VOL. 13, NO. 2, JANUARY 2018 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

ANALYSIS OF THE MALATHION MOLECULE STRUCTURE AND PROPOSAL OF A COMPOUND AS ITS REPLACEMENT

Jorge Eliecer Buitrago Salazar, Olga Lucia Ramos Sandoval and Dario Amaya Hurtado
Universidad Militar Nueva Granada, Facultad de Ingeniería en Mecatrónica, Bogotá, Colombia, Grupo de Aplicaciones Virtuales - GAV
E-Mail: tmp.jorge.buitrago@unimilitar.edu.co

ABSTRACT

Pesticides such as Malathion, have been considered harmful to health, reason why the search for new compounds that are friendly to humans and the environment becomes necessary. With knowledge of its properties and molecule structure, it is possible, to propose new compounds which are less toxic than the original without altering its organophosphorus characteristics. This paper presents the results of the analysis of the Malathion properties at molecular level, for the purpose of presenting a compound as a replacement, in order to reduce its toxicity. The properties of absorption, metabolism and toxicity of each possible molecule were evaluated, from which a less toxic compound that still preserves characteristics as an organophosphorus insecticide was obtained.

Index terms: malthion, ADMET properties, insecticide, organophosphorus.

INTRODUCTION

The organophosphorus compounds are characterized as inhibitors of the enzyme acetylcholinesterase (AChE), that inhibition produce an increase in concentration of Acetylcholine (ACh). The ACh is a chemical neurotransmitter, which performs the neural synapse in the central nervous system (brain, spinal cord) (Stenersen, 2004; Shibamoto & Bjeldanes, 1996; Dellamatrice & Monteiro, 2014; Pinheiro, *et al*., 2011). Increasing the concentration of ACh in muscle tissue, can cause a cardiovascular collapse in some muscles by overstimulation, generating cramps, tachycardia, hypertension and excessive salivation (ATSDR, 2013). Currently, the use of chemical pesticides for pest control is dominant, thereby; the number of poisoned people by pesticides is higher in agricultural areas (Stenersen, 2004). Malathion is part of the family of organophosphorus insecticides; it is toxicologically classified as slightly toxic to humans (EPA, 1995). This is traditionally used in crops of corn, cotton, avocado, soursop, among others (Mosquera & Peñuela, 2009; Corra, 2009). In some laboratory tests has been found that the Malathion is classified like a non-carcinogenic compound, however, at high doses of exposureit is possible develop this disease (Shibamoto & Bjeldanes, 1996), (Agency for Toxic Substances and Disease Registry, 2013). Malathion is susceptible to chemical changes due the reactivity of their functional groups. In certain cases, in presence of air and water it can produce Malaoxon, this compound is more toxic than Malathion. ANSES (2015).

Toxicological tests are extensive and complex, so it requires a system of prediction and simulation for properties, this process is called tests in-silico (Hansen *et al*., 2009). This process is mainly used in the pharmaceutical industry to improve the active compounds in drugs (Cheng *et al,* 2012; Li *et al*, 2014).

The in-silico method is based on the functional groups of each compound in order to determine the molecular behavior. First, the functionals groups that are present are determined, then these groups are compared with molecules that have the same functional groups to finally obtain a correlation in a property (Can, 2014; Jaramillo *et al*., 2013). The quantitative structure-activity relationships (QSAR) are used as method of prediction of properties for pesticides. (Levet *et al*., 2013).

For drugs are performed a further analysis, which include the analysis of properties of absorption, distribution, metabolism, excretion and toxicity (ADMET properties). (Cheng *et al*., 2012). With this analysis, it can be possible make a complete evaluation of the behavior of the molecule Based on the above, this paper proposes a new molecule that decreases the toxicological effects on humans and still has the phosphate functional group, characteristic of organophosphate insecticides. Furthermore, the molecule has a lower solubility and decreases the toxic effect on humans by increasing the lethal dose (LD 50).

MATERIALS AND METHODS

The evaluation of the chemical properties in pesticides, contains 3 steps, the evaluation of the method, the development of new molecules and the evaluation of properties in the new substances, this procedure verify the accuracy of the method for predict properties evaluated and ensures the search of new compounds based on the reactivity of Malathion.

