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The relationship between physico-chemical properties and maximum residue levels and tolerances of crop protection products for crops set by the US, EU and Codex

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The relationship between physico-chemical properties and maximum residue levels and tolerances of crop protection products for crops set by the US, EU and Codex

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ABSTRACT

Residues on foodstuffs resulting from the use of crop protection products are a function of many factors, e.g. environmental conditions, dissipation and application rate, some of which are linked to the physico-chemical properties of the active ingredients (a.i.). Residue limits (maximum residue levels (MRLs) and tolerances) of fungicides, herbicides and insecticides set by different regulatory authorities are compared, and the relationship between physico-chemical properties of the a.i.s and residue limits are explored. This has been carried out using simple summary statistics and artificial neural networks. US tolerances tended to be higher than EU MRLs. Generally, fungicides had the highest residue limits followed by insecticides and herbicides. Physico-chemical properties (e.g. aromatic proportion, non-carbon proportion and water solubility) and crop type explained up to 50% of the variation in residue limits. This suggests that physico-chemical properties of the a.i.s may control important aspects of the processes leading to residues.

Keywords: artificial neural networks, pesticides, foodstuffs, physico-chemical properties, crop type

Introduction

Residues of crop protection products on foodstuffs are highly regulated. Thus, maximum residue levels (MRLs) and tolerances (hereafter collectively termed residue limits), are based on carefully conducted supervised field trials, and represent the highest residue that would normally be expected when observing good agricultural practice (EC 1997b, EPA 1996, FAO/WHO 2002). When a crop protection product is used on a crop, residues of the active ingredient (a.i.) can be found on food and feed commodities at harvest. The level of residues depends on a large number of factors. Factors relating to effect of use pattern and growth conditions on residue levels have been extensively investigated. For example, application rate (Fletcher et al. 1994; Hoerger & Kenaga 1972, OECD 2002b, Pfleeger et al. 1996, Sadlo 2000), pre-harvest intervals (PHI) (Timme & Frehse 1980), number of applications (Timme & Frehse 1980) crop characteristics (Fletcher et al. 1994, Hoerger & Kenaga 1972, Pfleeger et al. 1996, Santier & Chamel 1998), climate (Elliot & Spurr 1993, Galera et al. 1997, Nigg et al. 1978, OECD 2002b), and growth dilution (Holland et al. 1996) all affect residues. The influence of the properties of the a.i. itself on residues is less well understood. However, there is some evidence that physico-chemical properties of formulations and a.i.s affect residues (Briggs & Bromilow 1994, Holloway & Western 2003, Spynu 1989).

Factors indirectly affecting residue levels include rain-fastness, foliar uptake, uptake through roots, volatilisation, photostability, degradation rate and persistence on the plant surfaces, all of which are linked to the physico-

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3 chemical properties of the a.i.s (Bentson 1990, Bromilow & Chamberlain
4 1991, Bromilow & Chamberlain 1995, Holloway & Western 2003, Trapp
5 2004). The physico-chemical properties may interact, and the relationship with
6 residues is not necessarily linear (Baker et al. 1992). For example, water
7 solubility and lipophilicity affect uptake as well as persistence on the plant
8 surfaces (Bromilow & Chamberlain 1995, Tice 2001, Willis & McDowell 1987).
9 Furthermore, there may be interactions among use patterns, crops, climate
10 and physico-chemical properties of the a.i.s (Bentson 1990, Galera et al.
11 1997, Schonherr et al. 1999). Consequently, data that cover a wide range of
12 crops, use patterns and climatic conditions are necessary in order to draw
13 generally applicable conclusions about the relationship between physico-
14 chemical properties of a.i.s and residues in foodstuffs. Since the trials used to
15 set residue limits are normally conducted under varying local and climatic
16 conditions, residue limits often provide a more substantial basis for modelling
17 residues than results from single experiments (EC 1997b, EPA 1996,
18 FAO/WHO 2002, Hoerger & Kenaga 1972).

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43 Here, the relationship between physico-chemical properties of crop protection
44 products and residue limits in foodstuffs are explored. This was done for
45 fungicides, herbicides and insecticides registered for use by the EU, Codex
46 and US. Furthermore, residue limits in different regions and for different crop
47 types were compared.

58 **Methods**

59 *Data collation and datasets*

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3 Four datasets were collated for analyses: one of physico-chemical properties
4 of a.i.s (Clarke & Delaney 2003) and three on residue limits for different
5 commodities from the EU (Liaison Database [Internet]), Codex (Liaison
6 Database [Internet]) and US (US Environmental Protection Agency [Internet]).
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8 Only a.i.s that had information on both physico-chemical properties and
9 residue limits were included in the analyses.
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20 *Physical and chemical properties of active ingredients.* The dataset containing
21 the physico-chemical properties of a wide range of a.i.s (Table I) was provided
22 by Eric Clarke and John Delaney (for details of sources and calculations
23 methods see Clarke & Delaney 2003). On the basis of their target organisms,
24 the a.i.s were grouped into fungicides, herbicides and insecticides (hereafter
25 collectively termed main uses). The physico-chemical properties of fungicides,
26 herbicides and insecticides differ (Bromilow & Chamberlain 1995, Clarke &
27 Delaney 2003, Tice 2001), so the three main uses were analysed separately.
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41 *Residue limits on crops in different legal regions.* Three datasets on residue
42 limits were collated: EU MRLs, Codex MRLs and US tolerances (Liaison
43 Database [Internet], US Environmental Protection Agency Tolerance Database
44 [Internet])). The EU and US cover real geographical regions, whereas Codex
45 does not cover a coherent region; hereafter the EU, US and Codex are
46 collectively termed legal region. The methods used to establish residue limits
47 by the EU, US and Codex are different (EC 1997a, FAO/WHO 2002, USEPA
48 1996), and the use patterns are not necessarily the same. Therefore, the
49 three datasets were analysed separately. In contrast to the US and Codex
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3 datasets, the EU MRLs included some a.i.s which were not registered for use
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5 in the EU; for those a.i.s the MRL was not set on the basis of residue trials but
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7 at the level of quantification (LOQ). Thus, in the EU dataset, it was not
8
9 possible to distinguish between the LOQs that represented genuinely low
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11 residues and those which were set at LOQ because the a.i. was not
12
13 registered for use. Consequently, the analyses of the EU MRL dataset were
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15 performed without MRLs set at LOQ.
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22 The datasets represented a wide range of a.i.s and crops (Table II, Table III).
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24 There was some but not a complete overlap between the a.i.s and crops in
25
26 the three datasets. Residues have been shown to differ between crops
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28 (Fletcher et al. 1994, Galera et al. 1997, Hoerger & Kenaga 1972, Pflieger et
29
30 al. 1996), so the crops were grouped into seven categories in order to allow
31
32 comparisons (Table II). The grouping was made on the basis of surface area
33
34 to weight ratio, direct exposure to spray, and consumers (humans or animals).
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36 For each a.i., the mean residue limit was taken for all the crops belonging to a
37
38 crop type, and this value was used in the data analyses. Thus, the models
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40 predict residue limits for a crop type rather than an individual commodity.
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42 Animal feed and 'others' were excluded from the analyses because residues
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44 in foodstuffs of plant origin intended for human consumption are the focus of
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46 this study.
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55 *Data analysis*

