Prediction of the endocrine disruption profile of pesticides

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Numerous manmade chemicals released into the environment can interfere with normal, hormonally regulated biological processes to adversely affect the development and reproductive functions of living species. Various in vivo and in vitro tests have been designed for detecting endocrine disruptors, but the number of chemicals to test is so high that to save time and money, (quantitative) structure–activity relationship ((Q)SAR) models are increasingly used as a surrogate for these laboratory assays. However, most of them focus only on a specific target (e.g. estrogenic or androgenic receptor) while, to be more efficient, endocrine disruption modelling should preferentially consider profiles of activities to better gauge this complex phenomenon. In this context, an attempt was made to evaluate the endocrine disruption profile of 220 structurally diverse pesticides using the Endocrine Disruptome simulation (EDS) tool, which simultaneously predicts the probability of binding of chemicals on 12 nuclear receptors. In a first step, the EDS web-based system was successfully applied to 16 pharmaceutical compounds known to target at least one of the studied receptors. About 13% of the studied pesticides were estimated to be potential disruptors of the endocrine system due to their high predicted affinity for at least one receptor. In contrast, about 55% of them were unlikely to be endocrine disruptors. The simulation results are discussed and some comments on the use of the EDS tool are made.

Keywords: pesticides; endocrine disruption profile; nuclear receptors; in silico; molecular docking; Endocrine Disruptome

1. Introduction

The past decades have seen increasing concern by the public, researchers, and authorities that pesticides and many other xenobiotics possess the ability to affect the hormonal regulation and the endocrine system of human and wildlife, and thus adversely impact their reproduction and development [1–13]. These manmade compounds, named endocrine-disrupting chemicals (EDCs), can adversely impact an organism’s endocrine system in various ways.

EDCs can mimic the biological activity of a hormone by binding to a cellular receptor, leading to an unwarranted response by initiating the cell’s normal response to the naturally occurring hormone at the wrong time or at an excessive level (agonist effect). EDCs can bind to a receptor without activating it, but the presence of the EDC on the receptor will prevent binding of the natural hormone (antagonist effect). EDCs can bind to transport proteins in the blood, thus altering the amounts of natural hormones present in the circulation. They can

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interfere with the metabolic processes in the body, affecting the synthesis or breakdown rates of natural hormones [14].

It is beyond the scope of this paper to catalogue all the possible ways by which a chemical can disrupt the endocrine systems of vertebrates and we refer readers to some interesting reviews [14–18]. Nonetheless, one of the major mechanisms interfering with normal homeostasis is the direct interaction of chemicals with receptors [19]. As a result, a number of studies have focused on them, especially on the estrogen and androgen receptors which are members of the nuclear receptor family [20]. In addition, given the wealth of information gathered on them, it has been possible to successfully derive (quantitative) structure–activity relationship ((Q)SAR) models for the prediction of the binding affinities of any kind of organic molecules from only their structure and/or physicochemical properties [21–30]. These in silico paradigms are now widely used to fill data gaps, and to screen and prioritise chemicals for further experiments, with a consequent reduction of time, costs and number of tested animals [31,32].

Recently, Kolšek and colleagues [33] proposed a new simulation tool, named Endocrine Disruptome, which simultaneously predicts the probability of binding of chemicals on the 12 following receptors: androgen receptor (AR); estrogen receptors α and β (ERα and ERβ); glucocorticoid receptor (GR); liver X receptors α and β (LXRα and LXRβ); peroxisome proliferator-activated receptor α, β/δ and γ (PPARα, PPARβ/δ and PPARγ); retinoid X receptor α (RXRα); and the thyroid receptors α and β (TRα and TRβ). In the meantime, Endocrine Disruptome was used by Plošnik and colleagues [34] on 558 structurally diverse compounds which were randomly selected from the CosIng (Cosmetic Ingredients and Substances) Inventory database. These authors showed that 122 compounds were estimated to be possible endocrine disruptors because they bound to at least one receptor and 21 were predicted to be probable endocrine disruptors because they bound to more than five receptors simultaneously [34].

In this context, the Endocrine Disruptome software was used to predict the endocrine disruption profile of 220 structurally diverse pesticides. However, because the experimental results obtained on them are very often contradictory or totally lacking for most of the receptors, in a first step, the simulation tool was applied to 16 pharmaceutical compounds known to target at least one of the studied receptors as a result of their therapeutic action.

2. Materials and methods

2.1 Simulation tool

2.1.1 Model design

To derive the models, three main types of chemicals were gathered from the DUD-E website (http://dude.docking.org/) [35] and/or the ChEMBL database (https://www.ebi.ac.uk/chemblDb/) [36]. The active compounds were obtained from binding and functional assays showing half inhibitory concentration (IC50) or half effective concentration (EC50) values <1 μM. Agonists were ligands with IC50 or EC50 values <1 μM filtered with ‘agonist(ic)’ in the functional assay description. Antagonists were ligands with IC50 or EC50 values <1 μM filtered with ‘antagonist(ic)’ in the functional assay description. An additional molecular weight (MW) filter of 600 was used except for TRs for which no limitation was applied due to the high MW of the endogenous ligands. Decoys, which are chemicals with similar physicochemical properties as ligands but with different structures and thus assumed to be no-binders, were obtained from the DUD-E website [35]. For each ligand, 50 decoys were considered. The active,
agonist and antagonist ligands and their corresponding decoys were merged to constitute three databases per receptor except when the number of ligands was too low. Reduced databases were also constituted for selecting the best receptor structures. Initially, up to six crystal structures were considered per receptor. Structures with the highest resolution were preferentially retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). Both agonist and antagonist conformers of receptors were considered, depending on their availability in PDB. This was the case for AR, ERα and ERβ, and GR [33]. Only chain A for each crystal structure was used for the docking experiments, except when the number of available crystal structures was reduced or when the predictions were not optimal. In these cases, other chains were also used. Receptors were prepared with the AutoDock tools [37] and the dockings were performed with AutoDock Vina 1.1.2 [38] using the default options.

Two validation parameters were calculated for each three-dimensional (3D) structure, namely the area under the curve (AUC) of the operating characteristic (ROC) curve and the ROC-based enrichment factor at 1% (EF1%). EF1% is the percentage of known ligands found in the top 1% of the ranked docking database [33]. For each target, the structure with the best validation parameter values was selected for the final validation which was performed on the full databases of ligands and decoys. Good results were obtained for all the receptors except for the mineralocorticoid and progesterone receptors, which were excluded from the first version of the software and hence are not available in the current version.