Model evaluation. Obtaining the ADMET properties was performed with the software AdmetSAR® (Cheng *et al*., 2012). It was considered the properties of absorption, metabolism and toxicity, for the analysis of each molecule, because they are the properties that has more relevance and variation in the analysis of these compounds (Can, 2014). The model evaluates the probability for the prediction, according to its internal database.

It is required insert the molecule in the format simplified molecular input line entry system (SMILE) for the use of the AdmetSAR® software, for which the molecules was drawn and optimized in MOPAC 2012 program version 15.156W, it was used the method FP7, the which decrease the quantity of energy inside the compound, then, the optimized molecules were converted

to the format specified in OpenBabel V.2.3.1 program (Maia *et al*, 2012;. O'Boyle *et al*., 2011).

CCOC(CC(C(=O)OCC)S[P](OC)(OC)=S)=O Smile Malathion

The model was evaluated, by performing a comparison between the data generated by the software and the data reported in the literature, from different governmental sources as the Colombian Agricultural Institute (ICA) and the Environmental Protection Agency's (EPA-US).

Development of new molecules. The alternatives substances were obtained through the possible reactions, that reactions can be the Malathion with the different places in which it is located, such as the atmosphere, soil and crops.

Through the reactions of the esters groups of Malathion (Figure-1), were obtained the new molecules, In addition, the bonds of sulfur group and the radicals of the molecule were modified

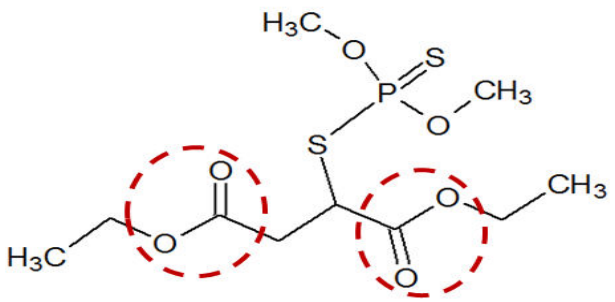

Figure-1. Malathion esters groups.

Evaluation of properties. The AdmetSAR® software was used, in which the properties of absorption, metabolism and toxicity of substances proposed were evaluated as possible replacements of Malathion.

The toxicological classification scale of the World Health Organization (WHO) for pesticides was used for evaluation of toxicological properties (Run, 2009). In the analysis of the qualitative values, it was necessary a conversion as shown in Table-1. In which the equation 1 was used for weighting of properties already mentioned.

$$R=\sum V*P \quad (1)$$

Where R is the result, V is the value obtained in the analysis of each characteristic of each property and P is the probability. Eight characteristics were obtained, which are specified in the Table-2. The results of model prediction of properties were compared with values from the literature. In addition, the relative error was calculated, which shows a measure of the accuracy of the system that is used as a reference to assess the veracity of the data obtained from the software.

Table-1. Conversions for qualitative data.

Assigned value	Qualitative property	Toxicity level
1,00	Less harmful[1]	V
0,50		IV
0,00		III
-0,50		II
-1,00	More harmful[1]	I

Quantitative toxicity properties were analyzed for the 4 best molecules in the previous analysis, to determine the most appropriate substance in the method in-silico. These properties are not taken into account in the initial evaluation, due the high error in the correlations used by the program (Cheng *et al.*, 2012).

RESULTS AND DISCUSSIONS

Eight characteristics of different properties were evaluated for the comparison between the model and the literature; these characteristics are shown in the Table-2. These properties were chosen because they are the most relevant for evaluating toxicity in different species and make an estimation of the toxicity in humans. Errors for solubility and toxicity in rats between 12.2% and 13.7% and of 1 to 2 categories were observed. The error is supported in an appropriate manner with the use of probability to determine the efficiency of the model used; it is a direct indicator of the precision of the system. It was found that the software has good accuracy, as evidenced in Table-2, however was observed an offset in the toxicity in rats, this information is directly related to the probability of the same. In the analysis of new molecules is counted directly the probability of the data, for evaluated the reliability of the data. It should be noted that the evaluation of the molecule F, obtained the worst result, this molecule is the Malaoxon, which is a derivative of Malathion, this compound is more toxic for the humans, this molecule also indicates good accuracy of the software.