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57 Summary statistics for legal regions, crop type and main uses were
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59 calculated. Artificial neural networks (three layer perceptrons) were used to
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3 analyse the relationship between residue limits and the physico-chemical
4 properties of the a.i.s. The three layer perception was chosen because it is
5 one of the most commonly used neural network architectures, and it is a
6 powerful tool for analysing data for prediction and classification (Bishop 1995).
7
8 Furthermore, the three layer perceptron is capable of modelling complex
9 linear and nonlinear relationships and is good at handling large numbers of
10 interdependent variables, which often complicates more traditional
11 approaches to statistical modelling (Bishop 1995). The datasets were also
12 analysed with general linear models (anovas, multiple regression and
13 combinations thereof), but as neural networks performed much better, results
14 from these more traditional statistical methods are not presented. The residue
15 limits were log-transformed prior to all analyses.
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34 *Variable selection and training of neural networks.* In order to train the neural
35 networks each of the datasets of residue limits from the three legal regions
36 were combined with the dataset containing physico-chemical properties of the
37 a.i.s. Neural networks require large datasets to be properly trained. As the
38 number of variables increases the more observations are required to train
39 neural networks (Bishop 1995). Consequently, variable selection and
40 reduction is paramount for successful training. The following procedure for
41 variable selection was used. Pair-wise correlations between residue limits and
42 all the physico-chemical variables were performed. Then feature selection
43 was applied with forwards, backwards and genetic selection. On the basis of
44 these two approaches, variables were chosen that appeared to be important.
45 Numerous networks were trained and sensitivity analyses were used to
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3 further reduce the number of variables. The variable reduction and training
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5 was continued until a balance between prediction accuracy and network
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7 complexity was achieved. Then a range of networks with similar accuracy of
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9 predictions, but with different input variables and architectures were chosen
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11 for further comparisons. The comparison included a check for over-learning,
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13 correlation between observed and predicted values, and a graphical
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15 inspection of the relationship between observed and predicted values. This
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17 showed whether the network performed well over the full range of observed
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19 residue limits. On this basis, the network(s) which gave the best predictions of
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21 residue limits were chosen and are presented in the results and discussion.
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29 All data analyses relating to neural networks were carried out using
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31 STATISTICA Neural Networks version 6 (©, StatSoft, Inc. 2003).
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36 **Results**

37 *General trends in residue limits*

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39 An initial inspection of the summary statistics of the three raw datasets of
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41 residue limits revealed some general trends relating to main use, crop types
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43 and legal region. Of the three main uses, fungicides had the highest residue
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45 limits, insecticide residue limits were intermediate and herbicide residue limits
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47 were lowest (Figure 1A). For food commodities, leafy vegetables had the
48
49 highest residue limits, whereas more 'compact' commodities such as fruits
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51 (e.g. apples) and compact vegetables (e.g. cucumbers) were intermediate
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53 (Figure 1B). The lowest residue limits were found for root and bulb vegetables
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3 and seeds, both representing commodities that have a low direct exposure to
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5 spray deposits compared to other crops.
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10 The residue limits varied among legal regions. Thus, US tolerances tended to
11
12 be higher than Codex MRLs and EU MRLs were lowest (Figure 1). However,
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14 interpretation of the differences among the legal regions should be made with
15
16 caution, because even though there is some overlap between the three
17
18 datasets with respect to a.i.s and crops, there are also some substantial
19
20 differences (Table III). Nonetheless, the trend remained the same for
21
22 fungicides and insecticides when the a.i.s found in all three datasets were
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24 compared (there were not enough herbicides in the Codex MRL dataset for
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26 this comparison).
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34 *Prediction of fungicides*

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36 Of the three main uses, neural networks generally performed best on
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38 fungicide residue limits. Thus, a higher proportion of the variation was
39
40 explained than for the other main uses (Table IV, Table V, Table VI). The
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42 general trends in residue limits were captured for EU MRLs, Codex MRLs and
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44 US tolerances (Table IV, Figure 2). On the basis of crop type and 2-4 physico-
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46 chemical variables it was possible to explain 40-50% of the variation in
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48 residue limits (Table IV).
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55 For each legal region there was more than one neural network that performed
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57 equally well with respect to precision of predictions. The neural networks
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59 differed both with respect to the variables included and network architecture
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3 (number of neurons in different layers). Even so, there were some general
4 trends with respect to variable selections. Crop type was an important variable
5 and was included in most neural networks. Variables describing non-hydrogen
6 atom characteristics (aromatic proportion, non-carbon proportion and halogen
7 proportion), also appeared in many neural networks, as did water solubility.
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17 The relationship between the physico-chemical variables and residue limits
18 was not straightforward. One of the simpler neural networks was used to
19 explain this point, namely the best Codex network, where three variables
20 (crop type, molecular weight and aromatic proportion) explained 50% of the
21 variation in Codex MRLs. Analysed separately, there was no obvious
22 relationship between molecular weight or aromatic proportion and residue
23 limits (Figure 3). However, when molecular weight and aromatic proportion
24 were combined a pattern emerged; at low aromatic proportions molecular
25 weight only had minor effect, but at higher aromatic proportions there was a
26 negative relationship between residue limits and molecular weight. Thus, the
27 highest residue limits were found for compounds, which had a high aromatic
28 proportion and low molecular weight (Figure 3). Although molecular weight
29 was not included in the neural networks for the EU MRL and US tolerance
30 datasets, the same pattern was still apparent (Figure 4). The a.i.s where high
31 residue limits were linked to low molecular weight and high aromatic
32 proportion, were a mixture of compounds with CAS dates before 1965 and
33 newer compounds with CAS date after 1965. Some of the other neural
34 networks performed as well as the one just described (Table IV), but they
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3 included more variables and the relationships between variables and residue
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5 limits were more complex.
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10 *Prediction of herbicides*

