International Journal of Chemical Modeling ISSN 1941-3955
Volume 5, Number 1, pp. 35-50 

# THE IMPORTANCE OF THE QSAR-QSPR METHODOLOGY TO THE THEORETICAL STUDY OF PESTICIDES

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## Abstract

In this paper, we reviewed various interesting applications of the Quantitative Structure-Activity/Property Relationships (QSAR-QSPR) Theory in pesticide research, with special emphasis on studies developed during the last decade. Different types of chemical structures were considered as pesticide agents. The environmental fate of pesticides is determined by partitioning between environmental compartments, and by transport and degradation processes. It is known that ecotoxicity assessment is essential before placing new chemical substances on the market, and so we reviewed the QSAR-QSPR applications on different properties, such as the Bioconcentration Factor, Soil/Sediment Sorption Coefficient, Toxicity, Aqueous Solubility, and Air to Water Partitioning. Finally, we revised different specific studies in this field.

## 1. Introduction

Most applications of data analysis involve attempts of correlating a model or pattern, usually of a quantitative type, with a set of experimental measurements. The reasons for fitting such models are varied. For example, a model may be purely empirical and be required for the purpose of designing new experiments. On the other hand, the model can be based on some theory or law, and an evaluation of the data correlation with the model can be used to gain a perspective of the process underlying the observations that were performed. In some cases, the ability to fit satisfactorily a model to a set of data can offer useful elements for the formulation of new hypotheses.

The type of model that can be fitted by a data set depends not only on the nature of the data but also on the use that the model will be submitted to. In many applications a model is expected to be used predictively, but predictions do not have to be necessarily quantitative [1]. It might be said that the origin of any theory is based on the observation, compilation of

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experimental information and modelling that derive into mathematical equations, for which a physical meaning is finally established.

There are methods that combine statistical tools and computational chemistry trying to obtain mathematical models able to relate numerical properties of the molecular structure to its activity. Quantitative structure-activity relationship or quantitative structure-property relationship research are attempts to correlate molecular structure, or properties derived from molecular structure, with a particular kind of chemical or biochemical activity. The kind of activity varies depending on the specific interest: quantitative structure-activity relationship is widely used in pharmaceutical, environmental, and agricultural chemistry in the search for particular properties. The term quantitative structure-property relationship is used, particularly when some property other than biological activity is concerned. The molecular properties used in the correlations relate as directly as possible to the key physical or chemical processes taking place in the target activity. Structure-activity relationships emerge from the observation how a certain change in the chemical structure of a compound generates a change in its (bio)chemical behaviour [2,3].

The central importance of the applications of the QSAR-QSPR methodology appears when quantitative predictions of an experimental property of a substance can be stated, remaining the substance unknown either because it is unstable or toxic or economically unattainable or its synthesis is long time demanding.

## 2. QSAR-QSPR Studies on Pesticides

The practical application of Quantitative Structure-Activity Relationships (QSAR) and Quantitative Structure-Property Relationships (QSPR)[1] has become possible after research in the area has vastly developed and has started to take the shape of a separate science [4]. Apart from the growing use of QSAR-QSPR in pharmaceutical research, the increased concern of environmental hazards arising from chemical pollutants has opened another area of application.

The underlying assumption in the QSAR-QSPR Theory is that the molecular structure contains, in principle, coded within it all of the information which predetermines the chemical, biological and physical properties of the chemical. If we elucidate in detail how such properties are determined by the chemical structure, we are able to predict such properties simply from the molecular structure. This is essential for the design of novel pesticides and herbicides since their properties may be predicted prior to synthesis and consequently the design may, in this way, be guided by the results of calculations.

In the realms of QSAR-QSPR, the molecular structure is translated into the so-called molecular descriptors, describing some relevant feature of the compounds, with mathematical formulae obtained from Chemical Graph Theory, Information Theory, Quantum Mechanics, Markov Chains Theory, etc. [5-7] There exist more than a thousand available descriptors in the literature, and many of these molecular descriptors are topological indices (TIs) or invariants obtained from the molecular graph, whose vertices are atoms weighted with different physicochemical properties (mass, polarity, electronegativity, charge) [4]. Even though the relationship between the structure and the activity remains unknown for a given dataset, the QSAR-QSPR technique has been based on statistically determined linear or

nonlinear models relating the chemical behaviour of compounds with descriptors, in order to find out useful parallelisms.

