Methodology for Predicting Cattle Biotransfer Factors

September 23, 2005

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Executive Summary

The main route of human exposure to many highly lipophilic compounds is through ingestion of contaminated agricultural products such as beef and milk (McLachlan, 1993). The transfer of contaminants from environmental media (e.g., air, soil, and water) into livestock products has historically been either determined by direct measurement of contaminants in food items, or predicted using regression models. When empirical data are lacking, one of the most widely used approaches is the regression model developed by Travis and Arms (1988), which relates the chemical octanol-water partition coefficient ($K_{ow}$) to its biotransfer into beef and milk. These regressions, however, are hampered by the limited log $K_{ow}$ range and questions surrounding the validity of the underlying biotransfer data set. To improve biotransfer estimates for risk assessments, this investigation sought to develop a new biotransfer model that reduced estimation uncertainty and was applicable over a wider range of log $K_{ow}$ values. The strategy in selecting a suitable screening methodology was to minimize the data requirements of the method to keep it widely applicable and to better predict biotransfer of contaminants from feed into beef and milk.

The analysis consisted of a period of data collection, an evaluation of existing models, and an evaluation of predicting biotransfer with multiple chemical properties. A literature review of biotransfer studies was conducted to assemble a biotransfer data set consisting of 72 references that covered 488 individual cattle and 55 chemicals. A parallel data collection effort was performed to gather chemical property data for the 55 chemicals according to a specified hierarchy of literature references. When compared to this data set, existing models did not prove significantly better at providing biotransfer factor (BTF) estimates than did the Travis and Arms regressions. In addition, including other chemical properties in the regressions did not appear to predict biotransfer better than log $K_{ow}$ alone. These options of using other existing models or including multiple chemical properties were also determined to be more data intensive and less easily applied than a regression using log $K_{ow}$ alone. Ultimately, we developed a polynomial regression model to predict BTFs using only log $K_{ow}$. The model’s assumptions and data were closely examined to ensure that they were appropriate by conducting various sidebar analyses (i.e., validation of the default factors in the analysis, adjustment of biotransfer data to steady-state conditions where possible).

The result is a new methodology that improves accuracy of biotransfer estimates in beef and milk and is easily implemented on a wide variety of chemicals. The underlying empirical data set marks a notable improvement in the quality and quantity of biotransfer data upon which the method was developed. Several improvements were implemented in direct response to criticism of existing approaches, including (1) expanding the data to include a wider log $K_{ow}$ range, (2) excluding highly metabolized chemicals (i.e., oxidizable and hydrolyzable), (3) limiting the beef data to nonlactating animals, and (4) extrapolating steady-state concentrations...
from time-series data. The approach also handles organic acids more appropriately by considering their ionization state in the cow’s digestive system.

The analysis found no significant difference between fat-adjusted concentrations in milk and beef. BTFs are predicted using the following single equation, which can be used to predict chemical concentrations in fat ($R^2=0.8259$; $F=716.31$):

$$y = - 0.099x^2 + 1.07x - 3.56$$

where

$$y = \log \text{BTF}(\text{mg/kg Fat}/\text{mg/day})$$

$$x = \log K_{ow} \text{ (unitless)}.$$

Application of this equation requires that the user know only the log $K_{ow}$ to estimate a BTF. The BTF can then be adjusted to account for the fat content of milk or beef. It is appropriate for organic chemicals lacking empirical biotransfer data and having a log $K_{ow}$ between -0.67 and 8.2. To improve BTF estimates for organic acids, the first-order dissociation constant (pKa) can be used to account for chemical ionization. The BTFs for oxidizable and hydrolyzable chemicals may be improved by using a metabolism factor. The BTF estimates, in concert with chemical concentrations in feed items, may be used to calculate the chemical concentrations in beef and milk products relevant to human consumption.
1.0 Introduction

The U.S. Environmental Protection Agency (EPA) has determined that there is a demonstrated need to improve existing models for predicting the transfer of chemical constituents from environmental media into agricultural products. Models that predict chemical transfer into beef and milk due to cattle ingestion of contaminated vegetation (e.g., forage and silage) often use a biotransfer factor (BTF). BTFs are currently used in virtually all multimedia risk assessments, ranging from national-scale screening analyses to site-specific analyses.

The goal of the research conducted was to develop a biotransfer model with improved predictive abilities over the current methods used by EPA. The project’s primary objectives were to (1) ensure that the methodology (i.e., model and supporting data) was transparent and easy to implement, (2) use only chemical properties for which data were readily available as predictors of BTFs, and (3) demonstrate improvements in the accuracy of biotransfer predictions over current methods. Additionally, we developed a database of biotransfer data that represents a significant improvement in the quality, quantity, and clarity of the underlying data compared with existing models. The methodology relies exclusively on chemical-specific properties (e.g., no site-specific or animal-specific parameters) to ensure broad applicability of the model.

1.1 Background

The main route of human exposure to many highly lipophilic compounds is through ingestion of agricultural products such as beef and milk (McLachlan, 1993). The transfer of contaminants from environmental media (e.g., air, soil, and water) to agricultural products has historically been either determined by direct measurement of contaminants in food items or predicted using regression models. Direct measurement is sometimes used to calculate exposure concentrations in site-specific assessments. Modeling is used when measured data are unavailable or inappropriate, such as during screening evaluations, non-site-specific assessments (e.g., national risk assessments), and predictive risk assessments.

