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RESEARCH COMMUNICATION

Bioconcentration modelling of alcohol ethoxylates by quantitative structure activity relationship approach: a first look

S.P. Ratnayake*
Sri Lanka Institute of Nanotechnology, Nanotechnology and Science Park, Mahenwatte, Pitipana, Homagama.

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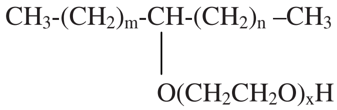
Abstract: Alcohol ethoxylates (AEs) are a class of nonionic surfactants. This study overviewed the environmental health effects and quantitative structure activity relationships generated for bioconcentration factors of seventeen alcohol ethoxylates, which are currently in commercial use as household detergents. The X-data matrix consisted of 560 molecular descriptors which was calculated by the DRAGON® molecular modelling environment. The logarithms of bioconcentration factors calculated by EPI® toxicology estimation suite were used as the response factor. Out of two quantitative structure activity relationships generated, one exhibited a model fit of 0.95 and a power of prediction of 0.42. The second was superior in terms of model fit, which was 0.92 and a power of prediction of 0.7. The predicted bioconcentration values exhibited a minimum percentage error of 10 % and a maximum of 37 %. Prediction accuracy became better with increasing bioconcentration factor. A convincing relationship between bioconcentration and calculated molecular descriptors for alcohol ethoxylates was obtained, hence the capability of quantitative structure activity relationship approach for modelling the environmental behaviour of AEs at a fully empirical level was demonstrated. Constructing a quantitative structure activity relationship having a realistic predictive power over a variety of commercial AEs may be challenging, but with the use of finely tuned chemical descriptors and better modelling tools it could be possible to accurately and rapidly predict toxicities as well as the environmental behaviour of AEs.

Keywords: Bioconcentration, molecular descriptors, quantitative structure activity relationship.

INTRODUCTION

Alcohol ethoxylates (AEs) are a subtype of nonionic surfactants. Most AEs contain a hydrophobic alkyl chain attached to a hydrophilic ethylene oxide (EO) chain by an ether linkage (Figure 1). The AE class also includes alcohol propoxylates and butoxylates. The general formula for an AE can be expressed as $CH_3–(CH_2)x–O–(CH_2CH_2O)y–H$ (Boeije *et al*., 2006).



$$CH_3\text{-}(CH_2)_m\text{-}\underset{\displaystyle O(CH_2CH_2O)_xH}{\underset{|}{CH}}\text{-}(CH_2)_n\ –CH_3$$

Figure 1: Structure of Softanol® : a commercial secondary AE (ENEOS, 2011).

AEs are commonly used to a larger extent in laundry detergents and all-purpose cleaners, and to a lesser extent in agriculture, cosmetics, and paper production (Talmage, 1994; HERA, 2009). In 2002 over 0.5 million tons of fatty alcohols and fatty-alcohol-based surfactants were estimated to have been consumed in North America, of which approximately 67 % consisted of AEs or sulfated forms of AEs (Modler *et al*., 2002). The solubility of AEs in water is due to the presence of a strong hydrophilic group (Aveyard, 1984; Swisher, 1987). A mixture of AEs could contain more than 100 different components, which are called ethoxymers. This is due to the presence of many possible combinations of lengths of alkyl chains and the variation of the degree of ethoxylation (Salager, 2002).

Upon entry to the environment, AEs go through processes such as abiotic degradation, adsorption to particles and microbial degradation. Volatilisation is highly unlikely due to the extremely low vapour

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* samanthaR@slintec.lk

pressures (Balson *et al*., 2002). The usual disposal pattern for most AEs is through a drainage system. Therefore, their biodegradation occurs mostly within the sewage processing system (Nielson *et al*., 2002). Studies have shown that a high percentage of AEs released to water are adsorbed to soil particles, and through the process of a sewage treatment plant, undergo anaerobic decomposition. The remaining portion in the aqueous solution undergoes aerobic decomposition (HERA, 2002). Aerobic microbial biodegradation happens to be the most significant process concerning the fate of AEs. Alcohol ethoxylates with multiple branches have shown a slower degradation rate than linear AEs (Birch, 1984; Cardellini & Ometto, 2001). Alcohol ethoxylates can produce intermediate degradation products, which may include free fatty alcohols, polyethylene glycols and carboxylic fatty acids. Literature suggests that AEs are absorbed rapidly through the gills of fish and are rapidly metabolised and eliminated (Bishop & Maki, 1980; Newsom *et al*., 1995; Kiewiet *et al*., 1997).