In QSAR-QSPR modelling, the Parsimony Principle (Occam's Razor Principle) [8] calls for using models and procedures that contain all that is necessary for the modelling but nothing more, i.e. given a number of models with nearly the same predictive error, that containing fewer parameters should be preferred because simplicity is desirable in itself. In addition, the applicability domain of the model (AD) must be defined [9] and the predictions for only those structures that fall in this domain can be considered reliable. The AD is a theoretical region in the space defined by the descriptors of the model and the modelled response, for which a given QSAR-QSPR should make reliable predictions. This region is defined by the nature of the chemicals in the training set and can be characterized in different levels of sophistication.

## 2.1. Bioconcentration Factor

The large number of organic pollutants is a direct result of the increasing use of toxic chemicals, such as herbicides, fungicides, pesticides, industrial solvents, or petroleum products [10] Bioconcentration is of great concern when defining toxic effects due to chronic exposure of chemicals. The experimental determination of Bioconcentration Factors (BCF) is expensive and time-consuming, so the QSPR technique is needed to predict this pesticide's property. A review summarized the correlations established in the past between structural descriptors and BCF [11]. One approach consisted on estimating a chemical's BCF based on its relationship with other physicochemical parameters such as the octanol/water partitioning coefficient ($K_{ow}$) [12,13] or the soil absorption coefficient ($K_{oc}$) [14] The $\log_{10}K_{ow}$ (logP) was employed for modelling BCF with Multivariable Linear Regression (MLR) [15-17] non-linear [18,19] bilinear [20] and polynomial [21] models. The main drawbacks of such models appeared with very large molecules having high $\log_{10}K_{ow}$, which may diffuse only slowly through membranes [22,23]

The QSPR models established for BCF used theoretical molecular descriptors such as molecular weight [24], molecular connectivity indices [19,25,26] geometrical [11] quantum-chemical descriptors [27] or combinations of different molecular descriptors [28,29]. An investigation was proposed for the use of the chromatographic retention in Biopartitioning Micellar Chromatography as an *in vitro* approach to evaluate the BCF of pesticides in fish [30] using a heterogeneous set of 85 pesticides from six chemical families.

Many studies obtained good results, but some models still lack robust validation, and the quality control of the data used for modelling was not always defined. New reliable and more strictly validated QSPR models on BCF were developed by Zhao et al. [31]. This work analyzed a large data set of 473 heterogeneous compounds, which combined MLR, Radial Basis Function Artificial Neural Network (RBF-ANN) and Support Vector Machine (SVM) methods, and was based on 2D-types of molecular descriptors calculated mainly from Dragon software [32].

Papa et al. [33] presented a properly validated QSPR for studying the persistence of 250 heterogeneous organic compounds, for which three *a priori* defined classes of environmental persistence were generated by Hierarchical Cluster Analysis, from the combination of half-life data in air, water, soil and sediment available for all the studied compounds. The

reliability of the proposed QSPR models was verified further with new data from the literature.

Jackson et al. [34] developed a validated model capable of predicting 109 high-quality fish BCF for the species *Lepomis macrochirus*. This QSPR involved descriptors such as the number of atoms for a given group (e.g., $-CH_3$) or the local topology of each atom as derived from electron counts. Another study employed the CAESAR model [35] on 635 compounds, which achieved better results than the BCFBAF v3.00 program for predicting BCF.

## 2.2. Soil-Sorption Coefficient

The soil/sediment sorption coefficient ($K_{oc}$) describes the extent to which a chemical is distributed between the solid and solution phases in soil, or between water and sediment in aquatic ecosystems, and indicates whether a chemical is likely to o be transported through the soil or would be immobile. One of the most comprehensive analyses in this area was carried out by Sabljic et al. [14], who evaluated the quality and reliability of the relationships between soil sorption coefficients and n-octanol/water partition coefficients for more than 400 compounds.

A frequently used descriptor in the estimation of $K_{oc}$ values was the first-order molecular connectivity index ($^1\chi$) [36]. A review of more than 200 QSPR for the estimation of $\log_{10}K_{oc}$ was presented by Gawlik et al. [37] showing that $\log_{10}K_{oc}$ values were most frequently modelled with aqueous solubility, n-octanol/water partition coefficient, Reversed Phase High-Performance Liquid Chromatography capacity factor, topological indices, or linear solvation energy parameters. Several efforts were done in this area in order to improve the results found with such empirical descriptors through the employment of constitutional, topological, quantum chemical, and WHIM (Weighted Holistic Invariant Molecular) types of descriptors [38] Also, the fragment contribution approach was quite successfully used to model soil sorption for large data sets [39,40]

Gramatica et al. [41] used the Genetic Algorithms (GA) approach for the selection of relevant descriptors for 185 non-ionic organic pesticides, while Duchowicz et al. [42] established a QSPR on this data set by using the Replacement Method (RM) variable subset selection approach. There were two attempts to model soil sorption with ANN [43,44]. Winget et al. used the results of quantum mechanical calculations to develop a set of effective solvent descriptors using SM5 solvational parametrization to characterize the organic carbon component of the soil [45].

