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Determination of Descriptors Which Influence the Toxicity of Organochlorine Compounds Using Qsar Method

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Authors' contributions

This work was carried out in collaboration among all authors. Author MOP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors BK and NNK managed the analyses of the study. Author ZN managed the literature searches. All authors read and approved the final manuscript.

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Short Research Article

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ABSTRACT

Organochlorine Pesticides (OCP) are organic compounds obtained by the chlorination of various unsaturated hydrocarbons. They are very toxic and therefore belong to the family of persistent organic pollutants. If formerly these pesticides were used to fight against certain vectors of diseases and thus improve the productivity of the host, today they are considered as "enemy" of the environment. To understand the origin of the toxicity of organochlorine compounds, we used 73 molecules (test set: 50 and validation: 23) containing at least one chlorine atom and for which the toxicity ($LogLC_{50}$) against *Poecilia reticulata* is known to establish QSAR models. Firstly, we used principal component analysis (PCA) to identify the best descriptors. Then, the different models were established using the method of multiple linear regression (MLR). Models established with quantum and physicochemical descriptors only showed satisfactory results. But the best model was determined with the combination of both quantum and physicochemical descriptors. The criteria of this model are as follows:

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$R^2 = 0.939$; $R^2_{ajusted} = 0.932$; $P_{value} < 0.0001$; $\alpha = 0.05$
$R^2_{CV} = 0.935$; $R^2 - R^2_{CV} = 0.004$; $MCE = 0.073$; F =134.701
These criteria show that the toxicity of organochlorine compounds is well described by the combination of quantum and physicochemical descriptors namely lipophilia (LogP), polarizability (pol), entropy (S), zero-point energy (ZPE) and the number of chlorine atoms (NCl).

Keywords: Organochlorine compounds; toxicity; QSAR; quantum descriptors and physicochemical descriptors.

1. INTRODUCTION

Organochlorine pesticides use began in the 1940s with the advent of dichlorodiphenyl-trichloroethane (DDT) which was synthesized for the first time by Othmar Zeidler in 1873 [1] and whose insecticidal properties were discovered by Paul Müller in 1939 [2]. These pesticides have contributed to improved and increased agricultural yields and have led to progress in the control of food resources [3]. The use of organochlorine pesticides has not been limited to increasing agricultural yields, it has also spread to other sectors. Indeed, organochlorine pesticides have long time been used to fight against certain diseases vectors [4-7]. DDT is one of the insecticides recommended by WHO for indoor residual spraying for malaria control [8].

After two decades of intense use, research [7,9] begun to show the dangerousness of these chemical compounds to the environment.

Over time, several studies [10-13] proved their presence in all ecosystems and their effects on elements which live there. The presence of organochlorine pesticides in all ecosystems is assumed to be due to both their persistence their volatility.

The persistence of organochlorine compounds in the environment is largely due to the stability of the carbon-chlorine bond that is resistant to degradation. But their presence throughout the food chain is the consequence of their lipo-solubility. This property gives them the ability to cross the phospholipid structure of biological membranes thereby reaching the adipose tissue in which they accumulate. The rate of these compounds increases in the body of the species that live in these environments with progress in the food chain in which humans are at the top [14-16].

As for volatility, it is generally due to the organochlorines' relatively high vapor pressure. This property allows them to travel great distances. Thus, according to some studies [17-19], organochlorine pesticides have been found in environments in which these pesticides have never been used and sometimes even far from the places where they were used. In view of all the above-mentioned, the use of organochlorine pesticides was therefore regressed from the 1970s and even several pesticides containing organochlorines were banned in some countries. But it was until the year 2001 that the first Conference on Persistent Organic Pollutants (POPs) was held. Indeed, in Sweden in 2001, the Stockholm Convention marked the first convention on POPs. This convention has been signed by 151countries. This high number of signatories of the convention shows its importance. Since then, it was decided to reduce or even to eliminate the production and the exploitation of persistent organic pollutants. Among the 12 organic pollutants covered by this convention, 9 represent organochlorine pesticides.

The main objective of this study is to perform a QSAR study of organochlorine compounds to determine the descriptors that influence their toxicity.

Crum-Brown and Frazer [20] were considered to be the precursors of the QSAR methodology. Indeed, already in 1868, they postulated that the biological activity of a molecule is a function of its chemical constitution. In 1893, Richet [21] discovered that the toxicity of organic compounds is inversely proportional to their solu bility in water. But the era of QSAR really begins in the 1960s with, on the one hand the publication of Hansch and Fujita [22] and on the other hand, the publication of Free and Wilson [23]. And from then, the number of publications containing the word "QSAR" continues to increase due its ability to predict the properties of chemical compounds.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Selection of data set

We investigated about 73 molecules as displayed in Table 2. These molecules were taken from Alan Katritzky et al.'s article [24]. For each molecule, LogLC_{50} is calculated where LC_{50} stands for the concentration that causes the death of 50% of the population of the test organism. Besides, the most toxic compound is assumed to display the smallest value of LogLC50. Furthermore, it should be noted that lethal dose (LD) and lethal concentration (LC) are identical. But the difference is related to the mode of penetration of the substance into the body. When the administered substance enters the body by inhalation, the notion of dose is replaced by that of concentration. Thus, the lethal dose 50 becomes the lethal concentration 50 [25]. According to Hodge and Sterner [26] chemicals products can be classified into 6 groups according to their toxicities (Table 1).