The tendency of a substance to bioconcentrate in aquatic organisms is usually expressed as its bioconcentration factor (BCF) (Cummins *et al*., 1996; Pavan *et al*., 2008). BCF is defined as the ratio of the concentration of a chemical in an aquatic organism to the concentration of the chemical in surface water, sediment, or soil (USEPA, 1999). It is a unitless quantity. It has been observed that, with the increasing length of the hydrophobic chain, the potential of bioconcentration increases for AEs (Balson *et al*., 2002). Further, increasing the length of the hydrophilic group decreases the hydrophobicity and results in a reduction of the BCF. When hydrophobicity was increased, higher uptake rates and BCFs for AEs have been observed (Balson *et al*., 2002). It has been concluded that AEs are not stored in the fish, yet are subjected to rapid biotransformation within their bodies (Tolls *et al*., 2000). The resultant metabolites of biotransformation were less toxic than the parent compounds. Most BCF values reported for AEs are less than 300, which is a safe number (Tolls *et al*., 2000). Octanol water partition coefficient (Log K_{ow}) values of most of the AEs have been estimated to range between 3 and 7, implying the bioaccumulation of some AEs (Muller *et al*., 1999).

The toxicity of an individual AE homologue is a function of its chemical structure and the toxicity has been shown to increase with increasing alkyl chain length and decreasing ethoxylate chain length (Macek & Krzeminski, 1975; Bishop & Perry, 1981; Yamane *et al*., 1984; Dorn *et al*., 1997; Lizotte *et al*., 1999; Raney, 2000). Linear AEs have been found to be more toxic than branched AEs (Dorn *et al*., 1997; Ghirardini *et al*., 2001). In primary and secondary alcohols, the location of attachment between the alcohol and ethoxylate chains have also been indicated to affect AE toxicity (Kurata *et al*., 1977). The hardness and temperature of water as well as the homologue distributions in the ethoxylate chain have also been identified to moderate AE toxicity (Lewis & Hamm, 1986; Garcia *et al*., 1996). The effects of AEs on reproduction of fish have been demonstrated by previous studies. However, the effects have been shown to be reversible. Change in the reproduction patterns was identified as the most sensitive indicator of AE surfactant effects on fish (Tovell *et al*., 1975; Dorn *et al*., 1997).

Current scientific data on the toxic effects of surfactants such as AEs are based mostly on laboratory experiments on a very few species of animals. Therefore, deriving information from existing laboratory data for environmental modelling is challenging. This study attempted to derive a model for BCF of AEs with the quantitative structure activity relationship (QSAR) approach.

METHODOLOGY

Twenty one AE structures were converted to simplified molecular input line entry system (SMILE) formulas. The derivation was achieved by EPIWEB 4.1 developed by the United States Environmental Protection Agency (USEPA-EPI, 2012). SMILEs data were used for the calculation of 560 molecular descriptors using the Dragon 1.0 molecular modelling environment, developed by the Virtual Computational Chemistry Laboratory of Milano Chemometrics and QSAR Research Group (VCC, 2011). SMILEs are provided in Table I of the Appendix. A brief description and the values of some selected descriptor types are provided in Table II of the Appendix (Todeschini & Consonni, 2000). BCFBAF, a sub-programme of EPI software suite was utilised to estimate the BCF and its logarithmic value of each compound for fish. This estimation method is currently used in the USEPA developed physico-chemical property and environmental fate estimation programme. Principle component analysis (PCA) and orthogonal partial least squares (OPLS) were used for the QSAR generation using the statistical software package SIMCA P+ 12.0. Four AEs were used as the prediction group against the generated QSAR models.

RESULTS AND DISCUSSION

The complete descriptor dataset was analysed with PCA (Mol. ID: 1 – 21 in Table I of Appendix). Five compounds (13, 14, 15, 18 and 19 in Table I of Appendix) were identified as vastly different from the rest of the group according to the hotelling rules of SIMCA, hence were excluded from further analysis. The refined overall set exhibited a segregation based on log BCF values (Y-response) according to PCA scores (Figure 2A). Multiple relationships seemed to exist between the molecular descriptors and respective log BCF values. The scores on two principle components (PC) exhibited two distinctive groups (denoted as G-1 and G-2 in Figure 2A and Table 1).

