroid system by DiStefano *et al.* (1975), DiStefano and Fisher (1976), Saratchandran *et al.* (1976), and DiStefano and Mori (1977). The model was calibrated by adjusting parameter values to generate output that falls within two percent of the steady-state values reported by Saratchandran *et al.* (1976). The output shown in figure 4 represents the normal hormone secretion levels for triiodothyronine (T3), thyroxine (T4), and thyrotrophin (TSH). Human health data indicates that perchlorate inhibits iodide uptake into the thyroid gland via a sodium-iodide transporter, resulting in decreased secretion of T3 & T4 and increased TSH (Saito *et al.* 1983). Currently studies are being conducted to provide laboratory data to derive the relationship between perchlorate concentration in the thyroid tissue and hormone secretion in the channel catfish.

Compartment	Lab Mean (ppb)	Lab S.D. (ppb)	Simulated Mean (ppb)	Simulated S.D. (ppb)
Poorly Perfused Tissue	7261	1279	5900	1438
Richly Perfused Tissue	1326	507	1798	1026
Liver	126	174	166	74
Kidney	950	440	878	560
Fat	Not Measured	Not Measured	466	43
Thyroid Tissue	7222	1314	6581	3630

**Table 1.** Comparison of means and standard deviations for measured and simulated concentrations for a 5-day 100 ppb dose calibration run.

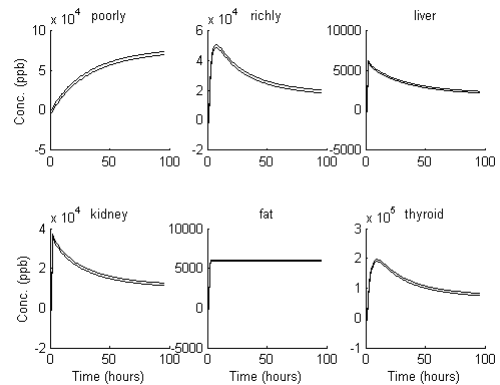


**Figure 4.** Normal secretion rates for T3, T4, and TSH.

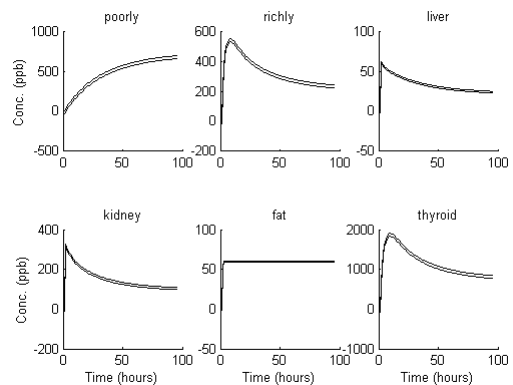
#### 4.0 MAXIMUM-DOSE APPROACH VS. MULTIPLE-MODEL APPROACH

To demonstrate the over-conservative nature of current risk assessment practices we compared the simulated organ concentrations for a 96-hour PBTK run using a maximum environmental concentration of 943 ppb from our lake plume as the inhaled dose (Figure 5) to those of the multiple-model approach using the entire lake and movement model to determine the dose (Figure 6). A population of 10 fish was used to generate mean concentrations and 95% confidence limits. The maximum-dose approach resulted in organ concentrations two orders of magnitude greater than those simulated with the multiple-model approach (Table 2). All of the organs in the multiple-model approach had less than 1000 ppb of perchlorate after 96 hours, compared to 5,000-80,000 ppb with the maximum-dose approach. Of particular concern is the thyroid tissue since it will govern the changes in hormone secretion for our effects model.

Until we define the relationship between hormone inhibition and thyroid perchlorate concentration we cannot determine the magnitude of the impact on our effects model.



