QSPR Study of Acceptable Daily Intake of Organophosphorus Pesticides

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Abstract

Organophosphourus (OP) agrochemicals represent an important group of chemicals used over the past 60 years for protecting crops, livestock, and human health and as warfare agents. OPs can raise environmental and health problems because of their toxicity and possibility to accumulate in the food chain as pesticide residues. The acceptable daily intake (ADI) can be considered as a measure on human health of the effect of pesticide residues in food. In this paper the influence of 46 OPs structure on their ADIs (expressed as pADIs) is studied. OP structural descriptors were calculated from the energy optimized structures using molecular mechanics calculations. Their pADI values were related to them using linear (multiple linear regression, MLR, combined with genetic algorithm for variable selection) and nonlinear (artificial neural network, ANN) approaches. 22 compounds were included in the models as training set, 6 in the prediction set and 18 OPs as external set. Robust models with predictive power were obtained using the linear MLR approach. The nonlinear modeling of pADIs gave an unstable model without predictive power. The robustness, overfitting and prediction power and applicability domain of the QSPR (quantitative structure-property relationship) models were checked. New experimental toxicological data would be needed for ten out of the 46 OPs, to revise their known ADI values. New ADIs for similar compounds could be predicted based on the linear QSPR models.

Keywords：organophosphourus compounds, accessible daily intake, MLR, ANN

1. Introduction

Agrochemicals are used as animal and bird repellents, food storage protectants, herbicides, insecticides and acaricides, rodenticides, plant growth regulators, mould-killing substances, antifouling products, soil sterilants, and wood preservatives (Renwick,

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2002).

Organophosphorus compounds (OPs) constitute an important group of chemicals used over the past 60 years for protecting crops, livestock, human health and as warfare agents (Elersek and Filipic, 2011). They are broadly used worldwide, and account for ca. 50% of total pesticide use in the world (Guodong et al., 2012). Despite their benefits in the fight against pests, the unreasonable use of organophosphate pesticides can generate environmental pollution problems due to their stability, high toxicity and capacity to accumulate in the food chain.

Organophosphate pesticide residues and their metabolites were found in human tissues and urine, including persons not exposed occupationally (Witczak et al., 2018; Rezg et al, 2010). A long-term exposure to low doses of pesticides may cause dysfunctions of the immune, respiratory and endocrine systems, producing negative neurological and reproductive effects, as well as dermal changes (Krieger, 2001).

The 'acceptable daily intake' (ADI) notion to evaluate the pesticide residue in food was first introduced by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1958 (FAO Nutrition meeting Report Series 17/WHO tech. Rep. Series 144, 1958) with insignificant modifications in 1962 (WHO tech. Rep. Ser. 240, 1962; FAO nutrition meetings Report series 31/WHO tech. Rep. Ser. 228, 1962), 1974 and 1987 (WHO Environmental health criteria 70, 1987). In the following years, hundreds of food additives and pesticide residues have been evaluated and reevaluated by these two international expert groups (Lu, 1988). The ADIs, used nationally and internationally in the elaboration of food standards, have proved satisfactory in permitting the cautious use of these chemicals and in protecting the health of the consumer (Rubery et al., 1990).

ADI was defined as "the daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk on the basis of all known facts at the time." (FAO nutrition meetings Report series 31/WHO Tech. Rep. Ser. 228, 1962). It is described as an estimate of the amount of a food additive, expressed on a bodyweight basis that can be ingested on daily over a lifetime without significant risk to health. The World Health Organization (WHO) and United States Environmental Protection Agency (U.S. EPA) have established an ADI for an actual risk management decision in the regulatory process of pesticides for setting safety standards.

The determination of acceptable daily intake (ADI) for the toxicological evaluation implies collecting all relevant data, determining the no-effect level using the most sensitive indicator of the toxicity, and applying an appropriate safety factor to arrive at the ADI for man (Lu, 1988). The ADI is established based on known facts at one time. This fact is consistent with the view that it is impossible to be absolutely certain about the safety of a chemical and the ADI may be revised with respect to the new toxicological data.

In a previous study Kim (2012) modeled ADI values, considered as health-based control, of several pesticides using the MLR approach. He pointed out that an approach using a robust QSAR technique would be useful to detect potential sources that might provide critical information about uncertainty of ADI values in addition to the model development as preliminary human health risk assessment for certain pesticides.

