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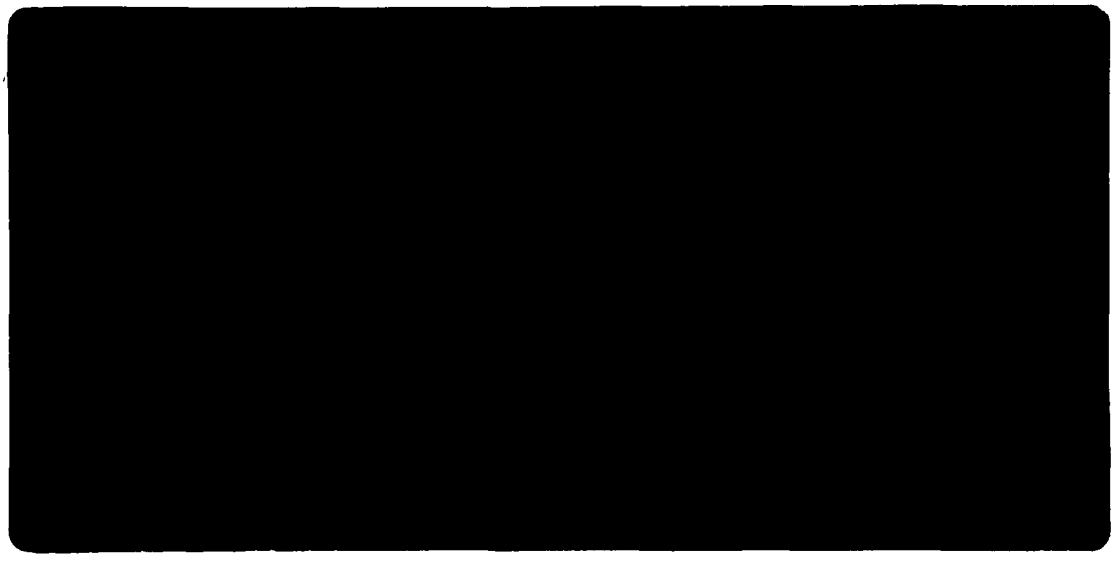

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AN IMPROVED METHOD FOR CALCULATING BIOCONCENTRATION FACTORS FROM STRUCTURE

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An Improved Method for Calculating Bioconcentration Factors from Structure

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AN IMPROVED METHOD FOR CALCULATING BIOCONCENTRATION FACTORS FROM STRUCTURE

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ABSTRACT

The relationship between bioconcentration and lipophilicity has numerous exceptions. Several medium and high molecular weight solutes bioconcentrate either to a small extent or not at all. Most of these exceptions cannot be anticipated, which greatly increases the uncertainty of environmental assessment. We have been able to attribute most of the exceptions to the relatively low solubility of these compounds in lipid. Correction for this effect leads to a surprisingly accurate (r=0.95) structure-bioconcentration equation. In addition, we have obtained preliminary evidence for the importance of lipid solubility in aquatic toxicity.

KEYWORDS

Aquatic Organisms Bioconcentration Lipid

INTRODUCTION

The bioconcentration factor in fish (BCF, the fish:water concentration ratio of a contaminant) is a major consideration in establishing health and environmental criteria. For simple hydrophobic compounds, BCF increases with K_{ow}, the octanol:water partition coefficient. For larger more complex substrates, BCF levels off and then falls with increasing K_{ow}. High K_{ow} compounds such as octachloronaphthalene and octachlorodibenzodioxin do not bioconcentrate at all (1,2), and a similar trend is observed for many dyes (3).

An enormous amount of work has gone into understanding why the BCF-K_{ow} relationship breaks down. It has been suggested that low BCFs occur because of (a) steric effects (the molecule is too big to pass through the gill membrane), (b) low lipid solubility, (c) slow uptake rates, (d) low bioavailability due to sorption and complexation with dissolved organics, (e) feces elimination, (f) growth dilution, and (g) metabolism. All of these possibilities are valid, at least within limited groups of compounds. For example, metabolism is important for some polynuclear aromatics, but usually not for polychloro derivatives.