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12 The neural networks were able to capture general trends in US tolerances for
13 herbicides on the basis of 4-5 physico-chemical variables. The neural
14 networks explained 40% of the variation in US tolerances (Table V), but
15 underestimated tolerances in the higher end (Figure 5B). For EU MRLs for
16 herbicides, the neural networks also captured the general trends in the lower
17 end, but the tendency to underestimate residue limits in the higher end was
18 even more pronounced than for US tolerances (Table V, Figure 5A). There
19 were not enough herbicides in the Codex dataset for analysis (Table III).
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34 In contrast to fungicides and insecticides, crop type did not appear to be
35 important for herbicide residue limits. As in the analyses of fungicides,
36 variables describing non-hydrogen atom characteristics (aromatic proportion,
37 non-carbon proportion and halogen proportion) tended to be influential. In
38 contrast to both fungicides and insecticides, acidity and basicity were also
39 important. There was a tendency for a downward trend in residue limits at
40 high hydrogen-bond acidity (Figure 5C), but other than that it was difficult to
41 discern the shape of the relationship between the physico-chemical variables
42 and residue limits (e.g. aromatic proportion, Figure 5D).
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58 *Prediction of insecticides*

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Neural networks were able to capture the general trends in EU MRLs and Codex MRLs on the basis of crop type and 3-4 physico-chemical variables (Table VI, Figure 6). The prediction of EU MRLs was best with 52% of the variation explained. The neural networks were able to explain 38% of the variation in Codex MRLs but only 28% of the variation in US tolerances for insecticides.

In the same way as for the fungicides, crop type was important for insecticide residue limits as were physico-chemical variables describing non-hydrogen atom characteristics (aromatic proportion, non-carbon proportion and halogen proportion) (Table VI). Again, the relationships between residue limits and the physico-chemical variables were not straightforward. As an example the simplest neural network for EU MRLs for insecticides was chosen. There was a negative relationship between halogen proportion and residue limits, but the effect of non-carbon proportion on residue limits could only be observed when combined with halogen proportion (Figure 7). Thus, a combination of high halogen proportion and low non-carbon proportion gave the lowest residue limits. One of the neural networks for Codex MRLs also included non-carbon proportion and halogen proportion. However, the compounds with high halogen proportion were compounds with CAS dates from before 1965, and some of them also had use as fumigants. The combination of halogen proportion and non-carbon proportion was not included in the neural networks for US tolerances (Table VI).

Discussion

General trends in residue limits

The summary statistics of the residue limits showed substantial variation among and within main uses, crop types and legal regions. Of the three main uses, herbicides had the lowest residue limits, fungicides the highest and insecticides were intermediate. Herbicide residues were expected to be low because they are often applied with long pre-harvest intervals (PHI). Fungicides tend to have higher application rates and shorter PHI than insecticides, which might explain why they had higher residue limits.

Our results indicate that residue limits are affected by commodity surface to weight ratio and exposure to direct spray. These factors along with application rate have been shown to cause variation in initial residues (Fletcher et al. 1994, Hoerger & Kenaga 1972, OECD 2002a, Pfleeger et al. 1996) and subsequent decline of residues (Galera et al. 1997).

In general, US tolerances were higher than Codex MRLs, which were higher than EU MRLs. Many factors might have contributed to these differences among legal regions. Firstly, there were differences with regards to which a.i.s were registered for use in the three legal regions. However, the trend remained the same even when only a.i.s and crop types that occurred in all three legal regions were included. Secondly, differences in pest and disease prevalence, use patterns and climatic conditions may contribute to the variation (Bruhn & Fry 1982, Galera et al. 1997, OECD 2002a, Willis & McDowell 1987). Thirdly, different calculation methods for residue limits may