2.1.2 Implementation and use
The final validation results were used to calculate three thresholds values per structure to define four probability binding classes (Table 1). For the threshold calculations, the true positive rate (sensitivity, SE) values were used. The docking scores for each threshold were calculated to broadly correspond to SEs of 0.25, 0.50 and 0.75 [33]. It is noteworthy that the selected threshold values are inclusive.

Table 1. Threshold values defining the four classes of probabilities of binding in the Endocrine Disruptome software [33].

| Target | Docking scores |
|--------|----------------|
| AR*    | -8.6           |
| ARa    | -8.4           |
| ERα    | -9.3           |
| ERαa   | -10.7          |
| ERβ    | -9.2           |
| ERβa   | -9.0           |
| GR     | -10.7          |
| GRa    | -9.8           |
| LXRα   | -11.9          |
| LXRβ   | -12.1          |
| PPARα  | -10            |
| PPARβ  | -10.5          |
| PPARγ  | -10.3          |
| RXRα   | -12.1          |
| TRα    | -10.2          |
| TRβ    | -10.5          |

*See text for details of significance.
Endocrine Disruptome software (EDS) is available as a free web-based system (http://endo
crinedisruptome.ki.si/) running on an open source platform called Docking interface for 
Target Systems (DoTS). The chemical of interest can be either drawn or introduced by means 
of its simplified molecular input line entry system (SMILES) string. It is crucial to note that 
stereochemistry has to be taken into account in the SMILES encoding. The EDS is able to 
simultaneously predict the binding affinity of a ligand on the 16 targets (Table 1). Results are 
provided as docking score values as well as a probability of binding expressed by means of a 
coloured code calculated from the SEs. ‘Red’ corresponds to SE <0.25 and indicates a high 
probability of binding. ‘Orange’ (0.25 < SE < 0.50) indicates a lower probability of binding 
but the class is higher than ‘yellow’ (0.50 < SE < 0.75) and ‘green’ (SE >0.75) which corre-
sponds to the lowest probability of binding.

The EDS is intended to be used as a screening tool easily interpretable from its colour 
 codes. However, it is preferable to not focus on the colour coded outputs but to instead anal-
yse the docking score values obtained with AutoDock Vina. Indeed, it is noteworthy that a 
unique SMILES string can lead to different colour coded outputs. This is explained by the 
fact that small differences can be obtained from one run to another one. If the docking score 
value is near a threshold value (Table 1), the result can change when the calculation is 
repeated. Consequently, when using the EDS it is essential to make enough repetitions with 
the same SMILES string.

Last, the EDS provides for each chemical, its structure and basic molecular physiochemi-
cal properties including MW, octanol–water partition coefficient (log P), number of hydrogen 
 bond acceptors, number of hydrogen bond donors, number of rotatable bonds, and the 
existence of pan-assay interfering compounds (PAINS) [39] which can give false positive 
results [33].

2.1.3 Studied chemicals
Sixteen pharmaceutical compounds known to bind against at least one of the studied 
receptors were selected for testing the EDS performances. We hypothesised that these com-
ounds, for which validated in vivo endocrine activities were available, represented a first 
necessary step to consider in order to give some confidence in the predictions made with this 
software. If the results were satisfactory, we could expect the EDS to be suitable for estimat-
ing the endocrine disruption profiles of pesticides.

In a second step, 220 structurally diverse pesticides were selected. Most of them are re-
presentative of the pesticides currently used on French farm land [40]. First and second gener-
ation anticoagulant rodenticides were also considered due to their impact on non-target wildlife 
species including numerous bird species [41–44]. Last, some pesticides were also selected 
due to their structural characteristics.

It is noteworthy that the endocrine disruption potential of chemicals including a silicon 
(e.g. flusilazole, CAS RN 85509-19-9) an aluminium (e.g. fosetyl-aluminium, CAS RN 39148-24-8), a manganese (e.g. maneb, CAS RN 12427-38-2), a sodium (e.g. metam-sodium, 
CAS RN 137-42-8) or a zinc (zineb, 12122-67-7) atom cannot be evaluated with the EDS. In 
the same way, pesticides with a too large molecular weight (e.g. abamectin, MW = 873) can-
not be evaluated.

When necessary, E and Z type isomerism as well as chirality were encoded in the 
SMILES strings of the studied chemicals. In these cases, the canonical SMILES strings were 
also experienced to evaluate the variation in the simulation results. Each SMILES string was 
tested at least seven times in different work sessions and different days.
The prediction results were expressed by four different classes of binding that were ranged from 1 (low probability of binding) to 4 (high probability of binding). They were calculated directly from the binding scores and the threshold values (Table 1). In other words, the colour codes were not gathered. When the different runs led to various probability values, the most frequent one was reported first. Thus, the code 4-3 means that the studied chemical showed more frequently binding scores leading to its allocation in class 4 rather than in class 3, while 3-4 was for the inverse situation. We claim that it is the most convenient way to use the EDS in practice. Last, because the EDS is not identified by a version number, it is worth noting that all our calculations were made between April and June 2015.

3. Results and discussion

3.1 Pharmaceutical compounds

The 16 selected compounds are listed in Table 2 under a target receptor for which a corresponding endocrine activity was unambiguously found due to their therapeutic action.

Danazol (CAS RN 17230-88-5) is a derivative of the synthetic steroid ethisterone, which is mainly used in the treatment of endometriosis. It exhibits hypoestrogenic and hyperandrogenic effects [45]. Barbieri and colleagues [46] showed that danazol bound to the AR of rat prostate cytosol and to the GR of rat liver cytosol, but it did not bind well to the ER of the rat uterus. These experimental results are in agreement with those found by using the EDS (Table 2). Oxandrolone (CAS RN 53-39-4) is an androgenic anabolic steroid with specific therapeutic applications [47,48] and which shows an affinity for the AR [49]. Consequently, it is not surprising that it presents a high binding affinity against the AR but also a significant affinity for the ERs shown in Table 2. Flutamide (CAS RN 13311-84-7) and bicalutamide (CAS RN 90357-06-5) are synthetic non-steroidal compounds used primarily to treat prostate cancer due to their anti-androgenic activity [50]. The simulation results obtained for these two compounds (Table 2) allows us to detect this effect. However, notice that bicalutamide is predicted as an agonist on the ERα and to a lower extent also as agonist on the ERβ while, except for its anti-androgenic activity, it has been identified as having no other endocrine activity [51].

