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Prediction of Acute Toxicity to Fathead Minnow by Local Model Based QSAR and Global QSAR Approaches

Youngyong In,[†] Sung Kwang Lee,[‡,*] Pil Je Kim,[§] and Kyoung Tai No[†,#,*]

[†]*Bioinformatics and Molecular Design Research Center, Seoul 120-749, Korea*
[‡]*Department of Chemistry, Hannam University, Daejeon 305-811, Korea. [*]E-mail: leesk@hnu.kr*
[§]*National Institute of Environmental Research, Incheon 404-170, Korea*
[#]*Department of Biotechnology, Yonsei University, Seoul 120-749, Korea. [*]E-mail: ktno@yonsei.ac.kr*
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We applied several machine learning methods for developing QSAR models for prediction of acute toxicity to fathead minnow. The multiple linear regression (MLR) and artificial neural network (ANN) method were applied to predict 96 h LC_{50} (median lethal concentration) of 555 chemical compounds. Molecular descriptors based on 2D chemical structure were calculated by PreADMET program. The recursive partitioning (RP) model was used for grouping of mode of actions as reactive or narcosis, followed by MLR method of chemicals within the same mode of action. The MLR, ANN, and two RP-MLR models possessed correlation coefficients (R^2) as 0.553, 0.618, 0.632, and 0.605 on test set, respectively. The consensus model of ANN and two RP-MLR models was used as the best model on training set and showed good predictivity (R^2=0.663) on the test set.

Key Words : QSAR, Fathead minnow, Acute toxicity, Consensus model, ANN

Introduction

Quantitative Structure-Activity Relationships (QSARs) have currently gained enormous importance in the field of environmental science as adoption of REACh (Registration, Evaluation and Authorization of Chemicals) legislation in EU. As QSAR could be useful in reducing time and cost of experiments and animals testing, many researchers have developed the method to prioritize untested chemicals for risk assessment and to fill data gaps for regulatory purposes.[1]

Risk assessment for aquatic ecosystems is assessed by acute toxicity of algae, daphnia, and fish in accordance with OECD guidelines. Especially, fish is important as a biological model in aquatic toxicology studies as it represents one of the trophic levels of the aquatic food web. US Environmental Protection Agency (EPA) produced acute toxicity data of fathead minnow, which later became the most widely used small fish model for regulatory ecotoxicology, with respect to mode of action.[2] Several researchers have used the EPA data to develop various QSAR models by group contribution method,[3,4] solvation parameter model,[5] artificial neural network[6-9] and GA-MLR(genetic algorithm-multiple linear regression).[10] Previous results of QSAR studies for acute toxicity of fathead minnow are summarized in Table 1. The models can be divided into two patterns; local models based QSAR and global QSAR. Local models based QSAR is mainly employed to build local models for each substructure or mode of action (MOA) and subsequently combine local models into a single model. Generally, local model is considered more confidential than global model due to smaller applicability domain. However, it is difficult to accurately predict the toxicity of unclear chemicals that have more than one substructures or misclassified MOA. Global QSAR is employed to build a model of diverse chemicals with various mechanisms. That can provide a simple and intuitive understanding of structural effects of chemicals and global toxicity independent of MOA.[11]

In this study, we present QSAR models for acute toxicity prediction of compounds with a wide range of diversity on fathead minnow. We have employed several methods for deriving reliable prediction of QSAR models. One of them is the consensus model that uses a number of different QSAR models for each endpoint. Empolyment of such methods can limit the possibility of error from a QSAR by cross checking the results with other QSARs. Another is the performance investigation of models by comparing and integrating local

Table 1. Summary of recent QSAR studies to fathead minnow

Authors	Used descriptors	Statistical method	MOA	No. of compounds		R^2	
				training	test	training	test
Gini *et al.*[6]	various descriptors from various software	NN/MLR	Y (implicitly considered)	454	114	-	0.760
Mazzatorta *et al.*[7]	physico-chemcial, tolopoligal descriptors	Fuzzy-NN	N	392	170	0.70	0.31
Mazzatorta *et al.*[8]	physico-chemcial, tolopoligal descriptors	NN	N	388	166	0.688	-
Mazzatorta *et al.*[9]	physico-chemcial, tolopoligal descriptors	CP ANN	N	282	286	0.97	0.56

model based QSAR and global QSAR approaches.