In order to better perceive the relationships between chemical descriptors and log BCF values, G-1 and G-2 were separately analysed by OPLS, hence two QSARs were obtained. G-1 exhibited a weak correlation with model fit (R2) = 0.95 and power of prediction (Q2) = 0.42. The scores on two PCs are shown in Figure 2B. Further, G-2 exhibited a decent correlation, also on two PCs in the OPLS analysis, with R2 = 0.92 and Q2 = 0.7. Unlike G-1, OPLS score positioning also exhibited a pattern of increasing log BCF from left to right, hence indicating a more systematic correlation than in G-1 (Figure 2C). The observed *vs* predicted log BCF values followed a linear pattern, which was also a sign of acceptable model fit (Figure 2D). Four unknown compounds with analogous

Table 1: Compound identification of QSAR-1 and QSAR-2

Group/QSAR	Compound ID
G-1/QSAR-1	3, 4, 6, 8, 9 10, 12, 15, 16, 19
G-2/QSAR-2	1, 2, 5, 7, 11, 20, 21

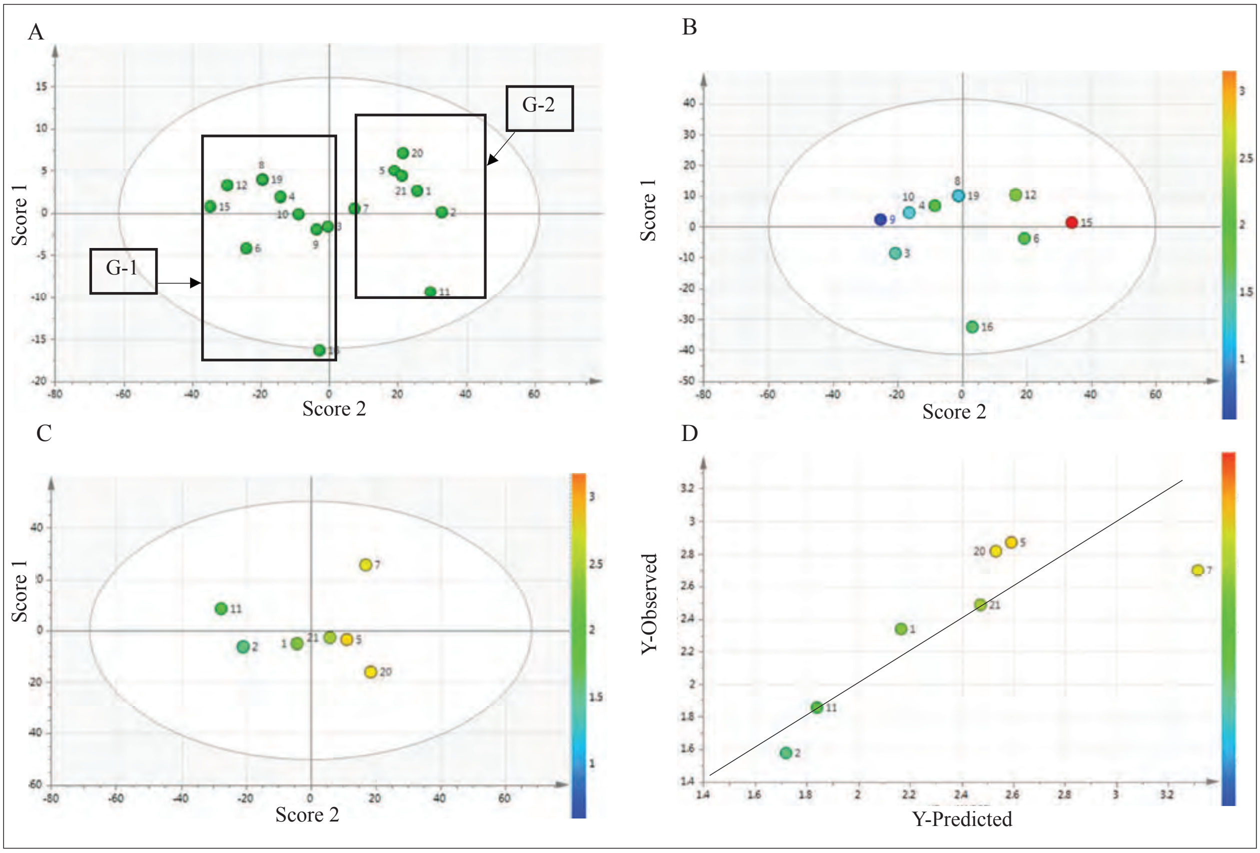

Figure 2: (A) PCA scores exhibiting two groups of AEs (denoted as G-1 and G-2); (B) OPLS scores of G-1; (C) OPLS scores of G-2; (D) observed *vs* predicted bioconcentration for the G-2 model set of AEs. Compounds colour coded according to BCF.