The log BCF-log K_{ow} profile curves at about log $K_{ow} \approx 5.5$ and compounds of greater log K_{ow} are termed superlipophilic. From a study of several compounds of varying size, Opperhuizen et al. (2) concluded that compounds of cross-section greater than 9.5Å are too large to cross the gill membrane. At some level this must be true; clearly, very large compounds cannot permeate a membrane of fixed pore size. However, the 9.5Å limit cannot be the sole cause of reduced BCFs, since large differences in BCF also occur between compounds of similar cross-section. For example, hexabromobenzene does not bioconcentrate at all, whereas a bromobiphenyl of similar cross-section bioconcentrates appreciably (1). Also, many disperse dyes have low BCFs even though their cross-section is well below the 9.5Å cut-off. Hence, cross-sectional effects cannot be implicated in all instances of reduced BCFs.

Gobas, Mackay and co-workers (1) have reviewed possibilities (a)-(g) and have convincingly argued that low lipid solubility is the most likely reason for the curvature. They reason that compounds that are miscible with *both* octanol and lipid follow the BCF-K_{ow} correlation. Thermodynamically, $BCF = \gamma_{water}/\gamma_{lipid}$, and $K_{ow} = \gamma_{water}/\gamma_{octanol}$, where γ is the activity coefficient. Thus, if γ_{lipid} and $\gamma_{octanol}$ are roughly constant, BCF will be related to K_{ow} since they are both governed by γ_{water}. Gobas et al. (4) reason that for compounds that lie beyond the cut-off, $\gamma_{octanol}$ and γ_{lipid} are no longer constant, and the log BCF-log K_{ow} relationship ceases to be linear.

Many other workers have noted the inadequacy of octanol in modeling lipid behavior. Chiou (5) used triolein:water partition coefficients (K_{tw}) in place of K_{ow} to model BCF. Triolein is a better lipid substitute than octanol. A slight leveling off of K_{tw} was observed for

large compounds, but the decrease observed with BCF was not reproduced. Gobas et al. (6) studied partitioning between L-a-phosphatidylcholine dymyristoyl membrane vesicles (MW) and water and found that plots of log K_{MW}-log K_{ow} leveled off at log K_{ow}=6-7. Again, K_{MW} values remained high for hexabromobenzene and some dyes that do not bioconcentrate. Both triolein and membrane vesicles are chemically closer to lipid than is octanol, but since they lack the physical structure of fish lipid, they are unable to reproduce the *drop* in BCF observed for large compounds.

RESULTS AND DISCUSSION

We have extended Gobas et al.'s (1) low lipid solubility hypothesis and have been able to develop what appears to be the most accurate structure-BCF relationship reported to date for compounds of widely differing structure.

The standard BCF-K_{ow} equation takes the form

$$\log BCF = c_1 + c_2 \log K_{ow} \quad (1)$$

where c_1 and c_2 are constants. In principle, c_2 should equal one (7), whereupon eq. (1) reduces to

$$\log BCF = c_1 + \log K_{ow} \quad (2)$$

Writing BCF and K_{ow} in terms of activity coefficients leads to

$$\log(\gamma_{water}/\gamma_{lipid}) = c_1 + \log(\gamma_{water}/\gamma_{octanol}) \quad (3)$$

which rearranges to

$$c_1 = \log(\gamma_{octanol}/\gamma_{lipid}) \quad (4)$$

Substituting c_1 in eq. (2) leads to

$$\log BCF = \log(\gamma_{octanol}/\gamma_{lipid}) + \log K_{ow} \quad (5)$$

For compounds that follow eq. 1, the $\log(\gamma_{octanol}/\gamma_{lipid})$ term is approximately constant. For large compounds, it is likely that γ_{lipid} changes much more sharply than $\gamma_{octanol}$ since lipid is much more structured than octanol (1). Other factors being equal, a structured or polymeric matrix tends to be much more non-ideal (as a solvent) than a simple monomeric liquid.

To a good approximation, the $\gamma_{octanol}/\gamma_{lipid}$ term in eq. 5 is a ratio of solubilities. The two major factors that govern solubility are the energy required to form a cavity in the solvent, and the solute-solvent interaction (8). The energy of cavitation is particularly important for large compounds since the solvent needs to reorganize around the solute to a greater degree. Owing to its tighter physical structure, reorganization within the lipid must, necessarily, require more energy than that within octanol, which is a much smaller entity.

Recasting eq. 5 in terms of solubilities leads to

$$\log BCF = \log S_{lipid} - \log S_{octanol} + \log K_{ow} \quad (6)$$

Since S_{lipid} data are generally unavailable, let us assume that $\log S_{lipid}$ is linearly related to $\log S_{octanol}$. Equation 6 now becomes

$$\log BCF = c_3 + c_4 \log S_{octanol} + \log K_{ow} \quad (7)$$

For small compounds, $S_{octanol}$ should be essentially constant since $\gamma_{octanol}$, the activity coefficient in octanol, will approximate 1, and eq. 7 will take the form of eq. 2. For large compounds, $S_{octanol}$ should decrease and give rise to the observed decrease in BCF.