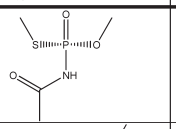
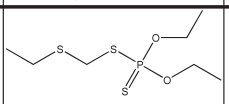
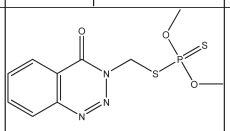
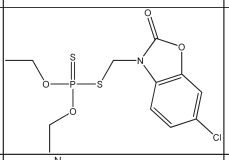
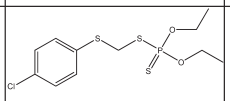
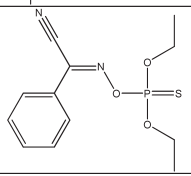
This paper presents the application of multiple linear regression (MLR) and artificial neural network (ANN) approaches to model the accessible daily intake dependence on the structural features of a series of 46 organophosphorous pesticides (http://www.inchem.org/pages/pims.html). Molecular mechanics calculations based on the MMFF94s force field were employed to model the pesticide structures. Structural features were computed from the minimum energy structures and were related to the ADI values using the multiple linear regression (MLR) and artificial neural network (ANN) approaches.

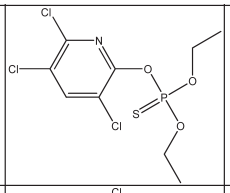
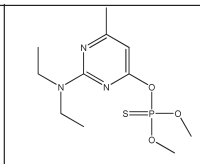
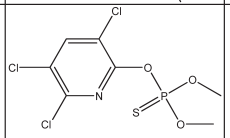
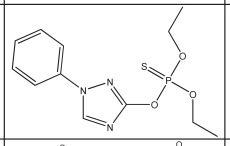
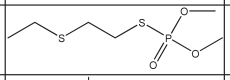
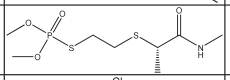
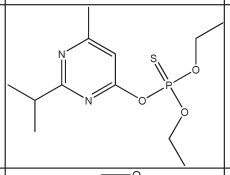
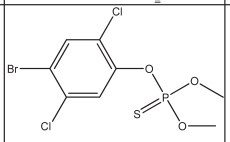
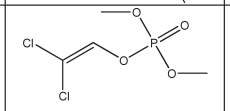
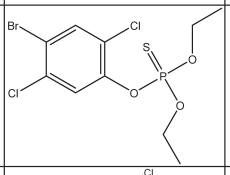
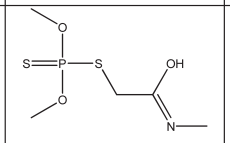
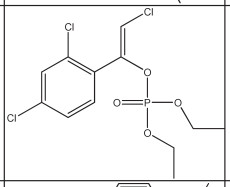
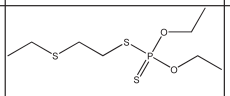
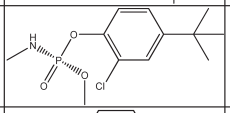
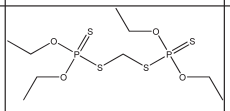
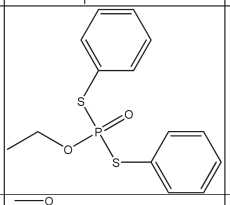
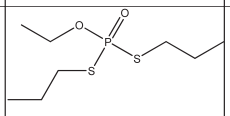
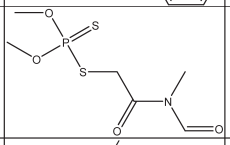
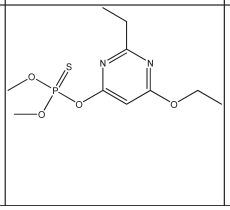
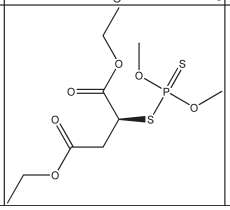
2. Methods

