HESI
ILSI Health and Environmental Sciences Institute

DRAFT 4: April 11, 2006

Models Section from submission to *Environmental Health Perspectives*

Title

Workgroup Report: Review of Fish Bioaccumulation Databases used for Identifying Persistent, Bioaccumulative, Toxic Substances

Authors

Anne V. Weisbrod[1]*, Lawrence P. Burkhard[2], Jon Arnot[3], David Powell[4], Ovanes Mekenyan[5], Phil Howard[6], Christine Russom[2], Robert Boethling[7], Yukimitsu Sakuratani[8], Theo Traas[9], Todd Bridges[10], Charles Lutz[10], Mark Bonnell[11], Thomas Parkerton[12], Kent Woodburn[13]

Affiliations

[1]Central Product Safety, The Procter & Gamble Company, Cincinnati, Ohio USA; [2]National Health & Environmental Effects Laboratory, US Environmental Protection Agency, Duluth, Minnesota USA; [3]Canadian Environmental Modelling Centre, Trent University, Peterborough, Ontario Canada; [4]Dow Corning Corporation, Midland, Michigan USA; [5]Laboratory of Mathematical Chemistry, Bourgas A. Zlatarov University, Bourgas, Bulgaria; [6]Syracuse Research Corporation, Syracuse, New York USA; [7]Office of Pollution Prevention & Pesticides, US Environmental Protection Agency, Washington DC USA; [8]Chemical Management Center, National Institute of Technology and Evaluation (NITE), Japan; [9]National Institute for Public Health and the Environment, Utrecht, the Netherlands; [10]US Army Engineer Research and Development Center, Vicksburg, Mississippi USA; [11]Environment Canada-New Substances, Ottawa, Ontario Canada; [12]ExxonMobil Biomedical Sciences, Annandale, New Jersey USA; [13]Toxicology, Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan USA.

Models for Predicting Bioconcentration and Bioaccumulation

Bioconcentration models

In 1974, the first relationship based upon the K_{ow} of the chemical was established for predicting BCFs of nonionic organic chemicals(Neely WB, Branson DR, Blau GE, 1974). This relationship was of the general form:

$$\log \mathrm{BCF} = a \log K_{ow} + b$$

where a and b are empirical constants derived by regression analysis of BCF-K_{ow} data sets. Numerous regression equations have been developed since then with varying amounts of bioconcentration data (Bintein S, Devillers J, Karsher W, 1993;Schüürmann G and Klein W, 1988;Veith GD, Defoe DL, Bergstedt BV, 1979). Based upon the analyses of BCF data and underlying partitioning theory (de Wolf W, de Bruijn JHM, Seinen W, Hermens J, 1992), the slope of the regression equation should be close to one and the intercept should be approximately zero for BCF-K_{ow} data sets of organic chemicals with these specific characteristics: nonionic, small molecular weight (< 1000 g/mol), very slowly or non-metabolized, and when BCF values are expressed by the chemical concentration in fish normalized to its lipid content and the bioavailable (or freely dissolved) concentration of the chemical in water.

BCFWIN: This QSAR model is contained within the Estimation Programs Interface (EPI) Suite®, developed by the U.S.-Environmental Protection Agency's Office of Pollution Prevention and Toxics and the Syracuse Research Corporation (SRC). The suite of models is publicly available on the Internet (http://www.epa.gov/oppt/p2framework/docs/epiwin.htm). The EPI Suite contains eleven programs for estimating physical-chemical properties, rate constants, and partition coefficients for organic chemicals. One of these programs is BCFWIN, which estimates the chemical's bioconcentration factor based upon its K_{ow} and structural features (e.g., functional groups and elemental composition) (Meylan WM, Howard PH, Boethling RS, Aronson D, Printup H, Gouchie S, 1999). The BCFWIN predictive algorithm is built upon a database of 694 chemicals; i.e., 610 nonionic organic compounds (which include 18 organometallics) and 84 ionic organic compounds (which include carboxylic acids, sulfonic acids and their salts, and quaternary nitrogen compounds).