BTFs are commonly used in environmental regulatory programs for estimating the transfer of chemicals from contaminated vegetation into agricultural food products. As shown in Equation 1, the BTF is the ratio of the concentration in either beef or milk to the chemical intake rate in mass of chemical per day:

\[
BTF = \frac{\text{Beef or Milk Concentration (mg/kg)}}{\text{Chemical Intake Rate (mg/d)}}
\] (1)
One of the most significant limitations in using BTFs to estimate concentrations in beef and milk is the lack of chemical-specific empirical data. Because studies using cattle are expensive, very few chemicals have been researched. In 1988, Travis and Arms published a methodology using octanol-water partition coefficients ($K_{ow}$) as a predictor of cattle BTFs. They compiled data from a review of literature sources to derive empirical BTFs for about 40 chemicals and developed linear regression equations relating these BTFs to log $K_{ow}$. This methodology has been adopted by the risk assessment community as the state of the science for well over a decade. For example, the Travis and Arms regressions are the current default methodology recommended in the draft EPA guidance entitled *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (HHRAP) (U.S. EPA, 1998a); however, more recent criticism of the Travis and Arms equations has led to questions on their validity (U.S. EPA, 2000b). Specifically, the regressions

- May overestimate BTFs for high log $K_{ow}$ chemicals (and thus beef and milk concentrations) because few such chemicals were included in the data set,
- Do not accurately predict concentrations for some rapidly metabolizing chemicals,
- Are based on a mix of steady-state and non-steady-state data, and
- May underestimate beef BTFs (and concentrations) because they are based on data from lactating and nonlactating animals.

### 1.2 Overview of This Study

The first step in this research was to validate the Travis and Arms linear log $K_{ow}$ regression. We collected the cited references and log $K_{ow}$ data set from Travis and Arms and developed linear regressions from the same input data using an updated approach (Birak et al., 2001). This validation exercise yielded new regressions not statistically different from those originally presented by Travis and Arms; however, some of the empirical biotransfer data spanned several orders of magnitude for a single log $K_{ow}$. Such variability in a development data set introduces uncertainty in the regression’s predicted BTF values (Finkel, 1990). This verification exercise was intended only to determine whether the results by Travis and Arms could be replicated and did not specifically address any of the challenges pointed out by peer reviewers.

Subsequent steps in the research involved investigating alternative modeling approaches to predict biotransfer that were developed after the Travis and Arms study was published. Dowdy et al. (1996) suggests that molecular connectivity indices (MCI) may be an accurate predictor of beef and milk BTFs; however, the MCI model performance decreased when applied to an independent data set from that used by Dowdy et al. (1996). Appendix B documents the MCI validation research conducted using BTFs from this study’s biotransfer database. Other researchers have developed fugacity-based models (MacLachlan, 1994) and sophisticated pharmacokinetic models (Derks et al., 1994) to predict biotransfer. Such models tend to be data intensive, require chemical data that may not be readily available, and do not achieve the level of
transparency and usability that was established as a primary objective of this research. As a result, the research presented in this report is a new methodology that satisfies all of the primary objectives and goals outlined in Section 1.0.

2.0 Methods

RTI began model development with an extensive period of data collection through literature review. During this phase, biotransfer and chemical data were gathered according to specified data quality objectives. Once this data set was complete, data gaps that required use of surrogate data to derive BTF values still existed. These parameter estimations were conducted using default values and/or using other data reported by researchers. Regressions were performed once all data gaps were filled and the data normalized.

2.1 Literature Review

An extensive biotransfer database was assembled by collecting data from literature. The literature search used the following databases to identify articles:

- Medline
- Toxline
- CAB (formerly the Commonwealth Agricultural Database)
- Environline
- Environmental Bibliography
- AGRICOLA (AGRIcultural OnLine Access).

In addition to collecting literature from these search engines, we gathered all references from the citation lists of Travis and Arns (1988) and Dowdy et al. (1996) containing biotransfer data. The criteria for including studies in the biotransfer database were as follows:

- The reference must be a primary source of data.
- The experiment must be a feeding study on cattle given a chronic chemical dose via ingestion,
- The investigators must report either a mass chemical intake rate or chemical concentration fed to animals,
- The investigators must provide chemical concentrations in beef tissue, beef fat, whole milk, or milk fat, on or near the last day of the feeding study, and
- The reported concentrations in beef or milk must exceed the detection limit for the study.
Articles that met these criteria were included in the biotransfer database. Twenty-one of the 34 studies cited by Travis and Arms were included in this analysis. Six of the papers could not be located; two were secondary sources of data that did not meet the data quality requirements of this analysis; four reported media concentrations below the studies' detection limits; and one raised serious quality concerns (e.g., concentrations in controls similar to concentrations in the experimental group). The biotransfer database for this study was expanded to include 72 references, covering 488 animals and 55 chemicals.

Qualitative performance and acceptance criteria were applied to the studies in the database to characterize each study’s overall data quality. The criteria were used to score each study on its experimental approach, its analytical quality, the completeness of its data, its success in reaching steady state, and the occurrence of chemical metabolism in the experiment. These scores were used to inform areas of further investigation in the biotransfer database. The performance and acceptance criteria were also intended to underscore the importance of transparency in the methods.

2.2 Data Collection

Appendix D provides detailed descriptions of each study, as well as animal metadata and chemical concentration data for each animal, shown as a time series where applicable. For papers in which multiple chemicals were studied, the chemicals are each presented as individual experiments. All the data are provided in the same units used in the original literature (e.g., mg/kg). The database also includes the chemical, analytical methods, and detection limits for each study.

When possible, every animal in a study was tracked separately. For each animal, the following metadata were tracked, as available:

- Animal type (e.g., beef or dairy)
- Lactation status
- Animal description (e.g., breed)
- Length of dosing period
- Feed intake rate
- Chemical concentration in feed
- Chemical intake rate
- Animal age
- Animal weight
- Rate of weight change
- Rate of milk production, if applicable.