The set of all 73 molecules that were used in this study are shown in Table 2.

2.1.2 Molecular descriptors

We have calculated several quantum and physicochemical descriptors to carry out the QSAR model.

- **Quantum descriptors**

For quantum descriptors we determined highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), total energy (E_T), dipole moment (DM), constant volume heat capacity (C_v), entropy (s), thermal energy (E_{th}), highest Mulliken electronic charge (*CAE*), lowest Mulliken electronic charge (*CAF*), ionization potential (PI); electronic affinity (*AE*), energy gap between E_{HOMO} and E_{LUMO} (ΔE), absolute electronegativity (χ), Chemical potential (μ), absolute hardness (η), mollesse ($\boldsymbol{S}$) and reactivity index (ω). We also considered the number of chlorine (N_{Cl}) atoms as a descriptor. These descriptors were generated or calculated by Gaussian 03 [27] technique. The calculations were performed, thanks to DFT method with B3LYP as the functional and 6-311++g (d,p) as basis set. Moreover, they were determined on reference to equations below.

$$PI = -E_{HOMO}\,;\ AE = -E_{LUMO}\,;\ \Delta E = E_{LUMO} - E_{HOMO}$$

$$\chi = \frac{E_{LUMO}+E_{HOMO}}{2} = \frac{AE+PI}{2} = -\mu\,;$$

$$\eta = \frac{E_{LUMO}-E_{HOMO}}{2} = \frac{PI-AE}{2}\,; \quad S = \frac{1}{\eta}\,; \quad \omega = \frac{\mu^2}{2\eta}.$$

- **Physicochemical descriptors**

For physico-chemical descriptors, we used ChemSketch [28] to determine lipophilicity (LogP), formula weight (M), molar refractivity (Rm), molar volume (Vm), parachlor (Pc), index of refraction (Ir), surface tension (γ), density (d) and polarizability (Pol).

2.2 Methods

2.2.1 Descriptive analysis

XLSTAT [29] software and the principal component analysis (PCA) method were used to realize the matrix of correlation. Principal component analysis (PCA) permits to examine descriptors set and to select the good ones that give the best model at prediction [30]. It allows to identify the descriptors which correlate well with the biological activity Log (LC_{50}).

Table 1. Class of toxicity according to the scale Hodge and Sterner [27]

Index or class of toxicity	Term commonly used	Toxicological parameter (DL_{50})
1	Extremely toxic	$DL_{50} \leq 1$ mg/kg
2	Highly toxic	1 mg/kg $\leq DL_{50} \leq$ 50 mg/kg
3	Moderately toxic	50 mg/kg $\leq DL_{50} \leq$ 500 mg/kg
4	Slightly toxic	500 mg/kg $\leq DL_{50} \leq$ 5000 mg/kg
5	almost not toxic	5000 mg/kg $\leq DL_{50} \leq$ 15000 mg/kg
6	relatively harmless	$DL_{50} \geq$ 15000 mg/kg

Table 2. Names and LogLC_{50} of 73 organochlorine molecules

N°	Compounds	Log LC_{50}			
Test set					
1	3-chloroaniline	2.02	38	2-chlorophenol	1.94
2	3-chlorophenol	1.70	39	3,4-dichloroaniline	1.61
3	4,5-dichloro-2-methoxyphenol	1.40	40	3,4-dichlorotoluène	1.40
4	4-chloro-3,5-dimethylphenol	1.34	41	3,5-dichloroaniline	1.38
5	4-chloroaniline	2.33	42	3-chlorotoluène	2.16
6	4-chlorophenol	1.82	43	chlorobenzene	2.23
7	4-chlorotoluène	1.67	44	lindane	-0.69
8	Chloroform	2.93	45	trichloroethene	2.58
9	dichloromethane	3.54	46	1,2,3-trichlorobenzene	1.11
10	hexachlorobutadiene	-0.20	47	1,3-dichlorobenzene	1.72
11	pentachlorobenzene	-0.15	48	2,4-dichlorophenol	1.41
12	pentachloroethane	1.74	49	2,5-dichlorophenol	1.42
13	pentachlorophenol	0.22	50	3,4,5,6-tetrachloro-2-hydroxyphenol	1.00
14	tetrachloroethene	1.98	**Validation set**		
15	tetrachloromethane	2.64	51	1,1-dichloroéthane	3.31
16	α,α-dichloro-m-xylyene	-0.16	52	1,2,3,4-tetrachlorobenzene	0.65
17	1,1,1-trichloroéthane	3.00	53	1,2,3,5-tetrachlorobenzene	0.57
18	1,1,2-trichloroéthane	2.82	54	1,2,4,5-tetrachlorobenzene	0.15
19	1,2-dichlorobenzene	1.60	55	1,2,4-trichlorobenzene	1.17
20	2,3,4,5-tetrachloroaniline	0.19	56	1,2-dichloroethane	3.06
21	2,3,5-trichlorophenol	1.08	57	1,2-dichloropropane	3.01
22	2,4-dichloroacetophenone	1.80	58	1,3-dichloropropane	2.87
23	2,4-dichloroaniline	1.59	59	1,4-dichlorobenzene	1.44
24	2-chloro-4-methylphenol	2.40	60	2,2,2-trichloroethanol	3.31
25	Dieldrin	-1.78	61	2,3,4,6-tétrachlorophenol	0.67
26	hexachloroethane	0.81	62	2,3,6-trichloroaniline	1.27
27	1,1,2,2-tetrachloroethane	2.23	63	2,4,5-trichlorophenol	0.80
28	1,2,3-trichloropropane	2.45	64	2,4,6-trichlorophenol	1.06
29	1,3,5-trichlorobenzene	1.26	65	2,4,α-trichlorotoluène	0.08
30	1-chlorobutane	3.02	66	2,4-dichlorotoluène	1.46
31	2,3,4,5-tetrachlorophenol	0.48	67	2,6-dichlorophenol	1.68
32	2,3,5,6-tetrachloroaniline	0.07	68	2-chloroaniline	1.69
33	2,3,5,6-tetrachlorophenol	0.74	69	3,4,5-trichloro-2,6-dimethoxyphenol	1.12
34	2,3,6-trichlorophenol	1.44	70	3,4,5-trichloro-2-methoxyphenol	1.03
35	2,4,5-trichloroaniline	1.08	71	3,4,5-trichlorophenol	0.92
36	2,4,5-trichlorotoluène	0.94	72	3,5-dichlorophenol	1.22
37	2,5-dichloroaniline	1.01	73	4-chloro-3-methylphenol	1.67