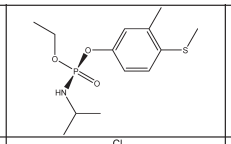
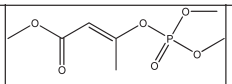
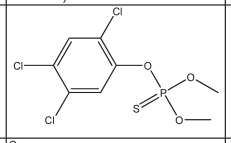
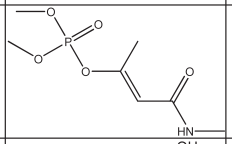
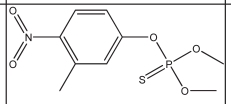
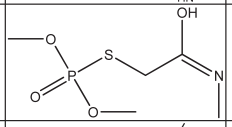
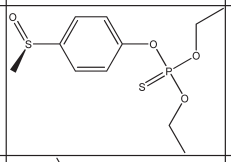
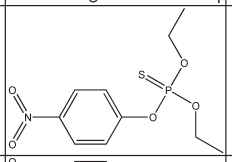
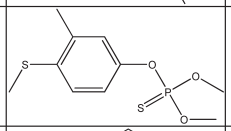
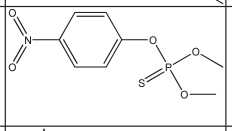
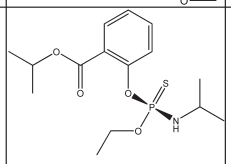
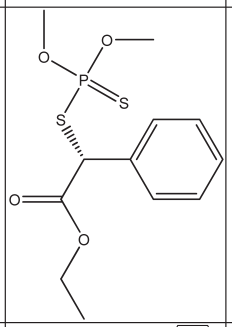
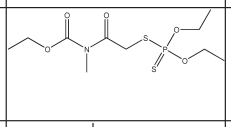
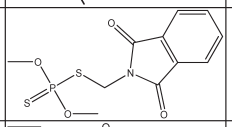
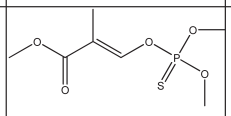
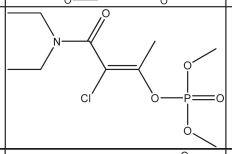
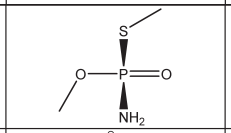
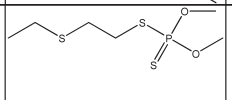
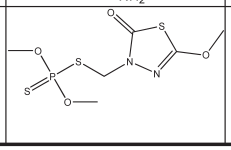
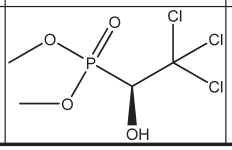
Definition of target property and molecular structures

The acceptable daily intake (ADI) (mg/kg bodyweight) of 46 organophosphorous pesticides with diverse structures (http://www.inchem.org/pages/pims.html) was molar converted to pADI (Table 1) and was used as dependent variable in this study.

Table 1. Structure of the organophosphorous pesticides and the pADI values.

No	Structure	$pADI_{exp}$	No	Structure	$pADI_{exp}$
1		6.79	**24**		9.11
2		7.8	**25**		8.57
3*		8.84	**26***		8.47

4**		7.54	**27**		7.01
5		7.51	**28**		8.5
6		8.89	**29**		7.56
7		8.18	**30****		6.96
8		7.74	**31****		6.99
9		7.36	**32****		8.25
10		8.96	**33****		6.46
11		8.28	**34****		8.01
12		8.91	**35****		7.11
13		7.99	**36****		7.22

14		8.78	**37****		8.17
15*		7.51	**38****		8.57
16*		7.74	**39****		8.85
17*		9.01	**40****		7.77
18*		8.44	**41****		7.12
19		8.54	**42****		8.03
20		8.22	**43****		7.20
21		7.6	**44****		8.78
22		7.55	**45****		7.91
23		8.48	**46****		7.41

* Test compounds in the MLR/ANN models.
** External set.

The OP structures were optimized using the conformer plugin (with MMFF94 as molecular mechanics force field) inside the MarvinSketch (MarvinSketch 15.2.16.0, ChemAxon Ltd. http://chemaxon.com) package. The lowest energy conformers were used to calculate the structural descriptors using the DRAGON (Dragon Professional 5.5, 2007, Talete S.R.L., Milano, Italy) and InstanJChem (Instant JChem 20.15.0, 2020, Chemaxon, http://www.chemaxon.com) software.

MLR method

The multiple linear regression (MLR) (Wold and Dunn III, 1983) approach was employed together with the genetic algorithm for variable selection included using the QSARINS v.2.2.4 program (Chirico and Gramatica, 2012; Gramatica et al., 2013; Gramatica, 2020). 1736 structural descriptors were calculated for the 46 OPs. In the MLR calculations the RQK fitness function (Todeschini et al., 2004) with leave-one-out cross-validation (Hawkins et al., 2003) correlation coefficient as constrained function to be optimized, a crossover/mutation trade-off parameter of T = 0.5 and a model population size of P = 50 were employed.

The OP derivatives were divided into training and test sets by response splitting (Gramatica et al., 2012; Gramatica, 2014) to verify if the chemicals in the model were included in the response domain (chemicals were ordered according to their increasing activity, and one out of every three chemicals was put in the prediction set, always including the most and the least active compounds in the training set). Six compounds in the test set were taken out of the total number of compounds: compounds 3, 15, 16, 17, 18, 26. In the external set following 18 compounds were included: 4, 30-46.