If the type of animal (e.g., beef or dairy) was not provided, an assignment was made based on the breed using data from the Oklahoma State University Breeds of Livestock Web site (Oklahoma State University, 2003).
Milk and beef concentrations were also entered into the database. For each concentration data point, the database includes the following media metadata:

- Sample’s fat content
- Day of sample collection
- Sample type (e.g., fat-separated, whole milk, or whole muscle tissue).

The majority of the studies analyzed milk and beef samples for the parent chemical originally fed; however, two chemicals, aldrin and heptachlor, metabolize so readily to other compounds that the parent chemical is not expected to be present in beef and milk in significant concentrations. Specifically, aldrin is metabolized to dieldrin, and heptachlor is metabolized to heptachlor epoxide (Claborn et al., 1960). Most feeding studies on aldrin or heptachlor either measured the metabolite directly or measured total chlorine, which, for the most part, would consist entirely of the metabolite (Claborn et al., 1960). For example, Rumsey and Bond (1974) found that dieldrin concentrations in muscle were 100 times greater than those of aldrin in animals fed aldrin. Because the chemical accumulating in milk or muscle tissue is the metabolite rather than the parent chemical, using chemical data for the metabolite rather than the parent chemical is more appropriate in these cases for deriving a BTF.

Chemicals other than aldrin and heptachlor also were reported to undergo metabolism; however, some chemicals, such as chlordane (Dorough and Hemken, 1973), have a series of byproducts with no single predominant metabolite. In most of these studies with metabolized chemicals, a total concentration was reported, which included the parent compound and all byproducts. For consistency, total concentrations were recorded even when papers did distinguish results between the parent compound and multiple metabolites.

The data for each animal often included multiple data points for different sampling days or tissues. If the researchers provided concentration data on multiple days, including days after the conclusion of the dosing period, all the concentrations were recorded individually. In addition, concentrations in the literature were generally not reported as concentrations in beef, but instead as concentrations in various specific muscle tissues. In such cases, priority was given to tissues typically used for human consumption. If more than one tissue sample per animal met that criterion, each sample was recorded separately. Further, if a single sample was separated into fat and tissue before analysis, both of these concentrations were recorded separately. Detailed descriptions of the data gathering process are provided in Birak et al. (2001).

In addition to the animal and concentration data, chemical property data were gathered for all the chemicals in the biotransfer data set. The chemical properties used to develop the regressions include the $K_{ow}$ and the first-order dissociation constant ($pK_a$). Other chemical properties, such as the Henry’s law constant, molecular weight, vapor pressure, solubility, and octanol-air partition coefficient, were also gathered for regression analysis, but these properties were not ultimately included in the model. These properties were considered because they would be widely available and would influence the mobility and behavior of a chemical in environmental media. As discussed further in Section 3.0, chemical oxidation and hydrolysis rates were also sought to provide an indicator of metabolism rate. No readily available source of biological rates was available; therefore, environmental rates were considered. Specifically, aqueous photolysis rates were considered because (1) the products of aqueous photolysis have
been shown to closely mimic those from biological metabolism, (2) aqueous photolysis rates would include both oxidation and hydrolysis reactions, and (3) these data were readily available for many chemicals in this analysis.

Log $K_{ow}$ and pKa data are provided in Table 1. These data were gathered from the following four references in the order listed:

- U.S. EPA’s Dioxin Reassessment (U.S. EPA, 2000a) for dioxins only,
- U.S. EPA’s Superfund Chemical Data Matrix (U.S. EPA, 1996),
- CHEMFATE (Syracuse Research Corporation, 2005a), and
- PhysProp Database (Syracuse Research Corporation, 2005b).

For organic acids, we also collected the log $K_{ow}$ for the ionized ($K_{ow,i}$) and the neutral form ($K_{ow,n}$) of the chemical, along with the acid dissociation constant (pKa). For these chemicals, the log $K_{ow}$ provided in Table 1 is a weighted value calculated based on the fraction of the chemical in the neutral form (FracNeutral):

$$K_{ow} = K_{ow,n} \times \text{FracNeutral} + K_{ow,i} \times (1-\text{FracNeutral}).$$

Accounting for the fraction of ionizable organics in the neutral form is important because $K_{ow}$ can vary considerably depending on pH. The cow’s small intestine, where chemicals can be absorbed, has a near neutral pH (Umphrey and Staples, 1992). Thus, the neutral fraction was determined using a pH equal to 7 in the following equation (Lee et al., 1990):

$$\text{FracNeutral} = \frac{[HA]}{([HA] + [A^-])} = \frac{1}{1 + 10^{(\text{pH} - \text{pKa})}}$$

where

- $\text{FracNeutral} =$ fraction of neutral species present for organic acids (unitless),
- $[HA] =$ equilibrium concentration of organic acid (mol/L),
- $[A^-] =$ equilibrium concentration of anion (mol/L), and
- $\text{pKa} =$ acid dissociation constant (unitless).