Model Development

Experimental Data. The procedure of model development is depicted in Figure 1. In this study, we have used EPA Fathead Minnow Acute Toxicity Database with experimental values for the median lethal concentration for 50% of a population of fathead minnow within 96 h (96 h LC_{50}, mmol/L) collected and reviewed by the Mid-Continent Ecology Division of the U.S. EPA's National Health and Environmental Effects Research Laboratory.[12] It can be used as good training set for developing predictive QSARs of toxicity that contain mode of action information. Generally, four classes of fish acute toxicity have been classified by the European Community legislation as shown in Table 2.[13]

The EPA fathead minnow dataset[14] contains 617 chemicals including organic, inorganic, and organometal chemicals. Inorganic molecules, organometal molecules, salt containing molecules, dimmer, and undefined structures were excluded from the original EPA data. The final dataset included 555 organic compounds as training set for developing the models and endpoint values were expressed as –log(mmol/L).

Molecular Descriptors. The molecular descriptors were computed using PreADMET v2.0 program.[15] An initial set of 228 2D descriptors was used to select useful those for the prediction. The descriptors consisted of 8 constitutional descriptors, 12 geometrical descriptors, 1 physicochemical descriptor, and 207 topological descriptors. In order to reduce the dimensionality of variables, objective descriptors reduction was carried out in the following way. We excluded the descriptors which had identical or missing values and possessed low correlation with given toxicity ($R^2 < 0.1$) from the original pool of descriptors. Finally, 95 descriptors were used in the following calculations.

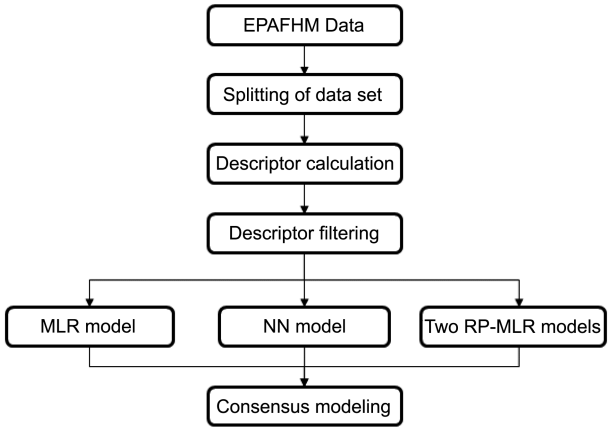

Figure 1. Schematic representation of the QSAR procedure for the prediction of acute fish toxicity.

Table 2. EC Classification for fish (Directive 92/32EEC Annex VI Point 5.1)

Class	LC_{50}	dangerous for the environment
I	< 1 mg/L	very toxic to aquatic organisms
II	1-10 mg/L	toxic to aquatic organisms
III	10-100 mg/L	harmful to aquatic organisms
IV	> 100 mg/L	in the aquatic environment

Splitting of Data Set. Toxicity data set of chemicals was split into a training, validation and test set based on sphere-exclusion algorithms[16] using in-house program. The sphere-exclusion method (SEM) provides the sampling of representative training set from the whole data set and can control the size of the training set by using different sphere radius values. The distance of SEM was generated from the score of principal components explained over 90% of the total variance of all descriptors. In this study, the splitting ratio between the training and the test compounds was set to 4:1. We also tried to divide them into the training and validation set for neural net learning with the ratio of 3:1.

Multiple Linear Regressions (MLR). The first step of this study involved the development of a multiple linear regression model for the entire training data. To determine the optimal subset of descriptors, we generated MLR equations based on all the possible combinations of the 95 descriptors. The number of descriptors in the MLR equations varied from 1 to 5. The best result of the MLR model is summarized in Table 3. The robustness of the models and their internal predictability were evaluated by test set. The computation of all the MLR models from one to five descriptors took about 12 hours for execution on a personal computer (Core2Duo 6600, 2GB RAM)). All the statistical analyses of the obtained MLR models were performed using the SAS JMP package(v8.0, SAS Institue Inc, Cary, NC, USA).

Artificial Neural Network (ANN). A feed-forward, three-layer network with Rprop (Resilient back-propagation) algorithm[17] as training algorithm was used to make non-

Table 3. Comparative statistical performance of developed QSAR models

Method	Classified Group	Training set			Test set		
		N	$R^{2\,a}$	MAE[b]	N	$R^{2\,a}$	MAE[b]
MLR (Model 1)	-	445	0.712	0.557	110	0.553	0.523
ANN[c] (Model 2)	-	445	0.776	0.499	110	0.618	0.478
RP(reactive) -MLR (Model 3)	reactive	119	0.755	0.623	32	0.552	0.610
	the others	326	0.741	0.510	78	0.686	0.431
	all	445	0.746	0.536	110	0.632	0.483
RP(narcosis) -MLR (Model 4)	narcosis	260	0.758	0.435	85	0.534	0.476
	the others	185	0.704	0.609	25	0.730	0.493
	all	445	0.758	0.506	110	0.605	0.480