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3 also have contributed to the variation (EC 1997b, FAO/WHO 2002, EPA
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5 1996).
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10 *How good were the predictions?*
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12 Neural networks explained 30 to 50% of the variation in residue limits and
13 although there was some noise, the general trends in residue limits were
14 captured on the basis of crop type and 3-5 physico-chemical variables. A
15 prediction of 40-50% of the variation could be considered fairly good
16 considering that information on use pattern had not been taken directly into
17 account. However, use pattern alone does not explain all variation in residue
18 limits either. Thus, even if only initial deposit is considered, application rate
19 only explains 20% of the variation for some crop types, but up to 90% for
20 others (Pfleeger et al. 1996). Nonetheless, many factors that have an effect
21 on residue limits were not included in our analyses (e.g. application rate,
22 number of applications, PHI and formulation) (Briggs & Bromilow 1994,
23 Frehse & Walter 1994, Hoerger & Kenaga 1972, Holloway & Western 2003,
24 Timme & Frehse 1980). Our results indicated that crop type and physico-
25 chemical properties of the a.i.s controlled important aspects of the processes
26 leading to a residue limit, irrespective of the use pattern.
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50 *Which variables were important?*
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52 Physico-chemical properties are likely to be important for rainfastness
53 (Mulrooney & Elmore 2000), photo degradation (Bentson 1990), volatilisation
54 (Bentson 1990), metabolism (Bates 1990), retention on plant surface (Willis et
55 al. 1994), degradation rate (Timme & Frehse 1980), uptake into plants and
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3 transport in plants (Bromilow & Chamberlain 1991, Bromilow et al. 1991,
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5 Schonherr & Baur 1994, Schonherr et al. 1999, Trapp 2004). Often more than
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7 one neural network gave similar predicted outcomes. This indicated that there
8
9 were several variables affecting the dissipation processes, and/or that
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11 variables were interdependent and therefore interchangeable.
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17 Crop type was included in the majority of neural networks. Non-hydrogen
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19 atom characteristics of the pesticides were also important, and at least one of
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21 aromatic proportion, non-carbon proportion and halogen proportion were
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23 included in all neural networks. The non-hydrogen atom characteristics affect
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25 water solubility, lipophilicity and polarisability, which are all factors that are
26
27 thought to be important for uptake into and transport around plants (Bromilow
28
29 et al. 1991, Clarke & Delaney 2003, Trapp 2004). Nonetheless, non-hydrogen
30
31 atom characteristics were more important for prediction of residue limits than
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33 water solubility, polarisability and lipophilicity themselves. This could have
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35 been caused by the non-hydrogen atom characteristics also affecting other
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37 properties of the a.i.s, such as stability, volatilisation, toxicity and metabolism
38
39 (Clarke & Delaney 2003), or because uptake into plants and transport around
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41 plants does not always control the final residues.
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51 The relationships between non-hydrogen atoms characteristics and residue
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53 limits were not straightforward. There were interactions between variables as
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55 well as non-linear relationships involved. These complex relationships might
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57 have been caused by non-hydrogen atom characteristics affecting different
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59 aspects of the dissipation processes simultaneously. For instance, non-
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3 hydrogen atom characteristics affect both water solubility and lipophilicity,
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5 which affect rainfastness as well as uptake into plants (Bromilow &
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7 Chamberlain 1995, Mulrooney & Elmore 2000, Trapp 2004). Non-hydrogen
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9 atom characteristics also affect the stability of the a.i.s, causing differences in
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11 degradation and metabolism rate (Clarke & Delaney 2003). Non-carbon
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13 proportion affects the solubility of the compound, its ability to permeate
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15 membranes and how well it sticks to a waxy surface (Bromilow & Chamberlain
16
17 1995, Tice 2001, Trapp 2004). However, the effect will depend on whether
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19 groups containing nitrogen and oxygen or halogens are added. This could be
20
21 the reason for non-carbon proportion and halogen proportion often appearing
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23 together in the neural networks. Aromatic proportion was included in many
24
25 neural networks. Aromatic proportion is likely to affect both stability and ability
26
27 to permeate membranes, and possibly also toxicity (Clarke & Delaney 2003,
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29 Tice 2001), which may affect efficacy and hence application rate. To
30
31 complicate things further, plants have different surface properties and
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33 morphology, which may be another reason why crop type was included in
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35 most networks.
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46 *How do main uses and legal regions vary with respect to variable selection*
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48 *and precision of predictions?*
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51 Neural networks performed best on fungicides followed by insecticides and
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53 had the poorest performance on herbicides. This reflected the general trends
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55 in residue limits among main uses. Thus, not surprisingly, it was easiest to get
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57 good predictions for the main uses with detectable residues, whereas it was
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3 more difficult for herbicides where residues were low and showed less
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5 variation.
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10 The three main uses differ in physico-chemical profiles and in systemicity
11 (Clarke & Delaney 2003, Tice 2001, 2002). Thus, most herbicides tend to be
12 systemic, whereas the majority of insecticides have contact action, and
13 fungicides are somewhere in between (Clarke & Delaney 2003, Tice 2001).
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15 This may explain the differences among the main uses with respect to which
16 variables appeared in neural networks.
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27 Crop type occurred in most fungicide and insecticide neural networks but not
28 in herbicides. This, was expected as herbicides are targeted at weeds rather
29 than the crop. Water solubility appeared in most fungicide models but less
30 frequently in insecticides. This may be explained by insecticides having more
31 uniform water solubility than fungicides.
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41 Aromatic proportion in combination with a measure of molecular size
42 (molecular weight or volume) and water solubility appeared to be important in
43 determining the residues of fungicides. In general, the highest residue limits
44 were found for compounds which had a high aromatic proportion and low
45 molecular weight. Newer a.i.s tend to have higher molecular weights and
46 lower application rates than old a.i.s (Tomlin 2000), and such correlations may
47 also have been picked up by the neural networks. However, the compounds
48 were a mixture of compounds with old and new CAS dates, and came from
49 different pesticide classes, so the pattern appeared to have general
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3 applicability. Another explanation may stem from the relationship between
4 molecular weight and aromatic proportion, where each addition of an aromatic
5 ring leads to a rather high increase in molecular weight leading to a complex
6 relationship.
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15 Halogen proportion appeared to be important for controlling the residues of
16 insecticides and there was a negative relationship between halogens and
17 residue limits. A closer inspection of the data showed that negative
18 correlations were to some extent driven by a few compounds which had high
19 halogen proportion and low residue limits. These were all compounds with
20 CAS date from before 1965, and some were also used as fumigants. It is
21 therefore questionable whether this trend has general applicability.
22 Nonetheless, as halogens are added to insecticides to make them more
23 stable with respect to insect metabolism (Clarke & Delaney 2003), a.i.s with
24 high halogen proportion may be more efficacious and persistent,
25 consequently requiring lower application rates.
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43 The variables, which were included in herbicide neural networks, were
44 different from those for fungicides and insecticides. For instance, acidity often
45 appeared in the herbicide neural networks. There tended to be a negative
46 relationship between acidity and herbicide residue limits. Acid groups are
47 more common in herbicides than in fungicides and insecticides, possibly
48 because acid groups tend to have phytotoxic effects (Tice 2001, Clarke &
49 Delaney 2003). Furthermore, acidity is linked to transport of chemicals within
50 plants (Trapp 2004). Additionally, Abraham's A is linked to hydrogen-bond
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3 donors, which are thought to have a negative correlation with stability (Clarke
4 & Delaney 2003, Platt et al. 1999). Thus, acidic herbicides may have lower
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6 residue limits because they are more efficacious and less stable.
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12 Overall, the best predictions were achieved for EU MRLs, and Codex MRLs
13 could also be predicted fairly well, whereas models predicting US tolerances
14 had the poorest performance. The variables that were used by the neural
15 networks varied among the EU, Codex and US, even for the same main use.
16 This could be caused by differences in which a.i.s were included in the
17 different datasets. Alternatively, if climate and physico-chemical properties
18 interact (Galera et al. 1997, Willis & McDowell 1987), this may also cause
19 differences between which variables were included in the different neural
20 networks. For instance, foliar uptake is affected by molecular weight, but the
21 relationship between foliar uptake and molecular weight changes with
22 temperature (Schonherr et al. 1999). Moreover, photodegradation not only
23 depends on photo-stability but also on uptake into leaves where compounds
24 are more stable (Bentson 1990).
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46 *Importance of use patterns*

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48 Use patterns were not included directly in the analyses, but we suspect that
49 the differences among main uses, crop types and legal regions are linked to
50 differences in use pattern. As main uses and legal regions were analysed
51 separately and crop type was included in most models, use pattern was
52 indirectly included in the analyses. Furthermore, if the physico-chemical
53 properties are linked to toxicity and stability this may affect use pattern. For
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3 instance, high toxicity for the target organisms may lead to lower application
4 rates, which will lead to lower residues. It would be interesting to include
5 information on use pattern as a future development of the models.
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10 11 12 **Acknowledgements**

13
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15 chemical properties of crop protection products. We are indebted to Anne
16 Taylor for help on collating the datasets on residue limits. We are grateful for
17 comments on earlier drafts of this report from Kim Travis, John Delaney,
18 Geoff le Patourel, Mike Skidmore, Leslie Bray and Nina Heard.
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Table I. Physico-chemical variables used to predict residue limits. For details of sources and calculation methods see Clarke & Delaney 2003.