We obtained Log $K_{ow,i}$ values from the ARS Pesticide Properties Database maintained by the U.S. Department of Agriculture (USDA, 2003a). In cases where the database provided a range of log $K_{ow}$ values, the lower value was selected for log $K_{ow,i}$. In cases where a value for log $K_{ow,i}$ was not identified, values were selected using a surrogate chemical with a similar structure. Otherwise, log $K_{ow,i}$ was estimated assuming a ratio of log $K_{ow,i}$ to log $K_{ow,n}$ of 0.015. This ratio is a conservative value developed by EPA to apply to organic acids without data for log $K_{ow,i}$ (U.S. EPA, 1996). For dicamba, the log $K_{ow}$ in CHEMFATE appeared to be for the ionized form. Dicamba’s log $K_{ow,n}$ was obtained from Physprop, which was confirmed to be for the neutral form of the chemical.
## Table 1. Chemical Properties

<table>
<thead>
<tr>
<th>CAS</th>
<th>Constituent</th>
<th>log $K_{ow}$ (unitless)</th>
<th>pKa (unitless)</th>
<th>log $K_{owi}$ (unitless)</th>
<th>log $K_{own}$ (unitless)</th>
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<td>Aldrin</td>
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<td>1918009</td>
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(continued)
Table 1. (continued)

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<th>CAS</th>
<th>Constituent</th>
<th>( \log K_{ow} ) (unitless)</th>
<th>pKa (unitless)</th>
<th>( \log K_{ow,i} ) (unitless)</th>
<th>( \log K_{ow,n} ) (unitless)</th>
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<td>19408743</td>
<td>Hexachlorinated dibeno-p-dioxin, 1,2,3,7,8,9-</td>
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<td>51207319</td>
<td>Tetrachlorodibenzoaluran, 2,3,7,8-</td>
<td>6.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>51630581</td>
<td>Fenvalerate</td>
<td>6.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>52315078</td>
<td>Cypermethrin</td>
<td>6.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>52645531</td>
<td>Permethrin</td>
<td>6.5</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>52756226</td>
<td>Flamprop-isopropyl</td>
<td>4.24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>52918635</td>
<td>Deltamethrin</td>
<td>6.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>53780340</td>
<td>Mefluidide</td>
<td>0.23</td>
<td>4.78</td>
<td>0.03</td>
<td>2.02</td>
</tr>
<tr>
<td>55511983</td>
<td>Buthidazole</td>
<td>0.34</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>55673897</td>
<td>Heptachlorinated dibenzofuran, 1,2,3,4,6,7,9-</td>
<td>7.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>57117314</td>
<td>PeCDF, 2,3,4,7,8-</td>
<td>6.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>57117416</td>
<td>Pentachlorinated dibenzofuran, 2,3,4,7,8-</td>
<td>6.79</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>57117449</td>
<td>Hexachlorinated dibenzofuran, 1,2,3,6,7,8-</td>
<td>7.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>57653857</td>
<td>Hexachlorinated dibeno-p-dioxin, 1,2,3,6,7,8-</td>
<td>7.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>60851345</td>
<td>Hexachlorinated dibenzofuran, 2,3,4,6,7,8-</td>
<td>7.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>67562394</td>
<td>Heptachlorinated dibenzofuran, 1,2,3,4,6,7,8-</td>
<td>7.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>70648269</td>
<td>Hexachlorinated dibenzofuran, 1,2,3,4,7,8-</td>
<td>7.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
2.3 Data Processing

After data entry, all values were normalized to standard units using automated data processing routines; these data are provided in Appendix E. Where data gaps existed, other parameters and/or default values were used. Table 2 provides the calculations and default values used by the automated data processor to estimate these parameters when necessary. In all cases, reported data were preferred over default values. Initially, most default values were selected to be consistent with those in Travis and Arms (1988). All default values were checked to confirm that they were internally consistent with data collected from the literature search (as will be discussed later in this section). Appendix E lists the standardized media concentration data, sorted alphabetically by author. For a given reference, the data are further grouped by chemical and animal. Time-series concentration data are shown, and the phase of the experiment is noted for each data point (e.g., uptake, last day of dosing, depuration).

Cattle feed intake rates can vary based on animal weight and period of lactation (for dairy cattle). The values selected by Travis and Arms were within a range of data provided by the National Research Council (1987) (i.e., approximately 10 to 25 kg/day for dairy cattle and 7 to 10 kg/day for beef cattle). These values also demonstrated consistency with feed intake rates reported in the biotransfer database. For cases in which a study reported an animal body weight but no feed intake rate, the daily feed intake rate was assumed to be 3 percent of the animal’s weight (Clark et al., 1975). This assumption was validated using studies reporting body weight and feed intake rate.

In some cases, researchers reported the chemical intake rate on a per-body-weight basis, which required the body weight of the animal to obtain the desired units (mg/day) for the chemical intake rate. If the researchers did not report an animal body weight, default body weight values were used. These values were 533 kg for lactating animals and 267 kg for nonlactating animals. These default body weights were derived using the default assumptions for feed intake rates and feed intake as a percentage of animal body weight.

For the fat content of milk, 4 percent is a common standard reported by the USDA (1896) and by several researchers (Zweig et al., 1961; Gannon et al., 1959). This value differs slightly from the fat content used by Travis and Arms for milk samples (3.68 percent); however, the adjustment is minor and is consistent with values observed in the literature. The default beef fat content of 19 percent was selected because it was the median fat content of several different beef cuts reported by Fries and Marrow (1977) and has also been used in other biotransfer models (Lorber et al., 1994). This value is lower than the default assumption of 25 percent fat content in beef used by Travis and Arms, but is certainly reasonable given the range of fat contents reported by the USDA (e.g., from 7.5 percent to more than 30 percent) (USDA, 2003b). As is discussed further in Section 3.0, the regression model was ultimately developed using fat-based concentrations to reduce the uncertainty in having to assume a fat content.
Methodology for Predicting Cattle Biotransfer Factors