In the Figure-2 is show the ten search possible compounds, on which the molecules B, F, G and I are produced by the hydroxylation with substances in the environment, the molecules C, D and E for degradation in the soil by the action of bacteria and solar energy and the H, J and K molecules by hydrolysis reactions due to acid medium. Software properties were evaluated for Malathion molecule as shown in Table-3, also the results of qualitative properties and the value obtained by Equation 1. The results of other molecules are shown in Figure-3.

Table-2. Comparison of the prediction model AdmetSAR®.

Parameter	Prediction	Probability	Real value[(1)]	Relative error
S (H2O)	162,67 mg/kg	0,8100	145 mg/kg	12,18 %
			143 mg/kg	13,76 %
Cancer	Carcinogenic	0,6261	Carcinogenic	No
Human Cancer	No	0,7437	No	No
			No carcinogenic	No
			A4; Not classifiable	No
			Negative	No
Fish toxicity	High	0,9402	Very high	1 Category
Rat toxicity DL 50	Alta	0,6130	Moderate	1 Category
			Moderate	1 Category
			Shortly dangerous	2 Categories
Bee toxicity	Alta	0,9117	Very high	1 Category
Bio degradability	No	0,8429	No	No
Metabolism CYP450 1A2	No inhibitor	0,8415	No inhibitor, substrate	No

[(1)](ANSES, 2015; ATSDR, 2013; Mosquera & Peñuela, 2009; Shibamoto & Bjeldanes, 1996)

