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Application of multilayer perceptron for prediction of the rat acute toxicity of insecticides

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Abstract

With the growing number of insecticides that can potentially contaminate the environment, the determination of their acute mammalian toxicity is of prime importance in risk assessment. Chemoinformatics presents an alternative to animal testing because laboratory tests are costly in time and money and actively opposed by animal rights activists. In this work, the Quantitative Structure-Toxicity Relationship (QSTR) model established by using the artificial neural network (ANN) has been used for estimating the acute oral toxicity (LD50) of these insecticides to male rats. The 123 insecticides of the training set and the sixteen insecticides of external testing set have been described by means of using molecular descriptors. The QSTR model was validated internally and externally. A good results (Q2 =0.96 and Q2ext =0.95) were obtained. The prediction results are in good agreement with the experimental values of LD50.

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Keywords: QSAR; Insecticides; Prediction; Artificial neural network; Domain applicability

1. Introduction

Insecticides are widely used in agriculture for plant protection and in domestic applications. They are also used to slow the spread of insects. Insecticides have also contributed to the control of many human diseases transmitted by insects. However, despite these advantages, insecticides have a major drawback such as toxicity [1, 2]. Due to the

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excessive use of these products, there is a widespread contamination of water, soil and air. For example, many studies [3-5] revealed the presence of insecticides in the atmosphere, in the fog, in droplets rain, in surface water and groundwater. Several studies on the contamination of food products revealed the presence of unacceptable levels of insecticide residues in food products such as cereals, vegetables, fruits, fish, milk, tea, honey and medicinal herbs [6, 7].

Exposure to these persistent insecticides has been associated with health effects including cancer, headache, skin and eye irritation, immune system problems, stomach, kidney, Parkinson and Alzheimer's disease, reproductive difficulties, birth defects, diabetes, Thyroid disease, cataracts and anemia [8-10].

Development of alternative methods that are designed to reduce and replace the use of animals to predict biological activity of chemical compounds is a widely explored area of research. This pathway is imposed for several reasons: economic considerations, reduction of time constraints, and pressure of public opinion [11]. These methods, which include quantitative structure–activity relationship (QSAR), are an indispensable tool for ecotoxicological risk assessment [12]. QSAR approaches, based on the hypothesis that the structure of a molecule should contain the element responsible for its chemical and biological properties, have been applied to prediction of toxicity [13]. In recent years, QSAR studies conducted by use of artificial neural network (ANN) modeling approaches have received considerable attention in modeling toxicity. Advantageously, a neural network (NN) model has a distinctive ability of learning nonlinear functional relation-ships. They do not require any prior structural knowledge of relationships that exist between important variables and processes to be modeled. There are many reports about QSAR prediction of toxicity of pesticides. However, among this abundant literature, studies specifically dedicated to QSAR prediction of insecticides acute oral toxicity appear rather limited.

In the present study, the basic requirements to develop a QSAR model were respected. The model must be evaluated in terms of its predictive power; its credibility was therefore evaluated through internal and external validation. As potential for toxicity to humans is often extrapolated from animal studies, the main objective of this work was to obtain a QSAR model that could be used to predict oral acute LD_{50} toxicity of a diverse set of 139 insecticides on rats. The stepwise MLR method was used to reduce the number of descriptors and to select the relevant ones. The QSAR model established by using artificial neural networks and molecular descriptors satisfies the guidelines required by the Organisation for Economic Cooperation and Development (OECD) [14].

2. Materials and method

2.1. Rat *LD_{50} data*

LD_{50} (lethal dose) is defined as a statistically derived expression of a single dose of a chemical that can be expected to kill 50% of animals in the experimental group. The LD_{50} is one way to measure the short-term poisoning potential (acute toxicity) of a material. Oral rat LD_{50} acute toxicity data were collected for 139 insecticides from internet databases. The data were selected from the Pesticide Properties DataBase (University of Hertfordshire, 2007–2013). The LD_{50} values were converted into mmol/kg body weight. Insecticides were divided into training, and test sets. The basis of 139 insecticides has been divided into 2 lots. The first with 123 insecticides (88.5%) is dedicated to develop the QSAR model. The second which included 16 insecticides (11.5%) that have not been used for the development of the QSAR model, is left for the external validation. The observed LD_{50} values in the training and test set were in the range 0.01–29.72 mmol/kg.

2.2. Descriptor calculation and Selection of relevant descriptors

SMILES strings were obtained from the Pesticide Properties DataBase (University of Hertfordshire, 2007–2013). These strings were used to generate 1666 descriptors. All descriptors were obtained from the online program E-Dragon 1.0 (www.vcclab.org).

To avoid the phenomenon of overfitting, the number of variables (descriptors) must be reduced. Several methods to simplify a database are used. The method used to select the most significant descriptors was described previously [15]. In the first step, invariant descriptors, namely those with absent values (represented by the code ''999''), were manually removed. Next, any descriptor that had identical values for >75% of the samples and any descriptors with a

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