Table 2. Parameter Extrapolation Procedures

<table>
<thead>
<tr>
<th>Value Required</th>
<th>Value Provided</th>
<th>Conversion</th>
<th>Defaults</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{whole milk}} )</td>
<td>( C_{\text{milk fat}} )</td>
<td>Divide ( C ) by FC</td>
<td>Default FC: milk = 0.04; beef = 0.19 (Zweig et al., 1961 and Lorber et al., 1994)</td>
</tr>
<tr>
<td>( C_{\text{beef tissue}} )</td>
<td>( C_{\text{beef fat}} )</td>
<td>Divide ( C ) by FC</td>
<td>Default FC: milk = 0.04; beef = 0.19 (Zweig et al., 1961 and Lorber et al., 1994)</td>
</tr>
<tr>
<td>( C_{\text{milk fat}} )</td>
<td>( C_{\text{whole milk}} )</td>
<td>Multiply ( C ) by FC</td>
<td>Default FC: milk = 0.04; beef = 0.19 (Zweig et al., 1961 and Lorber et al., 1994)</td>
</tr>
<tr>
<td>( C_{\text{beef tissue}} )</td>
<td>( C_{\text{beef fat}} )</td>
<td>Multiply ( C ) by FC</td>
<td>Default FC: milk = 0.04; beef = 0.19 (Zweig et al., 1961 and Lorber et al., 1994)</td>
</tr>
<tr>
<td>CIR</td>
<td>CIR per BW</td>
<td>Multiply CIR per BW by BW</td>
<td>See BW</td>
</tr>
<tr>
<td>C_{\text{feed}}</td>
<td>C_{\text{feed}} by FIR</td>
<td>Multiply C_{\text{feed}} by FIR</td>
<td>See FIR</td>
</tr>
<tr>
<td>BW</td>
<td>FIR</td>
<td>Divide FIR by PFIR</td>
<td>PFIR = 0.03 (Clark et al., 1975)</td>
</tr>
<tr>
<td>Lactation status</td>
<td>Set to defaults</td>
<td>BW_L = 533kg; BW_{NL} = 267kg</td>
<td>(derived by dividing FIR by PFIR)</td>
</tr>
<tr>
<td>FIR</td>
<td>BW</td>
<td>Multiply BW times PFIR</td>
<td>PFIR = 0.03 (Clark et al., 1975)</td>
</tr>
<tr>
<td>Lactation status</td>
<td>Set to defaults</td>
<td>FIR_L = 16kg; FIR_{NL} = 8 kg;</td>
<td>(Travis and Arms, 1988)</td>
</tr>
</tbody>
</table>

C = Concentration
FC = Fat content
CIR = Chemical intake rate
BW = Body weight
FIR = Dry-weight feed intake rate
PFIR = Percent feed intake rate per body weight
L = Lactating
NL = Nonlactating

2.4 Estimating Steady-State Concentrations

Using an automated data processor, steady-state concentration (Css) was first estimated based on the concentration reported on the last day of feeding. If concentration was not reported on the last day, the reported value nearest the last day—either during uptake or depuration (kd)—was selected. Next, depuration rates were determined for animals having time-series concentration data after the last day of feeding. From the depuration rates, we estimated the amount of time required to reach steady state. We also used this data to extrapolate steady-state concentrations. This amounts to using a simple, one-box pharmacokinetic model to mathematically describe chemical uptake from contaminated feed by the cow. Appendix A provides a detailed example of the process for extrapolating steady-state concentrations using the one-box model.

A thorough review of each experiment was conducted to ensure that the selections made by the automated processor were appropriate and to assess the overall quality of the data. The questions considered during this review include: (1) Did concentrations reach steady state? (2) Were concentrations measured on the last day of feeding? (3) Were concentrations at or near the analytical detection limits? (4) Do the data indicate two-compartment behavior during the
Methodology for Predicting Cattle Biotransfer Factors

depuration phase? and (5) Do the data indicate nonlinear behavior across chemical intake rates? These questions were considered for each experiment, and the results are fully documented in Appendix F.

In general, the approach taken for this review was to compare across all available data to determine the best data available and to reject data of lesser quality. For a given animal, concentrations below the detection limit were removed from the fit of the depuration data. For a given experiment, preference was given to animals fed higher chemical intake rates and having concentrations exceeding 5 times the detection limit. BTFs from such animals were typically less variable than those for animals with concentrations hovering around the detection limit. For a given chemical, preference was given to studies in which the animals were fed longer and concentrations were more likely to have reached steady state. As noted in these examples, data were removed only when other data was clearly more appropriate or of higher quality. For chemicals with minimal data, all data typically were accepted even when data quality issues may have been a concern. For example, if depuration data were not available to determine the amount of time required for concentrations to reach steady state, experiments were often still accepted.

As a result of this review, some modifications were made to the selections of the automated data processor. When concentrations were not measured on the last day, assuming that the concentration nearest to the last day was the best estimate of the Css was sometimes inappropriate. Consider an animal fed for 50 days with a concentration reported on day 40 and 51. The automated routines would have selected the concentration at day 51 as the closest value to the last day. If the chemical depuration rate is high, the concentration at day 51 could be significantly lower than the concentration reported at day 40. In this case, the concentration at day 40 might provide a better estimate of Css. For a more persistent chemical, the opposite could be true: the concentration at day 51 might be much higher than concentration reported at day 40.

In other cases, this review prompted us to limit the data used to derive depuration rates to those reported nearest the last day. Depuration rates were determined using time-series concentrations and by plotting the log of the concentration versus time. These data are fit using a linear regression in which the slope is equal to the depuration rate. Occasionally, we observed two distinct regions within these plots, each having its own slope. In the second region, chemicals are removed at a much slower then the first. Understanding this behavior is important when modeling concentrations out past the last day of feeding. The purpose of this modeling was to estimate Css, which is driven by the higher initial rate of removal. We did not attempt to model two-phase behavior; however, in some cases, we limited the data used to determine the kd to capture the initial rate of removal.