Estradiol valerate (CAS RN 979-32-8) is the 17-pentanoyl ester of 17β-estradiol. It is used to reduce menopausal symptoms (e.g. hot flushes, vaginal dryness) [45,51]. Consequently, it is not surprising that the EDS predicts that this chemical presents a high probability of binding on ERα and a little bit less on ERβ (Table 2).

Fulvestrant (CAS RN 129453-61-8) and tamoxifen (CAS RN 10540-29-1) are used in the treatment of hormone-dependant breast cancer due to their anti-estrogenic activity [45,51], which is correctly simulated by the EDS (Table 2). Conversely, while both compounds show no agonist activity on the ERβ, they show a strong agonist activity on the ERα (Table 2). If it is known that tamoxifen presents an estrogen agonist activity, fulvestrant is considered as a pure anti-estrogen [52].

Fludrocortisone (CAS RN 127-31-1) is a synthetic adrenocortical steroid showing very potent mineralocorticoid properties and high glucocorticoid activity. It is used in replacement therapy for primary and secondary adrenocortical insufficiency in Addison’s disease [51]. The simulation tool correctly predicts its agonist activity on the GR (Table 2). A low agonist and antagonist activity on the AR is also predicted. Only the agonist activity on the AR is described in the literature [53].
Table 2. Endocrine disruption profile of 16 pharmaceutical compounds estimated with the Endocrine Disruptome software [33].

| Compound                      | AR | ARa | ERα | ERαα | ERβ | ERβα | GR | GRα | LXRα | LXRβ | PPARα | PPARβ | PPARγ | RXRα | TRα | TRβ |
|-------------------------------|----|-----|-----|------|-----|------|----|-----|------|------|-------|-------|-------|------|-----|----|
| **Androgen receptor**         |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| Danazol                      | 4* | 4-3 | 1   | 1-2  | 1   | 1    | 2-3| 1   | 2-3  | 3-2  | 1     | 1     | 1     | 1    | 1    | 2   |
| Oxandrolone                   | 4  | 4   | 3-2 | 3-2  | 4   | 1    | 2  | 1   | 2    | 1    | 1     | 1     | 1     | 1    | 1    | 1   |
| Flutamide                     | 2  | 2-3 | 1   | 1    | 2   | 1    | 2-1| 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2    | 2   |
| Bicalutamide                  | 1  | 3-2 | 3-2 | 2-1  | 2-3 | 1-2  | 2  | 1   | 2-1  | 2-1  | 1     | 1     | 1     | 2-1  | 2-1  | 2-3 |
| **Estrogen receptors**        |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| Estradiol valerate            | 1  | 2-3 | 4   | 1-2  | 3-2 | 1-2  | 2  | 1-2 | 1    | 1-2  | 1     | 1     | 1     | 1    | 1    | 1-2 |
| Fluvestrant                   | 1  | 2   | 4-3 | 3-2  | 1   | 4    | 2-3| 1   | 2    | 1-2  | 2-3   | 1     | 2     | 1    | 1    | 1   |
| Tamoxifen                     | 1  | 2   | 4   | 3   | 1   | 3-4  | 2-1| 1   | 1-2  | 1    | 1     | 1     | 1     | 1    | 1    | 1   |
| **Glucocorticoid receptor**   |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| Fludrocortisone               | 2  | 3-2 | 1   | 1    | 1   | 1    | 3  | 1   | 1    | 2    | 1     | 1     | 1     | 1    | 1    | 1-2 |
| Mifepristone                  | 1  | 1   | 1   | 1-2  | 1   | 1    | 1-2| 3-4 | 1    | 1    | 1     | 1     | 1     | 1    | 1    | 1   |
| **Liver X receptors**         |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| (-)-Anthrabenzoxocinone       | 1  | 1   | 1   | 1    | 1   | 2    | 3  | 3-4 | 3-2  | 4    | 1     | 1     | 1     | 2-1  | 1-2  | 2-1 |
| **Peroxisome proliferator-activated receptors** |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| Rosiglitazone                 | 1-2| 2   | 1   | 1    | 1   | 1-2  | 1  | 2   | 1-2  | 1    | 1     | 1     | 1     | 1    | 1    | 2   |
| Farglitazar                   | 1  | 1   | 4   | 3-4  | 1   | 4    | 3-4| 3-4 | 3-4  | 2    | 4     | 4     | 4     | 4-3  | 3-2  | 1   |
| Muraglitazar                  | 1  | 1   | 2-3 | 2-3  | 1   | 2-3  | 2-3| 2-3 | 2-3  | 1-2  | 4-3   | 3     | 4-3   | 1    | 1    | 1   |
| **Retinoid X receptor**       |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| Bexarotene                    | 1  | 2   | 1   | 1    | 1   | 2-1  | 2  | 2-1 | 2    | 3    | 1     | 1     | 2-1  | 4    | 1    | 1-2 |
| **Thyroid receptors**         |    |     |     |      |     |      |    |     |      |      |       |       |       |      |     |    |
| DIMIT                         | 1  | 2   | 1   | 1    | 1   | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 4    | 3   |
| GC-1                          | 1  | 2   | 1   | 1    | 1   | 2    | 1  | 2   | 1    | 1    | 1     | 1     | 1     | 1    | 4    | 4   |

*See text for significance.
Mifepristone (CAS RN 84371-65-3) is a progestational and glucocorticoid hormone antagonist. Its inhibition of progesterone has led to its use for early pregnancy abortions. As a GR antagonist, the drug has been used to treat hypercortisolism in patients with non-pituitary Cushing syndrome [54]. The EDS correctly predicts the antagonist activity of the chemical on the GR (Table 2). It is worth noting that mifepristone has a weak anti-androgenic action which appears in animals after the prolonged administration of very high doses [51].

Herath and colleagues [55] have shown that anthrabenzoxocinones extracted from Streptomyces sp. presented an affinity for LXRα and LXRβ. This is in agreement with the results found using the EDS (Table 2). An antagonist activity on the GR is also predicted but no confirmation of this potential activity has been found in the literature.

