ACTUAL TRENDS IN COMPUTATIONAL TOXICOLOGY I. USING PHYSICAL-CHEMICAL DATA TO EVALUATE THE ACUTE TOXICITY (LD_{50})

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abstract: Aim of this work consists in evaluation of acute toxicity indices, expressed as LD_{50} values, based on physical-chemical data. Some basic considerations concerning actual trends in computational toxicology are exposed. The calculated LD_{50} values based on different physical-chemical data in a series of new synthesized acetanilides derivatives are discussed in relation with experimental ones.

Introduction

In present numerous companies and researchers are working on developing software to enable toxicology to be undertaken *in silico* rather than more conventionally *in vivo* or *in vitro*, with all their associated experimental and ethical problems [1]. Chemical Abstracts Service introduced TOXICENTER in February 2002, a database which carries toxicological information in more than five millions records [2]. The COmputerized Molecular Evaluation of Toxicity (COMET) project of the European Commission DG12 was completed in 2001 under coordination of Emilio Benfenati, chief of laboratory on Environmental Chemistry and Toxicology in Milan, Italy. Parameters for coupling molecular similarity and dissimilarity with activity using physical-chemical, topological and quantum chemical data have been defined.

The goal of this paper consists in evaluation of acute toxicity, defined as LD_{50} using only primary level of information, i.e. the physical-chemical data concerning a class of compounds as in precedent work [3]. Sure, our group can manage successfully with information received from quantum chemical computations [4].

Theoretical considerations

It is necessary to define concepts used in toxicology [5].

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Toxicant is a substance which introduced in organisms in relative high dose (unique or repeated at short periods) or in small doses (repeated for long time) determines alteration of organisms functions and may lead to death. Really, is established that every molecule, thermodynamic instable at temperatures higher than zero absolute, posses a reactivity which can be expressed by its toxicity.

The sphere of concept is larger; this can cover more classes of toxicants. For example the new proposed medicines (drugs) must be tested for toxicity.

DL_{50} (in mg/kg corp) is defined as acute toxicity induced by a substance (introduced in organism in oral/ parentheral mode) which determine a lethal effect for 50% from exposed animals.

A series of regression equations between CL_{50} (mM/l) and molecular weight (M), boiling point (t_b), melting point (t_m) and density (d) of organic volatile compounds have been established by Golubev [6]:

$$\log CL_{50}(mM/l) = 0.08 - 0.011\ M \quad (1)$$

$$\log CL_{50}(mM/l) = 0.02 - 0.09\ t_f \quad (2)$$

$$\log CL_{50}(mM/l) = 1.62 - 0.01\ t_m \quad (3)$$

$$\log CL_{50}(mM/l) = 0.11 - 0.2\ d \quad (4)$$

In this case indices of toxicity CL_{50} are defined after an exposure to toxic agent of 2 hours and a period of observation of 7 days and the physical chemical parameters of toxicants must be in corresponding interval:

$$30 < M < 300;\ 0.5 < d < 2;\ -100°C < t_b < 300°C;\ -190°C < t_m < 180°C$$

In works of Filov [7] and Sato [8] are done similar type of equations for TLV's*.

A very argumented regressional analysis [3] for aminic compounds indicates the following equations:

$$\log CMA = -1.04 - 0.006\ M \quad (5)$$

$$\log CMA = -1.62 - 0.012\ t_m \quad (6)$$

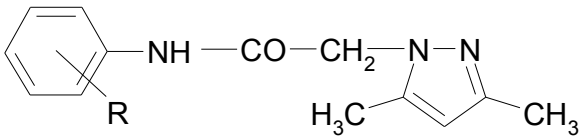
A better prediction for TLV's has been obtained using acute toxicity indexes [9,10]. For organic volatile compounds the corresponding equation is:

$$\log CMA\ (mM/m^3) = 0.88 \log DL_{50}\ (mM/l) - 2.29 \quad (7)$$

Results and discussions

To apply these considerations we extracted physical-chemical data from [11] for new substituted 2-(3,5-dimethyl- pirazol-1-yl)-acetanilides with pharmacological activity having general formula:

* - TLV's (Threshold Limits Values) – correspond in Romanian terminology to Maximal Admitted Concentration CMA's, expressed in mg/m^3.



where R – distinctive substituent given in Table 1.

Table 1. The physical-chemical data of named compounds

No	Distinctive radical R	M_{exp}	M.P (°C)
1	2'-Me	243	151-152
2	3'-Me	243	136-138
3	4'-Me	243	145-147
4	2'4'-diMe	257	158-159
5	2',6'-diEt	285	149-150
6	2'-NO_2	274	130-131

Using the equations (5) or (6) and consecutively (7) we obtained the values of log CMA and log DL_{50} from Table 2.

Table 2. Calculated log CMA and log DL_{50} values for named compounds

No	log CMA (5)	log DL_{50} (7)	log CMA (6)	log DL_{50} (7)
1	–2.498	0.236	–3.444	–1.311
2	–2.498	0.236	–3.252	–1.093
3	–2.498	0.236	–3.360	–1.215
4	–2.582	0.3318	–3.516	–1.393
5	–2.750	0.522	–3.408	–1.270
6	–2.684	0.4472	–3.18	–1.011

Analyzing results in columns two and three we can observe that computations after equation which use M values (determined with high precision by MS in [11]) can not discern between isomers. The compounds **1-3** appear as the most toxic in this series in contradiction with experimental data of authors [11]. But the results of computations done in fourth and fifth columns of Table 2 based on melting point determinations indicate that **6** (2'-NO_2) is the most toxic compound in this series and the least toxic is the compound number **4** (2',4'-diMe) in concordance with experimental data of cited authors [11].

Conclusion

Acute toxicity indices defined as log DL_{50}, obtained using melting point determinations can discern accurately the experimental observed variation of acute toxicity and can predict the most toxic compound in a series.

REFERENCES

1. Isfort, R.and Lederberg, J. (2000) *Annals NY Acad. Sciences* **IX**, 919.
2. Mandravel, C., (2003) *ARIO Book of Abstracts*, 8.
3. Mandravel, C., Stanculescu, I. and Chiosa, V. (2003) *An. Univ. Buc. (ser. Chimie)* **I-II**, 279-84.
4. Stanculescu, I., Mandravel, C., Delattre, F., Landy, D., Fourmentin, S., Woisel, P. and Surpateanu, G. (2003) *IEJMB* **2**, in press, http://www.biochempress.com
5. Mandravel, C., Stanescu-Dumitru R. and Chiosa V. (2003) **Relatii intre structura, proprietati si activitate biologica aplicate la poluantii industriali**, Ed. Univ. Buc., Bucuresti, 154-6.
6. Golubev, D. (1973) **Kolicestvenaia Toxicologia**, Medicina, Leningrad.
7. Filov V.A. (1962) *Biofizica* **7**(1), 73-79.
8. Sato, A. and Nakajima, F.N. (1979) *Arch. Env. Health* **2**, 69-75.
9. Spimu, I. and Ivanova, L.N. (1977) **Mathematical Prognostication and Prophylaxis of Environmental Pollution by Pesticides**, Medicina, Moscow.
10. Nikiforov, V. (1979) *Hygiena i Sanitaria* **10**, 56-60.
11. Zalaru, C., Iovu, M., Dumitrascu. F., Cristea E. and Tarcovnicu, I. (2004) *Anal. Univ. Buc (ser. Chimie)* **I-II,** in press.