Appendix B

Evaluation of the Molecular Connectivity Index

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Alternate Approach for Characterizing Biotransfer Factors

Final

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PROJECT SUMMARY

Under a previous work assignment with NCEA CTAC and OSW, RTI evaluated the Travis and Arms (1988) methodology used to predict biotransfer factors (BTF) of chemicals into beef and milk. The methodology based on the relationship between log K_{ow} and the chemical concentrations in beef tissue and milk. RTI investigated the basis for this relationship to evaluate the level of uncertainty associated with BTFs predicted using the Travis and Arms (1988) methodology. Despite the fact that this methodology has been the standard in risk assessment for more than a decade, our findings suggested that the BTFs were associated with considerable uncertainty (Birak et al., 2002). For example, our results for some chemicals indicated that the BTFs could vary over several orders of magnitude.

Based on these findings, NCEA CTAC and OSW tasked RTI with investigating alternative approaches to calculating BTFs. Specifically, we have been investigating the use of molecular connectivity indices (MCIs) as an alternative predictor of BTFs. Of particular interest was the BTF methodology for beef and milk presented by Dowdy et al. (1996) and based on methods originally developed by Meylan et al. (1992) to predict organic carbon partition coefficients (K_{oc}). Meylan et al. (1992) developed an approach for estimating K_{oc} using a two-step process in which (1) nonpolar chemicals were plotted against K_{oc} to examine the relationship between parameters (in this case, linear), and (2) correction factors were applied for polar chemicals based on the functional groups and deviations from their nonpolar regression line. Dowdy et al. used the polar correction factors from Meylan et al. to develop polar-adjusted molecular connectivity indices ($^1\chi_{pc}$), and found a strong linear relationship between the BTFs and MCIs.

To investigate this relationship further, RTI plotted the molecular connectivity indices for chemicals against BTFs, first for chemicals without polar correction factors and then for chemicals with polar correction factors as determined by Meylan et al. and Dowdy et al. Contrary to what other authors have found between K_{oc} and $^1\chi$, we found no relationship between the BTFs and $^1\chi$ for chemicals without polar correction factors. Using the method presented by Dowdy et al. to derive polar correction factors, we regressed the MCIs versus the BTFs and found that in this case a relationship does exist. Specifically, the R-square values for milk and beef are 0.55 and 0.54, respectively, as compared to the R-square values of 0.50 and 0.46 based on log K_{ow}.

In conclusion, we do not believe that the approach using molecular connectivity indices results in a substantial improvement in our ability to predict biotransfer factors. RTI recommends further investigation of the biotransfer database to improve understanding of the sources of uncertainty that confound this relationship. In addition, recent advances in molecular modeling have led to potentially hundreds of molecular descriptors that could be considered for predictive ability in terms of BTFs. The finding that molecular topology combined with polarity correction factors correlate with BTFs suggests that other shape and polarity/electrostatic descriptors should be examined. If appropriate, such factors could be applied without the use of additional correction factors. Examples are molecular electrostatic potential (MEP), dipole moment, the various STERIMOL shape descriptors, and the electrotopological state descriptors. Other methods presented in the literature that could be further investigated include pharmacokinetic modeling and fugacity modeling.

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ABSTRACT

Multimedia modeling simulations and sensitivity analyses suggest that the biotransfer factors (BTFs) are an important source of uncertainty in estimating exposure to animal products (e.g., beef and milk) through the farm food chain. There is a significant need for both the regulated and regulatory communities to reduce the uncertainty associated with BTFs to provide more reliable estimates of exposure and risk for agricultural pathways. For more than a decade, the methodology developed by Travis and Arms (1988) has served as the standard to predict BTFs in multimedia risk assessments, and risk assessors/managers have addressed the uncertainty inherent in those exposure estimates largely through the risk characterization process. Because the uncertainty in BTFs derived using the Travis and Arms approach can span several orders of magnitude, there is a need to improve our predictive capabilities for BTFs when measured data are unavailable (Birak et al., 2001). Recent research by Dowdy et al. (1996) that used molecular connectivity indices (MCIs) showed a strong linear relationship between BTFs and MCIs. The authors used the original data set published in Travis and Arms, supplemented by information gleaned from more recent literature reviews. In the current analysis, an expanded set of BTFs developed by Birak et al. are used to investigate the $^{1}\chi$ method proposed by Dowdy et al. Additional approaches to the linear regression techniques presented should be considered to reduce the uncertainty in predicted BTFs.

INTRODUCTION

One of the most important exposure pathways for lipohilic compounds involves the ingestion of agricultural products such as beef and milk (McLachlan, 1993; Travis and Hester, 1991). The transfer of chemical contaminants from feed crops to beef tissue and milk is often represented by chemical-specific biotransfer factors (BTFs). Although chemical concentrations in beef and milk can be measured, the collection and analysis of chemical samples in agricultural products is often prohibitively expensive. Consequently, the BTFs are frequently derived using the approach developed by Travis and Arms (1988) based on the linear relationship between the log of the octanol-water partition coefficient (log K_{ow}) and the concentration in beef and milk. Unfortunately, recent research on the methods used to predict BTFs indicates that this parameter is associated with uncertainty spanning several orders of magnitude (Birak et al., 2001). Given the importance of this parameter in predicting the exposure to chemical contaminants in beef and milk, it is clear that further research to improve the methods used to predict BTFs is warranted (Fries et al., 1999).