ANN method

ANNs (Zupan, and Gasteiger, 1999) simulate the functioning of human neurons and have been used as a nonlinear modeling approach. Among the various architecture and learning algorithms of ANN, the four descriptors in the best MLR model were used as input for a three-layer, fully connected, a feed-forward neural network with the back-propagation of errors. The number of input neurons was equal to the number of descriptors in the MLR model, and the output layer consists of one neuron for the pADI values. All input and output data were normalized 0 and 1. A commonly used log sigmoid function and the delta rule for the error correction formula were used in the networks. The calculation was performed using our in-house program.

Model validation

Internal and external validation criteria were verified to obtain robust and predictive models. To test the model predictive power following criteria were used: Q^2_{F1} (Shi et al., 2001); Q^2_{F2} (Schüürmann et al., 2008); Q^2_{F3} (Consonni et al., 2009) and the concordance

correlation coefficient (CCC) (Chirico and Gramatica, 2011), with the thresholds values higher than 0.85, as they have been rigorously determined by a simulation study (Chirico and Gramatica, 2012).

In addition the predictive parameter r^2_m (Roy and Mitra, 2012) was used, with the lowest threshold value of 0.65 used to be accepted.

For internal model validation the model robustness and overfitting were checked using the Y-randomization test. 2000 randomizations were employed to develop MLR models with minimal r^2 and q^2 values (Eriksson et al., 2001). In addition, the adjusted correlation coefficient (r^2_{adj}) and q^2 (leave-one-out, q^2_{LOO} , and leave-more-out, q^2_{LMO}) cross-validation coefficients were calculated, too. The model chance correlation was verified using the Y-scrambling or response permutation/randomization procedure. r^2_{scr} and q^2_{scr} parameters were obtained by randomly shuffling the dependent variable vector (Y-vector) using the original independent variable matrix.

The root-mean-square errors (RMSE) and the mean absolute error (MAE) of the training, crossvalidation and test sets were compared to check the model robustness and overfitting (Gramatica, 2020).

The Multi-Criteria Decision Making (MCDM) scores (Keller et al., 1991) were used to choose the best MLR models and were calculated based on the fitting, cross validated and external criteria.

3. Results and discussion

The data was normalized using the auto-scaling method:

$$XT_{mj} = \frac{X_{mj} - \overline{X}_m}{S_m} \qquad (1)$$

where for each variable m, XT_{mj} and X_{mj} are the j values for the m variable after and before scaling, respectively, $\overline{X}_m$ is the mean, and S_m is the standard deviation of the variable.

Several MLR models were obtained applying the genetic algorithm for variable selection. The internal and external validation criteria for these models are presented in Tables 2-4.

Table 2. Internal validation parameters of the MLR and ANN models (tr-training set)*

Model	$r^2_{training}$	q^2_{LOO}	q^2_{LMO}	r^2_{adj}	$RMSE_{tr}$	MAE_{tr}	CCC_{tr}	r^2_{scr}	q^2_{scr}	SEE	F
MLR1	0.874	0.802	0.776	0.844	0.229	0.194	0.933	0.191	-0.429	0.260	29.475
MLR2	0.832	0.765	0.744	0.805	0.263	0.235	0.908	0.134	-0.285	0.289	31.305
MLR3	0.711	0.585	0.559	0.665	0.345	0.269	0.831	0.137	-0.276	0.379	15.551
ANN	0.967	0.527		0.960	0.116	0.085	0.983				

* $r^2_{training}$ -correlation coefficient; q^2_{LOO} - leave-one-out correlation coefficient; q^2_{LMO} leave-more-out correlation coefficient; r^2_{adj} -adjusted correlation coefficient; $RMSE_{tr}$-root-mean-square errors; MAE_{tr}-mean absolute error; CCC_{tr}-the concordance correlation coefficient; r^2_{scr} and q^2_{scr} -Y-scrambling parameters; SEE-standard error of estimates; F-Fischer test.

Table 3. Crossvalidation (cv) results, MCDM values and final selected descriptors*

Model	$RMSE_{cv}$	MAE_{cv}	CCC_{cv}	MCDM	Descriptors included in the MLR model*			
MLR1	0.287	0.249	0.896	0.839	JGT	RDF090v	F03[C-N]	F06[C-P]
MLR2	0.311	0.282	0.872	0.819	JGT	RDF090v	F03[C-N]	
MLR3	0.413	0.323	0.758	0.736	nN	GGI7	JGT	
ANN	0.444	0.375	0.743		JGT	RDF090v	F03[C-N]	F06[C-P]

* JGT- global topological charge index (Galvez topological charge indices), RDF090v- Radial Distribution Function - 9.0/weighted by atomic van der Waals volumes (RDF descriptors), F03[C-N]-frequency of C-N at topological distance 3 (2D frequency fingerprints), F06[C-P]-frequency of C-P at topological distance 6 (2D frequency fingerprints), nN- number of Nitrogen atoms constitutional descriptors, GGI7- topological charge index of order 7 (Galvez topological charge indices).