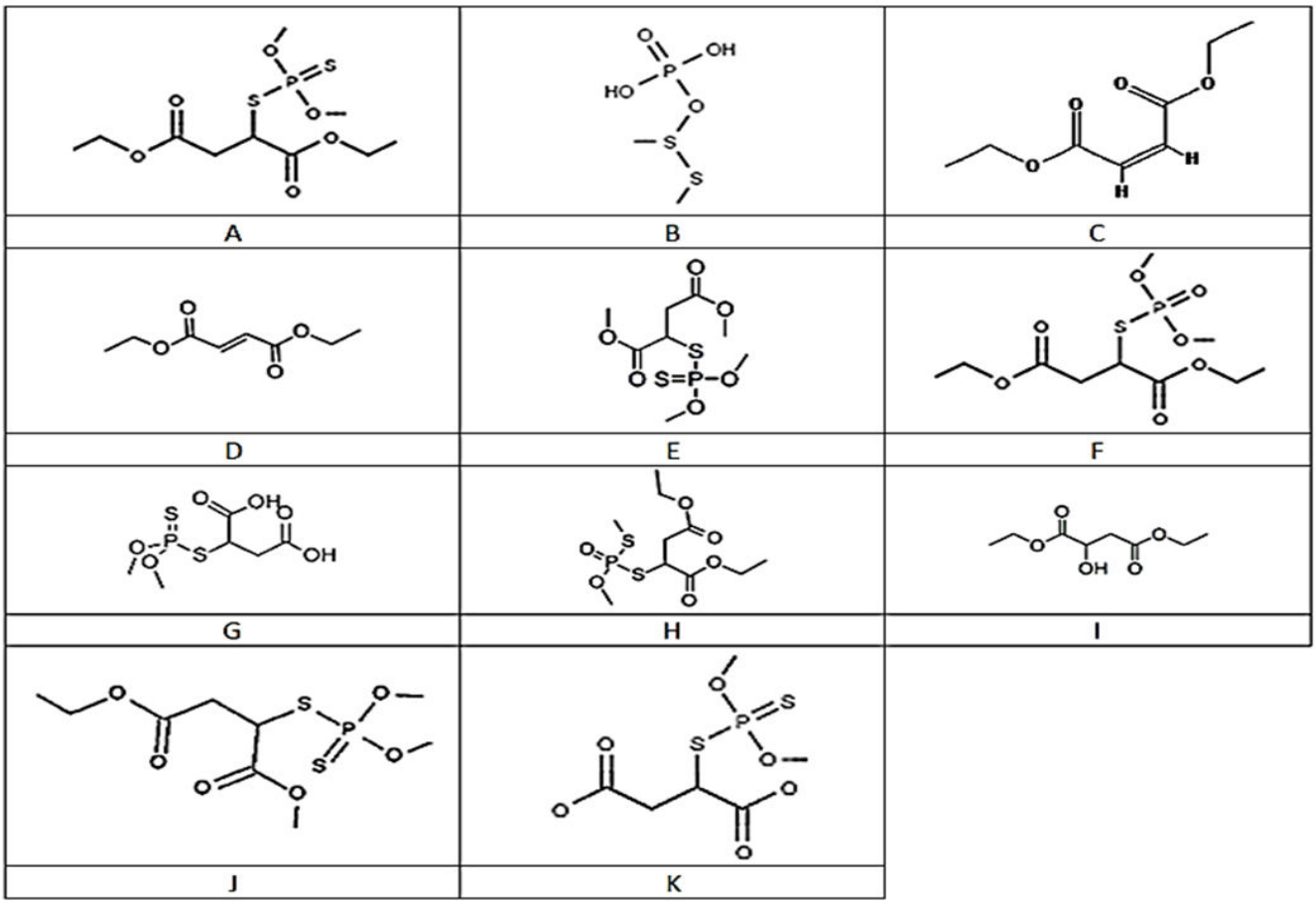

Figure-2. Molecules studied.

The molecules studied have similar behavior in their metabolic properties, because the phosphate group does not significantly affect the cytochrome P450 that is the main cytochrome affected by the pesticides. In absorption and toxicity, the differences are more significant for each compound, due to the different radicals that have each compound. In absorption the 3 best results are the molecules B, E and G. The main features of these compounds are sulfur-phosphorus and sulfur-oxygen bonds. These unions facilitate the absorption in the human body, because they are very reactive.

In absorption was worked with characteristics evaluated in different parts of the human body, the blood-brain barrier refers to a formation of cells in the cerebral cortex that prevent the passage of toxic substances (Cheng *et al*., 2012). The absorption in the intestine, the permeability of Caco-2, P-glycoprotein and the renal transporter,evaluate the ease of entry into the bloodstream through the different component of the digestive system (Stenersen, 2004).

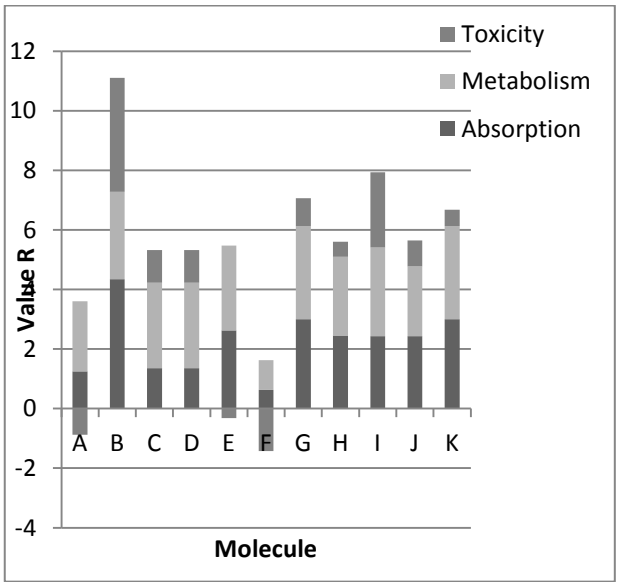

Figure-3. Qualitative assessment of molecules.

In the metabolic evaluation, it was considered the P450 cytochromes, which are part of the family of heme-proteins; usually they are part of the electron transfer chain, where it was metabolized substrates that need the body. Finally, the toxicity was evaluated in different species, which are characterized by a similar human metabolism.

Table-3. Evaluation of Malathion.