Various general and class-specific QSPR models for soil sorption of 344 organic pollutants were developed using a large variety of theoretical molecular descriptors based only on molecular structure [38]. Gonzalez et al. [46] applied the TOPological Sub-structural MOlecular DEsign (TOPS-MODE) approach to predict $K_{oc}$, achieving a QSPR accounting for more than 85% of the data variance and demonstrating the importance of the dipole moment, the standard distance, the polarizability, and the hydrophobicity descriptors. Goudarzi et al. [47] established QSPR models on 124 pesticides by using the Successive Projection Algorithm (SPA) method for descriptors selection, and the MLR and ANN techniques for model development.

## 2.3. Toxicity

Reproductive toxicity studies in animals are typically required for pesticides. Different QSAR models were established for the toxicity of organophosphorus compounds, which exhibit toxic behaviour as insecticides, pesticides, and mammalicides, with special incidence in respiration of living organisms [48,49]. Substituted benzaldehyde compounds are extensively used as intermediates to synthesize pesticides and are continuously being introduced into the environment. Jin et al. [50] found a parabolic relationship between the logarithm of the acute toxicity of 17 substituted benzaldehydes to *Daphnia magna* and the sum of Hammett $\sigma^*$ values of the substituent groups attached to the carbon of benzene cycle.

Devillers et al. [51] derived a QSAR for estimating the acute toxicity of pesticides against *Lepomis macrochirus*. The chemicals were described by means of autocorrelation descriptors encoding lipophilicity and the H-bonding acceptor and donor abilities of the pesticides. A three-layer Feed-Forward trained by the Back-Propagation algorithm (FFBP-ANN) was used as statistical engine for deriving a powerful QSAR model accounting for the weight of the fish, time of exposure, temperature, pH, and water hardness.

Vehraar et al. [52,53] developed a rule-based system to classify individual chemicals into four classes: inert, less inert, reactive and specifically acting chemicals such as pesticides. Modern classification techniques were applied by Mazzatorta et al. [54] for predicting the toxicity exhibited by 253 pesticides on trout, rat, daphnia, quail, and duck. This study involved 153 descriptors and constituted an alternative to the use of MLR-based QSAR. A later study involved linear and nonlinear models for the acute toxicity of 282 pesticides on rainbow trout [55].

A fragment-based QSAR approach was presented [56] to correlate acute toxicity to the rainbow trout (*Oncorhynchus mykiss*) for 282 pesticides. While there were other fragment-based modelling routes, this approach exploited the possibility of prioritizing fragments' contributions to toxicity. The correlation weights of three types of local graph invariants, the vertex degrees, the extended connectivity of first order, and the numbers of paths of length two, were used to obtain optimal descriptors [57] These descriptors were used in one-variable models to predict toxicity toward *Daphnia magna* for a set of 262 pesticides, achieving acceptable results.

In order to select high quality data sets of ecotoxicity values for pesticides, Benfenati et al. [58] derived a protocol to critically evaluate the quality of the underlying data. In another study, a dataset of 125 aromatic pesticides with well-expressed aquatic toxicity towards trout was subjected to a QSAR analysis [59].

Chlorinated compounds are largely used as insecticides and herbicides. Ivanciuc et al. [60] established a novel model for chloro-benzene compounds, with the (chloro-substitution) reaction network viewed mathematically as a partially ordered set (or poset). Different numerical fittings to the overall poset lead to different predictive QSAR, of which three were investigated: average poset, cluster expansion, and splinoid poset QSAR models, for the chloro-benzene´s toxicities against various species (*Poecilia reticulata*, *Pimephales promelas*, *Daphnia magna*, *Rana japonica*, etc).