The BCFWIN predictive model is, in essence, a refinement of the regression equation approach presented by Neely et al. with a much larger database of BCFs that permitted the development of correction factors for specific chemical class and structure molecular arrangements (Neely WB, Branson DR, Blau GE, 1974). The model reasonably predicts BCF values for chemicals within the model’s domain of applicability; based upon comparison of estimated and measured BCFs in the BCFWIN training set (i.e., 694 chemicals), 50 percent, 82 percent, and 90 percent the estimated log BCFs are one half, three quarters, and one log unit of their measured values, respectively.

As discussed previously, the BCF database assembly process did not evaluate the quality of individual studies incorporated into the database. Rules were developed for assigning a chemical's BCF value from the list of reported values assembled, and these assignments were made for the 694 chemicals. Any uncertainties incorporated into the list of 694 selected BCF values are directly translated into the predictive model. Uncertainties also arise from the quality of the K_{ow} data for individual chemicals used in the BCF-K_{ow} training set.

CONCAWE: The algorithms used by the BCFWIN program were extended to hydrocarbons by developing a correction factor for the hydrocarbon chemical class

(Stewart S, Aronson D, Meylan W, Howard P, 2005). The hydrocarbon correction factor was developed using the new set of recommended BCF values for 84 hydrocarbons. For the hydrocarbons, the mean absolute error and standard deviation for the log BCF was 0.43 ± 0.54.

Base-line Model, a.k.a. "POPs": The base-line concept for modeling the bioconcentration of chemicals is based on a reference curve delineating the empirically observed maximum bioconcentration driven by hydrophobicity of chemicals (Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O, 2005). In fact, this is the highest log *BCF* (log BCF_{Max}) which can be reached for a given log K_{OW} value assuming that small sized, nonionized molecules exhibit maximal bioavailability and are not metabolized (Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan OG, 2002;Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan OG, 2003) . The base-line model was theoretically justified by the multi-compartment diffusion model:

$$\log BCF_{MAX} = \log\left(\frac{{K_{OW}}^{n}}{(aK_{OW}+1)^{2n}} + F_W\right) \qquad \text{(Equation 1)}$$

where *a* and *n* are fitted model parameters, and F_w is the water content of the organism.

Mitigating chemical properties (molecular size and flexibility, ionization, volatilization, and adsorption) and organism specific properties (biotransformation and permeability) are used as reducing factors of the maximum bioconcentration determined via the base-line model:

$$\log BCF = \log\left(BCF_{MAX} \prod_i F_i\right) \qquad \text{(Equation 2)}$$

where F_i are the mitigating factors. Specific submodels have been developed for estimating $F_{\text{Metabolism}}$, $F_{\text{Ionization}}$ and $F_{\text{Molecular Size}}$. An example of the effect of the different mitigating factors on the predicted BCF value is provided for octadecenylsuccinic acid in Figure 1.

The model parameters were optimised by making use of the training set of experimental BCF values from 542 chemicals. The model performance for the training set showed a correlation coefficient of $R^2 = 0.84$; residual sum of squares SSR = 139.8 and variance $s^2 = 0.294$. For 88 percent of the training set chemicals, the difference between observed and calculated BCF values was found to be within 0.75 log unit. In an external validation exercise with 176 chemicals, the model demonstrated similar predictability of 80 percent, for chemicals belonging to model applicability domain (Dimitrov SD, Dimitrova GD, Pavlov T, Dimitrova N, Patlewics GY, Niemela G, Mekenyan OG, 2005;Mekenyan OG, Pavlov TS, Grancharov V, Todorov M, Schmieder P, Veith GD, 2005) .