The PPARs are a group of nuclear receptor proteins that function as transcription factors regulating the expression of target genes implicated in the cellular differentiation, development and metabolism of carbohydrates, lipids and proteins [14]. Rosiglitazone (CAS RN 122320-73-4) is an antidiabetic compound with anti-hyperglycemic and anti-inflammatory activities. It shows a selective affinity for PPARγ [45,56], which is not predicted by the EDS. The chemical is also predicted as no binder for PPARα and PPARβ (Table 2). In contrast, a high probability of binding is predicted on the three PPARs (Table 2) for the L-tyrosine analogue farglitazar (CAS RN 196808-45-4). It has been demonstrated that farglitazar is a full agonist of PPARγ and PPARα, although its affinity is lower on the latter receptor [56–58]. Note that high probabilities of binding were also predicted on other receptors, but without available literature data, it is impossible to discuss the reliability of these simulation results. Muraglitazar (CAS RN 331741-94-7) is also a dual PPARγ/α-agonist with strong PPARγ and moderate PPARα effects [59]. Originally, it was developed for the treatment of type II diabetes with the view to combining the insulin sensitising and anti-hyperlipidemic effects of the PPAR agonists [60]. A high probability of binding has been found on the three PPARs (Table 2).

Bexarotene (CAS RN 153559-49-0) is a RXR selective agonist mainly used in the treatment of cutaneous T-cell lymphoma [61]. This agonist activity is correctly estimated by the EDS (Table 2).

DIMIT (CAS RN 26384-44-1) is a non-halogenated artificial analogue of the thyroid hormone T3 which binds to the TRs [62,63]. The results found with the EDS are in agreement with these findings. A high binding affinity on the TRs is also found for the thyromimetic GC-1 (CAS RN 211110-63-3) (Table 2). However, it is well known that this compound shows a preference for binding to TRβ [63].

Analysis of the results obtained with the 16 pharmaceutical compounds (Table 2), known to have at least one affinity for the studied receptors, shows that there is an acceptable agreement between these affinities and the high probabilities of binding estimated with the EDS. However, the distinction between agonist and antagonist effects sometimes seems to be slightly less effective.

3.2 Pesticides
The prediction results obtained with the EDS for the whole set of 220 structurally diverse pesticides are given in Table 3. Analysis of the different endocrine disruption profiles listed in Table 3 shows that 54.5% of the studied pesticides present a profile only characterised by values of 1, 1-2, 2-1 and/or 2. Moreover, among these pesticides, 45.8% have one target with a value of 2, 1-2 or 2-1 while the 15 other targets present a value of 1 after at least seven repetitions at different days. Very often, the value of 2 is found for the antagonist form of the
Table 3. Endocrine disruption profile of 220 structurally diverse pesticides estimated with the Endocrine Disruptome software [33].

| Compound*                      | AR** | ARa | ERa | ERaa | ERβ | ERβa | GR | GRa | LXRa | LXRβ | PPARα | PPARβ | PPARγ | RXRα | TRα | TRβ |
|--------------------------------|------|-----|-----|------|-----|------|----|-----|------|------|-------|-------|-------|-----|-----|-----|
| Acetamiprid                    | 1**  | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Acetochlor                     | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Acifluorfen-methyl             | 3-2  | 2-3 | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 2     | 3   | 1   | 1   |
| Aclonifen                      | 2    | 3   | 1   | 1    | 2   | 1    | 1  | 1   | 1    | 1    | 1     | 2     | 2     | 2   | 1   | 1   |
| Amitraz                        | 1    | 1   | 1   | 1    | 1   | 2    | 2  | 2   | 1    | 1    | 1     | 2     | 1     | 1   | 1   | 2   |
| Amitrole                       | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 2   | 2   |
| Anthraquinone                  | 3    | 3   | 1   | 1    | 2   | 2    | 1  | 1   | 1    | 1    | 1     | 2     | 1     | 1   | 1   | 1   |
| Asulam                         | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2   | 1   | 1   |
| Beflubutamid                   | 3-2  | 3-2 | 4   | 2    | 2    | 3-4  | 2  | 1   | 1    | 2-1  | 1-2   | 1     | 3     | 3   | 1   | 1   |
| Benalaxyl                      | 1-2  | 2-3 | 2-3 | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Benfluralin                    | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Benfuracarb                    | 1    | 2   | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Benoxacar                      | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Bentazonate                    | 2    | 2-3 | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Benthiavalicarb                | 1-2  | 3-2 | 1-2 | 1    | 2-1  | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 2   | 1   |
| Bifenox                        | 2    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 2     | 2     | 2   | 1   | 1   |
| Bifenthrin                     | 1    | 2-3 | 1-2 | 2-3  | 1    | 2-3  | 4  | 1   | 3    | 2    | 1     | 4     | 4     | 3   | 2   | 3-4 |
| Boscalid                       | 1    | 2-3 | 2-3 | 2    | 2    | 3    | 2  | 1   | 1-2  | 1-2  | 1     | 1     | 1     | 1   | 1   | 1   |
| Brodifacoum                    | 1    | 1   | 1-2 | 4-3  | 1    | 4-3  | 1  | 4   | 4-3  | 1    | 1     | 1     | 1-2  | 3-2 | 1   | 1   |
| Bromadiolone                   | 1    | 1   | 3   | 4-3  | 1    | 3-2  | 2  | 4   | 4-3  | 1-2  | 3-2   | 3     | 4-3  | 1   | 1   | 1-2 |
| Bromopropylate                 | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Bromoxyln octanoate            | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 2   |
| Bromuconazole                  | 1    | 2-3 | 1   | 1    | 1-2  | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 2   |
| Bupirimate                     | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Carboxin                       | 2    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1-2 |
| Carfentrazone-ethyl            | 1-2  | 3   | 2   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Chlomethoxyfen                 | 2    | 3-2 | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 2     | 2     | 2   | 1   | 1   |
| Chlorantraniliprole            | 1    | 1   | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Chloridazon                    | 2    | 3   | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 2     | 1     | 1   | 1   | 1   |
| Chlorobenzilate                | 1    | 3   | 1-2 | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Chloropropylate                | 1    | 3   | 2-1 | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Chlorotoluron                  | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Chlorprophos-ethyl             | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   | 1   | 1   |
| Chemical Name               | SAR Code | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | C-10 | C-11 | C-12 | C-13 | C-14 |
|-----------------------------|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|
| Chlorpyriphos-methyl       |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Chlorsulfuron              |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Clethodim                  |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Chlorimuron-propargyl      |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 2    |
| Clomazone                  |          | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 2    |
| Clopyralid                 |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Cloquintocet-mexyl         |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 2    |
| Comatecaralyl              |          | 2   | 4   | 3   | 3   | 1   | 4   | 2   | 2   | 2   | 2    | 1    | 2    | 1    | 2    |
| Cyanamide                  |          | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Cyazofamid                 |          | 1   | 2   | 1   | 1   | 2   | 1   | 2   | 1   | 1   | 1    | 1    | 1    | 1    | 2    |
| Cyloxydim                  |          | 1   | 2   | 1   | 1   | 1   | 2   | 1   | 2   | 1   | 1    | 1    | 1    | 1    | 2    |
| Cyfluthrin                 |          | 1   | 2   | 2   | 3   | 1   | 2   | 2   | 3   | 2   | 1    | 1    | 2    | 1    | 2    |
| Cymoxanil                  |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| a-Cypermethrin             |          | 1   | 2   | 2   | 1   | 1   | 2   | 1   | 2   | 1   | 1    | 1    | 1    | 1    | 2    |
| Cyproconazole              |          | 1   | 2   | 3   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Cyprodinil                 |          | 1   | 3   | 1   | 1   | 1   | 2   | 1   | 1   | 2   | 1    | 1    | 1    | 2    |
| 2,4-D                      |          | 1   | 2   | 1   | 1   | 1   | 2   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| 2,4-DB                     |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    | 1    |
| Deltamethrin               |          | 1   | 2   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 2    | 1    | 1    | 2    |
| Desmedipham                |          | 2   | 3   | 1   | 1   | 1   | 2   | 1   | 1   | 1   | 1    | 1    | 1    | 2    |
| Diazinon                   |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    |
| Dimetabam                  |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    |
| Dichlorprop-P              |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 1    | 1    |
| Dicloprop-methyl           |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    | 2    |
| Difenoconazole             |          | 1   | 1   | 2   | 3   | 1   | 3   | 1   | 4   | 4   | 3    | 1    | 1    | 2    | 1    |
| Diethane                   |          | 1   | 1   | 3   | 1   | 4   | 1   | 4   | 3   | 4   | 1    | 1    | 2    |
| Difenofuran                |          | 1   | 3   | 4   | 3   | 2   | 4   | 3   | 2   | 3   | 2    | 1    | 1    |
| Dimethachlor               |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    |
| Dimethenamid-P             |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    |
| Dimebeose                  |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    |
| Dimethomorph               |          | 1   | 2   | 3   | 1   | 3   | 2   | 1   | 1   | 1   | 1    |
| Dinocap                    |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    |
| Diphacinone                |          | 1   | 3   | 3   | 3   | 4   | 3   | 3   | 3   | 2   | 1    |
| Diquat                     |          | 1   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1    |
| Dodemorph                  |          | 4   | 1   | 1   | 1   | 1   | 2   | 1   | 1   | 1   | 1    | 1    |