It is known that during a pest attack, many plants greatly increase their output of natural pesticides, such as allelochemicals or benzoxazinones. Thus, natural compounds could be an

alternative to synthetic pesticides, and Lo Piparo et al. [61] evaluated their toxicity behaviour by designing QSAR models for *Daphnia magna* toxicity prediction on benzoxazinone derivatives. Xue et al. [62] classified a diverse set of *Tetrahymena pyriformis* toxicity (TPT) chemical compounds, including pesticides, by using different statistical learning methods such as Logistic Regression, C4.5 Decision Tree, k-Nearest Neighbor (k-NN), Probabilistic Neural Network, and SVM on 841 TPT and 288 non-TPT agents which were more diverse than those in previous studies. The prediction accuracies were acceptable for TPT and for non-TPT agents based on 5-fold cross-validation studies, which were comparable to some of earlier studies despite the use of more diverse sets of compounds.

A later exhaustive study of 2008 from Zhu et al. [63] involved an international virtual collaboratory consisting of six independent groups, that compiled an aqueous toxicity data set containing 983 unique compounds tested in the same laboratory over a decade against *Tetrahymena pyriformis*. Each of the QSAR groups used their own modelling tools, and the established models were properly analyzed through internal and external validation, as well as with AD definitions.

A recent study [64] performed a QSAR for modelling the toxicity of 15 organothiophosphate pesticides to the invertebrate *Daphnia magna* and 10 compounds to fish (*Cyprinus carpio*). This work used quantum mechanical descriptors, and from the 100196 European Inventory of Existing Commercial Chemical Substances (EINECS), 83 compounds were identified for which one can obtain an indication of their toxicity without the need for additional experimental testing.

With the development of industrialization, phenols became widely used in chemical production of pesticides. In 2002, Cronin et al. [65] used the Partial Least Squares (PLS) technique on 108 molecular descriptors to analyze a large set of 200 heterogeneous phenols that simultaneously elicited different modes of toxicological action, such as polar narcotic (173), respiratory uncoupler (19), pro-electrophile (27), soft electrophile (27) and pro-redox cycler (4). The authors judged the quality of the final models with an external test set composed of 50 chemicals. In 2004, Devillers et al. [66] employed the same data set to derive alternative PLS models that improved previous statistical results, supplying also with two three-layer Perceptron ANN that displayed an even better statistics. Later, in 2008 Duchowicz et al. [67] proposed an alternative QSAR prediction of aqueous toxicities for the training set-test set of heterogeneous phenol derivatives chosen previously, using the Replacement Method and Dragon descriptors, which improved the performance of the previous models. Niu et al. [68] demonstrated that AdaBoost learning algorithm outperformed the performance of SVM, ANN and k-NN in predicting the mechanism of toxicity of 274 phenols based on molecular descriptors.

In 2009, Wang et al. [69] established interpretable QSAR models for assessing the aquatic toxicity of 1600 pesticides, involving 533 nontoxic, 287 slightly toxic, 329 moderately toxic, 231 highly toxic, and 220 very highly toxic compounds. The chemical structures were encoded into 196 molecular descriptors including the 2D topological, electrotopological state variables as well as the MlogP and AlogP parameters. Two methods, FSR and GA, coupled with the Linear Discriminant Analysis (LDA) were used to obtain stable and thoroughly validated QSAR.

## 2.4. Aqueous Solubility

Pesticide contamination of surface water and groundwater due to agricultural activities has been of concern for a long time. Aqueous solubility indicates the tendency of a pesticide to be removed from soil by runoff or irrigation and to reach surface water and indicates the tendency to precipitate at the soil surface. Even though many QSPR have been established in past years for predicting aqueous solubilities, the vast number of them were devoted to studying drug-like compounds [70].

A highly predictive QSPR model was derived and validated by Gao et al. [71], for estimating the aqueous solubility of 930 diverse compounds that included pesticide compounds. Yin et al. [72] developed a QSPR using GA-based variable-selection approach with quantum chemical descriptors derived from AM1 method, and efficiently predicted the aqueous solubility of 71 aromatic sulfur-containing carboxylates. Delgado et al. established a QSPR for 45 herbicides [73] demonstrating that the statistical and physical performance drops drastically when the model, obtained for a given phase (solid), is used to predict the solubility of the same set of compounds but in another phase (liquid). Deeba&Goodarzi [74] developed validated QSPR models using MLR, PLS, and ANN analyses with Dragon descriptors on 219 pesticides. Consistent with experimental studies, the results obtained offer excellent regression models having good prediction ability.