2.2.2 Statistical analysis

The establishment of QSAR model consists of making out mathematical relationship between biological activity and chemical descriptors. Thus, QSAR model is considered satisfied when the following conditions are satisfied. The choice of the best statistical model has to satisfy the following criteria that encompass the highest coefficient of determination (R^2), the highest of adjusted determination coefficient ($R^2_{ajusted}$), the highest coefficient of Fischer (*F),* the highest coefficient of cross validation *(*R^2_{CV}), the lowest values of Mean Square Error (*MSE*) and the difference $R^2 - R^2_{CV} < 0.3$.

The calculation of these parameters requires a statistical analysis. The most available methods allowing that calculation are Simple Linear Regression (SLR), Multiple Linear Regression (MLR), neurons networks and Partial Least Squares (PLS). In this article, MLR method of XLSTAT was used to perform the prediction [29].

3. RESULTS AND DISCUSSIONS

3.1 Matrix of Correlation

The principal component analysis permits to perform the matrix of correlation. Any descriptor having a partial correlation coefficient with the

biological activity Log (LC_{50}) less than 0.5 is removed from the descriptors set. For 2 descriptors having partial correlation coefficients with biological activity greater than 0.5 and whose partial correlation coefficient between both descriptors is greater than 0.95 then the one with the smallest partial correlation coefficient with the biological activity is also removed from the descriptors set. And we obtain the matrix of correlation presented in Tables 3 and 4. These Tables show that the selected descriptors correlate well with toxicity, because all of correlation's coefficients are higher than 0.5.

3.2 Quantum Descriptors Model

- **Equation of model 1**

Log LC_{50} = 3.11 – 12.66*E_{LUMO} – 0.049*S – 4.92E-04*ZPE – 0.51*NCl + 13.05*∆E

$N = 50$; $R^2 = 0.88$; $R^2_{adjusted} = 0.86$; $R^2_{CV} = 0.86$; $R^2 - R^2_{CV} = 0.02$;

$MCE = 0.15$; $F = 63.40$; P_{value} < 0.0001; $\alpha = 0.05$

Here, ***N*** is the number of molecule, ***MCE*** is Mean Square Error, $\boldsymbol{R^2}$ is the coefficient of determination, $\boldsymbol{R^2_{adjusted}}$ is the adjusted coefficient of determination, $\boldsymbol{R^2_{CV}}$ is the coefficient of cross validation and ***F*** is the coefficient of Fischer.

Furthermore, the small value of P_{value} means that the selected variables do bring a significant amount of information. The high values of $R^2\,(0.88)$ and $R^2_{adjusted}\,(0.86)$ and the low value of MSE (0.15) including $0.5 < R^2_{CV} < 0.9$ and $R^2 - R^2_{CV} < 0.3$ indicate that the proposed model is satisfactory and can predict our biological activity (LC_{50}).

$R^2_{adjusted} = 0.86$ indicates that the toxicity of 86% of our compounds are described with reliability by the selected descriptors. The high value of the coefficient of Fischer ($F = 63.40$) shows the strong relation which exists between the toxicity and the selected descriptors.

We can notice from the analysis of the equation of model 1 that Log (LC_{50}) increases when energy of the lowest unoccupied molecular orbital (E_{LUMO}), the entropy (*s*), the zero-point energy (ZPE) and the number of chlorine atoms (N_{Cl}) decrease while the gap energy (∆E) increases. Thus, the toxicity of organochlorine compounds evolves in the same direction as ∆E and in the opposite direction as E_{LUMO}, S, ZPE and N_{Cl}.

The regression line between the experimental and theoretical LogLC_{50} of the test and the validation set is illustrated in Fig. 1. The high value of determination coefficient $(R^2 = 0.88)$ and the low value of mean square error $MCE = 0.15$ prove a good similarity between the predicted and experimental values. This good similarity is highlighted also in Fig. 2.