physico-chemical characteristics (denoted as compound IDs: 1.1, 1.2, 1.3 and 1.4 in Table 2) were predicted against both generated QSARs (will be denoted as G-1 – QSAR-1 and G-2 – QSAR-2). QSAR-1-predicted log BCF values were much lower than those obtained by the log K_{ow} based USEPA-EPI programme. QSAR-2-predicted values were observed to be much more accurate. In both QSARs a higher accuracy was observed with increasing log BCF value. For compound ID 1.1 the percentage error was 37 % and for compound ID 1.4 it was 10 %. The observed *vs* predicted log BCFs are given in Figure 3 for QSAR-1 and in Figure 4 for QSAR-2. The exact values predicted from both QSARs are given in Table 2.

Table 2: Predicted log BCF values for designated compounds

ID	SMILE	CAS No [+]	USEPA based log BCF[*]	QSAR-1 predicted log BCF	QSAR-2 predicted log BCF
1.1	CCCCCCCOCC	70879-83-3	1.655	0.267	0.698
1.2	CC(C)CC(C)CC(C)CCCOCCOCCOCCOCCOCCO	68439-54-3	1.771	0.635	1.342
1.3	CCCCCCCCCCCCOCC	68526-94-3	1.901	0.979	1.947
1.4	CCCCCCCCCCCCCCCCCOCC	69227-20-9	3.074	1.282	2.995

[+] Chemical Abstracts Service registry number

[*] EPI version 4.1 developed by the USEPA

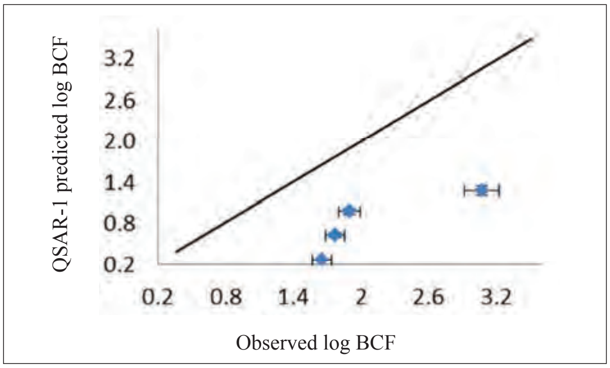

Figure 3: EPI-based *vs* QSAR-1 predicted log BCF (solid line represents a 100 % match of predicted log BCF to observed log BCF)

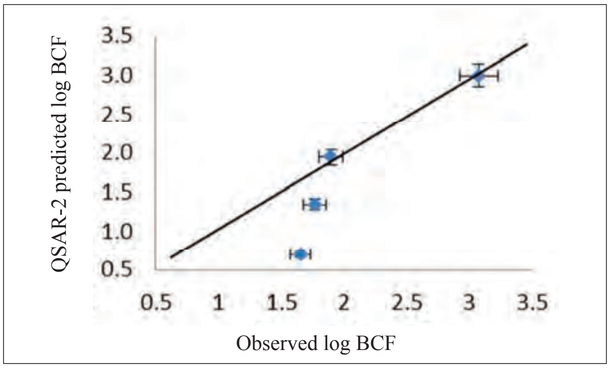

Figure 4: EPI-based *vs* QSAR-2 predicted log BCF

In comparison to this study, a QSAR constructed by Wong *et al*. (1997) for acute toxicities of AEs towards two aquatic organisms yielded R2 of 0.98 and 0.99 for *Daphnia magna* and *Pimephales promelas*, respectively. Nine AEs were used correlating alkyl and ethoxylate chain lengths to toxicity and the correlations were superior compared to that of the present study (0.92). Willing (2000) demonstrated a relationship for algae where R2 was 0.994. Another QSAR based relationship by Wind and Belanger (2005) produced a QSAR (n = 6) with a R2 of 0.586.

CONCLUSION

AEs seem to have lesser toxicities in both long and short run than other organic chemical compounds of wide use such as pesticides and halogenated flame retardants. The toxicity of AEs seems to increase with increasing alkyl chain length and decreasing ethoxylate chain length.