Because of the wide range of reported chemicals intake rates, we reviewed the data to determine whether or not high intake rates exceeded the linear range for the BTF. To test for nonlinear behavior, plots of concentration versus intake rate were examined for each experiment and chemical where multiple chemical intake rates were fed. Confidence intervals were determined for the intercept to ensure that they included zero. Such plots were used to examine the assumption that the BTF is constant across a wide range of intake rates and eliminate animals fed chemical intake rates outside of the linear range.
2.5 Estimating Biotransfer Factors

BTFs for beef and milk were calculated as follows:

\[ BTF = \frac{C_{ss}}{CIR} \]  

(3)

where

- BTF = Biotransfer factor ([mg/kg]/[mg/d])
- CIR = Chemical intake rate (mg/d)
- \( C_{ss} \) = Steady-state concentration (mg/kg).

Individual BTFs were calculated on a per-animal basis. Because several muscle samples were often recorded for one animal, these concentrations were averaged to avoid having one animal dominate the data set. Preference was given to data that used the fewest default assumptions.

For both beef and milk samples, we estimated fat-based and whole-tissue or milk concentrations. These were used to derive both fat-based and whole-tissue or milk-based BTFs. A ranking system was applied to the BTF values to easily identify the level of transformation used on each individual data point. For each BTF derived, the data were ranked from most to least preferred (1 to 3) based on the following criteria:

- Data were reported in the literature as needed to derive a BTF,
- Data were transformed using information from the feeding study (e.g., fat content), and
- Data required transformation with a default value.

3.0 Results

Figure 1 shows the fraction of biotransfer data corresponding to the ranking system discussed in Section 2.5. The figure demonstrates that the majority of beef data were reported as fat concentrations, whereas the majority of milk data were reported in whole milk. To convert between fat-based concentrations to whole-milk or tissue concentrations, an assumption must be made concerning fat content. As noted in Section 2.3, the fat content in beef tissue can vary widely, from 7.5 percent to more than 30 percent (USDA, 2003b). Despite variable tissue concentrations, research has demonstrated a general uniformity of chemical concentrations reported in fat samples (Fries and Marrow, 1977). In light of these facts, concentrations in fat were used for estimating BTFs, eliminating a potentially significant source of uncertainty with regard to the tissue data. Because milk concentrations were mostly provided in whole milk, these data required an adjustment to obtain concentrations in fat. Because there is significantly less
Methodology for Predicting Cattle Biotransfer Factors

Figure 1. Ranks of biotransfer data. The most preferred data underwent no transformation from information in the literature to BTF derivation. The figure demonstrates that the majority of beef data were reported as fat concentrations, whereas the majority of milk data were reported in whole milk.

Variability in milk fat contents, assuming a 4 percent fat content for this calculation is not expected to have introduced any significant bias in the model. Notably, other EPA risk assessments have also taken the approach of using fat-adjusted BTFs (U.S. EPA, 2000a).

One of the criticisms of the Travis and Arms regressions was the inclusion of highly metabolized chemicals. In the current research, all chemicals were flagged as to whether or not they were metabolized. Metabolic reactions typically result in compounds that are more hydrophilic than the parent compound, and thus more easily excreted. However, products of metabolism can, in some cases, be persistent, and even toxic. For example, DDT is metabolized to DDD and DDE, but remains persistent. As a result, no correlation was found between metabolism and biotransfer.

Further evaluation led to the discovery that chemicals capable of undergoing certain metabolic reactions are significant outliers. In Figure 2, the BTFs for hydrolyzable and oxidizable chemicals are shaded. These BTFs are significantly lower than are other values at the same $\log K_{ow}$, except at $\log K_{ow}$ 4.5, log BTF -0.43, which represents the chemical telodrin. Although this chemical is oxidizable, it also is highly chlorinated. Among all the chemicals, we examined how the degree of chlorination was related to biotransfer, but found no clear correlation. As noted in Section 2.2, we also attempted to correlate BTFs with reaction rates, in addition to $\log K_{ow}$. This approach was unsuccessful, in part, due to limitations in available data. Ultimately, the hydrolyzable and oxidizable chemicals were excluded from the final data set upon which the regression model was based.
An additional outlier in Figure 2 was noted at log Kow 5.5, log BTF -2.65. One common diagnostic tool in identifying outliers is the normal probability plot. This plot is used to test the underlying assumption that the data are normally distributed about the mean. During the development of the regression model, this point was the only significant outlier inconsistent with the assumption of normality. Further statistical tests indicated that this was also an influential point (i.e., based on DFFITS). In and of themselves, these facts are not a rationale to remove data from further analysis; rather, these are triggers to revisit the data. During the review of the data described in Section 2.4, this particular point had already been flagged as likely outside of the linear BTF range. We conducted statistical tests designed to identify when chemical intake rates were high enough to exceed the linear BTF range; however, these tests were not sensitive for small data sets. Given that this BTF was in conflict with other data from the same study and is likely outside of the linear BTF range, we did not include this BTF in the further development of the model.

Figure 3 presents all of the data remaining in the analysis. This figure clearly demonstrates the significant overlap between the fat-based beef and milk BTFs. The polynomials also considerably overlap. A covariance regression model was used to assess whether or not a single polynomial equation could be used to describe both sets of data. Based on a partial F-test, no statistically significant difference exists between the beef and milk BTFs. Therefore, one polynomial regression equation that can be used to predict fat-based cattle BTFs was derived and is provided in Figure 4. Depending on fat content, these BTFs can be adjusted to reflect concentrations in either milk or beef.
Methodology for Predicting Cattle Biotransfer Factors

Figure 3. Comparison between milk and beef BTFs. Each point represents a single animal. All data are adjusted to a fat basis. Based on analysis of covariance, there is no statistical difference between the polynomial regressions from milk and beef.

\[ y = -0.099x^2 + 1.07x - 3.56 \]
\[ R^2 = 0.8259 \]
\[ F = 716.31 \]

Figure 4. Polynomial regression model for predicting fat-based BTFs. Each point represents a single animal. All data are adjusted to a fat basis.
4.0 Discussion

Previously, an evaluation of the data and model derivation by Travis and Arms (1988) was performed (Birak et al., 2001). Although the linear regression development was verified in that research, variability that the linear model could not address with its univariate regression still existed in the BTF data. The wide variability in BTF values for a single log Kow was still unexplained after that analysis. The conclusion drawn at completion of the Travis and Arms verification work was that variability in BTF data and resulting uncertainty in the model suggested the following:

- A need exists for an expanded or further improved (standardized) data set to be truly representative of the patterns of biotransfer for different chemicals, and
- A linear regression using log Kow was not a suitable predictor for BTF values; other chemical properties or completely different models may better characterize biotransfer.

