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How to select relevant metabolites based on available data for parent molecules: Case of neonicotinoids, carbamates, phenylpyrazoles and organophosphorus compounds in French water resources

Jodie Melin[a,b,c], Amélie Guillon[b], Jérôme Enault[b], Mar Esperanza[b], Xavier Dauchy[c], Stéphane Bouchonnet[a]

[a] LCM, CNRS, École polytechnique, Institut Polytechnique de Paris, Route de Saclay, 91128, Palaiseau, France

[b] SUEZ - CIRSEE, 38 rue du Président Wilson, 78230 Le Pecq, France

[c] ANSES, Laboratory for Hydrology, Water Chemistry Department, 40 rue Lionnois, 54000 Nancy, France

Corresponding author: stephane.bouchonnet@polytechnique.edu

Abstract

The presence of pesticide in water resources is a topical issue in France as in many other countries. Resources can be contaminated by current-used pesticides and their metabolites but also by molecules banned 50 years ago. The number of reported studies on the impact of these substances on human health and environment increases every day. Currently, pesticides and their relevant degradation products are subjected to the European regulation for water intended for human consumption. It sets an individual quality limit of 0.1 µg/L, and another of 0.5 µg/L for the sum of their concentrations. The constant improvement of analytical methods allows laboratories to detect pesticides, at lower and lower concentrations but also more and more metabolites. However, regulation does not provide a national indicative metabolites list to be monitored. Each regional health agency offers their own list based on local agricultural practices and quantities of pesticides sold. This article reports a prioritization method allowing to identify new metabolites to be monitored in water resources, along drinking water treatment plants and in treated water; it describes its application in France in order to anticipate possible non-compliance with raw water and treated water and to provide solutions upstream of changes in sanitary control. This methodology has been developed to rank pesticides and to select the corresponding metabolites by combining three main criteria: use (sale and type of use), toxicity, and environmental fate (based on physical and chemical properties). Prioritization method was applied to four families of pesticides:

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carbamates, organophosphorus compounds, phenylpyrazoles and neonicotinoids, for which there is a real lack of knowledge as regards the occurrence of their metabolites in metropolitan France. 146 pesticides have been prioritized. The first 50 molecules were considered allowing the identification of 72 metabolites to be monitored in water resources and along drinking water treatment plants.

Keywords: pesticides; prioritization; metabolites; water resources; toxicity; environmental fate

Introduction

France is one of the most pesticide-consuming countries in Europe with more than 68.000 tons in 2015 according to the national database of phytosanitary product sales (BNV-D, 2015). Fungicides (46%) and herbicides (41%), are still intensely used in the agricultural sector for the control of pests and weeds or for curative purpose regarding plant diseases (BNV-D, 2016). Phenomena of runoff, leaching and spray drift result in the dispersion of pesticides from the intended target areas and lead to a global contamination of the different environment compartments: air, soil and water (Biodegradation of Pesticides, 2011; Pollutants in Buildings, Water and Living Organisms, 2015). Generally speaking, the environmental fate of these substances (persistence, mobility or degradation both in resources and treatments plants) (Farré et al., 2008; Li et al., 2016) and their toxicity towards human and animals (Burden et al., 2016; Hamadache et al., 2016; Mekonen et al., 2016; Morrissey et al., 2015) are a major concern. On September the 1st 2018, neonicotinoids were banned from the French market (Law, 2016, Article 125), after they had been assumed responsible for the decline of honeybees (Goulson, 2013; Bonmatin et al., 2015). Many studies have reported the occurrence of pesticides and their degradation products particularly in surface and ground waters (Gervais et al., 2008; Lapworth et al., 2015; Lopez et al., 2015). These substances have also been detected in raw water, along drinking water treatment plants (DWTPs), where they are not always fully removed by the conventional treatment processes, and in treated water used for human consumption. (Guillon et al., 2018; Klarich et al., 2017). According to the Regulation 1107/2009 (EC, 2009) a metabolite means any degradation products of an active substance, safener or synergist, formed either in organisms (biotic reactions such as biodegradation) or in the environment (abiotic reactions such as hydrolysis, photolysis,