As suggested above, the approach most commonly used to predict the contaminant concentrations in beef tissue and milk in an agricultural scenario involves the use of BTFs. The BTF is the ratio of the concentration in either beef or milk to the chemical intake in mass of chemical ingested by cattle per day (Equation 1).

$$BTF = \frac{Beef\ or\ Milk\ Concentration(mg/kg)}{Chemical\ Intake\,(mg/d)} \qquad \text{Eq. 1}$$

In 1988, Travis and Arms published a methodology to predict BTFs using a chemical's octanol-water partition coefficient (K_{ow}). Since publication, the regression equations developed by Travis and Arms have been widely used for predicting BTFs for beef and milk (U.S. EPA, 1998; U.S. ACE, 1996). However, subsequent research has called into question the validity of using K_{ow} to predict concentrations in beef and milk, particularly for chemicals with high log K_{ow} chemicals (McLachlan, 1993; Thomas et al., 1998; Fries et al., 1999) and chemicals with large uncertainty in K_{ow} values (Mackay et al., 1992). Figure 1 demonstrates the significant variability in BTF data for similar K_{ow} values.

Molecular topology and quantitative structure-activity relationship (QSAR) analyses use a chemical's structure as the basis for estimating properties, making them particularly useful for predictive modeling and risk assessments. Molecular connectivity employs a mathematical approach to characterize chemicals rather than using traditional physico-chemical characterizations in QSAR (e.g., log K_{ow}) (Randic, 2001). The normal path, first-order molecular connectivity index ($^1\chi$) has been used to estimate chemical properties, such as soil sorption coefficients (K_{oc}) and bioconcentration factors (BCFs) in fish (Meylan et al., 1992; Sabjlic, 1982). Dowdy et al. (1996) present an analysis that suggests that molecular connectivity indices may be an accurate predictor of beef and milk BTFs. In our analysis, we used the approach described by Dowdy et al. to examine the applicability of their regression to a separate BTF data set (Birak et al., 2001) and to evaluate the potential of molecular connectivity indices as an alternative approach for BTF estimation.

The $^1\chi$ methodology used in this analysis was developed by Randic (1975) and later refined by Kier and Hall (1986). A molecular connectivity index is calculated by drawing out a chemical in a hydrogen-suppressed molecular structure and designating a δ value for each atom. The δ value of an atom equals the number of adjacent nonhydrogen atoms. The δ values of each atom forming a bond pair designate a bond value, and the bond values are then summed over all the bonds in the chemical structure to calculate $^1\chi$, as shown in Equation 2.

$$^1\chi = \sum \left(\delta i \times \delta j\right)^{-0.5} \qquad \text{Eq. 2}$$

where *i* and *j* are adjacent atoms forming a bond pair in the structure, and δ is the number of adjacent nonhydrogen atoms.

Previous research by Meylan et al. (1992) and Sabjlic (1987) used $^1\chi$ to estimate K_{oc}, resulting in good predictive ability with nonpolar chemicals but weaker regressions with polar chemicals. However, when Meylan et al. added a polar correction component to the nonpolar regression equation, the K_{oc} values were accurately predicted for both nonpolar and polar chemicals (R^2=.988). The polar correction component of the regression was determined by applying a series of statistically derived polar fragment correction factors to the polar chemicals (Table 1). The polar correction factors for a chemical were selected based on the functional groups in its structure, the number of times they occurred in the molecule. In some instances, a correction factor was added based on the presence of certain functional groups, regardless of the number of times the group occurred. Combining the nonpolar regression equation with the polar correction component yielded

$$\log K_{oc} = m\left(^1\chi\right) + b + \Sigma\left(P_f N\right) \qquad \text{Eq. 3}$$

where

m	=	slope of regression
b	=	*y*-intercept of regression
P_f	=	polar fragment correction factor
N	=	number of times fragment occurs in molecule.

Dowdy et al. found that the polar correction factors developed by Meylan et al. could be used to calculate a polar-corrected molecular connectivity index that predicted BTFs well (R^2=0.9 for beef and 0.89 for milk). Their regression incorporated the polar correction factors into the connectivity index value rather than adding a separate polar correction component to adjust the nonpolar regression. With this suite of polar correction factors, Dowdy et al. estimated BTFs with a calculated polar-corrected molecular connectivity index, as shown in Equations 4 and 5.

$$\log BTF = m\left({}^{1}\chi_{pc}\right) + b \qquad \text{Eq. 4}$$

where

$^{1}\chi_{pc}$	=	the polar corrected first-order molecular connectivity index
m	=	slope of regression
b	=	*y*-intercept of regression

and

$$^{1}\chi_{pc} = \left({}^{1}\chi\right) + a''' \sum\left(P_f N\right) \qquad \text{Eq. 5}$$

where

$^{1}\chi$	=	the normal path first-order molecule connectivity index
a‴	=	constant estimated in regression
$\Sigma P_f N$	=	summation of polar correction factors multiplied by the number of times they occur in the chemical

Dowdy et al. optimized this regression equation to maximize the correlation coefficient and minimize the standard error of the estimator, determining that the best value for both the beef and milk regressions for a‴ is 1.89.

METHODS

The biotransfer data set used in this analysis calculates beef and milk BTFs on a per chemical basis for 54 chemicals. The BTFs in our database were developed using references cited by Travis and Arms (1988) in their development of the K_{ow}-based regression and additional references identified through a literature search. All papers, including those cited by Travis and Arms, had to meet our data quality criteria, which are detailed in Birak et al. (2001). The Log K_{ow} data selection is also provided in Birak et al. (2001).