## 2.5. Air to Water Partitioning

This is another important property of pesticides, as the tendency to volatilize from water solution into air is largely determined by its Henry's law constant ($K_H$). Although QSPR methods have been successfully used to predict many physicochemical properties, their use in predicting $K_H$ of pesticides has been rather limited and most of the existing models are derived from very limited data sets [75-77] Yao et al. [78] established linear correlations for a diverse set of 411 organic compounds. They used Forward Stepwise Regression (FSR) as feature selection and MLR and RBF-ANN for constructing linear and non-linear models, respectively.

Yaffe et al. [79] resorted to fuzzy ARTMAP (Adaptive Resonance Theoretic Map) and Back-Propagation ANN (BP-ANN) as a non-linear QSPR model for estimating $K_H$ of a heterogeneous set of 495 organic compounds. They built their model based on a set of molecular descriptors developed from PM3 Semiempirical Molecular Orbital Theory and the topological second-order molecular connectivity index. The fuzzy ARTMAP-based QSPR was superior than BP-ANN and MLR based QSPR models.

A recently reported QSPR study considers a well-known thermodynamic relationship between the logarithm of $K_H$ and the standard Gibbs free energy of solvation for 189 aliphatic hydrocarbons [80] where a fully-connected, Feed-Forward Multilayer Perceptrons ANN model with architecture 3-2-1 was employed. Modarresi et al. [81] established a QSPR on 940 organic compounds by making use of different descriptors of CODESSA software (Comprehensive Descriptors for Structural and Statistical Analysis), TSAR, and Dragon software, and a model based on a combined descriptor set from these packages. On the other hand, they used FSR and GA for feature selection and finally they performed a RBF-ANN to establish the model.

Duchowicz et al. [82] designed a QSPR for 150 aliphatic hydrocarbons by using the Replacement Method as feature selection based on MLR, achieving similar statistical results. A recent study [83] established a QSPR for a large data set of 96 heterogeneous organic pesticides by using GA, the Replacement Method, and four fully-connected FF-ANN based on Dragon descriptors.

## 3. Some Specific Studies on Pesticide Research

QSAR models were derived [84] on some famous pesticides with the Free-Wilson mathematical model in its Fujita-Ban variant [85]. In the case of sulfonylurea herbicides, the heterocycle connected with the amino group of the urea part was found to play an important role in inhibition of rape rooting, while for the case of benzoylphenylurea type insect-growth regulators a substituent at the benzoyl moiety caused the inhibition of insects' chitin synthesis. The Free-Wilson/Fujita-Ban model was also applied to model the insecticidal activity of 2,5-disubstituted-1,3,4-oxadiazoles against armyworm [86].

Various efforts have been done to model the activity of phosphoramidothioate (Ace II) compounds on housefly [87,88] and the competition binding of rodenticides to H1 receptor in rat and guinea pig brain [89] These studies were carried out by using topological descriptors alone or a combination of electronic, topological, hydrophobic and steric descriptors.

One role of monoterpenoids in the plants is to defend against plant-directed pathogens, herbivores, or competing plant species. New QSAR models were established for the insecticidal activity of monoterpenoids based on Dragon descriptors and MLR [90]. Another work [91] modelled the binding affinity of 18 substituted *N*-*t*-butyl-*N,N'*-dibenzoylhydrazine to intact Sf-9 cells, as this interaction leaded to strong insecticidal activity. The effects of the substituent on the binding affinity were analyzed quantitatively using the Hansch-Fujita QSAR method.

Gonzalez et al. [92] applied the TOPS-MODE approach in order to classify an heterogeneous series of organic herbicide and non-herbicide compounds, pre-processed by a k-Means Cluster Analysis in order to design the training and test sets. Gramatica et al. [93] ranked 54 pesticides in 4 *a priori* classes according to their environmental behaviour (sorbed, soluble, volatile and non-volatile/medium class) and finally assigned to the defined four classes by different classification methods, such as k-NN, using theoretical molecular descriptors. This QSPR approach allowed a rapid indication of the environmental distribution of pesticides.

QSPR studies were carried out on the gas chromatograph/electron capture detector (GC/ECD) system retention times of 38 diverse chlorinated pesticides, herbicides, and organohalides by using electronic, steric and thermodynamic descriptors and MLR and PLS techniques [94]. Praba and Velmurugan [95] established QSAR models for the activity of herbicides (30 benzodiazepinediones), insecticides (15 dioxatricyclododecenes), and larvides (18 N-oxalyl derivatives of tebufenozide) using the Molecular Operating Environment software.