Table 3. Matrix of correlation (Pearson (n)) of quantum descriptors used for model 1

Variables	Log LC_{50}	E_{LUMO}	S	ZPE	N_{Cl}	∆E
Log LC_{50}	1					
E_{LUMO}	0,522	1				
S	-0,848	-0,425	1			
ZPE	0,52	0,668	-0,542	1		
N_{Cl}	-0,569	-0,772	0,536	-0,9	1	
∆E	0,68	0,336	-0,581	0,182	-0,091	1

Table 4. Matrix of correlation (Pearson (n)) of Physico-chemical descriptors used for model 2

Variables	Log LC_{50}	LogP	M	Pc	Ir	ɣ	D	Pol
Log LC_{50}	1							
LogP	-0,847	1						
M	-0,871	0,826	1					
Pc	-0,777	0,668	0,779	1				
Ir	-0,728	0,622	0,628	0,576	1			
ɣ	-0,679	0,59	0,682	0,55	0,941	1		
D	-0,574	0,603	0,797	0,413	0,527	0,656	1	
Pol	-0,925	0,832	0,912	0,853	0,774	0,749	0,552	1

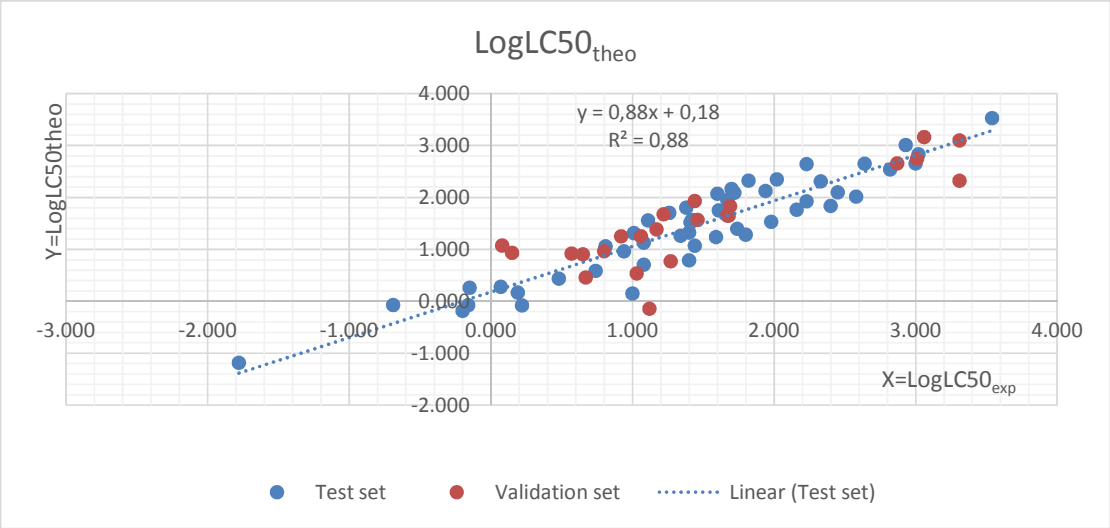

Fig. 1. Regression line of the test and validation sets

The regression line of the test set indicates that: $LogLC_{50theo} = 0.88 * LogLC_{50exp} + 0.18$

➢ **Contribution of descriptors**

The contributions of the quantum descriptors in the prediction of the organochlorine molecules toxicity were illustrated in the Fig. 3. The classification of the contribution of the descriptors in the model is as follows:

$$N_{Cl}(-0.74) > S(-0.57) > ZPE(-0.37) > \Delta E(0.35) > ELUMO(-0.19)$$

According to the contribution of these descriptors, the number of chlorine molecules (N_{Cl}) is the most important descriptor and lowest unoccupied molecular orbital energy (E_{LUMO}) is the least important descriptor for the prediction of toxicity of organochlorine molecules.

3.3 Physico-chemical Descriptors Model

➢ **Equation of model 2**

Log LC$_{50}$** = 9,95 - 0,11LogP** -3,31***Ir** + 0,03***ɣ** - 0,73***d** - 0,22***pol** ;* $N = 50;\ R^2 = 0.90;\ MCE = 0.12;$

$F = 80.29;\ P_{value} < 0.0001;\ \alpha = 0.05\quad R^2_{ajusted} = 0.89;\ R^2_{CV} = 0.89;\ R^2 - R^2_{CV} = 0.01$

The various calculated parameters prove that the model established with the physicochemical descriptors is predictive and reliable. In this model 89% of our compounds are described with reliability by the selected descriptors. Therefore, this model is shown to be satisfactory.

The toxicity of organochlorine compounds increases when lipophilicity (LogP), density (d), polarisability (pol) and index of refraction decrease and surface tension (ɣ) increases.

The regression line between the experimental and theoretical LogLC$_{50}$ of the test and the validation set is illustrated in Fig. 4. Here, the high value of determination coefficient $(R^2 = 0.90)$ and the low value of mean square error $MCE = 0.12$ prove a good similarity between the predicted and experimental values. This good similarity is emphasized also into Fig. 5.

➢ **Contribution of descriptors**

The contributions of the physicochemical descriptors in the prediction of the organochlorine molecules toxicity were illustrated in the Fig. 6. The classification of the contribution of the descriptors in the model is as follows:

$$Pol(-0.86) > ɣ(0.31) > Ir(-0.20) > d(-0.16) > LogP(-0.10)$$

According to this classification, polarizability is the most important descriptor and lipophilicity is the least important descriptor to prediction of toxicity of organochlorine molecules.