[a]R^2: coefficient of determination. [b]MAE: mean absolute error. [c]For ANN, original training set was divided into two sets as training and validation set. The validation set was used to prevent over-fitting. The number of compounds in training and validation sets was 334, and 111, respectively. The correlation coefficients (R^2) of training and validation set were 0.80 and 0.62. The number of compounds and results in Table 3 were derived from these two sets.

linear model. Rprop algorithm in comparison with general back-propagation method can be advantageous for two reasons; (a) fast convergence of training and validation set rather than online or batch weight updated back-propagation method; and (b) no choice of parameters such as learning rate and momentum is needed to obtain optimal condition. In this study, the top ranked 10000 equations from MLR models were selected to calculate ANN. The performance of ANN was evaluated by examining R^2 for the training set, the validation set, and the test set.

Recursive Partitioning (RP)-MLR. Acute toxicity compiled in the EPAFHM data is classified according to 11 types of MOAs such as narcosis, reactivity, *etc*.[12] Therefore, based on MOA, it is possible to build classification model for fish toxicity. Generally, it is agreed that QSAR model is suitable to predict chemicals within same MOA (mode of action), because it covers a more similar chemical domain. In order to develop MOA-based QSAR model, it is previously required to classify MOA of chemicals prior to local QSAR modeling. In this study, we tried to approach RP models of two types; one type classify narcosis group from other groups, and another type classify reactive group from other groups in the first step. The next was to build the local MLR model for narcosis and reactive group classified by RP model. The RP calculation was executed with cerius^{2}.[18]

Consensus Modeling. The consensus model, which can be derived by calculating average results for each model, might provide better complementary results than every individual model. In this study, we tried to test the validity and performance of 4 kinds of consensus models with combination of MLR, ANN and 2 RP-MLR models.

Results and Discussion

The QSAR models for acute fish toxicity were developed by using MLR, ANN, and two RP-MLRs. The criterions for model selection were the R^2 for the training set and the test set.

MLR Result. Among all the MLR equations based on all the possible combinations of the 95 descriptors, model 1 showed high stability for the regression equation owing to high R^2 value of the training and test set. The descriptors in

Table 4. List of descriptors for MLR, ANN and RP-MLR models

Model	Descriptor name	Description
MLR model (Model 1)	AlogP98	Calculated logP by Ghose's atom additive method
	ATS_MB_0_pol	Autocorrelation descriptor (Moreau-Bruto) of order 0 weighted by atomic polarizabilities
	$E_{state}S_{hydunsat}$	Sum of E-state hydrophobic unsaturated atoms
	$E_{state}SH_{dCH2}$	Sum of hydrogen E-state for $=CH_2$ type
	$FraVSA_{hydsat}$	Fraction of 2D van der Waals hydrophobic saturated surface area
ANN model (Model 2)	AlogP98	Calculated logP by Ghose's atom additive method
	ATS_MB_2_pol	Autocorrelation descriptor(Moreau-Bruto) of order 2 weighted by atomic polarizabilities
	$E_{state}S_{hba}$	Sum of E-state for Hydrogen bond acceptor
	$E_{state}SH_{dsCH}$	Sum of hydrogen E-state for =CH- type
	VChi4c	Kier & Hall valence connectivity index of order 4(cluster)
RP(reactive) -MLR others MOA set (Model 3-1)	AlogP98	Calculated logP by Ghose's atom additive method
	ATS_MB_2_AlogP98	Autocorrelation descriptor(Moreau-Bruto) of order 2 weighted by AlogP98 values
	ATS_MB_6_AlogP98	Autocorrelation descriptor(Moreau-Bruto) of order 6 weighted by AlogP98 values
	ATS_MB_6_Estate	Autocorrelation descriptor(Moreau-Bruto) of order 6 weighted by E-State values
	$E_{state}SH_{dCH2}$	Sum of hydrogen E-state for CH_2 type
RP(reactive) -MLR reactive MOA set (Model 3-2)	ATS_MB_0_pol	Autocorrelation descriptor(Moreau-Bruto) of order 0 weighted by atomic polarizabilities
	$E_{state}S_{hyd}$	Sum of E-state for hydrophobic atoms
	$E_{state}S_{aaCH}$	Sum of E-state for aaCH type (a: aromatic bond)
	$FraVSA_{hydunsat}$	Fraction of 2D van der Waals hydrophobic unsaturated surface area
	FraRotBonds	Fraction of Rotatable bond
RP(narcosis) -MLR narcosis MOA set (Model 4-1)	AlogP98	Calculated logP by Ghose's atom additive method
	ATS_MB_0_pol	Autocorrelation descriptor(Moreau-Bruto) of order 0 weighted by atomic polarizabilities
	ATS_MB_6_AlogP98	Autocorrelation descriptor(Moreau-Bruto) of order 6 weighted by AlogP98 values
	$E_{state}\_SH_{dCH2}$	Sum of hydrogen E-state for $=CH_2$ type
	$FraVSA_{hyd}$	Fraction of 2D van der Waals hydrophobic surface area
RP(narcosis) -MLR Others MOA set (Model 4-2)	AlogP98	Calculated logP by Ghose's atom additive method
	ATS_MB_10_pol	Autocorrelation descriptor(Moreau-Bruto) order 10 weighted by AlogP98 values
	$E_{state}\_SH_{hyd}$	Sum of hydrogen E-state for hydrophobic atoms
	$E_{state}\_SH_{polar}$	Sum of hydrogen E-state for polar atoms
	$FraVSA_{hydsat}$	Fraction of 2D van der Waals hydrophobic saturated surface area

