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In silico Acute Toxicity Prediction of Dimethyl Phthalate on Fish as Per Simulated Molecular Descriptors

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Abstract: ***An organic compound, dimethyl phthalate (DMP) is a category of plasticizer that is commonly utilized in plastic materials. The prediction of acute toxicity in fish through an in silico approach is an active assessment because fish is an edible diet of human beings. The objective of the present study was to predict an in silico acute toxicity (median lethal concentration or LC_{50} at 96hrs exposure) of DMP on fish as per simulated molecular descriptors by using toxicity estimation software tool (T.E.S.T.). The LC_{50} value of fish was predicted of about 15.97 mg/L or 4.09 -Log10(mol/L) as per similarity coefficient ≥0.5 of mean absolute error (MAE) of 0.03. Different molecular descriptors such as chi connectivity indices, topological descriptor, molecular properties, molecular distance-edge vector, burden eigenvalue descriptors, 2D autocorrelation descriptors, electrotopological state indices, information indices, molecular fragments, etc. were obtained. The average value was predicted for LC_{50} value as per all of these descriptors. It is concluded that the acute toxicity of fish for DMP was easily predicted after simulation of different molecular descriptors within T.E.S.T tool. It is suggested to evaluate fish toxicity with other phthalate compounds.***

Keywords: Acute toxicity prediction, Dimethyl phthalate, Fish toxicity prediction, *In silico* study, Plasticizer

1. Introduction

As per different regulatory bodies, worldwide the quantitative structure-activity relationship (QSAR) method encouraged, which recommended the usage of chemicals after the evaluation of the biological end points and probable risk factors.[1] Furthermore, the mathematical expression should be carefully validated before utilizing it to predict the modeled response as per similar chemical structure.[2]

Many studies reported the QSAR modeling is based on some tools of modern drug design and toxicity prediction of different organic chemicals. [3-5]

Traditionally, the objective of establishing toxicity of chemicals has been undertaken through the *in vivo* or *in vitro* models, where the test models or organisms are exposed to a chemical compound to acquire the toxic effects as median lethal concentration or LC_{50} value. An *in vivo* test requires animal harming, huge cost and more time consuming. [6] But an alternative method like QSAR is screened quicker the structure and biological end points of chemicals. For screening of toxicity with large-scale chemicals, efforts have developed by using QSAR modelling inbuilt in many tools. [3,7] A tool is called Toxicity estimation software tool (T.E.S.T), which helps toxicity screening of larger sets of chemicals in different test models viz. daphnids, fish and rat [8,9]

Among phthalate comounds, dimethyl phthalate (DMP) is a low molecular weight phthalate ester. [10,11] Several phthalates have already been established in which (DMP) is one of these derivatives [12] (Hlisníková et al., 2020). Some researchers observed toxicity of DMP in animal studies. [13,14]

In the present study, it was attempted to predict acute toxicity (median lethal concentration or LC_{50} at 96hrs exposure) of dimethyl phthalate on fish related to molecular descriptors by using toxicity estimation software tool (T.E.S.T.)

2. Materials and Methods

As per literature, the dimethyl phthalate (DMP) used in plasticizer was selected. [13-16] In this study, the test model like fish, commonly called Fathead minnow (*Pimephales promelas*) was selected as per the studied tool. The tool used as toxicity estimation software tool (T.E.S.T.) as per Martin et al. [8] For acute toxicity prediction, QSAR modelling was performed by using T.E.S.T (version, 4.1) for predicting median lethal concentration (LC_{50}) value of studied fish as per different molecular descriptors.

3. Results

Table 1 evaluates the prediction result of toxicity i.e., LC_{50} value as 4.09 -Log10(mol/L) and as per consensus method. The consensus method is the mean of different methods viz. Hierarchical clustering (3.72), Single model (4.06), Group contribution (3.94) and nearest neighbour (4.62), respectively (Table 2).

Table 1: LC_{50} value of fish of DMP as per consensus method

Endpoint	Predicted value	
	[-log10(mol/L)]	mg/L
Fathead minnow LC_{50} (96 hrs.)	4.09	15.97

Table 2: LC_{50} value of fish of DMP based on different models

Methods	Predicted value -Log10(mol/L)
Hierarchical clustering	3.72
Single model	4.06
Group contribution	3.94
Nearest neighbour	4.62

In Fig 2, the regression curve represented on DMP predicted with similar compound like Dimethyl nitroterephthalate as per similarity coefficient (SC) ≥0.5 (0.55) of mean absolute error (MAE) of 0.03.