63 oxidation, reduction). Breakdown of an active substance may also occur in treatment plants by
64 hydrolysis, biodegradation in sand filters, or activated carbon filters, degradation by
65 ozonation, photolysis during UV disinfection or oxidation by chlorine during final
66 disinfection (Martínez-Vidal et al., 2009). In 2014, 700 pesticides and metabolites were
67 monitored in French water resources. However, not all these molecules were found in raw
68 water: only 56% (389 substances) in surface water were quantified and 38% (265 pesticides)
69 in groundwater. (SOeS, 2016). Since, nearly half of these substances are banned today in
70 France; their presence in water is mainly due to their persistence and their mobility in the
71 environment and may also result of illicit uses. One-tenth of these quantified substances were
72 pesticides metabolites that might be more toxic than the parent compounds (Bletsou et al.,
73 2015). For example, oxon metabolites are 10 to 100 times more toxic than organophosate
74 itself (Sparling and Fellers, 2007). The same conclusion has been reported for three
75 metabolites of fipronil (Qu et al., 2016). The constant improvement of analytical methods
76 allows laboratories to detect more and more metabolites, at lower and lower concentrations
77 (ng/L or pg/L) in water resources, sometimes leading to regulatory non-compliances of these
78 resources.
79 Pesticides and their metabolites are subjected to several regulations, both at European and
80 national levels: (i) Regulation laying down the marketing of phytosanitary products
81 (Regulation 1107/2009/EC; EC, 2009), (ii) Water framework directive about the protection of
82 water resources (Directive 2000/60/EC; EC, 2000), (iii) Regulation on the drinking water
83 quality (Directive 98/83/EC; EC, 1998). In this last regulation, quality limits in raw waters are
84 set at 2 µg/L for a single substance and 5 µg/L for the sum of their concentrations (Directive
85 2000/60/EC; EC,2000). For water intended for human consumption, a 0.1 µg/L quality limit
86 is currently applied for single substances and 0.5 µg/L for the sum of pesticides and their
87 "relevant" metabolites (Directive 98/83/EC; EC, 1998). The French drinking water regulation
88 is governed by the public health code (PHC,2007, articles L. 1321-1 à 1321-10 and R. 1321- 1
89 to 1321-66), in application of European directive 98/83/EC with the same quality limits
90 mentioned above.
91 The concept of "relevance" in the regulation regarding waters intended for human
92 consumption is not yet defined in European regulations. Until early 2019, France considered
93 all metabolites detected in water intended for human consumption as relevant. In this context,
94 non-compliance management, for a given molecule (relevant metabolite or not), is based on
95 maximum health values (Vmax) that correspond to the maximum concentration of a pesticide
96 or metabolite in drinking water not to be exceeded to prevent harmful effects on human health

(AFSSA, 2004). Some countries (Austria, Netherlands, Croatia) rely on Guide Sanco/221/2000 (EC, 2003, rev.10-final -25 February 2003). In this document, metabolites are considered relevant in the context of the Regulation 1107/2009/EC in groundwater if one at least of the following conditions applies: (i) reasons exist to believe that the metabolite intrinsic properties are comparable to those of the parent substance in terms of biological activity, (ii) the metabolite poses a higher or comparable risk to organisms than the parent substance, (iii) the metabolite has unacceptable toxicological properties. In this DG SANCO guidance document, a sequential assessment scheme in 5 steps is given to determine the relevance of a metabolite. Other countries such as Germany and United Kingdom have developed their own alternative method.

In 2015, the French Ministry of Health requested ANSES (French Agency for Food, Environmental and Occupational Health & Safety) to define evaluation criterion of relevance of metabolites in water intended for human consumption in order to manage non-compliances at national level. On January the 30th 2019, the final evaluation was released (ANSES, 2019) allowing to evaluate metabolites relevance with a decisional tree based on (i) pesticidal activity, (ii) toxicological criterion (genotoxicity, carcinogenesis, reprotoxicity and endocrine disrupting character) and potential of transformation in DWTP into a dangerous product for human health. This evaluation is applicable to all metabolites, even those with very few toxicological data available and required extensive literature research. In absence of data for the pesticidal activity and genotoxicity of the metabolites, it is considered relevant by default. In absence of data for the other toxicological criterion, toxicity of parent molecule of the metabolites is considered to determine its relevance. Consequently, a metabolite is considered relevant for water intended to human consumption if it could cause (itself or its transformation products) a health risk unacceptable to the consumer and if it has a pesticidal activity similar to the parent molecule; limits values similar to those mentioned in Directive 98/83/EC are then applicable. On the contrary, a metabolite classified as non-relevant by ANSES methodology have a unique limit value sets at 0.9 µg/L. This value was defined according to TTC approach (Threshold of Toxicological Concern; EFSA and WHO, 2016). The final method was applied to 8 metabolites, 5 of them were classified as non-relevant and methodology will be used to others molecules to complete their evaluation. ANSES approach is intended to help the health authority to manage situations where regulatory quality limits are exceeded but it does not provide a national indicative list of metabolites to be monitored as part of the sanitary control.