Molecule	**Malathion** (A)	
	Value	**Probability**
Absorption		
Blood-Brain Barrier	1,0000	0,9236
Human Intestinal Absorption	-1,0000	0,9031
Caco-2 Permeability	-1,0000	0,5579
P-glycoprotein Substrate	-1,0000	0,7901
P-glycoprotein Inhibitor	1,0000	0,6817
	1,0000	0,9522
Renal Organic Cation Transporter	1,0000	0,9414
Total Absorción	1,2478	
Metabolism		
CYP450 2C9 Substrate	-1,0000	0,8308
CYP450 2D6 Substrate	-1,0000	0,9116
CYP450 3A4 Substrate	-1,0000	0,6132
CYP450 1A2 Inhibitor	1,0000	0,8415
CYP450 2C9 Inhibitor	1,0000	0,7963
CYP450 2D6 Inhibitor	1,0000	0,9114
CYP450 2C19 Inhibitor	1,0000	0,7480
CYP450 3A4 Inhibitor	1,0000	0,5673
CYP Inhibitory Promiscuity	1,0000	0,8504
Total Metabolism	2,3593	
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	1,0000	0,9228
	1,0000	0,8641
AMES Toxicity	1,0000	0,9132
Carcinogens	-1,0000	0,6261
Fish Toxicity	-1,0000	0,9402
Tetrahymena Pyriformis Toxicity	-1,0000	0,6168
Honey Bee Toxicity	-1,0000	0,9117
Biodegradation	-1,0000	0,8429
Acute Oral Toxicity	-0,5000	0,7605
Carcinogenicity (Three-class)	1,0000	0,7437
Total Toxicity	-0,8742	
Total	2,7330	

Table-4. Evaluation of quantitative properties for Malathion.

Property	**Valor**
Aqueous solubility (LogS)	-3,3076
Rat Acute Toxicity (LD50, mol/kg)	3,0259
Fish Toxicity (pLC50, mg/L)	1,7623
Tetrahymena Pyriformis Toxicity (pIGC50, ug/L)	0,0612

Table-5. Quantitative evaluation.

	Aqueous solubility (LogS)	**Rat Acute toxicity** (LD50, mol/kg)	**Fish toxicity** (pLC50, mg/L)	**Tetrahymena Pyriformis toxicity** (pIGC50, ug/L)
B	-18,1800	26,4270	21,0970	-0,5793
G	-1,8285	2,1748	2,1791	-0,2250
I	-0,7462	1,4513	2,6867	-0,1455
K	-1,8285	2,1748	2,1791	-0,2250

The quantitative characteristics were evaluated, in which are the solubility and toxicity in different species. The Table-4 shows the values for Malathion. Molecules with the best results qualitatively were the B, G, R and K, with these compounds was realized a quantitative analysis of properties (Table-5). The compound I is a straight chain, which does not contain sulfur or phosphorus that characterizes organophosphates, so it loses its insecticide power. It was found that the substance B, compared to the other three and with reference (substance A Malathion) have a lower solubility, so this substance will have a high octanol-water partition coefficient, which may eventually lead to bioaccumulation in adipose tissue.

In the property of toxicity were found to 4 (B, C, D and I), these are less toxic substances, the molecules C, D and I are little toxic because they do not contain sulfur atoms and phosphorus, thus at the moment of his degradation, they do not produce toxic compounds, however the substance B is an organophosphorus, wherein the toxic activity to humans is reduced compared with Malathion.

The toxicity values on different species show similarity in the G, I and K molecules with the reference value, otherwise, for the substance B values are higher, between more bigger be that value, show us that the lethal dose (LD 50) have to be higher to kill the half of a population sample. This indicates that this compound can reduce toxicity in the environment for the insects.

CONCLUSIONS

The software AdmetSAR® was evaluated to verify the accuracy; it is used to characterize organophosphate insecticides through the ADMET methodology for predicting new pesticides, which can decrease the toxicity in humans.

The analysis through the QSAR models complements aptly the ADMET analysis, in order to broaden the scope of prediction for new substances.

The molecule B was chosen due to his reduction in the toxic effect on humans, without change its functionality as organophosphate insecticide. After the in-silico method for prediction is time for evaluating its effect in-vitro to corroborate the data.

ACKNOWLEDGEMENTS

The authors would like to offer their special gratitude to the Research Vice-chancellorship of Nueva Granada Military University for financing the research project IMP_ING 1777 titled: "Análisis de residuos de plaguicidas en frutas tropicales en Colombia para la predicción de posibles efectos en la salud humana", 2015.