**Figure 5.** Simulated 96-hour PBTK output for maximum-dose approach.



**Figure 6.** Simulated 96-hour PBTK output for multiple-model approach.

Compartment	Maximum-Dose		Multiple-Model	
	Mean (ppb)	S.D. (ppb)	Mean (ppb)	S.D. (ppb)
Poorly Perfused Tissue	73,526	19,809	698	188
Richly Perfused Tissue	20,175	9,594	241	100
Liver	2,366	6,394	25	54
Kidney	12,596	1,036	108	10
Fat	6,076	622	60	6
Thyroid Tissue	82,780	37,776	800	354

**Table 2.** Comparison of 96-hour PBTK means and standard deviations for maximum-dose and multiple-model approaches

## 5. Conclusions

As can be seen with the example presented in this paper, very different results can be simulated with the use of a multiple-model integration approach compared to that of a maximum-dose approach. By relying on one maximum value that only represents 10m<sup>3</sup> of our lake we ignore the fact that the other 99% has a lower concentration, and that it may vary over time. Using a maximum-dose approach at each time step would remove the temporal variation, but not the spatial variation. By also taking behavior into account, through the use of movement models, we can arrive at more accurate risk assessments. The highest perchlorate concentrations in our example were near the surface, which we had eliminated from the catfish movement model since they are bottom dwelling fish. As a result of this behavior, basing any management decisions pertaining to catfish solely on the surface concentrations, where the maximum dose was located, would be inappropriate. By utilizing these real-world data and processes we can more accurately simulate a given risk, and subsequently save money, time, and resources that would otherwise be unnecessarily wasted on a prolonged remediation or risk management strategy.

Our future work is focusing on applying this approach to a real world risk assessment currently in progress and developing a 3-dimensional interactive simulation depicting the movement of perchlorate through lakes and streams, its intake into a moving catfish, and its subsequent effects on the endocrine system. The user will be able to zoom in to specific areas, rotate the image, view the concentration of the plume at a given point, PBTK output for a given fish, and any effects response. In essence, turning a lengthy report into an informative movie.

## 6. Acknowledgements

The authors would like to thank Dr. Chris Theodorakis and Carrie Bradford (TIEHH, Texas Tech University) for providing us with the data for the PBTK calibration run.

## 7. References

Brigham Young University (BYU), Groundwater Modeling System GMS Version 3.1 reference manual, Brigham Young University, 2001.

- Brigham Young University (BYU), Surface Water Modeling System SMS Version 8.0 reference manual, Brigham Young University, 2001.
- Brigham Young University (BYU), Watershed Modeling System WMS Version 6.1 reference manual, Brigham Young University, 2001.
- DiStefano, III, J.J., and D. A., Fisher, Peripheral distribution and metabolism of the thyroid hormones: a primarily quantitative assessment, *Pharmac. Ther.* B 2:539-570, 1976.
- DiStefano, III, J.J., and F. Mori, Parameter identifiability and experiment design: thyroid hormones, *Am. J. Physiol.* 233:R134-R144, 1977.
- DiStefano, III, J.J., K. C. Wilson, M. Jang, and P. H. Mak. Identification of the dynamics of thyroid hormone metabolism, *Automatica* 11:149-159, 1975.
- Marsh, L.M., and R.E. Jones, The form and consequences of random walk movement models, *J Theor Biol*, 133 113-131. 1988.
- Nichols, J.W., J.M., Anderson, M.E., Gargas, M.L., Clewell, H.J., III, Erickson, R.J, A physiologically based toxicokinetics model for the uptake and disposition of waterborne organic chemicals in fish, *Toxicol. Appl. Pharmacol.* 106:433-447, 1990.
- Nichols, J.W., J.M. McKim, M.E. Anderson, G.J. Lien, A.D. Hoffman, S.L. Bertelson, Physiologically based toxicokinetics modeling of three waterborne chloroethanes in rainbow trout (*Oncorhynchus mykiss*), *Toxicol. Appl. Pharmacol.* 110:374-389, 1991.
- Saito, K., K. Yamamoto, T. Takai, S. Yoshida, Inhibition of iodide accumulation by perchlorate and thiocyanate in a model of the thyroid iodide transport system, *Acta Endocrinol.* 104:456-461.
- Saratchandran, P., E. R. Carson, and J. Reeve, An improved mathematical model of the human thyroid hormone regulation, *Clinical Endocrinology* 5:473-483, 1976.
- White, G.C., and R.A. Garrot, Analysis of wildlife radio-tracking data, San Diego: Academic Press, 1990.
- Whyte, A.C. and I. Burton, Eds., Environmental Risk Assessment, SCOPE report 15, New York: John Wiley & Sons, 1980.