Normal path, first-order molecular connectivity indices and polar correction factors were obtained using the Estimation Program Interface (EPI) Suite™. The EPI Suite is a Windows®-based suite of physical-chemical property and environmental fate estimation models developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). PCKOCWIN™ is a component of the EPI Suite that estimates chemical soil adsorption coefficients (K_{oc}) from $^{1}\chi$ using the methodology developed by Meylan et al. (1992) and referenced by Dowdy et al. (1996). The polar correction factors applied in this analysis are identical to those cited in the Meylan et al. paper with one additional fragment documented in PCKOCWIN (Factor 29, Table 1) and one additional fragment derived by Dowdy et al. (Factor 28). Correction factors were applied to chemicals as recommended in PCKOCWIN with a few exceptions. In cases where a single ester was present in the chemical, the carbonyl (Factor 26) and aliphatic ether (Factor 19) polar correction factors were applied instead of the

ester correction factor (Factor 20). Also, where an aromatic organophosphorous fragment was present, the Dowdy-derived Factor 28 was used instead of PCKOCWIN's Factor 16. Both of these exceptions were applied to be consistent with the discrepancies documented by Dowdy et al. in application of the polar correction factors. To predict the polar-corrected normal path first-order molecular connectivity index ($^1\chi_{pc}$), the equation developed by Dowdy et al. was used (Equation 5).

The molecular connectivity indices from PCKOCWIN were compared with $^1\chi$ estimates from two other software programs, TOPIX and Molecular Modeling Pro. Chemical structures were also reviewed to identify discrepancies in the application of polar correction factors between PCKOCWIN and Dowdy et al. A limited literature search was performed to verify that the molecular connectivity indices documented have not been updated since the Dowdy et al. (1996) paper.

The log K_{ow} regressions shown here are also presented and discussed fully in Birak et al. (2001). For MCIs regressions were performed first using only the chemicals without polar correction factors versus the log BTFs for beef and milk separately. When a similar regression was performed with log K_{oc} and $^1\chi$, a strong correlation was observed (Sabjlic, 1987). Separate beef and milk log BTF regressions with the entire data set (i.e., including polar-corrected MCIs) were later performed, using our calculated polar-corrected molecular connectivity indices. The R^2 and F statistics were calculated using the software package Analyse-It.

RESULTS

Table 2 presents $^1\chi$ used in this analysis, $^1\chi$ reported in Dowdy et al., and BTF and log K_{ow} data for all chemicals that did not require polar correction factors. Table 3 presents analogous data for polar chemicals requiring correction factors. Also noted in Table 3 are the calculated $^1\chi_{pc}$ and polar correction factors applied in this analysis and the $^1\chi_{pc}$ and factors reported by Dowdy et al. (1996). The BTF and log K_{ow} data in these tables were developed by Birak et al. (2001).

The results from the linear regression analysis on chemicals not needing correction factors and $^1\chi$ are shown in Figure 2. In Figure 2a and 2b, log BTFs are plotted against $^1\chi$, as appropriate for milk and beef, respectively. The resulting regression equation for milk BTFs is

$$Log\ BTF\ milk = 0.0392\left(^1\chi\right) - 2.8857 \qquad \text{Eq. 6}$$

where N=27, R^2=0.01, and F=0.19.

The regression for beef BTF data is

$$Log\ BTF\ beef = -0.1163\left(^1\chi\right) - 0.8972 \qquad \text{Eq. 7}$$

where N=16, R^2=0.06, and F=0.84.

Figure 3 shows plots of the entire BTF data set and molecular connectivity indices calculated in this analysis (i.e., $^1\chi$ and $^1\chi_{pc}$). Chemicals that required polar-correction are noted differently in the plots from those that did not. Plots of the milk and beef data yielded somewhat similar regressions (see Equations 8 and 9).

$$Log\ BTF\ milk = 0.3057\left(^1\chi_{pc}\right) - 5.2704 \qquad \text{Eq. 8}$$

where N=53, R^2=0.55, and F=61.42.

$$Log\ BTF\ beef = 0.3683\left(^1\chi_{pc}\right) - 5.2968 \qquad \text{Eq. 9}$$

where N=33, R^2=0.54, and F=35.74.

DISCUSSION

The $^1\chi$ used in the analysis match those reported by Dowdy et al. for all chemicals also included in their analysis except toxaphene and arochlor 1254 (Table 2). Dowdy et al. specifically note that the structures they used for their analysis for these two chemicals were based on the most predominant structure in the chemical mixture, but the specific structure used was not noted. For this analysis, the structures used by EPIWIN for these chemicals were also used here.