4.1 Model Application

In lieu of empirical data, the regression equation in Figure 4 can be used to estimate a fat-based BTF for animals exposed to contaminated media (e.g., feed or forage). The regression is applicable to chemicals with log Kow ranging from -0.75 to 8.8 for both beef and milk BTFs. It is recommended that risk assessors use the bounds of the regression to make predictions for chemicals whose log Kow falls outside this range. Extrapolation of the equation to log Kow values beyond this range may produce inappropriate results. For example, Travis and Arms’ regressions were reported for a log Kow range of 1.3 to 6.9 for milk and 2.8 to 6.9 for beef. If these equations are used for chemicals with log Kow > 6.9, the model predicts increasing BTFs with increasing log Kow values. However, studies published since 1988 demonstrate that concentrations in beef and milk actually decrease with increasing log Kow for high log Kow chemicals (i.e., log Kow > 6) (McLachlan, 1993; Thomas et al., 1998; Fries et al., 1999). This study specifically sought to collect biotransfer data for high log Kow chemicals in order to examine this issue.

One of the main limitations in using this regression is the potential overestimation of BTFs for chemicals that are oxidized or hydrolyzed. One way to account for this overestimation is to rely upon a metabolism factor to improve model predictions. For example, a metabolism factor of 0.01 has been developed by EPA for bis(2-ethylhexyl)phthalate (U.S. EPA, 1998b). This factor is used to account for the fact that 99 percent of the chemical ingested is metabolized. If this factor is applied to the BTFs predicted for bis(2-ethylhexyl)phthalate using the presented regression model, the BTFs are reduced by two orders of magnitude. These metabolism-adjusted BTFs are close in magnitude to the BTFs for other chemicals that undergo ester hydrolysis, which supports the use of this metabolism factor. However, given the limited data set, EPA has not sought to develop default metabolism factors for all oxidized and hydrolyzed chemicals. This would appear especially inappropriate for the oxidized chemicals because they were not consistently underpredicted by the regression model. For example, telodrin is a chemical that...
does have a site for oxidation; however, it is also highly chlorinated and remains persistent. No clear trend could be identified whereby the degree of chlorination could be used to estimate the extent of metabolism.

In developing and applying any adjustment for metabolized chemicals, some important factors should be considered. First, the metabolized form of a chemical may in fact be as toxic as, or even more toxic than, the parent compound. Second, the metabolized form of a chemical may itself be persistent. In fact, many of the chemicals in the biotransfer data set that are well predicted by the regression line are metabolized to other compounds; DDT is metabolized to DDE, and lindane is metabolized to many different compounds. For DDT and lindane, BTFs are well predicted using the regression equation. Thus, if evidence shows that a chemical undergoes biotransformation to other compounds, it is not necessarily underpredicted by the regression equation.

4.2 Model Improvements

One of the primary objectives in conducting this research was developing a biotransfer model based on transparent data and methods. The databases for biotransfer and chemical properties were assembled so that original data sources and data quality were easily discernible. All information was entered into the database as reported in the original reference. Any data transformations performed to derive BTFs, such as unit conversions or fat adjustments, were conducted in separate steps, and both raw data and normalized data were maintained. Additionally, all data quality scores (as determined by the number of data transformations performed for derivation) were tracked for all the data used in the BTF regression. Upon reexamination of the linear log K_{ow} regressions (Travis and Arms, 1988), the results were not easily reproduced because of the difficulty in tracking data from cited references to the results shown in the paper. The clarity of procedures in this analysis, from data gathering to regression development, and the data that go along with these stages of analysis demonstrate a more transparent approach toward model development.

Another goal of this research was improving the data quality of the model. A significant obstacle to reproducing the linear log K_{ow} regressions (Travis and Arms, 1988) was a lack of clarity in the statement of the data quality standards of the research. Some of the studies included in that analysis were secondary sources of data that did not report the original study's methods. Other BTFs in the linear log K_{ow} regression were based on studies in which the chemical concentrations were near the detection limits of the study. The feeding study requirements and chemical reference hierarchy implemented in this study result in an improved, more uniform data quality. Using only primary references made including much more information about each study than is usually reported in secondary literature reviews possible.

The biotransfer data set also increased the quantity of BTF values on both ends of the log K_{ow} range due to gathering nearly double the references used in the Travis and Arms regressions. Peer reviewers noted that the linear regressions appeared to overpredict biotransfer for chemicals with high log K_{ow} (>6). In this research, that trend of decreasing BTFs at log K_{ow} of 6 or greater...
was confirmed by gathering more data on high log $K_{ow}$ chemicals; however, much of the data for the high log $K_{ow}$ chemicals were not available at the time of Travis and Arms’ research.