The analysis of the relative importance of the three mitigating factors showed that passive diffusion has a 69 percent contribution, metabolism 27 percent, whereas the rest of all mitigating factors was 4 percent. Unequivocally, these contributions show the primary importance of metabolism as compared to other mitigating factors. A screening exercise recently performed on the ~10,000 organic substances for Environment Canada DSL revealed that by including all mitigating factors, the number of chemicals identified as potentially B was reduced significantly, compared with the model using molecular size as

only mitigating factor (Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan OG, 2002;Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan OG, 2003) . About 12.5 percent of the chemicals were identified as potentially B with only molecular size as a mitigating factor, versus 1.5 percent of the chemicals identified as potentially B with all the mitigating factors accounted for.

Bioaccumulation models

Food web models can predict BCFs, BAFs, and BSAFs for aquatic organisms, and are being used increasingly in regulatory-driven assessments because they incorporate dietary sources and other environmentally relevant processes that contribute to exposure. Since the 1970s, food web models have been created using data from persistent organic pollutants. Many of these chemicals are very slowly metabolized by aquatic species, which has enabled greater understandings of key bioavailability, uptake, and elimination mechanisms in the environment. For substances that are subject to metabolic biotransformation, BAF values may be over-predicted if this loss rate is not included in the model's parameters(Burkhard LP, Endicott DD, Cook PM, 2003). Food web models have not been evaluated for all chemical classes, i.e., ionizing substances, as these field data are not available.

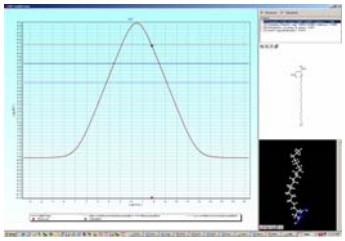
Application of food web models requires the specification of the food web, ecosystem conditions (e.g. sediment-water column disequilibria of the chemical, organic carbon content of the sediment, dissolved and particular organic carbon concentrations in water, average temperature), the biotransformation rates and other related factors for all organisms of the food web (e.g., weights, lipid and water contents, prey species). When properly constructed with high quality input data, predicted BAFs from food web models can be highly accurate. Based upon comparison of estimated and measured BAFs for three ecosystems, 60 percent and 96 percent of the estimated log BAFs were within 0.3 and one log unit of their measured values, respectively(Arnot JA and Gobas FAPC, 2003). Improving the accuracy of food web models beyond that obtained with current models will be difficult, because contaminant concentration vary widely among individual organisms in the environment. This variability is a key factor controlling the model accuracy when comparing estimated and measured BAFs (Arnot JA and Gobas FAPC, 2003).

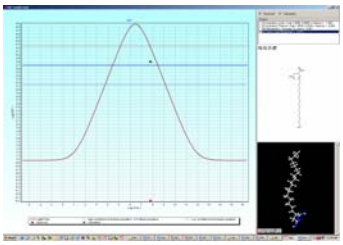
The application of typical food web models for screening large numbers of chemicals, such as for chemical management programs, is an arduous task because of the variability in site-specific ecosystem conditions and the input data required to simulate specific food webs. A semi-empirical mass balance bioaccumulation model was developed to address these limitations, providing a generic site assessment method (Arnot JA and Gobas FAPC, 2003) . The model circumvents many of the required site-specific input parameters by calibrating BAF predictions to measured BAF data. The model delivers a BAF prediction for a selected generic trophic level (e.g., lower, middle, upper) in a generic aquatic food web, requiring only a K_{OW} value for the chemical. Calibrating the model to BAF data for poorly metabolized chemicals allows for estimates of food web bioaccumulation potential. If reliable metabolic biotransformation data and scaling

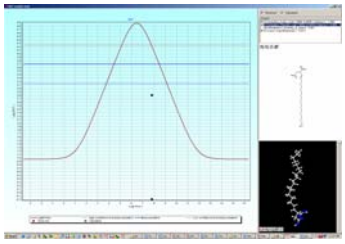
factors are available, these can be included in the mass balance calculations. The model can also provide BCF estimates by excluding dietary uptake. Environment Canada uses this model in their evaluations of bioaccumulation potential for new and existing substances.