In many cases, the $^1\chi_{pc}$ reported in Dowdy et al. (1996) do match values calculated in this analysis (Table 3). However, there are some notable exceptions. Specifically, the chemical structures for dieldrin, eldrin, and heptachlor epoxide all have an aliphatic ether group in a three-membered ring; an example is shown in Figure 4. These chemicals are assigned Factor 19 (Table 1) in PCKOCWIN, but not in Dowdy et al., possibly because Dowdy did not consider ethers in aliphatic rings for Factor 19. Flamprop-isopropyl and benzoylprop-ethyl both possess a nitrogen attached to an aliphatic carbon in their structures (Figure 4). Dowdy et al. assigned no polar correction factors for these functional groups, whereas PCKOCWIN assigned Factor 6 for both chemicals. In another example, PCKOCWIN assigned Factors 1, 2, and 7 (aromatic amine, aromatic ether, and carbamate groups) to oxadiazon. Dowdy et al. selected to apply correction factors for the aromatic ether (Factor 2), aliphatic ether (Factor 19), and carbonyl groups (Factor 26) to this chemical. The carbamate factor (Factor 7) was not presented by Dowdy et al. (1996); it may have been purposely excluded from the analysis. Regardless, each of these examples demonstrate discrepancies in interpretation and application of the polar correction factors, illustrating the difficulty in applying the $^1\chi_{pc}$ methods consistently for BTF estimation.

The regression analyses shown in Figures 2a and 2b did not reveal any correlation between $^1\chi$ and BTFs. The analysis that Meylan et al. conducted was initially based on a correlation between K_{oc} and $^1\chi$. Thus, it was anticipated that this regression would also show positive correlation between the $^1\chi$ and BTFs. By including chemicals with $^1\chi_{pc}$ in the regression, the regressions do improve and indicate a relationship between MCIs and BTFs, as

shown in Figures 3a and 3b, but this method does not appear to be a significant improvement over current methods (e.g., log K_{ow}). Specifically the R-square values for milk and beef are 0.55 and 0.54, respectively, compared with 0.50 and 0.46 based on log K_{ow}.

Some modifications could be made to this method that would likely improve the R-square value for the regressions. If the chemicals with aliphatic esters in them were no longer assigned a polar correction factor, as was done in Dowdy these chemicals would have BTFs closer to the current regression line. However, it is notable that pentachlorophenol does not currently have a polar correction factor applied, although it does contain a polar functional group (-OH). If that group were considered, pentachlorophenol would actually deviate further from the regression line because BTFs for this chemical are already underpredicted based on the MCI methodology. Interestingly, both pentachlorophenol and hexaclorobenzene are currently underpredicted by the current method and are aromatic ring structures that are highly chlorinated.

Theoretically, a correction factor for these chemicals could be derived that could either decrease or increase the $^1\chi$ value and provide a better fit to the regression line; however, this is not recommended. Rather, this example further demonstrates the limitations of the methodology. Specifically, the methodology developed by Dowdy et al. for their regressions could not be applied to an expanded data set of chemicals successfully. Creating additional rules and correction factors is likely to increase potential for errors and different interpretations, limiting the potential for widespread use.

In conclusion, the BTFs predicted using MCIs do not appear to represent a significant improvement over using Log K_{ow}. Although the use of a computer program such as EPIWIN can reduce discrepancies in how $^1\chi$ are calculated, the use of polar correction factors appears to be somewhat limited in applicability to groups of chemicals with similar structure and functional moieties. These limitations notwithstanding, the finding that molecular topology combined with polarity correction factors correlate with BTFs suggests that other shape and polarity/ electrostatic descriptors should be examined.

REFERENCES

Birak, P., J. Yurk, F. Adeshina, M. Lorber, K. Pollard, and S. Kroner. 2001. Travis and Arms revisited: a widely used bioconcentration algorithm. *Toxicology and Industrial Health,* 17 (in press).

Dowdy, D.L., T.E. McKone, and D.P.H. Hsieh. 1996. Prediction of chemical biotransfer of organic chemicals from cattle diet into beef and milk using the molecular connectivity index. *Environmental Science and Technology,* 30: 984-989.

Fries, G.F., D.J Paustenbach, D.B. Mather, and W.L. Luksemburg. 1999. A congener specific evaluation of transfer of chlorinated dibenzo-*p*-dioxins and dibenzofurans to milk of cows following ingestion of pentachlorophenol-treated wood. *Environmental Science and Technology,* 33:1165-1170.

Kier, L.B., and L.H. Hall. 1986. *Molecular Connectivity in Structure-Activity Analysis*. Research Studies Press: Letchworth, England.

MacKay, D., W.Y. Shiu, and C.K. Ma. *Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals.* Lewis Publishers: Chelsea, MI.

McLachlan, M.S. 1993. Mass balance of polychlorinated biphenyls and other organochlorine compounds in a lactating cow. *Journal of Agricultural and Food Chemistry, 3:474-480.*

Meylan, W., P.H. Howard, and R.S. Boethling. 1992 Molecular topology/fragment contribution method for predicting soil sorption coefficients. *Environmental Science and Technology,* 26:1560-1567.

Randic, M. 1975. On the characterization of molecular branching. *Journal of American Chemical Society,* 97:6609-6615.

Randic, M. 2001. The connectivity index 25 years after. *Journal of Molecular Graphics and Modelling,* 20:19-35.

Sabjlic, A., and M. Protic. 1982. Molecular connectivity: a novel method for prediction of bioconcentration factor of hazardous chemicals. *Chemico-Biological Interactions,* 42:301-310.

Sabjlic, A. 1987. On the prediction of soil sorption coefficients of organic pollutants from molecular structure: application of molecular topology model. *Environmental Science and Technology,* 21:358-366.

Thomas, G., A.J. Sweetman, W.A. Ockenden, D. Mackay, and K.C. Jones. 1998. Air - pasture transfer of PCBs. *Environmental Science and Technology*, 32:936-942.

Travis, C.C., and A.D. Arms. 1988. Bioconcentration of Organics in Beef, Milk, and Vegetation. *Environmental Science and Technology*, 22: 271.