Physiochemical property	Description
ClogP	Log of the partition coefficient between octanol and water. Values from clogP v4© software
MWT	Molecular weight
N_Rot_bond	Number of single non-terminal bonds
N_Donor	Number of hydrogen-bond donors
N_acceptor	Number of hydrogen-bond acceptors
Aromatic proportion*	Number of non-hydrogen atoms in aromatic systems divided by total number of non-hydrogen atoms
Non-carbon proportion*	Number of non-carbon non-hydrogen atoms divided by total number of non-hydrogen atoms
Halogen proportion*	Number of halogen atoms divided by the total number of non-hydrogen atoms
N_Cation	Number of positive charges
N_Anion	Number of negative charges
Charge	Formal charge at pH 7
A	Abraham's A (a measure of hydrogen-bond acidity). Values from Absolv v1.4 ©
B	Abraham's B (a measure of hydrogen-bond basicity). Values from Absolv v1.4 ©
S	Polarisability. Values from Absolv v1.4©
E	Excess molar refraction. Values from Absolv v1.4©
L	Length of molecule. Values from Absolv v1.4©
V	McGowan volume. Values from Absolv v1.4©
DOH	Difference between log of the partition coefficient between octanol and water and log of the partition coefficient between hexadecane and water
Water solubility	Log of the measure of water solubility from Absolv v1.4©
ESOL	Log of ESOL, a measure of water solubility (Delaney, 2004)

* collectively termed non-hydrogen atom characteristics; which equate to heavy atom characteristics in Clarke & Delaney 2003.

Table II. Number of crops with residue limits in the three legal regions and grouping of crops.

Crop type	Number of crops			Example of typical crops
	EU	Codex	US	
Leafy vegetables	20	24	190	Leafy salad, spinach, leafy brassica, herbs
Compact vegetables	29	28	54	Head cabbages, head salad, tomatoes, squash
Root and bulb vegetables	21	22	90	Onions, potatoes, radish, carrots
Fruits	44	54	102	Apples, melons, berries, grapes
Seeds	45	79	254	Cereals, corn, nuts, oil seeds, legumes
Animal feed*	-	36	577	Hay, alfalfa, fodder beet, forage crops
Other*	-	64	575	Animal produce, milk, tea, processed commodities

* excluded from data analyses

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Table III. Number of active ingredients (a.i.s) and observations included in the datasets.

	Main use	EU MRLs including LOQ	EU MRLs excluding LOQ	Codex MRLs	US tolerances	a.i.s shared by all datasets
Fungicides	Number of a.i.s	62	37	45	47	22
	Number of cases*	260	176	196	173	
Herbicides	Number of a.i.s	94	52	9	112	4
	Number of cases*	335	137	44	305	
Insecticides	Number of a.i.s	92	40	72	72	40
	Number of cases*	407	217	316	295	

*Number of cases counted after the crops had been grouped into crop types.

Table IV. Performance of neural networks used to analyse the relationships between residue limits of fungicides and crop types and the physico-chemical properties of the active ingredients. R^2 indicate the proportion of the variation in residue levels that was explained by the neural network. Over-learning occurs when a neural network fits the model to the noise rather than real patterns.

Dataset	Variables included in neural network	R^2	Graphical inspection of predicted plotted against observed residues	Check for over-learning
EU MRLs	ClogP, aromatic proportion, non-carbon proportion, halogen proportion, ESOL	0.48	Good over all fit. Captures high, but overestimates low residues	No over-learning
	Crop type, non-carbon proportion, B, ESOL	0.46	Captures high values, but overestimates most lower and lower intermediate values	No over-learning
	Crop type, non-carbon proportion, halogen proportion, B, ESOL	0.52	Captures high values, but overestimates most lower and lower intermediate values	Moderate over-learning
Codex MRLs	Crop type, aromatic proportion, halogen proportion, V	0.44	Good fit	Moderate over-learning
	Crop type, MWT, aromatic proportion	0.50	Good fit	Moderate over-learning
	Crop type, V, ESOL	0.41	Good fit	Moderate over-learning
US tolerances	Non-carbon proportion, halogen proportion, water solubility	0.41	Good fit in mid-high range, does not capture low residues	Minor over-learning
	Non-carbon proportion, halogen proportion, ESOL	0.42	Good fit in mid-high range, does not capture low residues	Minor over-learning
	Non-carbon proportion, halogen proportion, aromatic proportion	0.41	Good fit in mid-high range, does not capture low residues	Minor over-learning

Table V. Performance of neural networks used to analyse the relationships between residue limits of herbicides and crop types and the physico-chemical properties of the active ingredients. R^2 and over-learning as in Table IV.

Dataset	Variables included in neural network	R^2	Graphical inspection of predicted plotted against observed residues	Check for over-learning
EU MRLs	Aromatic proportion, non-carbon proportion, ESOL or Non-carbon proportion, A, ESOL or Aromatic proportion, A,B	0.30	Fit only reasonable in mid-range, i.e. underestimate high values, and overestimate low residues	Moderate over learning. Several models with similar fits
Codex MRLs		Too few observations for analysis		
US tolerances	Aromatic proportion, halogen proportion, S, ESOL, DOH	0.41	Poor fit	Minor over-learning
	Aromatic proportion, A, L, ESOL	0.41	Capture general trend but underestimated tolerances in high end	Moderate over-learning

Table VI. Performance of neural networks used to analyse the relationships between residue limits of insecticides and crop types and the physico-chemical properties of the active ingredients. R^2 and over-learning as in Table IV.