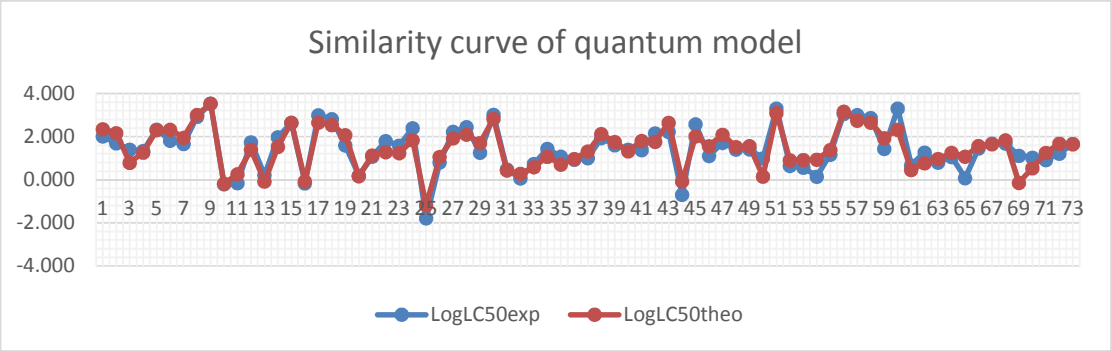

Fig. 2. Similarity curve of the experimental and predicted values of the quantum descriptors model

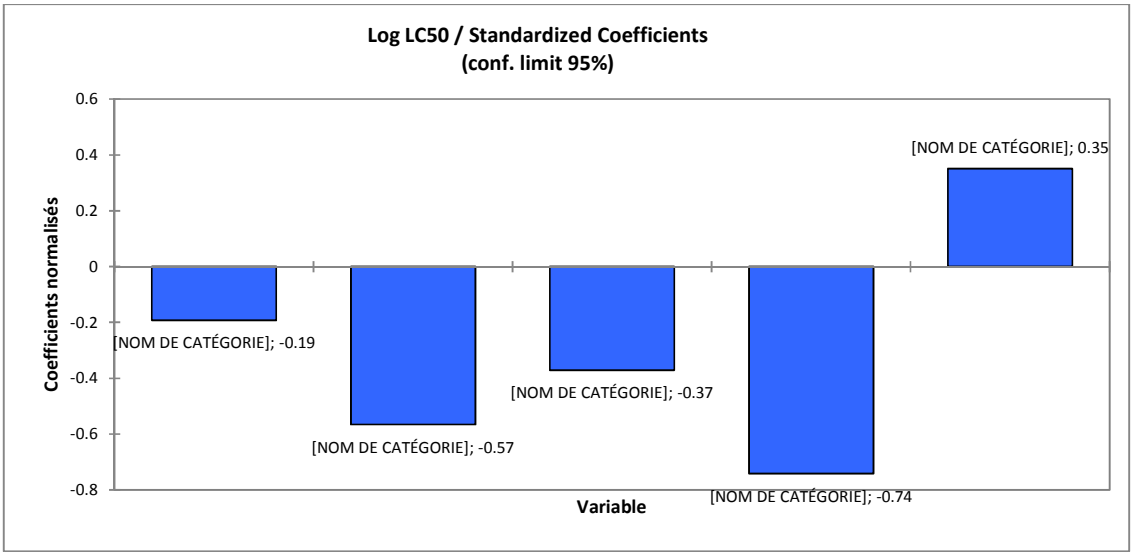

Fig. 3. Contribution of descriptors in model 1

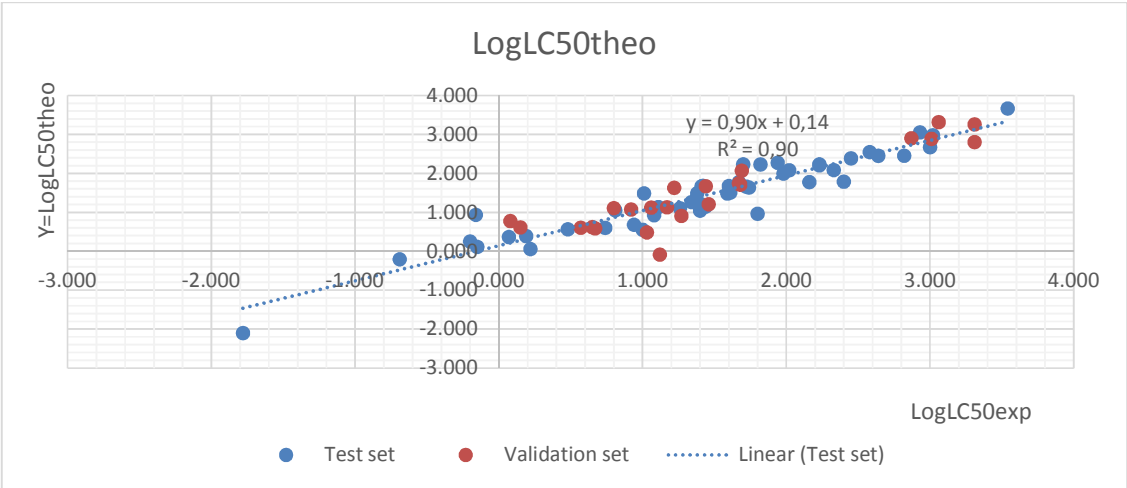

Fig. 4. Regression line of the test and validation set

The regression line of the test set indicates that: $LogLC_{50theo} = 0.90 * LogLC_{50exp} + 0.14$