BCF and related data were collected from the literature for 36 compounds varying in size and functionality. BCFs calculated from eq. 1 (c_1=-0.78; c_2=0.75) are compared to measured values in Fig. 1. The quality of fit is poor (r=0.74) since dyes and other large compounds deviate substantially. Equation 7 with c_3=-1.18 and c_4=0.782 gives a much better fit (r=0.95) as shown in Fig. 2 (9).

Since bioconcentration is related to aquatic toxicity for narcotic chemicals, one might expect lipid solubility considerations to also be important in this area. A notable difference between Figures 1 and 2 is that even compounds of low log K_{ow} (to which the cut-off does not apply) are better correlated by Figure 2. The implication is that the scatter in Figure 1 is caused

substantially by differences in lipid solubility. This suggests that for narcotic chemicals where toxicity is frequently related to BCF, the quality of LC_{50}-K_{ow} relationships should be improved markedly by including a term in octanol solubility. This should be particularly apparent for compounds that tend to be non-ideal in lipid or octanol.

Nitro-compounds fall into this category. Deneer et al.'s (10) toxicity data for guppies are provided in Fig. 3. There is, essentially, no relationship with K_{ow}. Inclusion of a log $S_{octanol}$ term leads to the Fig. 4 relationship, which is much improved despite the residual scatter. Thus, our hypothesis is supported by bioconcentration and (to a lesser extent) aquatic toxicity data, and has implications in both areas.

In sum, we hypothesize that the physical rather than the chemical structure of lipid dictates the extent to which uptake will occur for compounds that are non-ideal in lipid. Although our work only applies to aquatic organisms, there is evidence that large compounds do not concentrate in man (11). These relationships will be discussed along with their implications for the pulp and paper industry.

LITERATURE CITED

1. Gobas, F.A.P.C.; Shiu, W.Y.; Mackay, D. in "QSAR in Environmental Toxicology-II". K.L.E. Kaiser Ed. Reidel, Dordrecht, Holland 1987.

2. Opperhuizen A.; v.d.Velde, E.W.; Gobas, F.A.P.C.; Liem, D.A.K.; v.d.Steen, J.M.D. *Chemosphere* 1985, **14**, 1871.

3. Anliker, R.; Moser, P. *Ecotoxicol. Environ. Saf.* 1987, **13**, 43.

4. Gobas, F.A.P.C.; Clark, K.E.; Shiu, W-Y.; Mackay, D. *Environ. Toxicol. Chem.* 1989, **8**, 231.

5. Chiou, C.T. *Environ. Sci. Technol.* 1985, **19**, 57.

6. Gobas, F.A.P.C; Lahittete, J.M.; Garofalo, G.; Shiu, W.Y.; Mackay, D. *J. Pharm. Sci.* 1988, **77**, 265.

7. Mackay, D. *Environ. Sci. Technol.* 1982, **16**, 274.

8. Yalkowsky, S.H.; Banerjee, S. "Aqueous Solubility: Methods of Estimation for Organic Compounds". Marcel Dekker, NY 1992.

9. Banerjee, S.; Baughman, G.L. *Environ. Sci. Technol.* 1991, **25**, 536.

10. Deneer, J.W., Sinnige, T.L., Seinen, W. and Hermens, J.L.W. *Aquatic Toxicol.* 1987, **10**, 115.

11. Geyer, H.J.; Scheunert, I.; Korte, F. *Chemosphere* 1987, **16**, 239.

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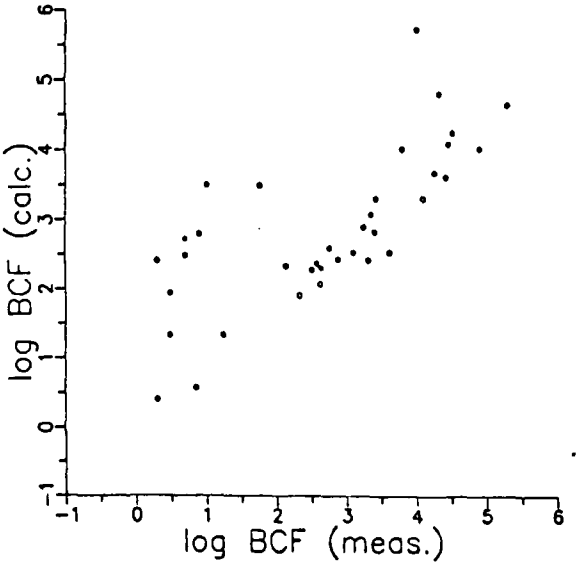