Dataset	Variables included in neural network	R^2	Graphical inspection of predicted plotted against observed residues	Check for over-learning
EU MRLs	Crop type, clogP* aromatic proportion, halogen proportion	0.52	Good fit	No over-learning.
	Crop type, non-carbon proportion, halogen proportion	0.49	Good fit (but larger spread at high values than model with 4 variables)	Moderate over-learning
Codex MRLs [#]	Crop type, non-carbon proportion, halogen proportion, DOH, water solubility	0.38	Reasonable to good fit in all range	Moderate over-learning.
US tolerances	Crop type, clogP, aromatic proportion, ESOL	0.26	Poor fit	No over-learning
	Crop type, aromatic proportion, S	0.28	Poor fit	Moderate over-learning

*ClogP may be substituted by ESOL

One observation excluded because MRL was very high

FIGURE LEGENDS

Figure 1. General trends of residue limits relating to target organisms (main uses), crop type and legal region. Means of residue limits for (A) main uses, and (B) crop types (for details on grouping see Table II). Error bars show 95% confidence limits.

Figure 2. Predictions of fungicide residue limits by neural networks. (A) EU MRLs; variables used by neural network: crop type, non-carbon proportion, halogen proportion, B, ESOL. (B) Codex MRLs; variables used by neural network: crop type, molecular weight, aromatic proportion. (C) US tolerances; variables used by neural network: non-carbon proportion, halogen proportion, aromatic proportion. Black circles: predictions. Dotted lines indicate perfect prediction, thus circles above line are over-predictions and circles below line are under-predictions.

Figure 3. Relationship between physico-chemical variables and Codex MRLs for fungicides. (A) Aromatic proportion. (B) Molecular weight (MWT). (C) Aromatic proportion and MWT where the surface was fitted with distance-weighted least squares smoothing procedure. (D) Response surface used by neural network.

Figure 4. Relationship between fungicide residues and molecular weight (MWT) and aromatic proportion. (A) EU MRL. (B) US tolerances. The surfaces were fitted with distance-weighted least squares smoothing procedure.

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3 Figure 5. Predictions of herbicide residue limits by neural networks. (a) EU MRLs.
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5 Variables used by neural network: aromatic proportion, A, B. (B) US tolerances.
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7 Variables used by neural network: aromatic proportion, A, L, ESOL. Black circles:
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9 predictions. Dotted lines: perfect prediction, thus circles above line are over-
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11 predictions and circles below line are under-predictions. (C) Relationship between US
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13 tolerances and A (hydrogen-bond acidity). (D) Relationship between aromatic
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15 proportion and US tolerances.
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22 Figure 6. Predictions of insecticide residue limits by neural networks. (A) EU MRL;
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24 variables used by neural network: crop type, non-carbon proportion, halogen
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26 proportion. (B) Codex MRLs; variables used by neural network: crop type, non-
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28 carbon proportion, halogen proportion, DOH, water solubility. Black circles:
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30 predictions. Dotted lines: perfect prediction, thus circles above line are over-
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32 predictions and circles below line are under-predictions.
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39 Figure 7. Relationship between physico-chemical variables and EU MRLs for
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41 Insecticides. (A) Non-carbon proportion. (B) Halogen proportion, where the surface
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43 was fitted with distance-weighted least squares smoothing procedure. (C) Non-carbon
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45 proportion and halogen proportion, where the surface was fitted with distance-
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47 weighted least squares smoothing procedure. (D) Response surface used by neural
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49 network.
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FIGURES

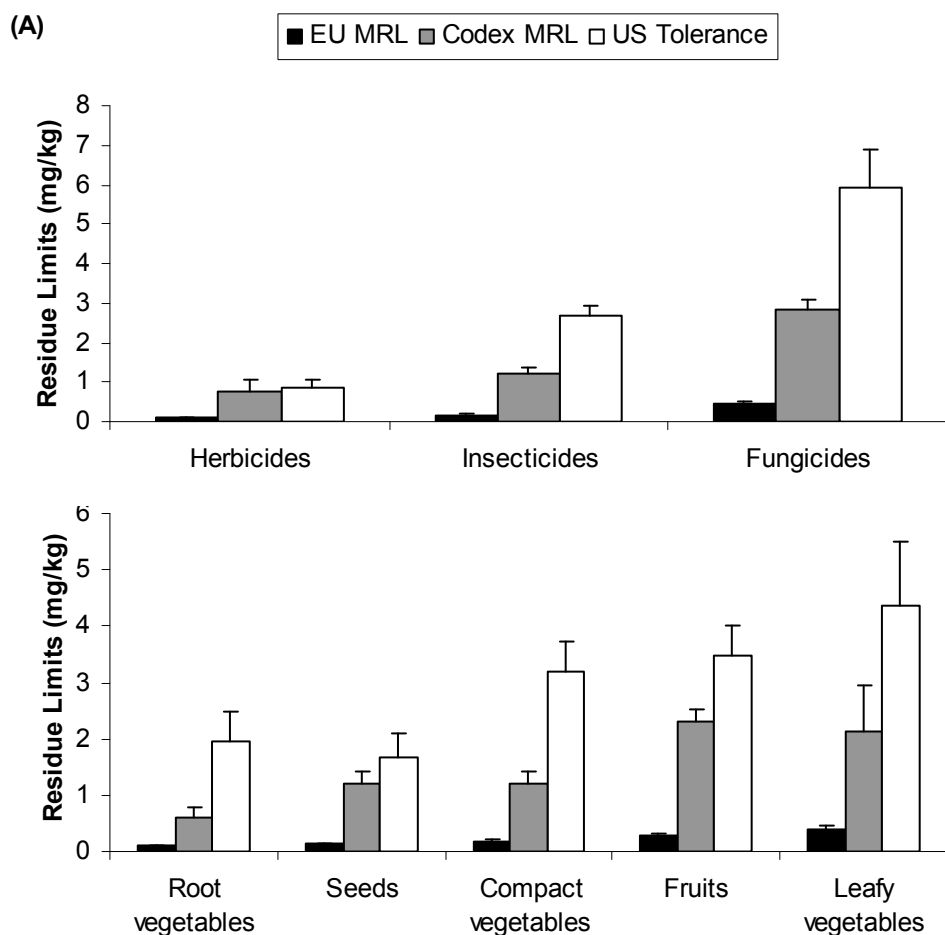


Figure 1.