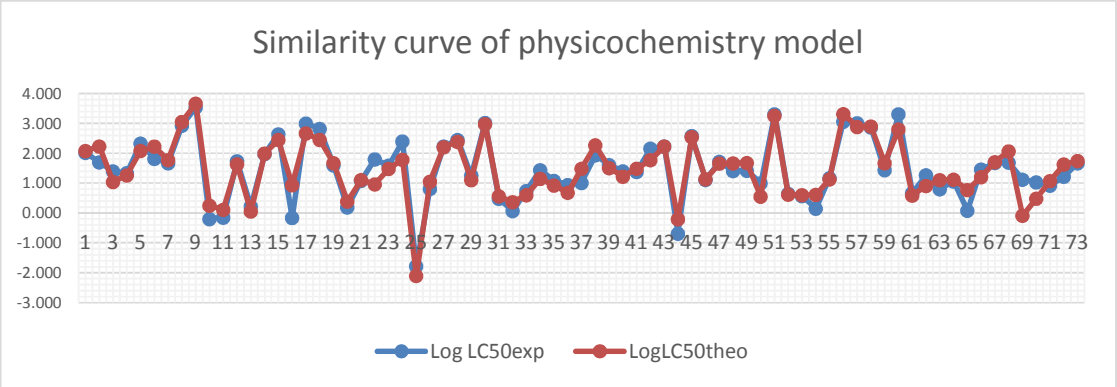

Fig. 5. Similarity curve of the experimental and predicted values of the physicochemical descriptors model

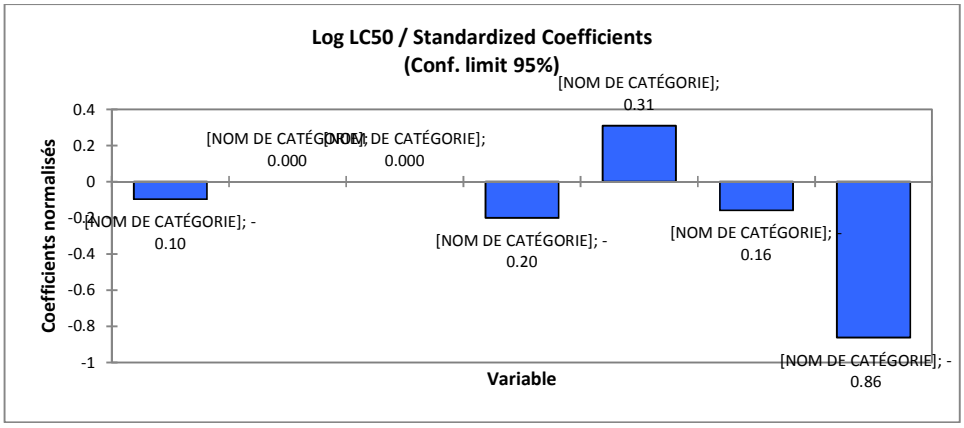

Fig. 6. Contribution of descriptors in model 2

3.4 Quantum and Physicochemical Descriptors Model

➢ **Equation of model**

Log LC_{50} = 3,72 **-** 0,14***LogP* -** 0,29***pol* +** 3,17E-02***S* -** 5,70E-04***ZPE* -** 0,36***N_{Cl}***

$R^2 = 0.94$; $R^2_{ajusted} = 0.93$; $R^2_{CV} = 0.93$; $R^2 - R^2_{CV} = 0.004$; $MCE = 0.07$; F =134.70;

$P_{value} < 0.0001$;

$\alpha = 0.05$

The greatest values of R^2 ; $R^2_{adjusted}$ and F and the lowest values of MCE and P_{value} shows the strong relation which exists between the toxicity and the selected descriptors. In this model 93% of our compounds are described with reliability by the selected descriptors. Then $R^2_{CV}(= 0.93) > 0.9$ *and* $R^2 - R^2_{CV}(= 0.004) < 0.3$ prove that this model is excellent. This equation shows that LogLC50 of organochlorine molecules increases when LogP, Pol, ZPE and NCl decrease and S increases.

The regression line between the experimental and theoretical LogLC50 of the test and the validation set is illustrated in Fig. 7. The high value of determination coefficient $(R^2 = 0.94)$ and the low value of mean square error $MCE = 0.073$ prove a good similarity between the predicted and experimental values. This good similarity is demonstrated also through Fig. 8.

➢ **Contribution of descriptors**

The contributions of the five descriptors in the prediction of the organochlorine molecules toxicity are illustrated by the Fig. 9. The classification of the contribution of the descriptors in the model is as follows:

$$Pol(1.14) > N_{Cl}(0.53) > ZPE(0.43) > S(0.37) > LogP(0.13)$$

According to the contribution of these descriptors, polarizability is the most important descriptor and lipophilicity is the least important descriptor for prediction of toxicity of organochlorine molecules.

3.5 Comparison of Different Models

The comparison of the criteria of validation enables us to choose the best model for the toxicity of the organochlorine molecules prediction. These criteria are summarized in the Table 5.