Table 3 predicts LC_{50} value [-Log10(mol/L)] in fish as per different simulated models. The range between 3.51-4.93 -Log10(mol/L). Different molecular descriptors such as chi connectivity indices, topological descriptor, molecular properties, molecular distance-edge vector, burden eigenvalue descriptors, 2D autocorrelation descriptors, electrotopological state indices, information indices, molecular fragments, etc. were obtained. The average value was predicted for LC50 value as per all of these descriptors.

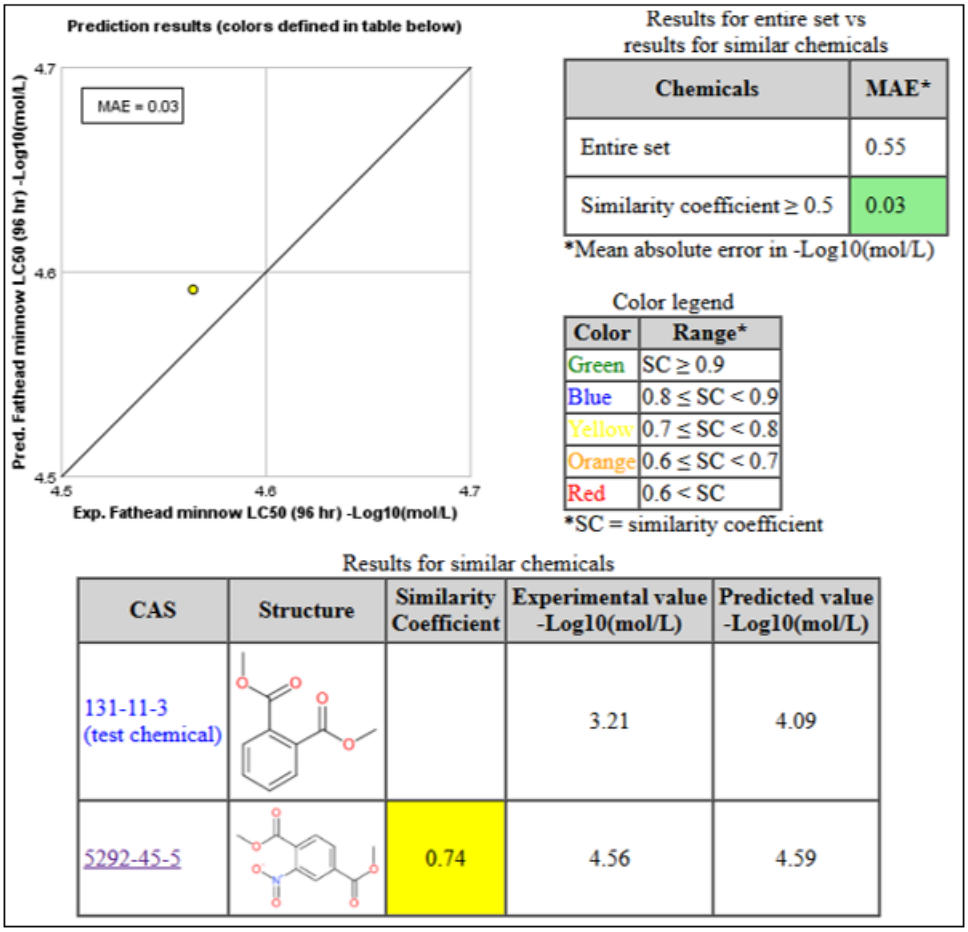
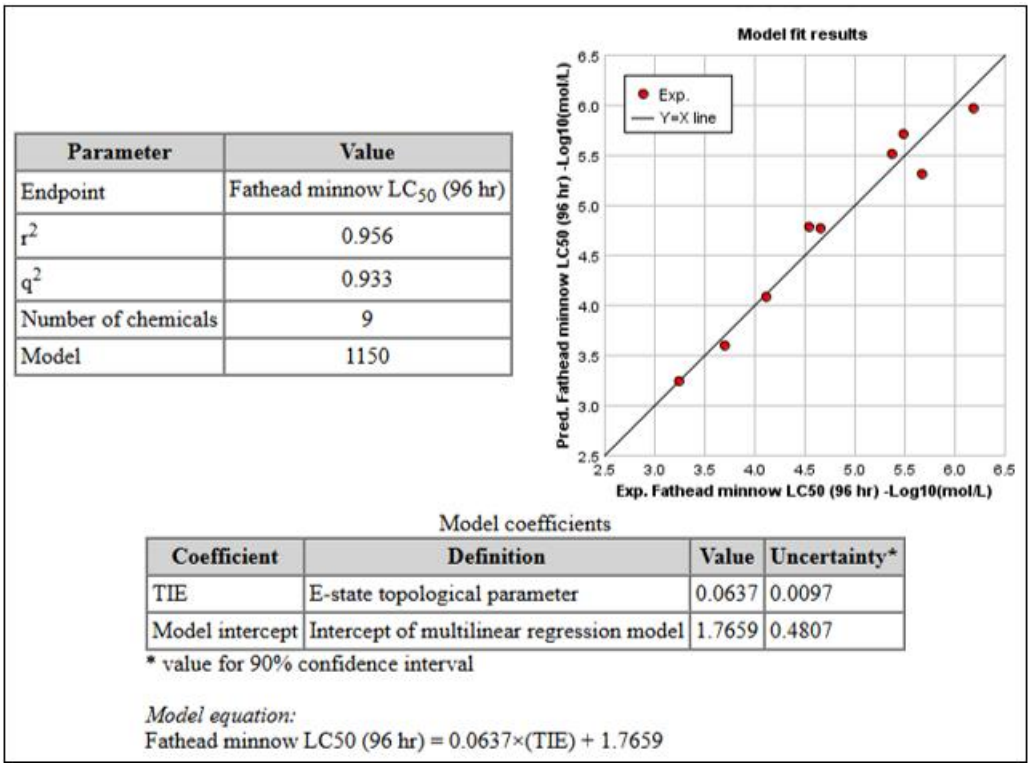