Regarding the milk and beef concentration data gathered, data quality objectives were intended to improve the clarity of BTF derivation. All concentration data represent the time nearest to steady state for a particular animal. For cases in which steady state was not reached, data from the last day of dosing or the day nearest the last day of dosing were used as the concentration for BTF derivation. However, for approximately 20 percent of the animals, steady-state concentrations were extrapolated or already provided in the study. These steady-state BTFs mark an improvement in the acceptability of the model's assumptions. The extrapolation exercise also demonstrated that, in the case of most chemicals, a significant difference did not exist between BTFs based on data as reported and BTFs based on data extrapolated to steady state.

One of the major changes made in this model, compared with existing biotransfer models, was the use of fat-based BTFs. The shift from a tissue-based BTF to a fat-based BTF was made for several reasons. First, the majority of beef concentration data (90 percent) was reported as fat concentrations. Changing the BTF to a fat-based factor required fewer transformations on the majority of the biotransfer data and, therefore, improved the data transparency of the model. Additionally, fat content varies widely in different cuts of beef, although concentrations in fat samples remain relatively constant regardless of cut (Fries and Marrow, 1977). Switching to a fat-based BTF allows risk assessors to adjust the fat content to the specific medium of interest and reduces uncertainty in the application of this model.

Peer review comments on the linear log $K_{ow}$ model (Travis and Arms, 1988) suggested that the regression may not accurately predict BTFs for metabolized chemicals. Approximately 40 percent of the chemicals included in this analysis are metabolized to some extent during digestion. Chemicals that metabolize were tracked by the quality criteria scores assigned to each study. A separate analysis was conducted to see if biotransfer of these chemicals was significantly different than for chemicals that are not metabolized. Removing the metabolized chemicals from the regression did not improve the model because too many data points in the regression were eliminated. Additionally, these chemicals did not appear to be outliers. Further examination of the data revealed that hydrolyzable and oxidizable chemicals were consistent outliers. Overwhelmingly, such chemicals had lower BTFs compared to other chemicals having similar log $K_{ow}$ values.

### 4.3 Data Limitations and Uncertainties

This study was limited by the literature that comprised the biotransfer database did not use—for the most part—analytical methods that are the state of the science, which is largely an artifact of the publishing period for the majority of the papers (mostly prior to 1980). Due to the quality of analytical methods used in much of the biotransfer studies, parameter uncertainty exists in the model, which could be reduced if the biotransfer database relied on more recent studies that utilized modern analytical methods.
Also, the focus of many feeding study articles was not to measure biotransfer of chemicals from contaminated feed into beef or milk. For example, Martin et al. (1976) designed an experiment to measure the dissipation rates of DDT in cows. To meet this objective, the experimental design did not aim to reach steady state or measure precise chemical and feed intake rates. This disjunction between feeding study objectives in the literature and the objectives of this study also contributes to variability in the BTF values upon which this model is based.

Because metabolized chemicals were not analyzed and reported in a consistent fashion in the literature, these metabolized chemicals introduce some uncertainty into BTF derivation. For rapidly metabolized chemicals such as heptachlor and aldrin, the predominant metabolites are well known and have readily available chemical property data. Other metabolized chemicals, such as chlordane, may have many metabolites for which little chemical information is available. As a result, a BTF may be derived based on a chemical concentration that characterizes the parent compound but does not really capture the overall chemical concentration of concern in the cow. The chemical property data used for the regression may also be inappropriate if the parent compound is metabolized rapidly and other byproducts with markedly different chemical property data (e.g., log K\text{ow}) persist in the cow’s milk or tissues.

The chemical property data used in the analysis have some limited variability associated with them. Reported log K\text{ow} values can vary among references. A validation of log K\text{ow} values reported from the chemical data references listed earlier showed that the log K\text{ow} for a chemical may vary +/- 0.5 among these different references. Chemical data for this study were collected according to a reference hierarchy that was based on data quality; therefore, the chemical property data used are not a significant limitation of the model.

5.0 Conclusion

Overall, the biotransfer database constructed for this analysis demonstrates a marked improvement in the data quality, data quantity, and data transparency relative to data sources used in existing models. Weaknesses in the data collection approach of other biotransfer models were closely examined to ensure that metadata of interest were collected (e.g., the lactation status of cattle in the beef BTF model). The chemical properties database also represents a significant improvement in data quality and quantity over those of existing biotransfer models. The chemicals included in the analysis improved the representativeness of the model for chemicals across the entire log K\text{ow} range.

The model itself underwent close evaluation. Sidebar investigations confirmed that the default values of the analysis were reflective of real data. The assumption of steady-state conditions was considered by extrapolating data to steady state where possible and comparing the change in BTF values known to be at steady state and those that were not. The results of this investigation demonstrated that assuming steady-state conditions for the model did not preclude use of all biotransfer data that could not be proven to be at steady state.
Finally, the model’s proposed relationship between a chemical’s log $K_{ow}$ and structure and biotransfer into beef and milk was rigorously examined. Properties other than $K_{ow}$ were analyzed, and biotransfer models with entirely different approaches were also examined to see if a better relationship existed between BTF values and other chemical parameters. These model evaluations confirmed that log $K_{ow}$ does predict biotransfer, but the metabolism of a chemical may also affect the observed BTF of a chemical into beef or milk.

The strategy in selecting a suitable screening methodology was to minimize the data requirements of the model, which precluded some of the more complicated pharmacokinetic and fugacity-based methods for estimating biotransfer. Only readily available chemical property data were considered for predicting BTF values because simple implementation was desired for this approach. The regression presented was developed with the goals of easy implementation, improved data quality, and better prediction of BTFs. Application of this regression in assessments should improve the accuracy of biotransfer estimates relative to existing methods.

6.0 References


NRC (National Research Council). 1987. *Predicting Feed Intake of Food-Producing Animals*. Board on Agriculture, Committee on Animal Nutrition, Subcommittee on Feed Intake, Washington, DC.