Travis, C.C., and S.T. Hester. 1991. Global chemical pollution. *Environmental Science Technology*, 25:814-819.

U.S. ACE (Army Corps of Engineers). 1996. *Risk Assessment Handbook, Volume II: Environmental Evaluation*. EM 200-1-4. June.

U.S. EPA (Environmental Protection Agency). 1998. *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities*. EPA 530-D-98-001A. Solid Waste and Emergency Response. July.

U.S. EPA (Environmental Protection Agency). 2000. EPI Suite, PCKOCWIN. Software downloaded from http://www.epa.gov/opptintr/exposure/docs/episuite.htm.

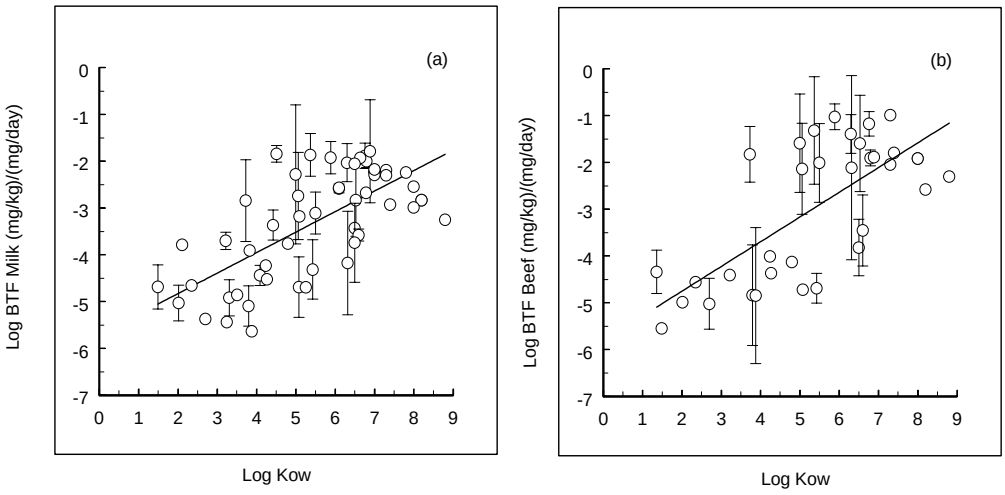

Figure 1. **Regression analysis of BTFs and log K_{ow} (Birak et al., 2002). Data for milk (a) and beef (b) are presented separately. Each point represents a mean BTF value per chemical. The error bars are the 95th percentile confidence interval from the mean. The r^2 for milk and beef are 0.50 and 0.46, respectively. For the milk regression, F = 44.28; for beef, F = 30.88.**

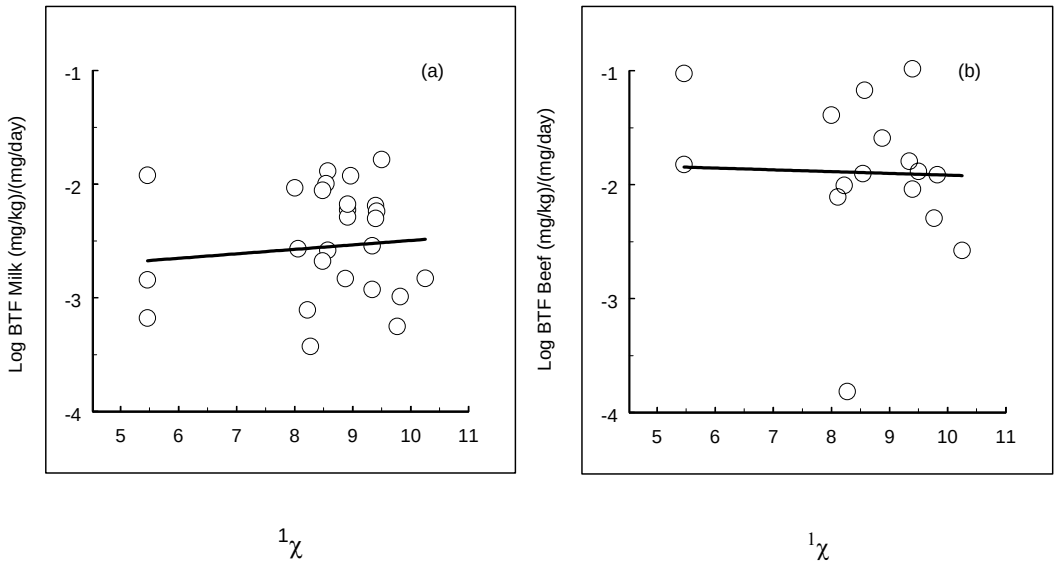

Figure 2. **Regression analysis of BTFs and $^1\chi$ for chemicals without polar correction factors in data set. Meylan et al. (1992) also performed a regression on nonpolar chemicals in their data set as a basis for their regression of molecular connectivity indices and K_{oc}. Data for milk (a) and beef (b) are presented separately. The r^2 for milk and beef are 0.01 and 0.06, respectively.**

