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Study on Classfication Model of Chemicals for Ecotoxicity QSAR System, KATE

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Quantitative Structure-Activity Relationships (QSARs) have the potential to provide information on hazards of chemicals, while reducing time, monetary cost and animal testing currently needed.[1] Also in Japan, they would be a powerful tool for data gap filling in initial risk assessment under Chemical Substances Control Law.

In this study, we exhibit the feature of the classes in KATE[2] and its classification. The trial web version of KATE, which is a QSAR model for ecotoxicity prediction, was published in January, 2008. The KATE system uses a chemical substance's substructure to predict median lethal concentration (LC50) in for acute toxicity tests and median effective concentration (EC50) in Daphnia acute immobilization tests. Chemical substance data can be entered using SMILES.† The ecotoxicity tests (fish and daphnia) gathered by the Ministry of the Environment, Japan[3] by 2006 and the fish acute toxicity tests from the US Environmental Protection Agency (EPA)'s Fathead Minnow database[4] were used as reference (training set) chemicals of the QSARs. As the same concept as the EPA ECOSAR ecotoxicity system,[5] the QSAR equations in the KATE model express the correlations between a compound's LogP (octanol-water partitioning coefficient) and its aquatic toxicity by simple linear regression analyses.

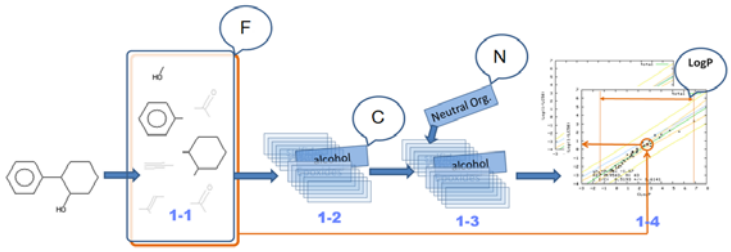

Fig.1 the KATE system and its judgments. A chemical is separated into substructures (1-1), classified by using the substructures (1-2), and added to the neutral organics class if necessary (1-3). Then the toxicity is estimated by the QSAR equation (1-4). The *F-*, *C-*, and *N-judgments* are delivered if each substructure of the chemical is found in the substructures of *all chemicals*, *the chemicals of its own class*, and *the chemicals of neutral organics*, respectively, in the training sets of the model. *LogP-judgment* is based on the range of the LogP of the training sets of its own class.

The overview of the KATE system is described in Fig. 1. Almost classes are based on their chemical structures. Only a class named *neutral organics* is based on the mode of action *narcosis*.[6] The substances belonging to narcosis is independent of a chemical structure and is dependent on its hydrophobicity. The narcosis's toxicity is also called 'baseline' or minimum toxicity. In the KATE model, the neutral organics consists of the classes: *sulfoxides*, *aliphatic HC (hydrocarbon)*, *aliphatic ether*, *aromatic/aliphatic ether*, *aliphatic ketone*, *aromatic ketone*, and

† *An identifier that expresses the molecular structure, etc. of a chemical compound in a line notation using printable ASCII characters*

aliphatic alcohol ether.[7b]

The current KATE system can be validated by using the ecotoxicity tests[3] by the Ministry of the Environment, Japan after 2006. Following the criteria decided by Hulzebos and Posthumus,[7] the estimations of KATE should not deviate from the experimental value with a factor of 10 to be considered as acceptable. As shown in Table 1 and 2, the chemicals having under and overestimating with a factor 10 criteria are 4 (5) of 31 (36) chemicals and 5 (6) of 29 (31) chemicals excluding (including) the neutral organics class at the fish and daphnia endpoint, respectively. In the daphnia endpoint, five of 29 chemicals cannot be estimated due to the lack of the QSAR schemes. The re-classification of chemicals covering the more variety of the chemical and/or multiple regression equation are required to improve the predictive and applicability of the QSAR model. We will show you the details of the re-classifications on the poster.

Table1. Acute toxicity of chemicals having under or overestimating with a factor 10 to fish LC50.

Chemical's name	KATE's class	Judgments				LC50/mg L^{-1}	
		N	C	LogP	F	Explt	KATE
1,8-Naphthylenediamine	aromatic amines 2	○	○	○	○	5.6	89.9
Trichloroacetonitrile	benzyl halides halo-ketone	○	×	○	○	0.07	1.5
(Z)-1,4-Bis(benzyloxy)but-2-ene	vinyl/allyl ethers	○	○	○	○	4.6	0.02
1-sec-Butyl-2-methoxy-3,5-dinitrobenzene	aromatic/alipatic ether	×	×	○	○	1.4	14.5
1-sec-Butyl-2-methoxy-3,5-dinitrobenzene	neutral organics	×	×	○	○	1.4	22.7

Table2. Acute toxicity of chemicals having under or overestimating with a factor 10 to daphnia EC50.

Chemical's name	KATE's class	Judgments				EC50/mg L^{-1}	
		N	C	LogP	F	Explt	KATE
1,8-Naphthylenediamine	aromatic amines 2	○	○	×	○	0.17	7.9
Trichloroacetonitrile	benzyl halides halo-ketone	×	×	○	○	0.04	7.6
3,4,5,6-Tetrachlorobenzene-1,2-dicarbonitrile	o-conjugated aromatic system	×	×	○	○	0.3	4.6
(Z)-1,4-Bis(benzyloxy)but-2-ene	vinyl/allyl ethers	○	×	×	○	1.4	14.8
1,1,2,2-Tetraphenylethane-1,2-diol	aliphatic alcohol ether	○	○	○	○	0.02	2.6
1,1,2,2-Tetraphenylethane-1,2-diol	neutral organics	○	○	○	○	0.02	1.1

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(b) In the OECD monograph, chasses of organic compounds for minimal toxicity were selected by the group, *aliphatic alcohols*, *aliphatic ketones*, *aliphatic ethers* and *alkoxyethers*, *aliphatic halogenated hydrocarbons*, *saturated alkanes*, and *halogenated benzenes*
7. E.M. Hulzebos, and R. Posthumus, *SAR and QSAR in Environmental Research*, 2003 **14**, 285.