Table 4. External validation parameters of the MLR and models (test set)*

Model	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	$RMSE_{ext}$	MAE_{ext}	CCC_{ext}	R^2_{ext}	r^2_m
MLR1	0.925	0.915	0.900	0.172	0.128	0.945	0.925	0.875
MLR2	0.928	0.916	0.897	0.174	0.169	0.945	0.928	0.894
MLR3	0.969	0.776	0.727	0.284	0.214	0.791	0.969	0.517
ANN	0.333	0.215	0.442	0.482	0.437	0.660	0.215	0.808

* Q^2_{F1}; Q^2_{F2} ; Q^2_{F3} , R^2_{ext}, r^2_m -external validation parameters; $RMSE_{ext}$-root-mean-square errors; MAE_{ext} -mean absolute error; CCC_{ext}-the concordance correlation coefficient

Experimental versus predicted pADI values, Williams and Y-scramble plots are included for the MLR1 best model in Figures 1, 2 and 3, respectively.

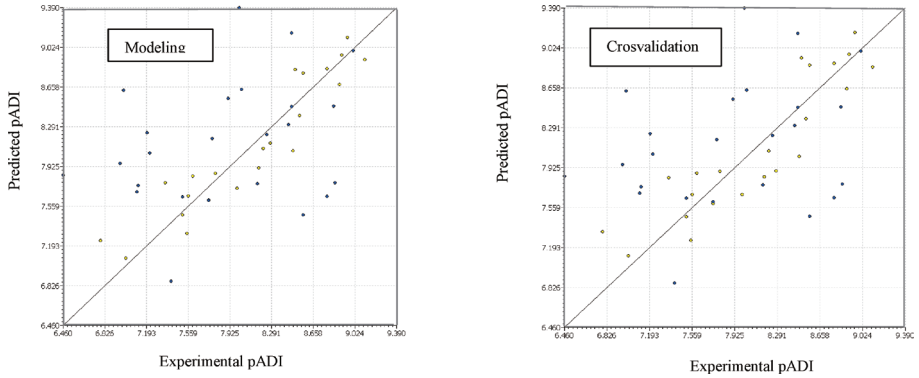


Figure 1. Experimental versus predicted pADI values for the MLR1 model predicted by the model (left) and by the leave-one-out (right) crosvalidation approach (yellow circles-training compounds, blue circles-test and external compounds).

The Williams plots for the training/crossvalidation/prediction/external sets establish the applicability domain of the models within ±3.0 σ and a leverage threshold h^* of 0.6818 ($h_i > h^*$; hi =leverage of a given chemical; h^*= the warning leverage). All compounds in the dataset are within the applicability domain of the best MLR1 model, as presented in Figure 2, except 9 out of 18 OPs in the external set: no. 30, 31, 33, 34, 36, 38, 39, 43, and 44, and one compound in the prediction set: no. 26, which were found as outliers. For these compounds other new toxicological data would be needed to establish appropriate ADI values.

MLR1 model overfit was checked after 2000 trials, using the y-scrambling test. Significant low scrambled r^2 (r^2_{scr}) and cross-validated q^2 (q^2_{scr}) values obtained for MLR1 model, indicate the model robustness and no chance correlation. Figure 3 suggests that in case of all the randomized models, the values of r^2_{scr} and q^2_{scr} were < 0.682 (r^2_{scr}/q^2_{scr} of 0.191/-0.429).

The intercorrelation analysis of the selected molecular descriptors from the MLR1 model is presented in Table 5. The selected descriptors are not intercorrelated.

Table 5. Correlation matrix of the selected descriptors included in the MLR1 model

	JGT	RDF090v	F03[C-N]	F06[C-P]	Standardized coefficients
JGT	1.0000				-0.638
RDF090v	-0.2107	1.0000			0.573
F03[C-N]	-0.1120	0.3673	1.0000		-0.475
F06[C-P]	-0.3393	0.2330	0.3157	1.0000	-0.238