The application of ANN to spinosyns, novel fermentation derived insecticide [96] identified new directions for improved activity in the chemistry, which subsequent synthesis and testing confirmed. The ANN-based analogues coupled with other information on substitution effects resulting from spinosyn structure activity relationships lead to the

discovery of spinetoram. Launched in late 2007, spinetoram provides both improved efficacy and an expanded spectrum while maintaining the exceptional environmental and toxicological profile already established for the spinosyn chemistry.

For the development of new fungicides against rice blast, QSAR analyses for fungicidal activities of thiazoline derivatives were carried out using MLR and ANN [97] achieving predictive models. Bitencourt and Freitas [98] modelled a series of sulfonylurea herbicides using a 2D image-based QSAR approach known as MIA-QSAR (Multivariate Image Analysis applied to QSAR), and highly predictive models were achieved for predicting AHAS (Acetohydroxyacid synthase) apparent inhibition constants.

Mastrantonio et al. [99] studied the acetylcholinesterase (AChE) enzyme inhibition ability by 10 organophosphorus pesticides, through QSAR based on conformational descriptors. Knaak et al. [100,101] provided parameters for the development of quantitative structure physiologically based pharmacokinetic / pharmacodynamic QSAR for assessing health risks to carbamates pesticides. Parameters specific to each carbamate are needed in the construction of the models along with their metabolic pathways.

The environmental contamination caused by an extensive use of chemical insecticides is a well-known problem, leading to the need of replacing these agents by insecticides of natural origin. A recent study of Duchowicz et al. [102] derived useful models that relate 46 experimentally measured $pED_{50}$ feeding inhibition on the common cutworm *Spodoptera litura* exhibited by aurones, chromones, 3-coumarones and flavones to their molecular structure. This work resorted to the Replacement Method based on MLR, and analyzed 1500 Dragon theoretical descriptors. A later QSAR from the same authors applied this modelling strategy on the insecticidal activity of 14 structurally-related flavone compounds towards the fall armyworm *Spodoptera frugiperda* [103].

The inhibition of essential amino acid biosynthesis in plants is an attractive mode of action of herbicidal activity. AHAS has been identified as the target of action of several structurally different types of chemicals (sulfonylureas, sulfonamides, imidazolinones and pyrimidylsalicylates) with high herbicidal activity. Unlike sulfonylureas and sulfonamides, AHAS inhibition by pyrimidylsalicilates has been scarcely studied by QSAR [104,105].

The often observed scarcity of physical-chemical and well as toxicological data hampers the assessment of potentially hazardous chemicals released to the environment. A recent work of Carlsen [106] reviewed the application of QSAR/QSPR in combination with Partial Order Ranking technique, which enabled to prioritize a series of chemical substances based on a simultaneous inclusion of a range of parameters. Rouhollahi et al. [107] established a QSAR study on a data set of 33 diphenyl ether herbicide with their inhibition data on protoporphyrinogen oxidase enzyme, using MLR and PLS combined with FSR, achieving acceptable results.

Many pesticides are endocrine-disrupting chemicals (EDCs), interfering with the body's endocrine system and producing adverse developmental, reproductive, neurological, and immune effects in both human and wildlife. A recent study of Li&Gramatica [108] established QSAR models on a big data set of EDCs-androgen receptor (AR) antagonists, and the strictly externally validated models were also used to distinguish AR binders as agonists and antagonists. The k-NN, local lazy IB1, and ADTree methods and the consensus approach were used to build the different models, involving Dragon types of descriptors.

## 4. Conclusion

We reviewed different QSAR-QSPR applications on properties of pesticides, such as the Bioconcentration Factor, Soil/Sediment Soption Coefficient, Toxicity, Aqueous Solubility, and Air to Water Partitioning, including different specific studies. This is essential for the design of novel pesticides and herbicides since their properties may be predicted prior to synthesis and consequently the design may, in this way, be guided by the results of calculations.

The QSAR-QSPR methodology is effected by various factors from which the most important are: (a) the size and the composition of the training and test sets; (b) the experimental error; (c) the appropriate selection of molecular descriptors that should include maximum information of structures and minimum co-linearity between them; (d) the use of suitable modelling methods; and (e) the employment of validation techniques to quantify the predictive performance of the developed models. Research is being carried out in this line in order to improve the predictive performance of the quantitative structure-activity/property relationships.

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