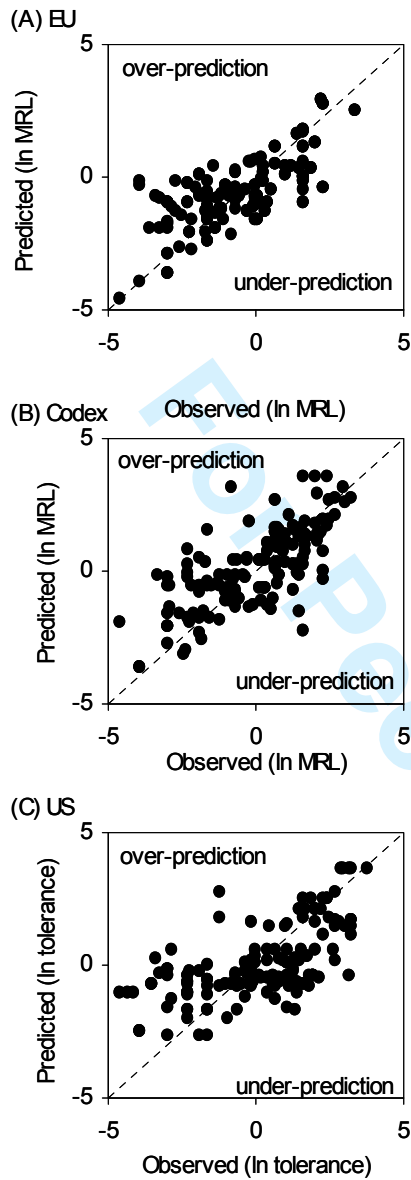


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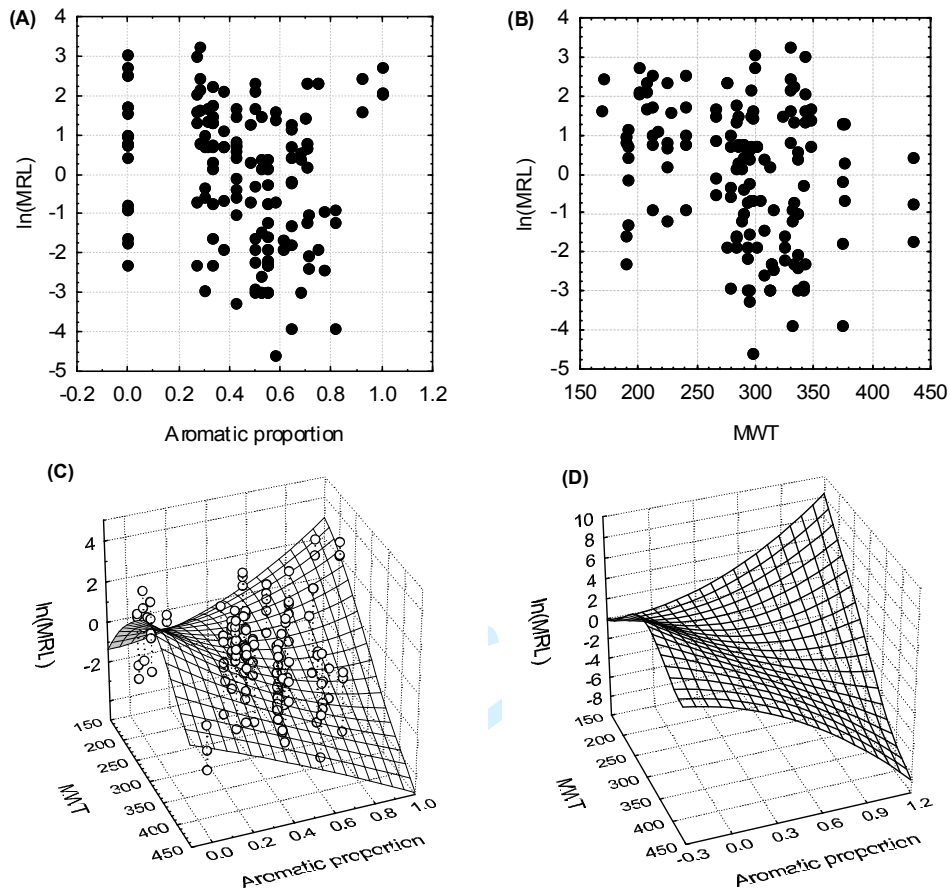
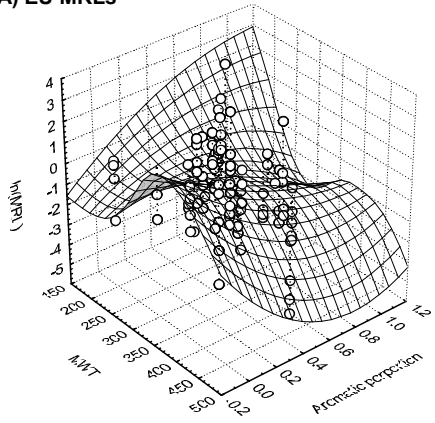


Figure 3.

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(A) EU MRLs



(B) US tolerances

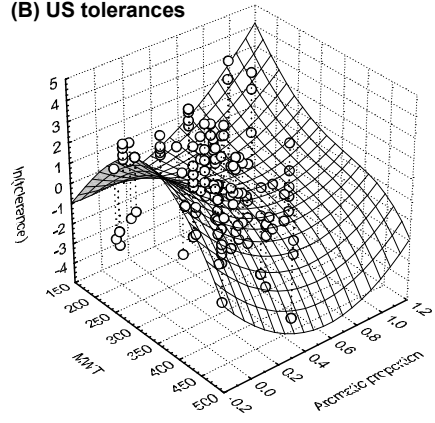


Figure 4.