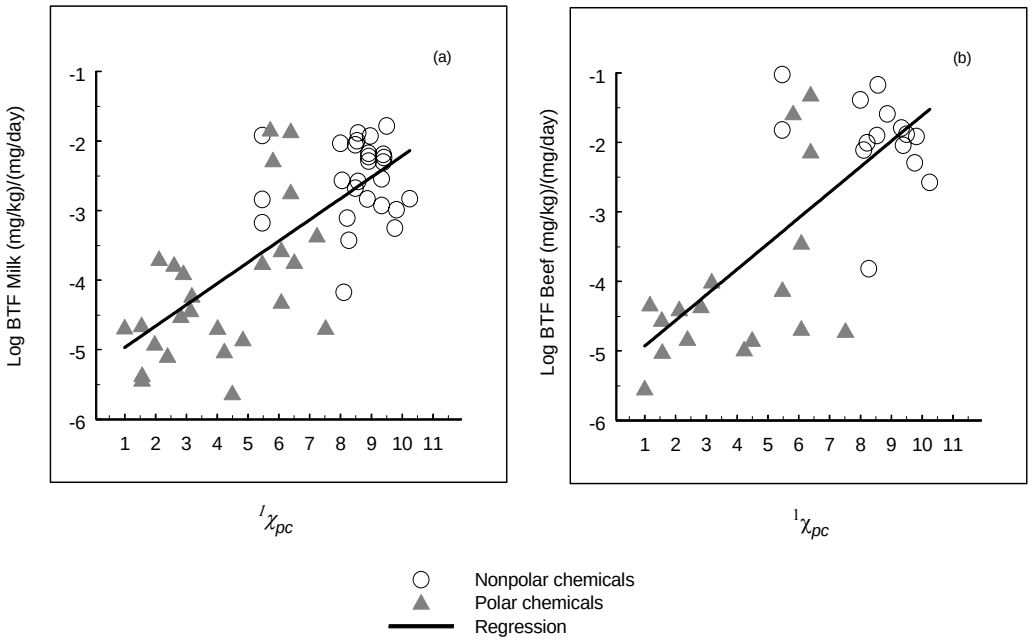

Figure 3. **Regression analysis of BTFs and $^{1}\chi_{pc}$ for all chemicals in data set. The chemicals without correction factors (○) and chemicals with polar correction factors (▲) are noted separately, but were both included in the linear regression. Data for milk (a) and beef (b) are presented separately. The r^2 for milk and beef are 0.55 and 0.54, respectively.**