REFERENCES

ANSES. 2015. Agence Nationale de sécurité sanitaire alimentation, environnement, travaill. Francia Avis ANSES relatif aux subtances actives biocides pouvant être utilisées dans le cadre de la prévention d'une épidémie de chinkungunya en Guyane.ANSES, 2014, 64p. Disponible en: <https://www.anses.fr/sites/default/files/documents/BIOC2014sa0060.pdf>Consultado el: 18 Mar.

ATSDR. 2013. Agencia para sustancias Toxicas y el Registro de Enfermedades. Resumen de Salud Pública Malation. ATSDR, 2003, 9p. Disponible en: < www.atsdr.cdc.gov/es>Consultado el: 20 Sep.

CAN A. 2014. Quantitative structure-toxicity relationship (QSTR) studies on the organophosphate insecticides. Toxicology Letters. 230: 434-443.

Cheng F.; LI W.; Zhou Y.; Shen J.; WU Z.; Liu G.; Tang Y. 2012. admet SAR: A Comprehensive Source and Free Tool for Assessment of Chemical ADMET Properties. Journal of Chemical Information and Modeling. 52: 3099-3105.

Corra L. 2009. Herramienta de capacitación para el manejo responsable de plaguicidas y sus envases - Efectos sobre la salud y prevención de la exposición.2. Ed. Buenos Aires: Organización Panamericana de la Salud OPS p. 302.

Dellamatrice P. M.; Monteiro R. T. R. 2014. Principais aspectos da poluição de rios brasileiros por pesticidas. Revista Brasileira de Engenharia Agrícola e Ambiental. 18: 1296-1301.

Hansen K.; Mika S.; Schroeter T.; Sutter A.; Ter Laak A.; Steger-Hartmann T.; Müller K.-R. 2009. Benchmark Data Set for in Silico Prediction of Ames Mutagenicity. Journal of Chemical Information and Modeling. 49: 2077-2081.

Jaramillo B. E.; Martelo I.; Duarte E. 2013. Toxicidad aguda de pesticidas organo fosforados y análisis de la relación cuantitativa de estructura actividad (QSAR). Biotecnología En El Sector Agropecuario Y Agroindustrial. 11: 76-84.

Levet A.; Bordes C.; Clément Y.; Mignon P.; Chermette H.; Marote P.; Lantéri P. 2013. Quantitative structure–activity relationship to predict acute fish toxicity of organic solvents. Chemosphere. 93: 1094-1103.

Li X.; Chen L.; Cheng F.; WU Z.; Bian H.; XU C.; Tang Y. 2014. In Silico Prediction of Chemical Acute Oral Toxicity Using Multi-Classification Methods. Journal of Chemical Information and Modeling. 54: 061-1069.

Maia J. D. C.; Urquiza Carvalho G. A.; Mangueira C. P.; Santana S. R.; Cabral L. A. F.; Rocha G. B. 2012. GPU Linear Algebra Libraries and GPGPU Programming for Accelerating MOPAC Semiempirical Quantum Chemistry Calculations. Journal of Chemical Theory and Computation. 8: 3072-3081.

Mosquera R.; Peñuela G. A. 2009. Biodegradación del malatión utilizando microorganismos nativos de suelos agrícolas. Revista Colombiana de Ciencias Pecuarias (Colombian Journal of Animal Science and Veterinary Medicine). 22: 189-198.

O'boyle N.; Banck M.; James C.; Morley C.; Vandermeersch T.; Hutchison G. 2011. Open Babel: An open chemical toolbox. Journal of Cheminformatics. 3: 25-33.

Pinheiro A.; Moraes J. C. S.; Silva M. R. Da. 2011. Pesticidas no perfil de solos em áreas de plantação de cebolas em Ituporanga, SC. Revista Brasileira de Engenharia Agrícola e Ambiental. 15: 533-538.

Shibamoto T.; Bjeldanes L. F. 1996. Introducción a la toxicología de los alimentos. 1.ed. Acribia. p. 216.

Stenersen J. 2004. Chemical Pesticides Mode of Action and Toxicology. Why is a toxicant poisonous?, CRC Press. Cap. 2, pp. 48-66.