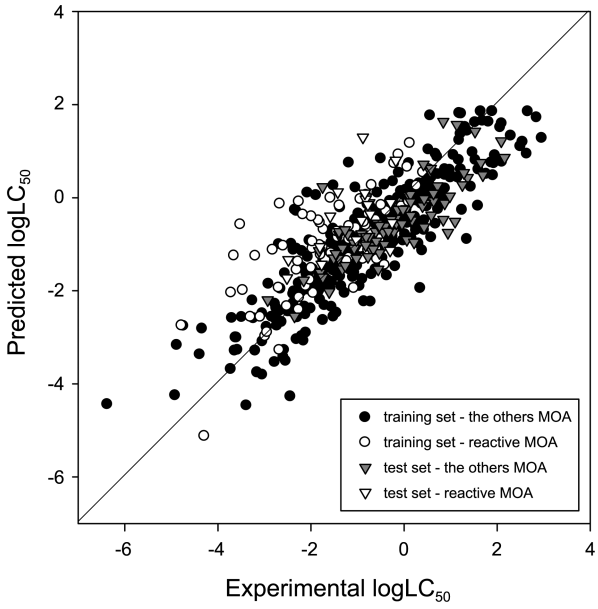

Figure 2. A plot of experimental *vs* predicted $logLC_{50}$ values by MLR model.

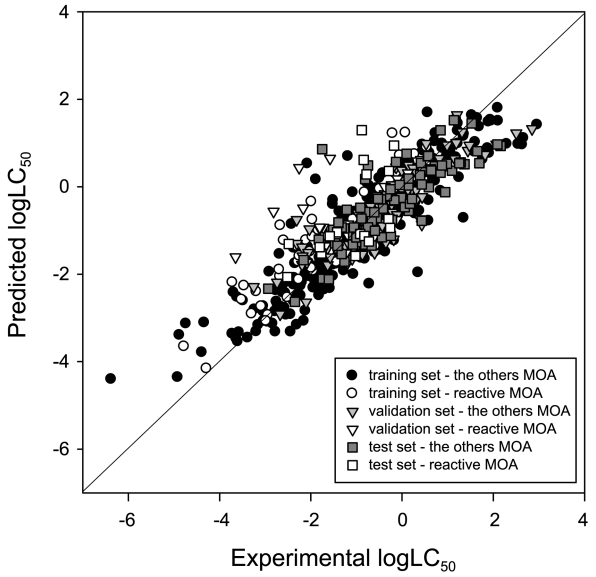

Figure 3. A plot of experimental *vs* predicted $logLC_{50}$ values by ANN model.

this model are summarized in Table 4. The calculated $logLC_{50}$ of the training and test set were plotted against the experimental values, as shown in Figure 2 for model 1.

Model 1.

$$\log LC_{50} = -0.77469679 \times AlogP98 - 0.0247932 \times ATS\_MB\_0\_pol + 0.0454004 \times E_{state}S_{hyd\_unsat} - 0.7148743 \times E_{state}SH_{dCH2} + 1.45112205 \times FraVSA_{hydsat} + 0.07012133$$

(Training set) n = 445, R^2 = 0.712, MAE = 0.557
(Test set) n = 110, R^2 = 0.553, MAE = 0.523

Where n is numbers of chemicals in the data set, R^2 is the coefficient of determination, and MAE is mean absolute error. The model 1 contains five molecular descriptors. Upon comparison of the residuals for chemicals of each MOA, the model 1 tended to overestimate value for most of the reactive group compounds. About 26.3% of reactive group compounds on the training and test set had larger residual than 1.0 $logLC_{50}$ (see Figure 2). Moreover, mean absolute error of reactive group compound on the training and test set (MAE=0.74 and 0.80) is larger than that of the others group compound (MAE=0.52 and 0.47) . The results revealed that the reactive chemicals were responsible for increase in error in the MLR model. Subsequently, the result led us to develop local RP-MLR models for reactive group chemicals.