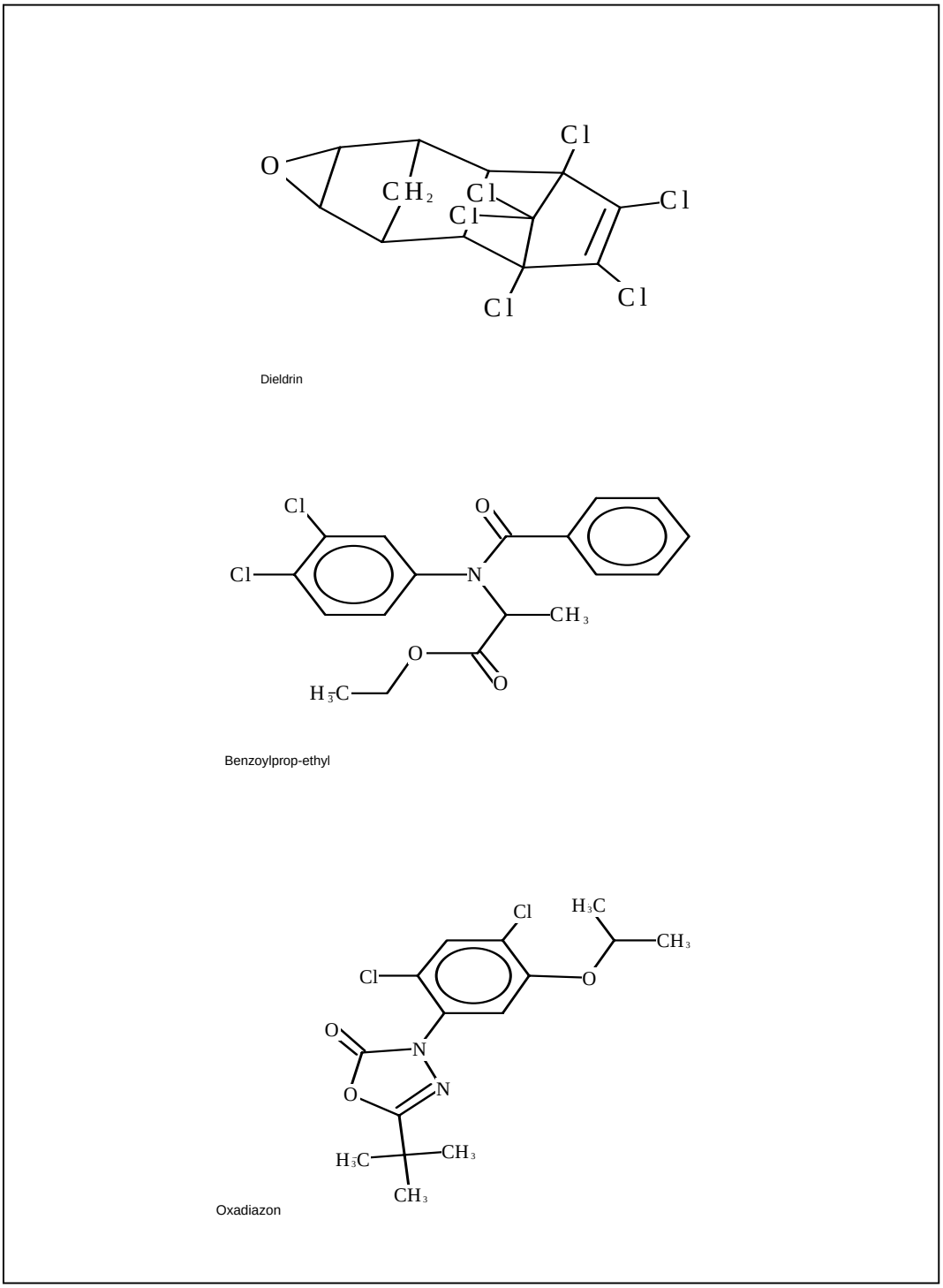

Figure 4. Examples of chemicals assigned different chemical functional groups by PCKOCWIN and Dowdy et al. (1996).

Table 1. Polar Correction Factors

	Fragment	Value
1.	Amine, aromatic (nonfused ring)	-0.7770[a]
2.	Ether, aromatic [-C-O-C-]	-0.6431[b]
3.	Nitro [-NO_2]	-0.6317
4.	N-CO-C (acetamide-type)	-0.8112
5.	Urea [N-CO-N]	-0.9222
6.	Nitrogen to carbon, aliphatic [-N-C]	-0.1242[c]
7.	Carbamate [N-CO-O] or [N-CO-S]	-1.0249
8.	Triazine ring	-0.7521
9.	Nitrogen-to-cycloalkane, aliphatic	-0.8220
10.	Uracil [-N-CO-N-CO-C=C- ring]	-1.8060
11.	Organic acid [-CO-OH]	-1.7512[a]
12.	Ketone [-C-CO-C-]	-1.2477
13.	Aliphatic alcohol [-C-OH]	-1.5193
14.	Nitrile/cyanide [-C≡N]	-0.7223[a]
15.	Thiocarbonyl [C=S]	-1.1002
16.	OrganoPhosphorus [P=S]	-1.2634[a,h]
17.	OrganoPhosphorus, aliphatic [P=O]	-1.6980[a,d]
18.	N-CO-O-phenyl carbamate	-2.0022
19.	Ether, aliphatic [-C-O-C-]	-1.2643
20.	Ester [-C-CO-O-C-] or [HCO-O-C]	-1.3089[g]
21.	Sulfone [-C-SO_2-C-]	-0.9945
22.	Azo [-N=N-]	-1.0277
23.	N-CO-O-N carbamate	-1.9200
24.	Aromatic ring with 2 nitrogens	-0.9650
25.	OrganoPhosphorus, aromatic [P=O]	-2.8781[a]
26.	Miscellaneous carbonyl [C=O] group	-1.2000[e]
27.	Pyridine ring (NO other fragments)	-1.7001[f]
28.	OrganoPhosphorous, aromatic [P=2]	-2.3300[h]
29.	Miscellaneous [S=O] group	-0.9000[i]

(continued)

Table 1. (continued)

[a] Counted only once per structure, regardless of number of occurrences.
[b] Either one or both carbons aromatic; if both carbons aromatic, cannot be cyclic.
[c] Any nitrogen attached to double bond is **not** counted; also carbonyl and thiocarbonyl are **not** counted as carbons.
[d] This is the **only** fragment counted, even if other fragments occur.
[e] Not included in regression derivation; estimated from other carbonyl fragments.
[f] A pyridine ring is counted **only** when no other fragments in this list are present.
[g] If more than one ester was present, Fragment 20 was used. When a single ester was present, the ester was treated as an ether and carbonyl group (Fragments 2, 19, 26) to be consistent with Dowdy et al. (1996).
[h] Dowdy et al. estimated a separate polar correction factor for aromatic organophosphorous groups (Fragment 28). The factor value is the average deviation of this set of compounds from the Dowdy et al.-derived curve.
[i] Polar correction factor used in PCKOCWIN but not presented in Dowdy et al. (1996) or Meylan et al. (1992).

Table 2. Chemicals with Unmodified Molecular Connectivity Indices ($^1\chi$)