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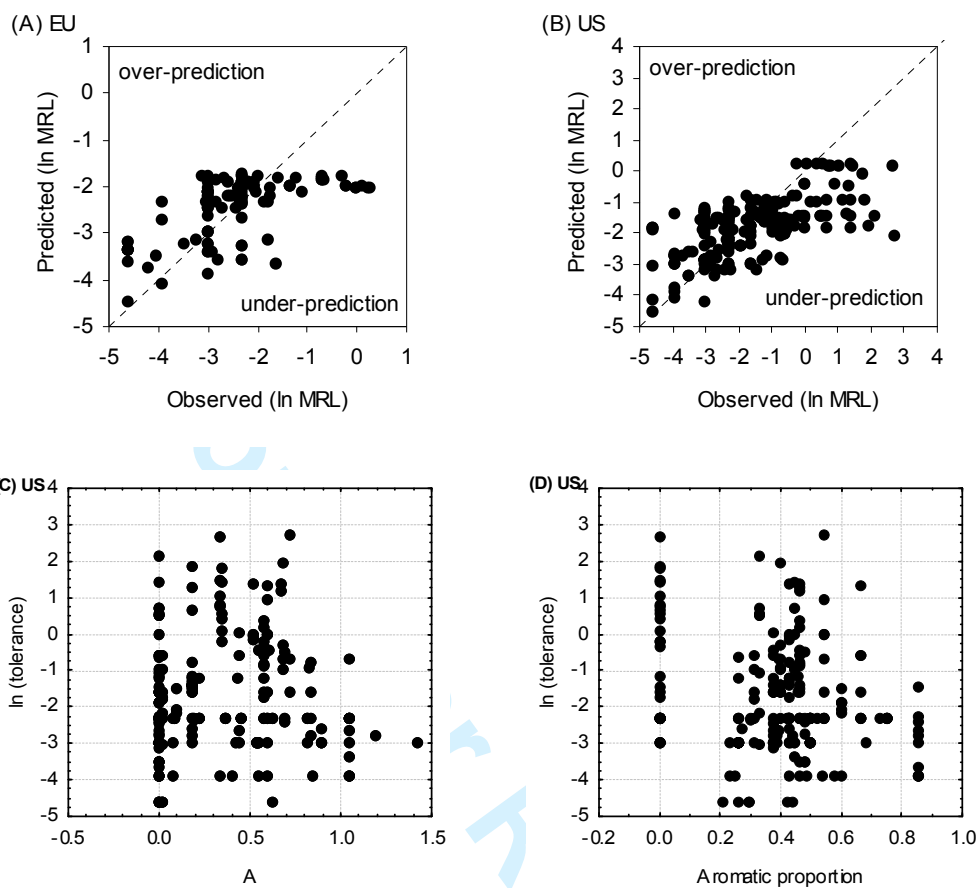


Figure 5.

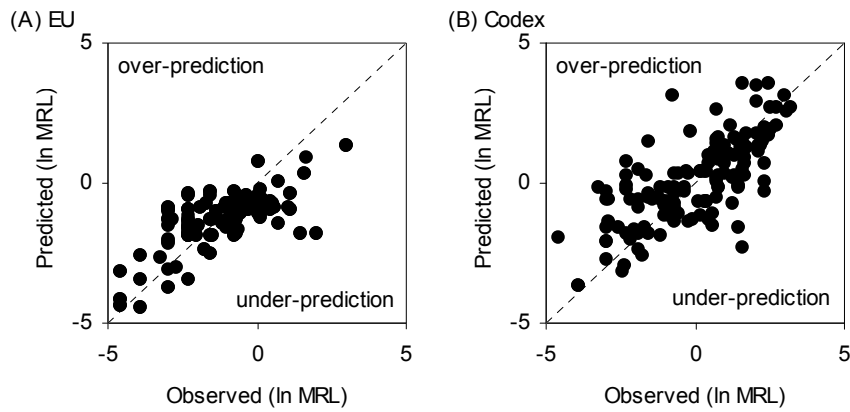


Figure 6.

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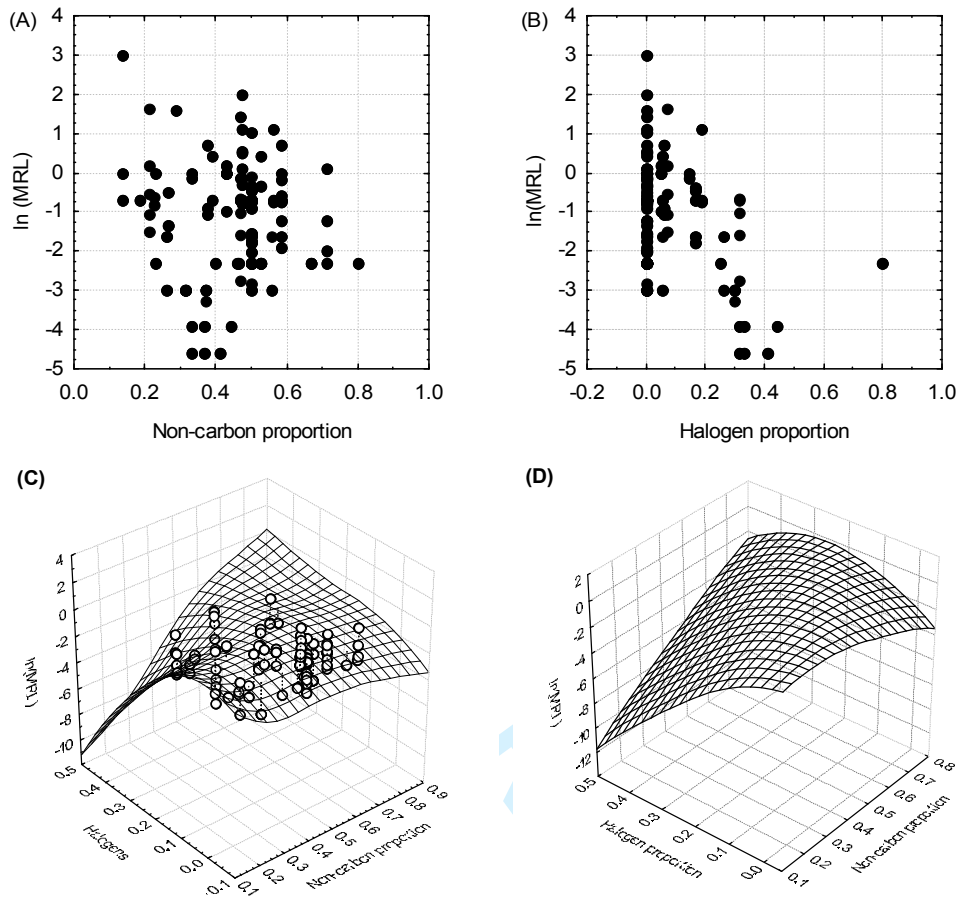


Figure 7

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