No study has been reported in the literature on prioritization methodology dedicated only to metabolites identification and focused only on water resources. This is a very challenging task because many metabolites likely to be present in the environment remain unknown and there is a severe lack of toxicity information on known ones. Furthermore, many analytical standards are not commercially available for metabolites, which makes their quantification impossible with classical analytical processes (Baran and Bristeau, 2018). However, two major institutes in France have developed micro-pollutants prioritization methods including pesticides, in surface water (INERIS; Dulio and Andres, 2012) and ground water (BRGM; Blum et al., 2011). Numerous prioritization methodologies - also referred as hierarchization methodologies - applied to micropollutants such as pesticides (Dabrowski et al., 2014; Tsaboula et al., 2016; Kuzmanović et al., 2015; Gros et al., 2017) and emerging substances (von der Ohe et al., 2011) in aquatic environment have been reported in the literature; some of them are listed in the supplementary data file S1. Generally, hierarchization approaches have a common objective that is to prioritize chemicals according to the concept of risk assessment (Guillén et al., 2012). The assessments mentioned above are based on two main parameters: exposure and dangerous effects for the environment and/or humans. Thus, the main differences between methodologies arise from the choice of criterion, their combination, and the processes followed to express exposure and effects. These choices are generally guided by the issues a given institution has to deal with regarding chemicals and the type of resources they focus on.

This work aims to identify new metabolites that might be non-compliant in the DW regulation, above the quality limits in raw water or in treated water. A prioritization method was developed and applied to pesticides, with the further aim of selecting metabolites to be taken into consideration on the basis of parent molecule ranking. The final ranking allows to select the corresponding metabolites belonging to four families: carbamates, neonicotinoids, organophosphorus compounds and phenylpyrazoles, to provide a list of molecules to be monitored in water resources and treated water. Hierarchization is based on three main criterion: (i) use of parent molecule, (ii) toxicity, and (iii) environmental fate of parent molecule. These criteria are declined in subcriterion and combined using a scoring system to provide a final ranking of molecules. The final list of pesticides allowed the selection of the corresponding metabolites by data extrapolation. This methodology can be applied on the scale of a territory. The use of pesticides is so different from one European country to the other that this study focuses on the application of this method on the French territory.

Methodology

Context and objectives of the prioritization method

Carbamates, neonicotinoids, organophosphorus compounds and phenylpyrazoles were retained for this study because of the lack of knowledge about the occurrence in water resources, toxicity and treatability of their metabolites in treatment plants in France. Concerning the occurrence, one condition has been retained: lack of information about metabolites concentrations (case of carbamates, for example). To date, data on metabolites are insufficient to permit a relevant prioritization based on metabolites themselves. The latter are generally less toxic and more polar than the parent molecules but, in some cases, they may be more persistent, more toxic and determined at higher concentrations than the pesticide itself (Bletsou et al., 2015). They may also have different properties (e.g. mobility) that allow them to reach water resources more quickly (Martínez-Vidal et al., 2009). In the present study, metabolites were selected according to data available for parent molecules; the degradation potential of the pesticide was considered and intrinsic toxic properties of metabolites were assumed to be comparable to those of parent molecules. **Fig. 1** displays the different ecological phenomena taken into account to develop this hierarchization methodology. The occurrence of pesticides and their metabolites in the environment and their fate from application on crops to tap water is influenced by five main parameters:

(i) The quantity of active substances sold and used in France. The assumption is that intensive use of pesticides increases contamination of water resources and exposure of humans. In such a way, Dabrowski et al. removed pesticides used in small quantities (< 1000 kg/an) from their prioritization method (Dabrowski et al., 2014).

(ii) The use on various crops (wine, beetroot, wheat, etc.), which reflects its ubiquity on the French territory and allows a rapid assessment of the degree of use of a given substance.

(iii) The stability of the parent compound, giving its potential to be degraded into metabolites, either in the environment (air, soil, water) or along drinking water treatment plants. These transformations can be caused by hydrolysis (reaction with water), photolysis (induced by sunlight), biodegradation, oxidation, reduction, ozonation, chlorination, etc.

(iv) The mobility of molecules that can reach surface water or groundwater through runoff, leaching, or permeation phenomena. This parameter is mainly governed by the weather (in particular rainfall, temperature and wind), the physicochemical properties of the substance and the environment where pesticides are spread.