ANN Results. In our study, ANN architecture consists of three layers: input layer, hidden layer and output layer. As Rprop neural network do not need to choose learning rate and momentum parameter, the optimization of ANN model only depend on the number of hidden neurons. The number of hidden neurons from 4 to 31 in the ANN models had been tried. The optimum ANN model was achieved for the training set, validation set, and test set with high correlation coefficient (R^2). Based on statistical results, 5 descriptors and 14 hidden neurons were required as the best protocol. The correlation coefficients (R^2) of the training, validation, and test set in the best ANN model were 0.802, 0.625, and 0.618, respectively. The predicted $logLC_{50}$ of the best ANN are shown in Figure 3. The five descriptors used for the best ANN model are shown in Table 4. The results of ANN model represented a similar tendency as that of MLR model. About 19.8% of reactive group compounds on the training and test set had larger residual than 1.0 ($logLC_{50}$). The mean absolute error (MAE) of reactive group compound on the training and test set (MAE=0.640 and 0.721) was larger than that of the others group compound (MAE=0.469 and 0.434). The reactive group compounds had overestimated toxicity values in the ANN model (see Figure 3).

RP-MLR Results. The prediction of MLR and ANN model represented a similar tendency for reactive MOA. The MLR and ANN model overestimated the results of most of the reactive MOA compounds and provided a good prediction for the narcosis MOA chemicals. The solution in the overestimated prediction of reactive MOA chemicals would be to develop a local based QSAR model for reactive MOA. In this study, we have tried to classify all the chemicals according to two patterns (reactive MOA *vs*. the others MOAs, and narcosis MOA vs. the others MOAs) using recursive partitioning (RP) method and then, build local MLR models within the same MOA. A detailed description of descriptors in the models is summarized in Table 4.

The RP(reactive)-MLR. In order to investigate the performance of local QSAR model, the training and the test set were classified into two subsets (reactive and the others MOA chemicals), respectively. The RP tree for classification of reactive and the others MOA are represented in Figure 4(a). The structure of the tree consists of four terminal and three non-terminal nodes, and the value of terminal node