CAS	Constituent	$LogK_{ow}$	$^1\chi_{calculated}$	$^1\chi_{reported}$*	Log Milk BTF		Log Beef BTF	
					Average	StDev	Average	StDev
50-29-3	DDT	6.5	8.9	8.9	-2.8	0.4	-1.6	0.5
57-74-9	chlordane	6.3	8.1	8.1	-4.2	0.6	-2.1	1.0
58-89-9	lindane	3.7	5.5	5.5	-2.8	0.4	-1.8	0.3
72-54-8	DDD	6.1	8.6	8.6	-2.6	0.0		
72-55-9	DDE	6.8	8.6	8.6	-1.9	0.1	-1.2	0.1
87-86-5	pentachlorophenol	5.1	5.5		-3.2			
118-74-1	hexachlorobenzene	5.9	5.5		-1.9	0.2	-1.0	0.1
309-00-2	aldrin	6.5	8.3	8.3	-3.4		-3.8	0.3
1746-01-6	TCDD, 2,3,7,8-	6.8	8.5	8.5	-2.0	0.1	-1.9	0.1
2385-85-5	mirex	6.9	9.5	9.5	-1.8	0.6	-1.9	
3268-87-9	OCDD	8.2	10.3		-2.8		-2.6	
8001-35-2	toxaphene	5.5	8.2	7.2	-3.1	0.2	-2.0	0.4
11097-69-1	aroclor 1254	6.3	8.0	8.4	-2.0	0.2	-1.4	0.2
19408-74-3	HxCDD, 1,2,3,7,8,9-	7.3	9.4		-2.2		-2.0	
35822-46-9	HpCDD, 1,2,3,4,6,7,8-	8.0	9.8		-3.0		-1.9	
39001-02-0	OCDF	8.8	9.8		-3.3		-2.3	
39227-28-6	HxCDD, 1,2,3,4,7,8-	7.8	9.4		-2.2			
40321-76-4	PeCDD, 1,2,3,7,8-	6.6	9.0		-1.9			
51207-31-9	TCDF, 2,3,7,8-	6.1	8.1		-2.6			
55673-89-7	HpCDF, 1,2,3,4,7,8,9-	8.0	9.3		-2.5			
57117-31-4	PeCDF, 2,3,4,7,8-	6.5	8.5		-2.1			
57117-41-6	PeCDF, 1,2,3,7,8-	6.8	8.5		-2.7			
57117-44-9	HxCDF, 1,2,3,6,7,8-	7.0	8.9		-2.2			
57653-85-7	HxCDD, 1,2,3,6,7,8-	7.3	9.4		-2.3		-1.0	
60851-34-5	HxCDF, 2,3,4,6,7,8-	7.0	8.9		-2.3			
67562-39-4	HpCDF, 1,2,3,4,6,7,8-	7.4	9.3		-2.9		-1.8	
70648-26-9	HxCDF, 1,2,3,4,7,8-	7.0	8.9		-2.2			

* 1χ values reported by Dowdy et al. (1996).

Table 3. Chemicals That Used Polar Correction Factors

CAS	Constituent	$\log K_{ow}$	$^1\chi$	$^1\chi_{pc}$	Polar Correction Factors (P_f)	$^1\chi_{pc}$ [a]	Polar Correction Factors (P_f)[a]	Log Milk BTF		Log Beef BTF	
								Average	StDev	Average	StDev
55-38-9	fenthion	4.1	7.5	3.1	28	3.1	28	-4.4	0.1		
56-38-2	parathion	3.8	8.5	2.9	3, 28			-3.9	0.0		
60-57-1	dieldrin	5.4	8.8	6.4	19	8.8		-1.9	0.2	-1.3	0.6
72-20-8	endrin	5.1	8.8	6.4	19	8.7		-2.7	0.5	-2.1	0.5
72-43-5	methoxychlor	5.1	10.0	7.5	2			-4.7	0.3	-4.7	
93-72-1	fenoprop (silvex)	3.8	6.9	2.4	2, 11	2.4	2, 11	-5.1	0.2	-4.8	0.5
93-76-5	2,4,5-T	3.3	6.5	2.0	2, 11	2	2, 11	-4.9	0.2		
94-74-6	MCPA	3.3	6.1	1.6	2, 11	1.6	2, 11	-5.4			
94-75-7	2,4-D	2.7	6.1	1.6	2, 11	1.6	2, 11	-5.4		-5.0	0.3
297-78-9	telodrin	4.5	8.1	5.7	19			-1.8	0.1		
314-40-9	bromacil	2.1	6.5	2.6	6, 10			-3.8	0.02		
1024-57-3	heptachlor epoxide	5.0	8.2	5.8	19	8.2		-2.3	0.7	-1.6	0.5
1918-00-9	dicamba	2.4	6.1	1.5	2, 11	1.6	2, 11	-4.7		-4.6	
1918-02-1	picloram	1.4	5.9	1.2	1, 11					-4.3	0.2
2921-88-2	chlorpyrifos	5.3	8.4	4.0	28	4	27, 28	-4.7			
19666-30-9	oxadiazon	4.8	10.1	5.5	1, 2, 7	4.2	2, 19, 26	-3.8		-4.1	
20354-26-1	methazole	3.2	7.5	2.1	1, 5, 6, 7			-3.7	0.1	-4.4	
22212-55-1	benzoylprop-ethyl	4.3	11.5	2.8	1, 6, 19, 26	3.1	1, 19, 26	-4.5		-4.4	
23950-58-5	kerb	3.5	7.3	4.8	6, 26	4.8	6, 26	-4.9			
35367-38-5	di-flubenzuron	3.9	10.0	4.5	1, 5, 26			-5.6		-4.8	0.7
51630-58-1	fenvalerate	4.4	14.5	7.2	2, 14, 19, 26	7.3	2, 14, 19, 26	-3.4	0.2		
52315-07-8	cypermethrin	6.6	13.3	6.1	2, 19, 26			-3.6	0.1	-3.4	0.4
52645-53-1	permethrin	6.5	12.4	6.5	2, 19, 26			-3.70.4			
52756-22-6	flamprop-isopropyl	4.2	11.8	3.2	1, 6, 19, 26	3.4	1, 19, 26	-4.2		-4.0	
52918-63-5	deltamethrin	5.4	13.3	6.1	2, 19, 26			-4.3	0.3	-4.7	0.2
53780-34-0	mefluidide	2.0	8.9	4.2	1, 4, 29			-5.0	0.2	-5.0	
55511-98-3	buthidazole	1.5	7.8	1.0[b]	1, 5, 6, 13, 24			-4.7	0.2	-5.5	

[a] Data reported in Dowdy et al. (1996).
[b] Overcorrection adjustment to lower limit $^1\chi_{pc}$.