(Continued)
Table 3. (Continued).

| Compound* | AR** | ARα | ERα | ERαα | ERβ | ERβα | GR | GRα | LXRα | LXRβ | PPARα | PPARβ | PPARγ | RXRα | TRα | TRβ |
|-----------|------|-----|-----|------|-----|------|----|-----|------|------|-------|-------|-------|------|-----|-----|
| α-Endosulfan | 2-1  | 3   | 2-1 | 2-1  | 1   | 2-1  | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| EPN       | 1    | 3-2 | 1   | 1    | 2-1 | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2-1 | 2   |
| Epoxiconazole | 1    | 4-3 | 3-4 | 3-2  | 2   | 2-1  | 1  | 2   | 1    | 2    | 1     | 1     | 1     | 2    | 2   |
| Ergocalciferol | 1    | 1   | 1   | 1    | 1   | 2-3  | 2  | 2-3 | 3    | 1    | 1     | 1     | 1     | 1    | 2-1 | 2   |
| Esfenvalerate | 1    | 2   | 2   | 2    | 1   | 2-3  | 2-1| 1-2 | 2    | 1-2  | 2    | 1     | 2-3  | 2    | 2   |
| Ethephon   | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Ethofumesate | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Ethoprophos | 1    | 1   | 2   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Ethylene dibromide | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Ethylene dichloride | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Fenamidone | 2    | 3-4 | 1-2 | 2    | 1   | 1-2  | 2  | 1   | 1    | 1    | 1     | 1     | 2     | 2-3  | 2   |
| Fenarimol | 1    | 2   | 3-2 | 2    | 1   | 4    | 2-1| 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fenazaquin | 1    | 3   | 2   | 2    | 2   | 1-2  | 2  | 1   | 2    | 2    | 1     | 1     | 1     | 1    | 3   |
| Fenoxaprop-P-ethyl | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| Fenpropidin | 1    | 3   | 1   | 1   | 1    | 1   | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fenpropimorph | 1 | 3-2 | 1-2 | 1   | 1   | 1   | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 2   |
| Fenvalerate | 1    | 2   | 2   | 2    | 1   | 1-2  | 2  | 1-2 | 1-2  | 1-2  | 1     | 1     | 2-3  | 3-2 | 2   |
| Flocoumafen | 1    | 1   | 3   | 4    | 1   | 4    | 2-3| 4   | 3    | 4-3  | 3     | 2     | 4-3  | 2-1 | 1   |
| Flonicamid | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1   |
| Florasulam | 1    | 3   | 2   | 2    | 2   | 1-2  | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fluazifop-butyl | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 |
| Fluazinam | 1    | 2   | 1   | 1    | 1    | 1   | 2  | 1   | 2    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fluicycloxuron | 1 | 1 | 1 | 2 | 1 | 4 | 2 | 4 | 2 | 3 | 1 | 1 | 1 | 1 | 1 | 1 |
| Flucyclotine | 1    | 2   | 2-3 | 3-4 | 1   | 1-2  | 2-3| 1   | 2    | 2    | 1     | 1     | 2     | 2   |
| Fluoxonil | 2    | 3   | 1   | 1    | 1    | 1   | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fluopicolide | 1    | 3   | 2   | 1    | 2    | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fluoxastatin | 1    | 2   | 1   | 1    | 1    | 2-1 | 3  | 2   | 2-1  | 1-2  | 3     | 1     | 1     | 2-1 | 2   |
| Flupyradisulfuron-methyl | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 2-1 | 1 | 1 |
| Flurochloridone | 3 | 3 | 2 | 1-2 | 2 | 1-2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 |
| Flurtamone | 1    | 3   | 3   | 2   | 2    | 3   | 2  | 1   | 2    | 1    | 1     | 1     | 1     | 1    | 2   |
| Fluthiamine | 1    | 3   | 1   | 1    | 1    | 1   | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Flutolanil | 2    | 3   | 2   | 2    | 2    | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Flutriafol | 1-2  | 3   | 3-2 | 2    | 2    | 2    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   |
| Foramsulfuron | 1    | 1   | 1   | 1    | 1    | 1   | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   |
| Glyphosate | 1    | 2   | 1   | 1    | 1    | 1   | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1 |