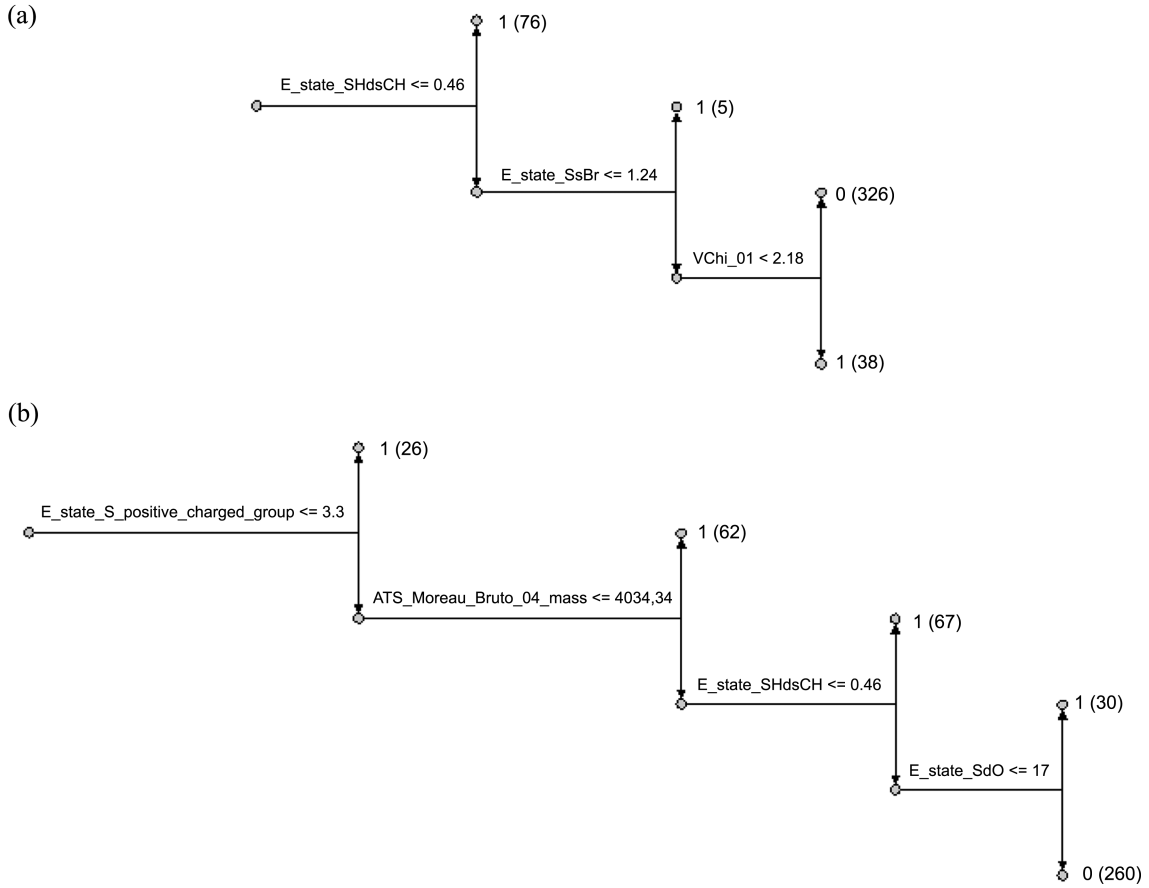

Figure 4. Recursive partitioning tree for MOA classification, (a) The trees for the RP(Reactive)-MLR model, (b) The trees for *RP(Narcosis)-MLR model*.

means class number by RP method (1 means reactive MOA and 0 means the others MOA). The descriptors, E-state_SHdsCH(Sum of hydrogen E-state values for =CH- type), E-state_SsBr(Sum of E-state values for -Br type), VChi_01(Kier & Hall valence connectivity index of order 1) were employed for the construction of final tree. The main structural information reflected by these descriptors was related to bond-polarity and molecular topology. The descriptors, E-state_SHdsCH and E-state_SsBr characterizes the bond polarity of C-H, A-Br, that is the reaction ability of =CH- and Any atom-Br. VChi_01 describes molecular connectivity and shape. In the tree, true response in agreement with the condition on tree stem follows the branch towards the downside and false response follows the branch to the upper side. The prediction accuracy of the RP(reactive MOA) model was 79.33%. The MLR (RP(reactive MOA)-MLR) model using 119 chemicals classified as reactive MOA is the following five-descriptors model (Model 3-1). And the MLR (RP(the others MOA)-MLR) model using 326 chemicals classified as the others MOA is presented as the following equation (Model 3-2).

Model 3-1.

$$\log LC_{50} = -0.1054478 \times \text{ATS\_MB\_0\_pol} - 0.0431803 \times E_{state}S_{hydrophobic} + 0.10296219 \times E_{state}S_{aaCH} - 3.208933 \times \text{FraVSA}_{hydunsat} + 6.1780578 \times \text{FraRotBonds} + 2.23251849$$

(Training set) n = 119, R^2 = 0.755, MAE = 0.623
(Test set) n = 32, R^2 = 0.552, MAE = 0.610

Model 3-2.

$$\log LC_{50} = -0.7086855 \times \text{AlogP98} - 0.3109225 \times \text{ATS\_MB\_2\_AlogP98} + 0.14222876 \times \text{ATS\_MB\_6\_AlogP98} - 0.0024411 \times \text{ATS\_MB\_6\_E}_{state} - 1.0087035 \times E_{state}SH_{dCH2} + 0.99742408$$

(Training set) n = 326, R^2 = 0.741, MAE = 0.510
(Test set) n = 78, R^2 = 0.686, MAE = 0.431

The absence of AlogP98 in the Model 3-1 illustrates absence of influence of hydrophobicity because the reactivity of compounds is more related to reactivity of functional groups than the hydrophobicity of whole molecule. Figure 5(a) describes the plot of the experimental versus predicted $\log LC_{50}$ values of RP (reactive)-MLR model for the training and test set. There were some improvements when compared to model 1, where the R^2 values for training set and test set were 0.712 and 0.553, respectively. Therefore, it can be seen that local model 3-1 and 3-2 gives better

