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Ecotoxicity quantitative structure–activity relationships for alcohol ethoxylate mixtures based on substance-specific toxicity predictions ☆

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Abstract

Traditionally, ecotoxicity quantitative structure–activity relationships (QSARs) for alcohol ethoxylate (AE) surfactants have been developed by assigning the measured ecotoxicity for commercial products to the average structures (alkyl chain length and ethoxylate chain length) of these materials. Acute *Daphnia magna* toxicity tests for binary mixtures indicate that mixtures are more toxic than the individual AE substances corresponding with their average structures (due to the nonlinear relation of toxicity with structure). Consequently, the ecotoxicity value (expressed as effects concentration) attributed to the average structures that are used to develop the existing QSARs is expected to be too low. A new QSAR technique for complex substances, which interprets the mixture toxicity with regard to the "ethoxymers" distribution (i.e., the individual AE components) rather than the average structure, was developed. This new technique was then applied to develop new AE ecotoxicity QSARs for invertebrates, fish, and mesocosms. Despite the higher complexity, the fit and accuracy of the new QSARs are at least as good as those for the existing QSARs based on the same data set. As expected from typical ethoxymer distributions of commercial AEs, the new QSAR generally predicts less toxicity than the QSARs based on average structure.

Keywords: QSAR; Alcohol ethoxylate; Mixture toxicity; Additivity; Toxic units; Ecotoxicity; Nonionic surfactant; Risk assessment

1. Introduction

Quantitative structure–activity relationships (QSARs) for ecotoxicity are mathematical relationships between molecular structure descriptors (Roberts, 1991; Morrall et al., 1999), and ecotoxicological effects values of these structures. For well-defined single substances, both the ecotoxicity and the molecular descriptors can be determined "exactly". Hence, QSARs for such substances can be good descriptions of reality—albeit limited by inaccuracies in the underlying experimental data and potential "lack of fit" of the applied mathematical model.

Complex substances, as described here, are not well-defined single chemical structures but are mixtures containing multiple structurally similar chemicals. Ecotoxicity data are rarely available for the individual chemicals but are usually available for the commercial multi-component substances. The ecotoxicity of a complex substance can be highly dependent on the shape of the distribution of its

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different components. This is because toxicity is usually not linearly related to molecular descriptors. For example, for surfactants, ecotoxicity will typically increase logarithmically with a linear increase in alkyl chain length. Hence, based on the principle of additive mixture toxicity (Loewe, 1953), the measured ecotoxicity of a complex substance may be largely driven by a limited number of components, i.e., those that are orders of magnitude more toxic than the others. The presence of these highly toxic components is not necessarily reflected in the calculated average structure of a complex substance. As a consequence, for complex substances, there is not always a meaningful relationship between the measured toxicity and the molecular descriptors of the average structure.

In such cases of nonlinearity, the most highly toxic components have an impact on toxicity that is disproportionate to their molar abundance, whereas their impact on the calculation of the substance's average structure is proportionate to molar abundance. Hence, it is possible that a complex mixture will in reality be significantly more ecotoxic than the single substance representing its average structure. Consequently, when for the purpose of QSAR derivation a mixture's measured ecotoxicity is assigned to the average structure (as if it were a single substance), this is expected to result in a QSAR that will—on average—overpredict the toxicity of most individual components of the mixture.

The mode of ecotoxic action for surfactants is generally accepted to be nonspecific, with exposure resulting in disruption of biological membrane integrity (Roberts, 1991; Roberts and Marshall, 1995). Roberts and Marshall (1995) state that the assumption of additivity (concentration addition model) for nonionic surfactants, specifically alcohol ethoxylates (AEs), is valid. Escher and Hermens (2002), Escher et al. (2002), and Dyer et al. (2000) demonstrated that baseline toxicants and related alcohol-based surfactants also follow a concentration addition model.