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Continued
| Compound*                  | AR** | ARα | ERα | ERαα | ERβ | ERβα | GR | GRα | LXRα | LXRβ | PPARα | PPARβ | PPARγ | RXRα | TRα | TRβ |
|----------------------------|------|-----|-----|------|-----|------|----|-----|------|------|-------|-------|-------|------|-----|-----|
| Metobenzuron               | 1    | 1   | 1   | 2    | 1   | 2-1  | 3  | 2   | 2    | 2    | 1     | 1     | 1     | 1    | 1   | 1   |
| S-Metolachlor              | 1    | 2   | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Metosulam                  | 1    | 2   | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 2   |
| Metrafenone                | 1    | 2   | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Metribuzin                 | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Metsulfuron-methyl         | 1    | 2   | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Myclobutanil               | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 2   |
| Napropamide                | 2    | 3   | 2   | 1    | 2-1 | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 2     | 2    | 1   | 1   |
| Nicosulfuron               | 1    | 1   | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Nonylphenol ethoxylate     | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Oxadiargyl                 | 1    | 2   | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   | 2   |
| Oxadiazon                  | 1    | 2   | 1   | 1    | 1   | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Oxyfluorfen                | 3-2  | 3-2 | 1    | 2    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 2   | 3   |
| Paclorbutrazol             | 1    | 2-3 | 1    | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   | 2   |
| Penconazole                | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 2   | 1   |
| Pencycuron                 | 1-2  | 3-4 | 2-3  | 2    | 1    | 4-3  | 2  | 1   | 1-2  | 1    | 1     | 1     | 1-2   | 1    | 2   | 3   |
| Pendimethalin              | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   | 1   |
| Permethrin                 | 1    | 2-1 | 2-3  | 1-2  | 1-2 | 2-1  | 1  | 1   | 2-1  | 1    | 1     | 2     | 2     | 2    | 2   | 3   |
| Phenmedipham               | 2    | 3   | 2   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 3   |
| 2-Phenylphenol             | 2    | 3   | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   |
| Picolinafen                | 4    | 4   | 4    | 3    | 4    | 3    | 2  | 3   | 3    | 3    | 2     | 3     | 2     | 4    | 4   |
| Pinoxadion                 | 1    | 1   | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   |
| Pirimicarb                 | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   |
| Prochloraz                 | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   |
| Procyomidone               | 3    | 3   | 2   | 2    | 2    | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 2   |
| Propanocarb                | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   |
| Propaquizafop              | 1    | 2   | 1   | 1    | 1    | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   |
| Propiconazole              | 1    | 2-3 | 2-1  | 1    | 1    | 2-1  | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   |
| Propyzamide                | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   |
| Proquinazid                | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   |
| Prosulfocarb               | 1    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 1    | 1   |
| Prosulfuron                | 1    | 2   | 1   | 1    | 1    | 1    | 2  | 1-2 | 1    | 1-2 | 1     | 1     | 1     | 1    | 1   |
| Prothioconazole            | 2    | 3   | 1   | 1    | 2    | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1-2 |
| Pyremetrazine              | 2    | 2   | 1   | 1    | 1    | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 1   |
| Pyraclostrobin             | 1    | 2   | 1   | 1    | 1    | 1    | 2  | 1   | 1    | 1    | 1     | 1     | 1     | 2    | 2   |
| Compound                  | SAR and QSAR in Environmental Research | SAR and QSAR in Environmental Research |
|---------------------------|----------------------------------------|----------------------------------------|
| Pyrazoxyfen               | 1 3 3 2 1 3 2 1 2 1 1 1 2 1 2 2      |
| Pyridate                  | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 2 2      |
| Pyrimethanil              | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 2 2      |
| Pyriproxyfen              | 2 2-3 2 1 2-3 1 2 1 1 1 1 1 1 3-2 3-2|
| Pyroxasulam               | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 1 1      |
| Quinmerac                 | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 2 1      |
| Quinoxyfen                | 3 4 3 1 2 1 2 1 1 1 1 1 1 1 3 2      |
| Quinoxyfen-ethyl          | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 2 2      |
| Quinoxyfen-P-ethyl        | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 2 2      |
| Rimsulfuron               | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 1 1      |
| Rottenone                 | 1 1 1 1 1 1 1 2-2 1 1 1 1 1 1 1      |
| RU 15525                  | 1 2-3 3 2 1 2-1 2 1-2 2-1 2 1-2 2-1 3-2 2 2 2 3-2|
| Spiroxamine               | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 2 2      |
| Sulfotrolone              | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 1 1      |
| Sulfosulfuron             | 1 1 1 1 1 1 1-2 1 1 1 1 1 1 1 1      |
| Sulfaramid                | 4 4 3 2 4 3 2 1 2 1 1 1 1 1 1 3 3    |
| Tefluthrin                | 3-2 4 3 2-3 2 2 2 1-2 2 3 1 1 1-2 2 2 2 3|
| Tembotrione               | 1 2-3 1 1 1 1 1 1 1 1 1 1 1 2-1 2 2   |
| Tetraconazole             | 1 3 2-1 1 2-1 1 2 1 1 1 1 1 1 1 1 2 2 |
| Thiacloprid               | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Thiamethoxam              | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Thifensulfuron-methyl     | 1 2 1 1 1 1 1 2 1 2 1 1 1 1 1 1 1    |
| Thiocyclam                | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Thiophanate-methyl        | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Thiram                    | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Transfluthrin             | 4-3 4-3 3 2-1 3-2 1 2 1 1 1 1 1 1 1 1 1 2 3 |
| Triadimefon               | 1 3-2 1 1 1 1 1 1 1 1 1 1 1 1 2 2    |
| Triadimenol               | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Triallate                 | 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1    |
| Triazoxide                | 2-1 2 1 1 1 1 2 1 1 1 1 1 1 1 1 1 1    |
| Tribenuron-methyl         | 1 2 1 1 1 1 2 1 1 1 1 1 1 1 1 1 2    |
| Triflurisoxystrobin       | 1 2 2-1 1 1 1 2 1 1 1 1 1 1 1 2 2 2-3 |
Table 3.  (Continued).