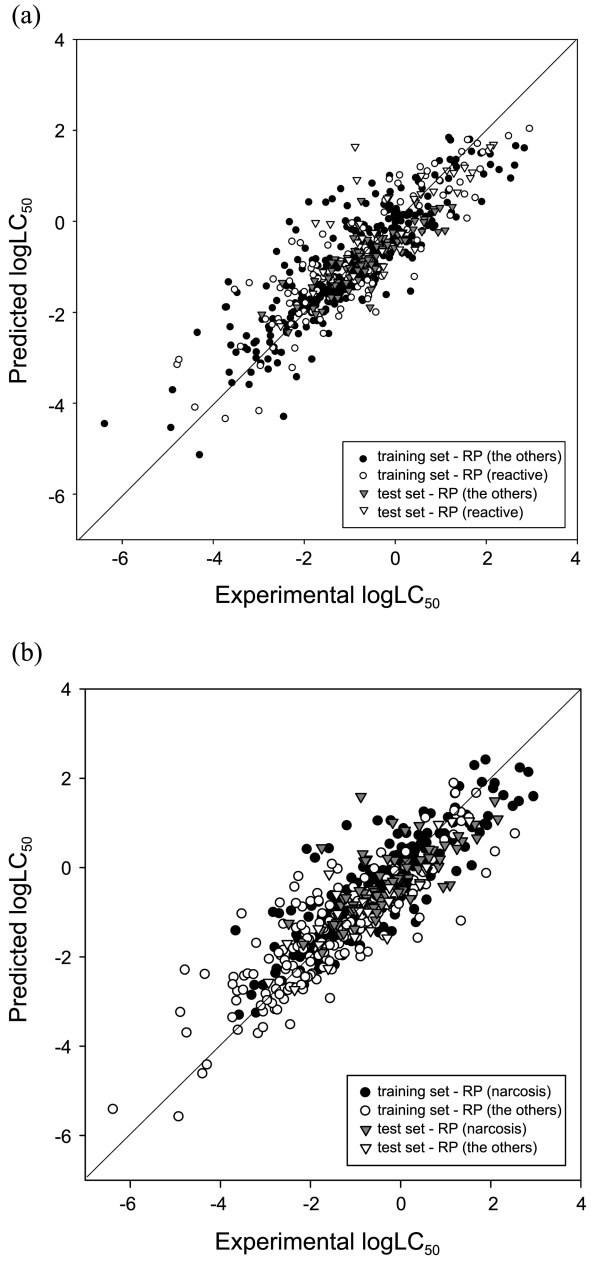

Figure 5. Plots of experimental vs predicted $logLC_{50}$ values by RP-MLR models after (a) classification of reactive MOA and the others MOA (b) classification of narcosis MOA and the others MOA.

results than global MLR model 1 (see Table 3). As the performance of Model 3-1 is worse than that of Model 3-2 for test set, it is apparent that informative descriptors are needed for representing reactive MOA. Further study is necessary to investigate good descriptors for applying QSAR model to the reactive MOA chemicals.

The RP(narcosis)-MLR. We have applied RP method to classify the data which were labeled as narcosis and others MOA and constructed local QSAR model for the obtained groups of chemical. The RP tree for classification of narcosis and the others MOA are shown in Figure 4(b). The structure of the tree consists of five terminal and four non-terminal nodes and the value of terminal node signifies class number by RP method (1 means narcosis MOA and 0 means the others MOA). The descriptors, E-state_S_positive_charged_group (Sum of E-state values for positive charged group), ATS_Moreau_Bruto_04_mass (Autocorrelation descriptor (Moreau-Bruto) order 4 weighted by atomic masses), E_state_SHdsCH (Sum of hydrogen E-state values for =CH- type) and E_state_SdO (Sum of hydrogen E-state values for =O type) were employed for the construction of the final tree. The descriptors in the RP model were all related to functional groups (for example positive charged, hydrogen of -CH=, carbonyl and nitro group) and size (atomic mass of molecules). The prediction accuracy of the RP (narcosis MOA) model was 74.16%. Local QSAR models were built by multiple linear regressions for each MOA chemicals classified as narcosis and the others MOA (Model 4-1 and 4-2).

Model 4-1.

$$\begin{aligned}\log LC_{50} = &-0.8266561 \times AlogP98 - 0.0288907 \\ &\times ATS\_MB\_0\_pol + 0.32083556 \\ &\times ATS\_MB\_6\_AlogP98 - 0.6461915 \\ &\times E_{state}\_SH_{dCH2} + 1.35188388 \times FraVSA_{hydrophobic} \\ &+ 0.41972596\end{aligned}$$

(Training set) n = 260, R^2 = 0.758, MAE = 0.445
(Test set) n = 85, R^2 = 0.534, MAE = 0.476

Model 4-2.

$$\begin{aligned}\log LC50 = &-0.7583831 \times AlogP98 - 0.0565768 \\ &\times ATS\_MB\_10\_pol + 0.11159603 \times E_{state}SH_{hydrophobic} \\ &- 0.1228881 \times E_{state}SH_{polar} - 1.88773629 \\ &\times FraVSA_{hydsat} - 1.3515789\end{aligned}$$

(Training set) n = 185, R^2 = 0.704, MAE = 0.609
(Test set) n = 25, R^2 = 0.730, MAE = 0.493

The predictions for the RP(narcosis)-MLR model are shown in Figure 5(b). The RP(narcosis)-MLR model and RP(reactive)-MLR model represented similar performance for the training and test set and outperform the MLR model (Table 3). The results confirmed the advantage of local model over the global model.