Alcohol ethoxylates are a class of nonionic surfactants that are complex substances. An AE molecule consists of a fatty alcohol, which is ester-linked to a polyethylene glycol (or ethoxylate) chain. The general formula for AE is CH_3–$(CH_2)_x$–O–$(CH_2CH_2O)_y$–H. For typical commercial AE materials, x can range from 8 to 17 and y can range from 0 to >20. Thus, an AE mixture could contain over 100 individual components ("ethoxymers") due to all possible combinations of alkyl chain lengths and ethoxylation degrees. The notation C_xEO_y will be used below to denote AEs with alkyl chain lengths of x and polyethylene glycol chain lengths of y. Different commercial materials may have different distribution shapes (e.g., narrow or wide) in accordance with the starting alcohols and the routes of synthesis. Logically, the "fingerprint" of AE in the environment also consists of a matrix with all possible ethoxymers. Further, the shape of the environmental distribution is likely to be different from the distribution shape of any of the commercial mixtures of AE.

Several QSARs have been developed to describe the ecotoxicity of AE surfactants. Wong et al. (1997) have derived AE-specific QSARs for acute toxicity to *Daphnia magna* and *Pimephales promelas*, using C length and EO number as molecular descriptors. Willing (2000) presented a QSAR to determine the acute algal toxicity of AE, using C length and EO number. Wind and Belanger (2005) used the same underlying data set to develop a QSAR for chronic algal toxicity (E_bC_{20}). Belanger et al. (2000) calculated an AE-specific QSAR to describe mesocosm NOEC and LOEC as a function of log K_{ow}. Finally, Morrall et al. (2003) developed a chronic ecotoxicity QSAR, based on log K_{ow}, for *D. magna*. An overview of these existing QSARs is given in Table 1.

Except for the algal work, the toxicity of commercial AE materials has previously always been related to the average structure of the exthoxymer distribution to develop the above QSARs. This approach is relevant for interpolation between commercial AE mixtures with distributions strongly centered around the average structures. However, it may not be appropriate for mixtures that have radically different distributions, such as those measured in environmental matrices, or for single ethoxymers. Based on the above reasoning, it can be suspected that these published QSARs overpredict ecotoxicity in those cases.

The research described in this paper aims (1) to verify whether the toxicity of a complex substance (in the case of AE) is indeed inadequately represented by the toxicity of the average structure, (2) to develop (based on the mixture toxicity concepts) a method for deriving QSARs specifically for complex substances, and (3) to apply this new method to derive new QSARs for AE ecotoxicity.

Table 1
Existing AE-specific ecotoxicity QSARs

Ecotoxicological endpoint	QSAR	Unit	Ref.
Forty-eight-hour EC_{50} *Daphnia magna*	$\log(EC_{50}) = -0.38\,C + 0.1\,EO - 1.77$	(mol/L)	1
Ninety-six-hour LC_{50} Fathead minnow	$\log(LC_{50}) = -0.34\,C + 0.05\,EO - 1.65$	(mol/L)	1
Seventy-two-hour ErC_{50} algae	$\log(EC_{50}) = -0.314\,C + 0.237\,EO + 2.96$	(mg/L)	2
Seventy-two-hour EC_0 algae	$\log(EC_0) = -0.168\,C + 0.182\,EO + 0.9$	(mg/L)	3
Twenty-one-day NOEC *Daphnia magna*	$\log(NOEC) = -0.84 \log K_{ow} - 2.0$	(mol/L)	4
NOEC mesocosm	$\log(NOEC) = -0.66 \log K_{ow} + 2.41$	(mg/L)	5
LOEC mesocosm	$\log(LOEC) = -0.748 \log K_{ow} + 3.16$	(mg/L)	5

Refs: (1) Wong et al. (1997); (2) Willing (2000); (3) Wind and Belanger (2005) based on Willing (2000); (4) Morrall et al. (2003); (5) Belanger et al. (2000).