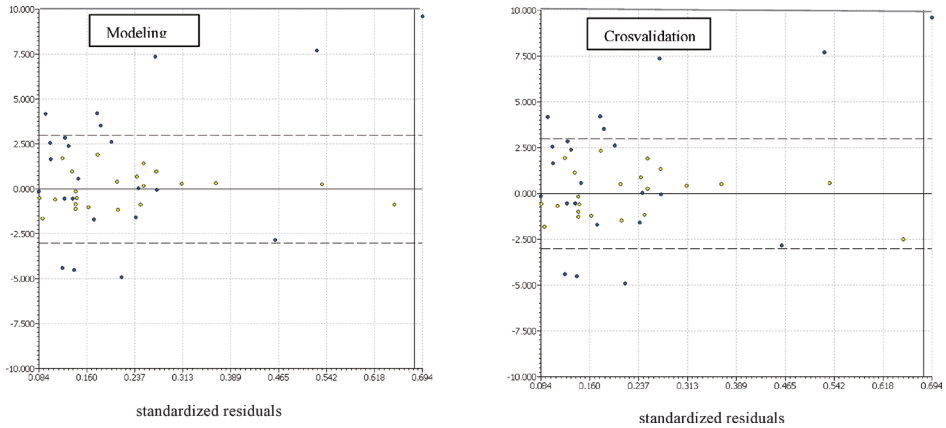


Figure 2. Williams plot predicted by the MLR1 model predicted (left) and by the leave-one-out (right) crosvalidation approach (yellow circles-training compounds, blue circles-test and external compounds).

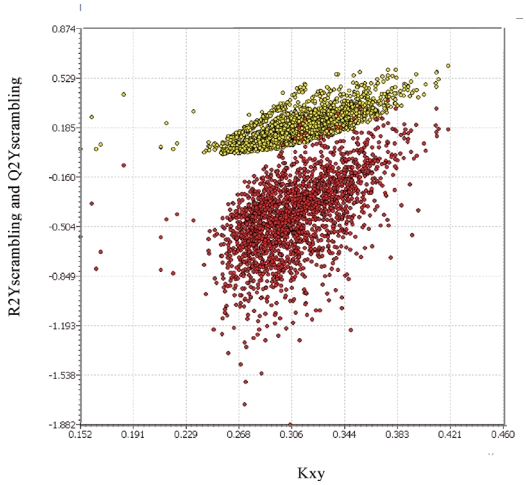


Figure 3. Y-scramble plots for the MLR1 model(yellow circles-r^2_{scr} ; red circles-q^2_{scr}).

Four descriptors are included in the best MLR1 model: JGT, RDF090v, F03[C-N], and F06[C-P]. Highest contribution to the pADI is given by the JGT, and RDF090v descriptors. Topological charge indices were proposed to evaluate the charge transfer between pairs of atoms, and therefore the global charge transfer in the molecule (Gálvez, Jet al., 1994). The GGI7 descriptor evaluates charge transfer in molecule carried out from the adjacency topological matrix. Helguera et al. (2008) consider that these indices represent a strictly topological quantity, being plausibly correlated with the charge distribution inside the molecule.

Radial Distribution Function (RDF) of an ensemble of atoms can be interpreted as the probability distribution of finding an atom in a spherical volume of certain radius, also incorporating different atomic properties in order to differentiate the contribution of atoms to activity (Duchowicz et al., 2008; Hemmer et al., 1999).

Higher values of the RDF090v descriptor and lower values of the JGT, F03[C-N] and F06[C-P] descriptors would favor lower ADI values.

The nonlinear ANN model performed for the four descriptors included in the best MLR model is not stable from statistical point of view. Different values for the RMSE and MAE parameters were obtained for the training/test/cross-validation sets. The fitting results are good, but the ANN model is without predictive power (see Tables 3-5).

The statistical results and intercorrelation coefficients presented above confirm that the MLR method associated with a proper variable selection procedure generates an efficient QSPR model for modeling the ADI values. Nonlinear simulation of pADIs gave worse results. Based on the proposed best MLR1 model ADI values could be predicted for other similar OPs.

4. Conclusion

46 organophosphorus compounds were modeled in this paper using QSPR models for their acceptable daily intake (ADI), an important measure of the pesticide residues in food. Multiple linear regression and artificial neural networks were employed to relate the pADI values to the computed structural descriptors of the OPs. Good linear QSPR models with predictive power were obtained. The nonlinear ANN model is not stable and does not have predictive power. The linear MLR model could be useful in the design of new similar compounds and in the prediction of their ADI values, based on the QSPR proposed models, for qualitative and quantitative risk assessments.

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References

Chirico, N., Gramatica, P.: Real external predictivity of QSAR models: how to evaluate it? Comparison of different validation criteria and proposal of using the concordance correlation coefficient. *J. Chem. Inf. Model.* 51, 2320-2335 (2011).

Chirico, N., Gramatica, P.: Real External Predictivity of QSAR Models. Part 2. New Intercomparable Thresholds for Different Validation Criteria and the Need for Scatter Plot Inspection. *J. Chem. Inf. Model.* 52, 2044-2058 (2012).