| Compound* | AR** | ARα | ERα | ERαα | ERβ | ERβα | GR | GRα | LXRα | LXRβ | PPARα | PPARβ | PPARγ | RXRα | TRα | TRβ |
|-----------|------|-----|-----|------|-----|------|----|-----|------|------|-------|-------|--------|------|-----|-----|
| Triflumizole | 1    | 3-2 | 1   | 1    | 1   | 2    | 1  | 1   | 1    | 1    | 1     | 1     | 1      | 1    | 2   | 1   |
| Trifluralin  | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 2    | 1    | 1     | 1     | 1      | 1    | 1   | 1   |
| Triflusalauron- methyl | 1   | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 2    | 1    | 1     | 1     | 1      | 1    | 2   | 1   |
| Trifenapac-ethyl | 1   | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1      | 1    | 2-1 | 1-2 |
| Triticonazole | 1   | 3-2 | 2   | 1    | 2   | 1    | 2  | 1   | 2    | 1    | 1     | 1     | 1      | 1    | 1   | 1   |
| Vinclozolin  | 2    | 3   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1      | 2    | 2   | 2   |
| Warfarin     | 1-2  | 4   | 2   | 2    | 2-1 | 2-1  | 2  | 1   | 1    | 1    | 1     | 1     | 1      | 2-1  | 1   | 2   |
| Zoxamide     | 1    | 2   | 1   | 1    | 1   | 1    | 1  | 1   | 1    | 1    | 1     | 1     | 1      | 1    | 2   | 2-1 |

*CAS RN is given in the supplementary material which is available via the multimedia link on the online article webpage.

**See text for details of significance.
androgen receptor (ARa). This finding might be related to the size of class 2 for ARa, which seems to be disproportionate in comparison with the other classes in Table 1.

This rate of pesticides with very low or low predicted probabilities of binding on the whole set of studied receptors might seem high. Nonetheless, it is not far from the results found by Kojima and colleagues [64] who used *in vitro* cell-based transactivation assays to screen 200 pesticides for their potential agonist and antagonist effects on human ERα (hERα), human ERβ (hERβ) and human AR (hAR), and for their potential agonist effects on PPARα and PPARγ. The results were ranked into four activity classes according to the REC20 (20% relative effective concentration) and RIC20 (20% relative inhibitory concentration) values. With this ranking, 56.5% of pesticides presented negative responses for all the targets [64].

Thus, for example, very low probabilities of binding were predicted by the EDS for sulfo-sulfuron (Figure 1, Table 3), which is a selective pre- and post-emergent sulfonylurea herbicide used for the control of various annual grasses and broadleaf weeds in winter and spring wheat as well as various non-food crops [65]. The simulation results are in agreement with the recent review by the European Food Safety Authority (EFSA) [66]. The same profile was also observed with rotenone (Table 3), a non-systemic insecticide with contact and stomach action [67]. Youssef and colleagues [68] have demonstrated that, although rotenone produced histological and biochemical effects similar to those produced by corticosterone, rotenone did not directly activate the glucocorticoid receptor. A lack of binding affinity is also predicted with the EDS because most of the time a class value of 1 is obtained on GR. Moreover, the simulation tool does not detect a binding affinity on the other studied receptors (Table 3). This is in line with the conclusion made by Ott [69] on the lack of endocrine disruption behaviour for this insecticide.

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**Figure 1.** Endocrine disruption profile of sulfo-sulfuron estimated with the EDS tool.
EPN (O-ethyl O-(4-nitrophenoxy) phenylphosphonothioate) is a non-systemic insecticide and acaricide [67], which seems to present an antagonist effect on AR but no agonist effect on this receptor (Table 3). This is in agreement with the in vitro assays of Kojima and colleagues [64], who also found slight agonist effects on ERα and ERβ but no antagonist effects [64]. A slight agonist effect was only predicted on ERβ in some runs with the EDS (Table 3). No effect was found on PPARα and PPARγ using the EDS (Table 3) and by Kojima and colleagues [64].

Permethrin is a non-systemic insecticide with a contact and stomach action. Moreover, it shows a slight repellent effect [67]. Kojima and colleagues [64] showed that permethrin only presented a slight agonist effect on hERα. Conversely, Brander and colleagues [70] did not detect an ER agonist effect on permethrin with the CALUX (Chemical Activated Luciferase Gene Expression) mammalian cell bioassay. However, concentrations of 0.1, 1 and 10 μg/L of permethrin significantly induced the expression of choriogenin in juvenile *Menidia beryllina* compared with methanol controls [70]. The value obtained with the EDS seems to confirm an estrogenic effect, especially on ERα (Table 3). A class value of 3 was also found for TRβ (Table 3) but no binding data have been found in the literature. Nevertheless, it is interesting to note that permethrin provides adverse effects on the thyroid [71]. No effects were found on PPARα and PPARγ by Kojima and colleagues. [64]. With the EDS tools, class values of 1 and 2 were found for PPARα and PPARγ, respectively (Table 3).