After comparing the validation criteria contained in Table 5, we notice that the best model is that obtained with the union of both quantum and physicochemical descriptors. This is proven by the highest value of $R^2, R^2_{ajusted}, F\ and\ R^2_{CV}$ and the lowest values of $MCE\ and\ R^2 - R^2_{CV}$. The values of R^2_{CV} superior to 0,9 and $R^2 - R^2_{CV}$ lower than 0,3 show that the established model is excellent [31]. Besides, The Table6 below summarizes the different molecules, the experimental values of toxicity (Log (LC_{50})) $_{exp}$, the theoretical values of toxicity (Log (LC_{50}))$_{theo}$ and the ratio (Log (LC_{50}))$_{exp}$ / (Log (LC_{50}))$_{theo}$.

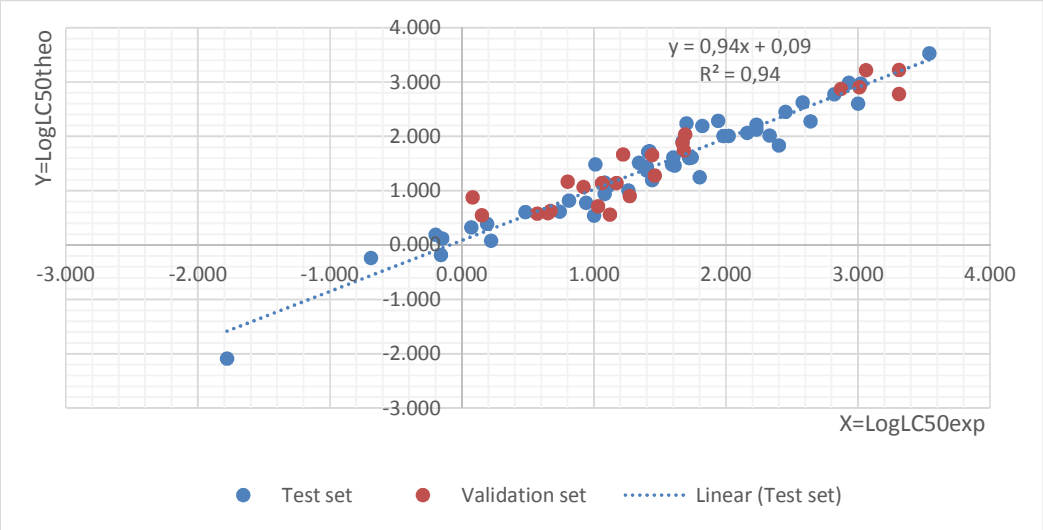

Fig. 7. Regression line of the test and validation sets

The regression line of the test set indicates that: $LogLC_{50theo} = 0.94 * LogLC_{50exp} + 0.09$

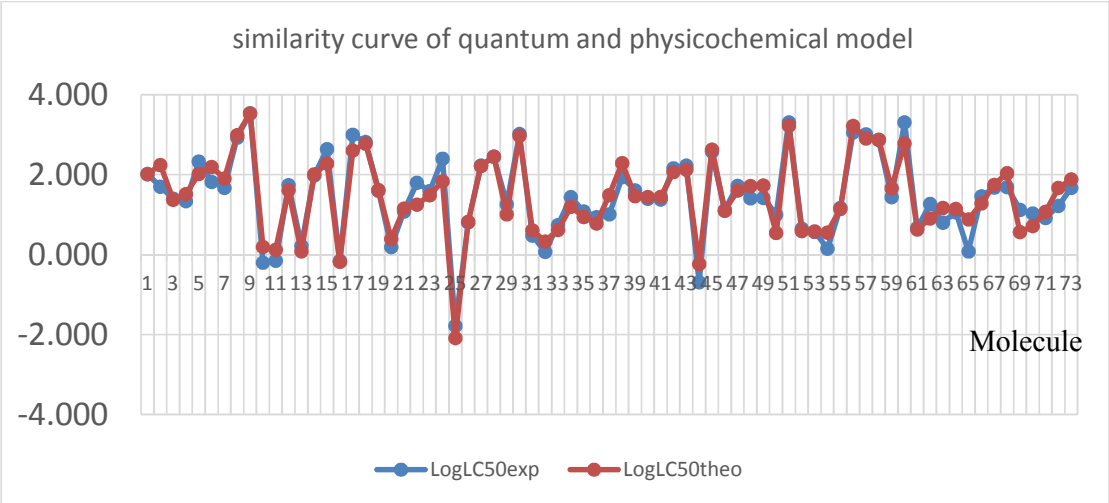

Fig. 8. Similarity curve of the experimental and predicted values of the quantum and physicochemical descriptors model

Table 5. Table of comparison of different models

Nature of descriptors Criteria	Quantum	Physicochemical	Quantum and physicochemical
N	50	50	50
R^2	0.88	0.90	0.94
$R^2_{ajusted}$	0.86	0.89	0.93
MCE	0.15	0.12	0.07
F	63.40	80.29	134.70
R^2_{CV}	0.86	0.89	0.93
$R^2 - R^2_{CV}$	0.02	0.01	0.004
P_{value}	< 0.0001	< 0.0001	< 0.0001
α	0.05	0.05	0.05

