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IN SILICO AND IN VIVO STUDY OF ACUTE TOXICITY OF THE SUBSTANCE OF THE MEE SERIES

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Abstract
This scientific work examines forecasts and real experiments to study the acute toxicity of a substance of the MEE series. Predicted screenings were carried out using the online GUSAR program. This made it possible to reduce the number of animal deaths. Afterwards, real-life tests were carried out on outbred white mice and the results were compared. According to the final results of the study, the substances of the MEE series in the GUSAR program on rats, he predicted that the substances of the MEE series belong to 4 slightly toxic and 5 non-toxic classes of acute toxicity. In an in vivo study of the MEE-2 substance in mice, the dose was 145 mg/kg. According to the toxicity classification of substances, the substance “MEE-2” belongs to toxicity class III, moderately toxic.

Keywords: Bis-carbamate, dimethyl sulfoxide, methanol, MEE substance, toxicity, in silico, in vivo, GUSAR online, pharmacology, LD50.

Introduction

Currently, carbamates are used in many industries such as agriculture, medicine, pharmaceuticals, technology, chemistry and petrochemistry, etc. Research on derivatives of carbamates and bis-carbamates, carried out recently, is motivated not only by theoretical, but also by practical needs. From this point of view, carbamate derivatives are of undoubted interest as substances with various biological activities. They are widely used in agriculture as bactericides, herbicides, fungicides, insecticides, and growth stimulants. And also, of particular interest is the use of these compounds in medicine as antiviral, antitumor, anti-inflammatory, antidiabetic, antiarrhythmic, vasodilator and other pharmaceuticals [1-4]. Thus, studying the acute toxicity of drugs such as N,N'-hexamethylene-bis-[(o-cresolyl)-carbamate] i.e. MEE-1, N,N'-hexamethylene-bis-[(m-cresolyl)-carbamate] i.e. MEE-2 and MEE-3 is important. The first step was to make predictions using computer programs to prevent the death of the mice. But to confirm the forecast, the MEE-2 substance was studied in reality, which is the goal of this scientific work.

2. Materials and Methods

To study the substance of the MEE series, *in silico* prediction of LD_{50} values for rats with four types of administration (oral, intravenous, intraperitoneal, subcutaneous, inhalation) were studied using the GUSAR program [5-9]. For prediction, training sets were created using data from the

SYMYX MDL toxicity database. The acute toxicity of the test substance "MEE-2" was studied by the generally accepted method described in the literature [10], a single administration of drugs with determination of the toxicity class.

3. Results and Discussions

GUSAR software was developed to generate QSAR/QSPR models from corresponding training sets presented as an SD file containing chemical structure and quantified endpoint data. QNA descriptors and their polynomial transformations do not provide information about the shape and volume of the molecule, although this information may be important for determining structure-activity relationships. Therefore, these parameters were added to the variables obtained from the Chebyshev polynomials. The topological length of a molecule is the maximum distance calculated by the number of bonds between any two atoms (including hydrogen). The volume of a molecule is equal to the sum of the volumes of each atom. To study the substance of the MEE series, we entered the structures of molecules in the MOL.file format and obtained the following predictions in Tables 1 and 2.

Table 1 Rat acute toxicity predicted by GUSAR

Substance	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
MEE-1	564,500 in AD	76,220 in AD	1873,000 in AD	413,200 in AD
MEE-2	587,600 in AD	60,980 in AD	2884,000 in AD	238,900 in AD
MEE-3	523,800 in AD	71,090 in AD	2196,000 in AD	486,400 in AD

Here: IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration.

Table 2 Acute Rodent Toxicity Classification of Chemicals by OECD Project

Substance	Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
MEE-1	Class 5 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD
MEE-2	Class 5 in AD	Class 4 in AD	Class 5 in AD	Class 4 in AD
MEE-3	Class 5 in AD	Class 4 in AD	Class 5 in AD	Class 4 in AD

Here: in AD - compound falls in applicability domain of models; out of AD - compound is out of applicability domain of models.

After the prediction results by the GUSAR program, the acute toxicity of the test substance "MEE-2" was studied by the generally accepted method described in the literature, a single administration of drugs with determination of the toxicity class. The experiment used white outbred mice weighing 19 - 21 g. During the experiments, the mice were kept in a vivarium at an air temperature of +20 – 22 °C, humidity no more than 50%, air exchange volume 8:10, day-night light mode. The mice were kept on a standard diet. For the experiment, a 1.5% solution of the drug 30 mg MEE-2 + 1.5 ml of methanol were prepared. The animals were divided into 5 groups of 6 animals each and a solution of MEE-2 substance was administered intragastrically once. The results are shown in Table 3.

Table 3 *In vivo* study of the acute toxicity of the MEE-2 substance in mice

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Substance	Route of administration	Mice LD50 (mg/kg)	Classification
MEE-2	Oral	145 (118-178)	Class 3

According to the toxicity classification of substances, the substance “MEE-2” belongs to toxicity class III, moderately toxic.

4. Conclusion

When *in silico* studying the substances of the MEE series in the GUSAR program on rats, he predicted that the substances of the MEE series belong to 4 slightly toxic and 5 non-toxic classes of acute toxicity. In an *in vivo* study of the MEE-2 substance in mice, the dose was 145 mg/kg. According to the toxicity classification of substances, the substance “MEE-2” belongs to toxicity class III, moderately toxic. But we believe that the toxicity of the solution would have been lower if we had prepared it in dimethyl sulfoxide DMSO instead of toxic methanol and would have matched the prediction of the GUSAR program.

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