Fig. 1 Comparison of measured BCFs with estimates from eq 1

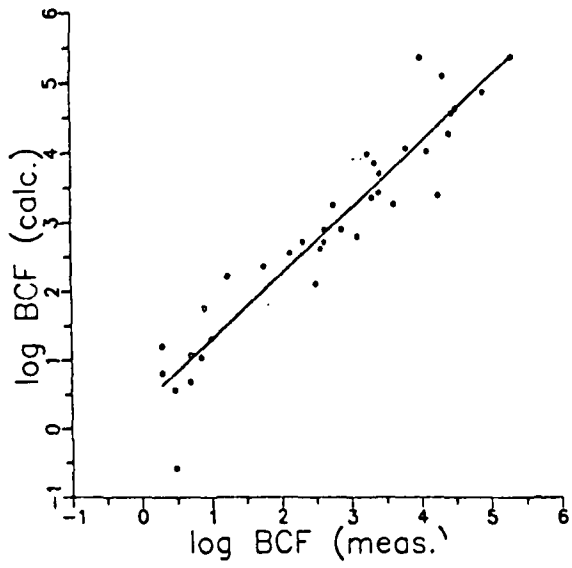


Fig. 2 Comparison of measured BCFs with estimates from eq 7

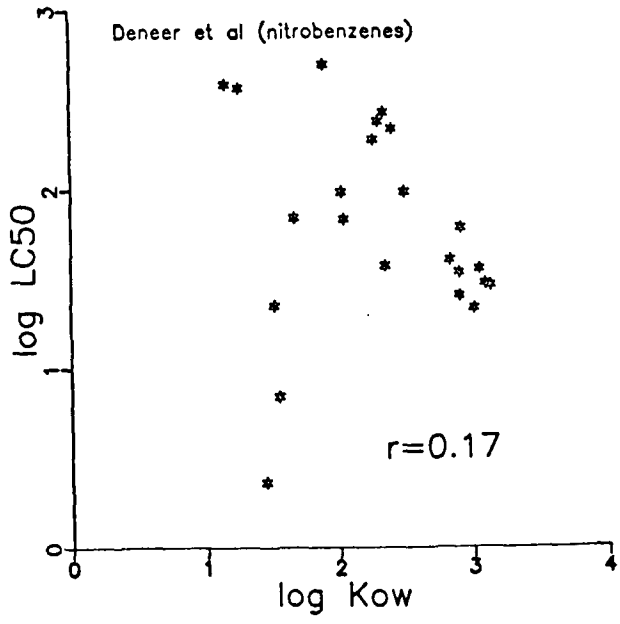
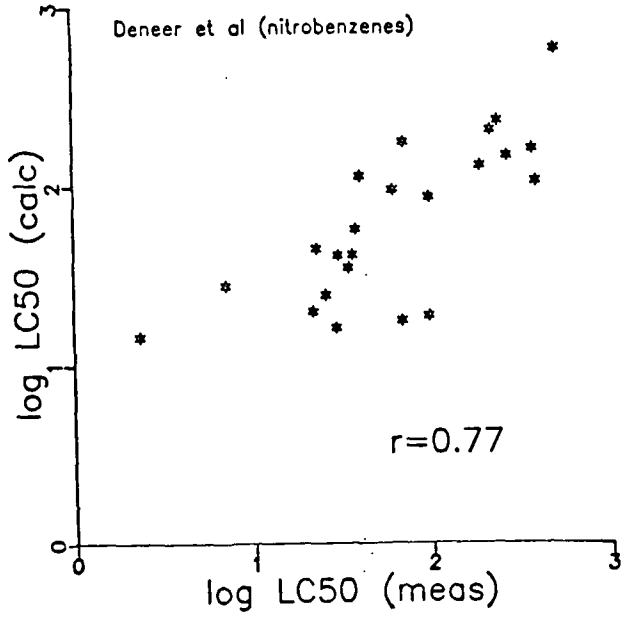


Fig. 3 Toxicity of nitrobenzenes towards the guppy uncorrected for lipid solubility



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