Table 6. Ratio (Log (LC50))$_{exp}$ / (Log (LC50))$_{theo}$ of mixed model

N°	Compounds	Log(LC_{50exp})	Log(LC_{50theo})	Log(LC_{50exp})/ Log(LC_{50theo})
Validation set				
51	1,1-dichloroéthane	3.31	3.225	1.026
52	1,2,3,4-tetrachlorobenzene	0.65	0.590	1.101
53	1,2,3,5-tetrachlorobenzene	0.57	0.583	0.978
54	1,2,4,5-tetrachlorobenzene	0.15	0.552	0.272
55	1,2,4-trichlorobenzene	1.17	1.145	1.022
56	1,2-dichloroethane	3.06	3.221	0.950
57	1,2-dichloropropane	3.01	2.908	1.035
58	1,3-dichloropropane	2.87	2.875	0.998
59	1,4-dichlorobenzene	1.44	1.660	0.867
60	2,2,2-trichloroethanol	3.31	2.783	1.189
61	2,3,4,6-tétrachlorophenol	0.67	0.632	1.060
62	2,3,6-trichloroaniline	1.27	0.905	1.403
63	2,4,5-trichlorophenol	0.8	1.170	0.684
64	2,4,6-trichlorophenol	1.06	1.145	0.926
65	2,4,α-trichlorotoluène	0.08	0.882	0.091
66	2,4-dichlorotoluène	1.46	1.282	1.139
67	2,6-dichlorophenol	1.68	1.746	0.962
68	2-chloroaniline	1.69	2.038	0.829
69	3,4,5-trichloro-2,6-dimethoxyphenol	1.12	0.565	1.982
70	3,4,5-trichloro-2-methoxyphenol	1.03	0.717	1.437
71	3,4,5-trichlorophenol	0.92	1.073	0.858
72	3,5-dichlorophenol	1.22	1.670	0.730
73	4-chloro-3-methylphenol	1.67	1.884	0.887

The ratio (Log (LC50))$_{exp}$ / (Log (LC50))$_{theo}$ varies around 1 for most compounds, which justifies that our model is excellent

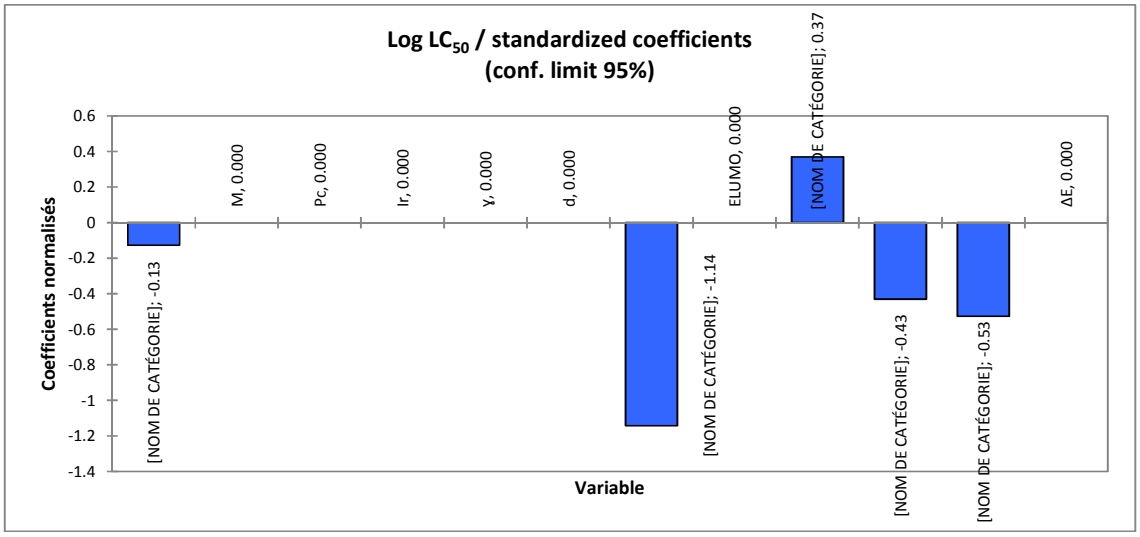

Fig. 9. Contribution of descriptors in model

4. CONCLUSION

The organochlorine pesticides constitute a subgroup of the organochlorine compounds. These compounds are well-known for their toxicity. What led us to determine, by QSAR method, the theoretical descriptors which could better explain this toxicity. Firstly, we determined on the one hand the quantum descriptors and on the other hand the physicochemical descriptors. Then, a Principal component analysis enabled us to select the best descriptors. Finally, three QSAR models were established. If the models established with the quantum descriptors only and the physico-chemical descriptors only gave good results with respectively $R^2 = 0.88$; $R^2_{ajusted} = 0.86$; $R^2_{CV} = 0{,}86$; $R^2 - R^2_{CV} = 0.02$; $MCE = 0.15$; $F = 63.40$ and $R^2 = 0.90$;

$R^2_{ajusted} = 0.89$; $R^2_{CV} = 0.89$; $R^2 - R^2_{CV} = 0.01$; $MCE = 0.12$; F =80.29, the best model was obtained with the combination of the two types of descriptors whose equation and criteria of validation are:

Log LC_{50} = 3,72 - 0,14***LogP*** - 0,29***pol*** + 3,17E-02***S*** - 5,70E-04***ZPE*** - 0,36***N_{Cl}***

$R^2 = 0.94$; $R^2_{ajusted} = 0.93$; $R^2_{CV} = 0.94$; $R^2 - R^2_{CV} = 0.004$; $MCE = 0.07$; $F =$ 134.70 ; $P_{value} < 0.0001$; $\alpha = 0.05$.

In perspective, it is determined the descriptors that influence the half-life time and the bioaccumulation factor of organochlorine compounds and then propose less toxic, less bio-accumulative and less persistent organochlorine pesticides.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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