Pyrazoxyfen is selective systemic herbicide belonging to the family of pyrazoles. It is absorbed through the young stems and roots of weeds, with a translocation into the whole plant [67]. A slight antagonist activity for pyrazoxyfen on hERα, hERβ and hAR was detected in vitro by Kojima and colleagues [64], while no effects were detected on PPARα and PPARγ. The antagonist activity on AR and ERβ was predicted by the EDS but an agonist activity rather than an antagonist effect was simulated on ERα. No effect was predicted on the PPARα but a value of two was obtained on PPARγ (Table 3). Inspection of Table 3 also shows that 12.7% of the studied pesticides present a probability of binding of 3-4, 4-3 and/or 4.

Bifenthrin is a pyrethroid insecticide and acaricide effective against a broad range of foliar pests [67]. High probabilities of binding have been predicted with the EDS on GR, PPARβ and PPARγ (Figure 2, Table 3). To our knowledge, there is not available information to verify whether these simulation results are realistic. The chemical is also classified in 3-4 on TRβ by the EDS. Inspection of Figure 2 shows that a docking score of -10.5 kcal/M was obtained on TRβ, which corresponds to the upper limit of class 3 for this receptor (Table 1). Consequently, it is not surprising that other simulation results lead an allocation in class 4. Experimental binding data on TR are lacking. However, Akhtar and colleagues [72] showed that when bifenthrin was orally administered to young adult rats for 21 days (Talstar, 0.5 mg/rat), a significant suppression of serum triiodothyronine (T3) and thyroxine (T4) levels was observed with a concomitant stimulation of thyrotrophin (TSH) concentration. The results obtained on ERα and ERβ might suppose a slight anti-estrogenic activity for this chemical (Table 3). Brander and colleagues [70] reported that the CALUX test did not detect ER agonism for bifenthrin. Conversely, in the ER antagonism assay, an initial bifenthrin concentration-dependent decrease in the ability of E2 to induce ER-dependent reporter gene activity (1–100 ng/L) was observed with a recovery of estrogenic activity at concentrations >100 ng/L. However, juvenile *Menidia beryllina* exposed to bifenthrin (1, 10, 100 ng/L) presented significantly higher levels of choriogenin measured as ng/mL in whole body homogenate than the controls. Interestingly, Wang and colleagues [73] have studied the effect of the two enantiomers of bifenthrin on its estrogenic activity. In the in vitro human breast carcinoma MCF-7 cell proliferation assay
(E-Screen), the relative proliferative effect ratios of $1S$-cis-bifenthrin and $1R$-cis-bifenthrin were 74.2% and 20.9%, respectively. Furthermore, proliferation was blocked by co-administration with the ER antagonist ICI 182,780, suggesting interaction with the estrogen receptor. Measurement of vitellogenin induction in Japanese medaka (*Oryzias latipes*) showed that, at an exposure level of 10 ng/mL, the response to $1S$-cis-bifenthrin was about 123 times greater than that to the $R$ enantiomer [73]. It is worth noting that the score values displayed in Table 3 are EDS simulation results obtained on the $S$ and $R$ enantiomer forms of bifenthrin which were each tested seven times.

A maximum loss in ovarian weight and enhanced follicular atresia were observed in rats after the absorption of a single oral sublethal dose of 0.14 mg/kg of floucomafen. This dose also affected the lipid metabolism as higher levels of total lipids, triglycerides and cholesterol, and lower levels of phospholipids, free fatty acids and glycolipids were observed in treated rat ovaries compared with the control [74]. These results might be not contradictory with the endocrine disruption profile obtained with the EDS for this chemical (Table 3), but no direct links have been made between the observed toxicological effects and binding activity on receptors. Brodifacoum, bromadiolone, coumatetralyl, difenacoum, difethialone, diphacinone and warfarin are also rodenticides showing endocrine disruption profiles of concern with the EDS (Table 3), but there is a lack of experimental studies on these chemicals to confirm these predicted receptor binding affinities. This is also the case for numerous pesticides in Table 3 such as beflutumid, hydramethylyn and mesotrione.

For many of the pesticides listed in Table 3, it is impossible to verify the reliability of the prediction results due to the unavailability of experimental data. *In vitro* data allow us to fill
gaps for some of them even if the results obtained with such tests can be prone to variations for a same chemical. *In vivo* results are invaluable, but their number is very limited in the face of the huge number of pesticides available on the market. Moreover, the availability of the information on binding affinities is not the same for all the different receptors. Indeed, the endocrine disruption potential of xenobiotics, including pesticides, has been much more studied on estrogen and androgen receptors than on the other receptors [21]. As a result, most of the available SAR/QSAR models for detecting the endocrine disruption potential of chemicals are also restricted to these two receptors [21,75].

From a large set of 11,416 structurally diverse chemicals analysed with the PASS (Prediction of Activity Spectra for Substances) system [76], Devillers and colleagues [77] have demonstrated definitive interest in considering endocrine disruption profiles, instead of focusing on a limited number of endpoints, to better gauge the complexity of endocrine disruption phenomena and to favour the ranking of the chemicals in the hazard and risk assessment schemes. The results obtained in the present study are in the line of those previously found with the PASS system [77]. They allow to better rank the pesticides according to their potential endocrine disruption potential. Chemicals falling in classes 3-4, 4-3, or 4 for at least one receptor have to be considered a priority for further *in vitro* and *in vivo* investigations.

4. Conclusion
The goal of this study was to estimate the endocrine disruption profile of pesticides using the Endocrine Disruptome software tool, which is freely available on the internet. The main advantage of this computational devise is the possibility of simultaneously estimating the potential binding affinity of the studied chemicals on different receptors for which, very often, experimental data but also SAR and QSAR estimation results, are not available. In a first step, the EDS was successfully tested on 16 pharmaceutical compounds known to be active on at least one studied receptor. Then, the EDS was used to predict the endocrine disruption potential of 220 structurally diverse pesticides. Even if, for most of them, experimental results are missing for comparison purposes, we claim that the Endocrine Disruptome software tool provides useful information for prioritising these pesticides according to their potential impact on the endocrine system of human and wildlife species. Recently, Plošnik and colleagues [34] used the EDS to estimate the endocrine disruption potential of cosmetic ingredients. It is expected that additional studies will be carried out against other chemical categories in order to obtain a full evaluation of this interesting computational tool. To be useful, it is necessary that Kolšek and colleagues [33] clearly identify the changes made in their software through a version number and/or the availability of a true bug list when problems have been identified.

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Disclosure statement
No potential conflict of interest was reported by the authors.
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