Consonni, V., Ballabio, D., Todeschini, R.: Comments on the definition of the Q2 parameter for QSAR validation. *J. Chem. Inf.* Model. 49, 1669-1678 (2009).

Elersek,T., Filipic, M.: Organophosphorous Pesticides - Mechanisms of Their Toxicity, In: *Pesticides - The Impacts of Pesticides Exposure*, Stoytcheva, M. (Ed.), Chapter 12, IntechOpen, (2011), https://www.intechopen.com/books/pesticides-the-impacts-of-pesticides-exposure/organophosphorous-pesticides-mechanisms-of-their-toxicity.

Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wold, S.: *Multi and megavariate data analysis: principles and applications*, Umetrics Academy, Umea, pp. 92-97, 489-491, (2001).

Duchowicz, P. R., Vitale, M. G., Castro, E. A., Autino, J. C., Romanelli, G. P., Bennardi, D. O.: QSAR modeling of the interaction of flavonoids with GABA(A) receptor. *Eur. J. Med. Chem.* 43, 1593-1602 (2008).

Gálvez, J., Garcìa, R., Salabert, M.T. and Soler, R.: Charge indexes: new topological descriptors. *J. Chem.Inf. Comput. Sci.* 34, 520-525 (1994).

Gramatica, P., Chirico, N., Papa, E., Cassani, S., Kovarich, S.: QSARINS: A new software for the development, analysis, and validation of QSAR MLR models. *J. Comput. Chem.*, 34, 2121-2132 (2013).

Gramatica, P.: Principles of QSAR Modeling: Comments and Suggestions From Personal Experience. *International Journal of Quantitative Structure-Property Relationships*, 5, 1-37 (2020).

Gramatica, P., Cassani, S., Roy, P. P., Kovarich, S., Yap, C. W., Papa, E.: QSAR Modeling is not "Push a Button and Find a Correlation": A Case Study of Toxicity of (Benzo-) triazoles on Algae. *Mol. Inf.*, 31, 817-835 (2012).

Gramatica, P.: External Evaluation of QSAR Models, in Addition to Cross-Validation: Verification of Predictive Capability on Totally New Chemicals. *Mol. Inf.*, 33, 311-314 (2014).

Guodong, D., Pei, W., Ying, T., Jun, Z., Yu, G., Xiaojin, W., Rong, S., Guoquan, W., Xiaoming, S.: Organophosphate pesticide exposure and neurodevelopment in young Shanghai children. *Environ Sci Technol.* 46, 2911-2917 (2012).

Hawkins, D.M., Basak, S.C., Mills, D.: Assessing Model Fit by Cross-Validation. *J. Chem. Inf. Comput. Sci.* 43, 579-586 (2003).

Helguera, A., Combes, R., González, M.: Applications of 2D descriptors in drug design: A DRAGON tale. *Curr. Top. Med. Chem.* 8, 1628-1655 (2008).

Hemmer, M.C., Steinhauer, V., Gasteiger, J.: The prediction of the 3D structure of organic molecules from their infrared spectra. *Vibrat. Spectrosc.* 19, 151-164 (1999).

Keller, H.R., Massart, D.L., Brans, J.P.: Multicriteria decision making: a case study. *Chemom. Intell. Lab. Syst.*, 11, 175-189 (1991).

Joint FAO/WHO Expert Committee on Food Additives, World Health Organization & Food and Agriculture Organization of the United Nations: *Procedures for the testing of intentional food additives to establish their safety for use*: second report of the Joint FAO/WHO Expert Committee on Food Additives [meeting held in Geneva from 17 to 24 June 1957]. *WHO techn. Rep. Ser.*, No. 144, *FAO nutrition meetings. Report series*, No. 17 (1958), https://apps.who.int/iris/handle/10665/40403.

Joint FAO/WHO Expert Committee on Food Additives, World Health Organization & Food and Agriculture Organization of the United Nations. (1962). Evaluation of the toxicity of a number of antimicrobials and antioxidants: sixth report of the Joint FAO/WHO Expert Committee on Food Additives [meeting held in Geneva from 5 to 12 June 1961]. *WHO tech. Rep. Ser.* No. 228, *FAO nutrition meetings. Report series* No. 31 (1962), https://apps.who.int/iris/handle/10665/40518

Kim, J. H..: Is it Possible to Predict the ADI of Pesticides using the QSAR Approach?. *J. Environ. Health. Sci.* 38, 550-560 (2012).

Krieger, R. *Handbook of Pesticide Toxicology*, Academic Press, San Diego, 2001.

Lu, F.C.: Acceptable daily intake: inception, evolution, and application. *Regul. Toxicol. Pharmacol.* 8, 45-60 (1988).