The QSAR presented by this study signifies the possibility of the QSAR approach for modelling the environmental behaviour of AEs. This study demonstrates that structure-derived parameters such as molecular descriptors of AEs could be successfully correlated to activity parameters such as BCF at a fully empirical level. One of the developed QSAR models exhibited a decent model fit and predictive power. However, more AEs would have to be included for the generation of a QSAR relationship that can be used to predict the behaviour of chemically diverse AEs. Since the end result of this type of a model is governed by purely mathematical quantities, for the moment, predictions on environmental fate may have to be made equally based on model predictions and experimental data. Considering the vast number of variables that govern the behaviour of AEs, this type of models have always been complex and challenging to interpret. Besides the inclusion of chemically diverse AEs in the modelling process, additional data such as biodegradation rate and adsorption capability must be studied in detail to generate better elucidations on the complete mechanisms of environmental fate and effects exerted by AEs. With such knowledge it will be possible to select an AE surfactant for each purpose with minimal persistence, bioconcentration potential and toxicity.

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APPENDIX

Table I: Chemical and toxicological data of AEs, used for model construction

Mol. ID	BCF	SMILE *	CAS No
1	2.337	CCCCCCCCC=CCCCCCCCCOCCOCCOCCOCCOCCO	61791-28-4
2	1.577	CCCCCCCCCCOCC	66455-15-0
3	1.442	CCCCCCCCCCOCCOCCOCCOCCO	68002-97-1
4	1.909	CCCCCCCCCCCCOCCOCCOCCOCCOCCO	68131-39-5
5	2.873	CCCCCCCCCCCCCCOCC	68154-96-1
6	1.734	CCCCCCCCCCCCCCOCCOCCOCCOCC(C)OC(C)CO	68154-98-3
7	2.699	CCOCCCCCCCCC=CCCCCCCCC	68155-01-1
8	1.183	CCCCCCCCCCCCCCOCCOCCOCCOCCOCCO	68213-23-0
9	0.613	CCCCCCCCOCCOCCOCCOCCOCCO	68439-45-2
10	1.261	CCCCCCCCCCOCCOCCOCCOCCOCCO	68439-46-3
11	1.853	CCC(CCCCCCCC)OCC	68551-14-4
12	2.337	CCC=CCCCCCCCCCCCCCCOCCOCCOCCOCCOCCO	68920-66-1
13	2.313	CCCCCCCCOCC	69013-19-0
14	2.303	CCCCCCCCCOC	71243-46-4
15	3.439	CCCCCCCCCCCCCCCCCCOCCOCCOCCOCC(C)OCC(C)O	73049-34-0
16	1.620	C(C)CC(C)CC(C)C(C)COCCOCCOCCOCCO	106232-83-1
17	2.328	C(C)CC(C)CC(C)CC(C)CCOCC(CC)OCC(CC)OCC(CC)OCCOCCOCCO	111905-53-4
18	1.264	C(C)CC(C)CC(C)CC(C)CCOCCOCCOCCOCC(C)OCC(C)O	111905-54-5
19	1.183	CCCCCCCCCCCCCCOCCOCCOCCOC(C)COC(C)CO	139626-71-4
20	2.900	CCCCCCCCCCCCCCCCOCC	68002-96-0
21	2.800	CCCCCCCCCCCCCCOCC	68951-67-7

* SMILE – simplified molecular input line entry system

Table II: A sample of calculated molecular descriptors

Mol. ID	Mv	nSK	Sv	RBF	DELS
1	0.503	15	22.6	0.273	4.30
2	0.502	13	19.6	0.263	4.21
3	0.518	23	31.6	0.333	20.2
4	0.519	28	38.4	0.342	24.4
5	0.503	17	25.7	0.280	4.36
6	0.518	32	44.5	0.318	26.6
7	0.512	21	31.3	0.283	6.01
8	0.518	30	41.5	0.342	24.5
9	0.521	24	32.3	0.344	23.9
10	0.520	26	35.4	0.343	24.2
11	0.502	14	21.1	0.244	5.38
12	0.523	34	47.0	0.337	25.8
13	0.500	11	16.5	0.250	4.09
14	0.502	11	16.1	0.247	4.05
15	0.517	36	50.6	0.320	27.1
16	0.517	24	33.1	0.286	22.7
17	0.518	38	52.9	0.287	36.7

Continued –

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Mol. ID	Mv	nSK	Sv	RBF	DELS
18	0.518	31	43.0	0.280	3.16
19	0.518	30	41.5	0.342	24.5
20	0.490	17	25.2	0.270	4.27
21	0.503	16	24.9	0.277	4.34

Mv – Molecular volume
nSK – Number of non H atoms
Sv – Sum of atomic van der Waals volumes (scaled on carbon atom)
RBF – Rotatable bond fraction
DELS – Molecular electrotopological variation