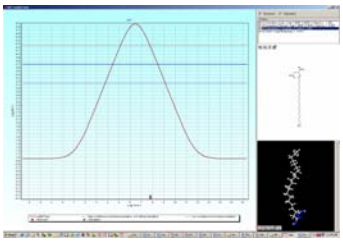
The growing field of determining the chemical absorption, distribution, metabolism, and excretion (ADME) processes in fish is the subject of the ILSI-HESI SETAC *In-vitro*/ADME Workshop conducted in March 2006. Those workshop participants explored the development and validation of techniques for extrapolating subcellular or *in vitro* measurements to whole body biotransformation rates or enzymatic activity rates across species, which could then be used as "stand-alone" assessments or incorporated into BCF and BAF model predictions.

Fig 1. Predicted BCF values for octadecenylsuccinic acid (CAS 028299-29-8) using the baseline model with no mitigating factors (a), molecular size as an mitigating factor (b), molecular size and ionization as mitigating factors (c), and molecular size, ionization, and metabolism as mitigating factors (d).

a 

b 

c 

d 

References

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci. 22. 337-345.

Bintein S, Devillers J, Karsher W. 1993. Nonlinear dependence of fish bioconcentration on n-octanol/water partition coefficient. SAR QSAR Env Res. 1. 39.

Burkhard LP, Endicott DD, Cook PM. 2003. Evaluation of two methods for prediction of bioaccumulation factors. Environ Sci Technol. 20. 4626-4634.

de Wolf W, de Bruijn JHM, Seinen W, Hermens J. 1992. Influence of biotransformation on the relationship between bioconcentration factors and octanol-water partition coefficients. Environ Sci Technol. 26. 1197-1201.

Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O. 2005. Base-line model for identifying the bioaccumulation potential of chemicals. SAR QSAR Env Res. 16. 531-554.

Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan OG. 2002. Predicting bioconcentration factors of highly hydrophobic chemicals. Effects of molecular size. Pure Appl Chem. 74. 1823-1830.

Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan OG. 2003. Bioconcentration potential predictions based on molecular attributes – an early warning approach for chemicals found in humans, birds, fish and wildlife. QSAR Comb Sci. 22. 58-68.

Dimitrov SD, Dimitrova GD, Pavlov T, Dimitrova N, Patlewics GY, Niemela G, Mekenyan OG. 2005. A stepwise approach for defining applicability domain of SAR and QSAR models. J Chem Inf Model. 45. 839-849.

Mekenyan OG, Pavlov TS, Grancharov V, Todorov M, Schmieder P, Veith GD. 2005. 2D-3D Migration of Large Chemical Inventories with Conformational Multiplication: Application of the Genetic Algorithm. J Chem Inf Model. 45. 283-292.

Meylan WM, Howard PH, Boethling RS, Aronson D, Printup H, Gouchie S. 1999. Improved method for estimating bioconcetration/bioaccumulation factor from octanol/water partition coefficient. Environ Toxicol Chem. 18. 664-672.

Neely WB, Branson DR, Blau GE. 1974. Partition coefficient to measure bioconcentration potential of organic chemicals in fish. Environ Sci Technol. 8. 1113-1115.

Schüürmann G, Klein W. 1988. Advances in bioconcentration prediction. Chemosphere. 17. 1551-1574.

Stewart S, Aronson D, Meylan W, Howard P. 2005.Critical evaluation of BCF hydrocarbon database and recalibrate of BCFWIN specifically for petroleum hydrocarbons: Syracuse Research Corporation Report for CONCAWE. FA429. Syracuse, NY:

Veith GD, Defoe DL, Bergstedt BV. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J Fish Res Board Canada. 36. 1040-1048.