Figure 1: Regression curve for similar compound like Dimethyl nitroterephthalate as per SC value

Table 3: LC_{50} value of fish as per different models

Model no.	LC_{50} value [-Log10(mol/L)]
1047	4.24
1150	3.51
1164	3.65
1210	4.93
1244	4.27
1284	3.70
1296	3.78
1301	4.46
1305	4.33

In Fig 2, the regression curve represented on DMP predicted as per model equation in which Pearson's correlation coefficient (R^2) values were obtained 95.6%, respectively, which are significantly higher for these toxicity predictions in fish like test model.



Parameter	Value
Endpoint	Fathead minnow LC_{50} (96 hr)
r^2	0.956
q^2	0.933
Number of chemicals	9
Model	1150

Model coefficients

Coefficient	Definition	Value	Uncertainty*
TIE	E-state topological parameter	0.0637	0.0097
Model intercept	Intercept of multilinear regression model	1.7659	0.4807

* value for 90% confidence interval

Model equation:
Fathead minnow LC50 (96 hr) = 0.0637×(TIE) + 1.7659

Figure 2: Regression curve represented on DMP predicted as per model equation

4. Discussion

In the present study, the acute toxicity (measured as 96-h LC_{50}) of DMP was predicted of about 15.97 mg/L to fathead minnows as per T.E.S.T tool. Past studies were reported for LC_{50} value for fathead minnows was 39 mg/L (flow-through) and 121 mg/L (static). [17]

On the other hand, the experimental study to determine toxic effects of organics requires the high laboratory costs together with regulatory restrictions and the international force to reduce animal testing inspire greater necessity on predictive *in silico* methods based on QSAR models. [5]

5. Conclusion

It is concluded that the *in silico* prediction of acute toxicity of DMP in fish (*Pimephales promelas*) which was easily predicted after simulation of different molecular descriptors within the T.E.S.T. tool. The toxicity screening by QSAR modelling is an important technique for any chemical compound to the environment and adverse effects in organisms. It is suggested that the prediction of other phthalate compounds on *P. promelus* fish should be conducted in future.

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Conflict of interest
Authors declare no conflict of interest.

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