Table 5. Comparative statistical performance of consensus QSAR models

Model No.	Model No.	Training set (N=445)		Test set (N=100)	
		$R^{2\,a}$	MAE^b	$R^{2\,a}$	MAE^b
5	1,2	0.778	0.485	0.630	0.471
6	(3-1,3-2), (4-1,4-2)	0.780	0.485	0.649	0.455
7	2,(3-1,3-2)	0.795	0.472	0.666	0.445
8	2,(4-1,4-2)	0.794	0.467	0.639	0.459
9	1,2,(3-1,3-2)	0.788	0.473	0.655	0.457
10	1,2,(4-1,4-2)	0.785	0.472	0.634	0.465
11	2,(3-1,3-2), (4-1,4-2)	0.800	0.460	0.663	0.446
12	1,2,(3-1,3-2), (4-1,4-2)	0.791	0.465	0.653	0.453

[a]R^2: coefficient of determination. [b]MAE: mean absolute error.

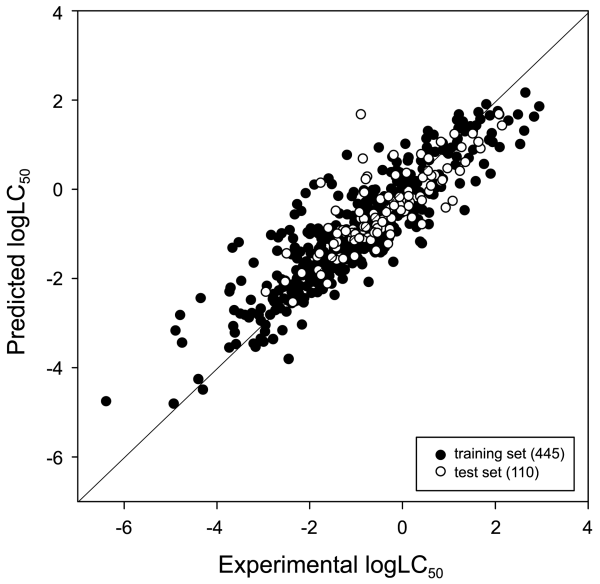

Figure 6. A plot of experimental vs predicted $logLC_{50}$ values by the consensus model 11.

Consensus Approach. To improve the predictions of acute toxicity of the test set, all the four models obtained in this study were used for consensus approach. Consensus prediction for the toxicity of a compound was calculated by averaging the predicted toxicity from four individual models. Table 5 compares the performances of the consensus models. It is clear from Table 4 and 5 that all the consensus models were shown to outperform individual models. In addition, it was proved that the Model 11 was the most predictive model for predicting toxicity among all the consensus models, resulting in improvements of R^2 and MAE for the test set. Figure 6 shows the plot of predicted versus experimental $logLC_{50}$ values by consensus Model 11. By comparison of the results of reactive MOA chemicals, Model 11 was found to have the MAE of 0.581 for reactive MOA chemicals on the training set, and 0.708 for those on the test set. It can be seen that the MAE of consensus Model 11 for reactive MOA chemicals were lower than that of MLR and ANN model. The result indicates that performance of Model 11 was obtained by improvement of consensus prediction for reactive MOA chemicals.

According to regulation class of Table 2, the model 11 also correctly classified 83.6% for the training set and 88.2% for the test set. This result demonstrates that Model 11 would aid in prioritizing the chemicals for acute toxicity testing and in categorizing the chemicals for regulation of the use.

Conclusion

In this study, we developed four QSAR models using MLR, ANN and two RP-MLR methods and evaluated a consensus models from individual models. As QSAR models only used 2-dimensional descriptors by easily drawing 2D chemical structures, they can allow model users to treat a large set of chemicals for priority setting. The best model was consensus model from ANN, two RP-MLR models and showed correlation coefficients (R^2) as 0.80 and 0.66 on training set (445 compounds), and test set (110 compounds), respectively and was better than previous studies. In best model, some of the reactive MOA chemicals had larger error than the others MOA chemicals. Therefore, it is necessary to develop new molecular descriptors for reactive MOA chemicals. In further studies, we will attempt to build new models by considering characteristics of reactivity of toxicity.

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