Renwick, A.G.: Pesticide residue analysis and its relationship to hazard characterisation (ADI/ARfD) and intake estimations (NEDI/NESTI), *Pest. Manag. Sci.* 58, 1073-1082 (2002).

Rezg, R., Mornagui, B., El-Fazaa, S., Gharbi, N.: Organophosphorus Pesticides as Food Chain Contaminants and Type 2 Diabetes: A Review. *Trends Food Sci. Technol.* 21, 345-357 (2010).

Roy, K., Mitra, I.: On the use of the metric r_m^2 as an effective tool for validation of QSAR models in computational drug design and predictive toxicology. *Mini-Rev. Med. Chem.*

12, 491-504 (2012).

Rubery, E. D., Barlow, S. M., Steadman, J. H.: Criteria for setting quantitative estimates of acceptable intakes of chemicals in food in the U.K., *Food Additives & Contaminants*, 7, 287-302 (1990).

Shi, L.M., Fang, H., Tong, W., Wu, J., Perkins, R., Blair, R.M., Branham, W. S,. Dial, S.L., Moland, C.L., Sheehan, D.M.: QSAR models using a large diverse set of estrogens. *J. Chem. Inf. Model.* 41,186-195 (2001).

Schüürmann, G., Ebert, RU., Chen, J., Wang, B., Kühne, R.: External validation and prediction employing the predictive squared correlation coefficient test set activity mean vs training set activity mean. *J. Chem. Inf. Model.* 48, 2140-2145 (2008).

Todeschini, R., Consonni, V., Mauri, A., Pavan, M.: Detecting "bad" regression models: multicriteria fitness functions in regression analysis. *Anal. Chim. Acta* 515, 199-208 (2004).

WHO Expert Committee on Pesticide Residues, World Health Organization & Food and Agriculture Organization of the United Nations: Principles governing consumer safety in relation to pesticide residues : report of a meeting of a WHO Expert Committee on Pesticide Residues held jointly with the FAO Panel of Experts on the Use of Pesticides in Agriculture [meeting held in Rome from 9 to 16 October 1961]. *WHO Tech. Rep. Ser.*, No. 240 (1962), https://apps.who.int/iris/handle/10665/40536 .

WHO International Programme on Chemical Safety, Joint FAO/WHO Expert Committee on Food Additives, WHO Task Group on Updating the Principles for the Safety Assessment of Food Additives and Contaminants in Food, International Labour Organization. et al.: Principles for the safety assessment of food additives and contaminants in food, published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization in collaboration with the Food and Agriculture Organization of the United Nations. *WHO, Environmental health criteria* No. 70 (1987), https://apps.who.int/iris/handle/10665/37578.

Witczak, A., Pohoryło, A., Abdel-Gawad, H., Cybulski, J.: Residues of some organophosphorus pesticides on and in fruits and vegetables available in Poland, an assessment based on the European union regulations and health assessment for human populations, *Phosphorus, Sulfur* 193, 711-720 (2018).

Wold, S., Dunn III, W. J.: Multivariate quantitative structure activity relationships (QSAR): Conditions for their applicability, J. Chem. Inf. Comput. Sci. 23, 6-13 (1983).

Zupan, J., Gasteiger J.: *Neural networks for chemistry and drug design; an introduction*, 2nd Edition, Wiley-VCH Publisher, Weinheim (1999).

有機リン系殺虫剤の1日摂取許容量のQSPR解析

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有機リン系農薬（OPs）は、これまで60年以上にわたって、農産物の収穫を増やし、家畜や人間の健康に悪影響が少ない農薬として広く使われてきた。しかし、OPsは農薬残基が生物濃縮によって蓄積し、アセチルコリン分解酵素阻害以外の毒性もあり、急性毒性だけではなく、慢性毒性や有機リン独特の遅発性神経毒性が問題になっている。植物防疫に使われた後の残留農薬を評価するために使われる指標に1日摂取許容量（ADI）がある。本研究では、46種のOPsについて、それらのADIのデータと化学構造との相関をQSPRの手法によって解析した。OPsの構造記述子は、分子力学計算を使用してエネルギー最適化構造から計算し、ADI値との相関を検討した。相関関係は、線形の重回帰分析（MLR）と非線形のニューラルネットワーク（ANN）の手法を適用した。その結果、MLRモデルによるADI値の計算値と実測値は良好な相関を示し、また十分な予測機能を有することが確認できた。しかし、ANNモデルは予測性能でMLRモデルに劣り、新規の類似化合物のADI値の予測にMLRモデルを適用できることを確認した。