(v) The efficiency of water treatment plants: substances can be fully, partially or not removed at all from water resources, along drinking water treatment plants and in distributed water. Toxic effects have to be also considered and are evaluated based on the toxicity of the parent molecules as in the ANSES approach, in particular their short-term and long-term effects and their significant carcinogenic, mutagenic, and/or endocrine disruptor properties. Two parameters were not considered in this prioritization method: (i) pesticides ecotoxicity for aquatic life, since their impact on human health was the core focus; (ii) data on occurrence of metabolites, since such data are poor (lack of data) because very few are included in monitoring lists.

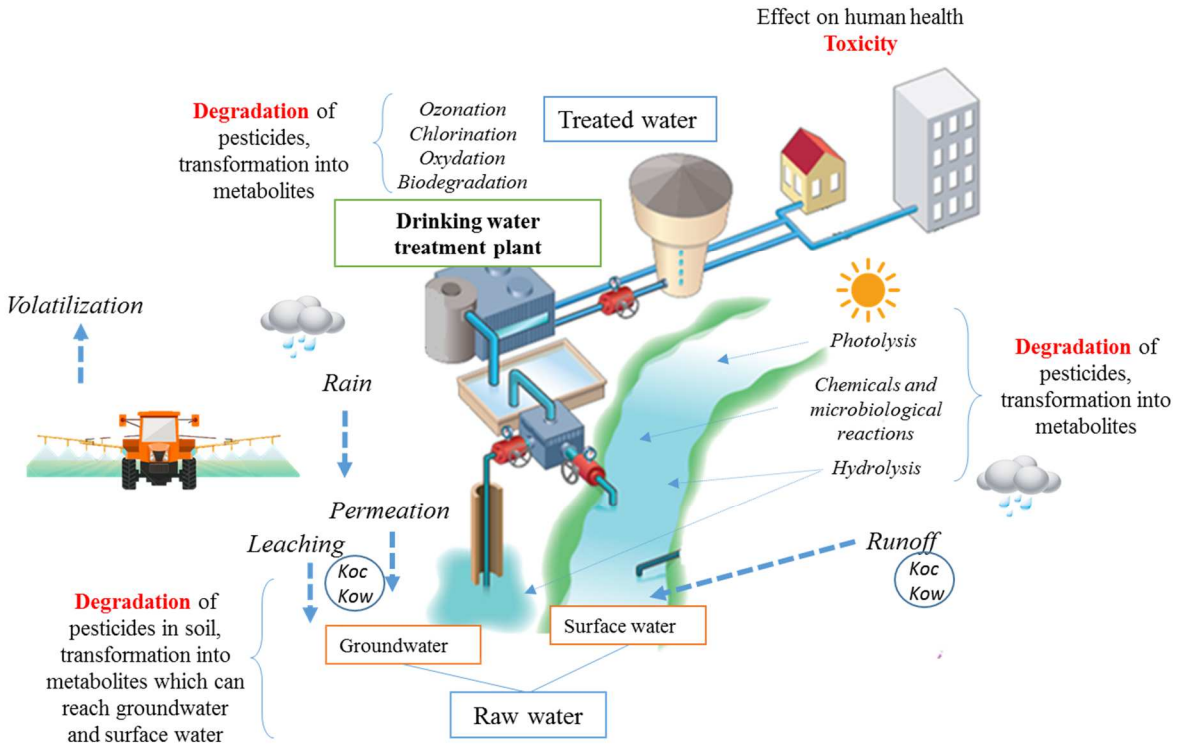


Fig. 1. Fate of pesticides in drinking water resources and drinking water treatment plants

Building of the starting list

In the literature (such as Pesticides Properties Database (PPDB, 2017)), 218 parent molecules belonging to the four selected families banned or not in the world were reported (130 organophosphorus compounds, 70 carbamates, 9 phenylpyrazoles and 9 neonicotinoids). To build the starting list, a first filter was applied by consulting the 2017 database "E-phy" (ANSES, 2017), which references all the pesticides authorized today or in the past in France. Pesticides that have never received any market authorization for the national territory were excluded, reducing the list to 146 parent molecules (80 organophosphorus compounds, 56 carbamates, 7 neonicotinoids and 3 phenylpyrazoles). Consequently, prioritization methodology was applied to 146 parent molecules. Approximatively 280 metabolites of these compounds were identified using the Pesticides Properties Database (PPDB, 2017). Among these 280 metabolites, only 160 metabolites have a CAS number, moreover, no physico-chemical information is available in the literature for many of them. An analytical standard is commercially available for 139 of them.

Definition of criteria and scores

Unlike for metabolites, data on parent molecules are widely available, which guarantees a relevant prioritization. A long process of data collection (use, toxicity and fate in the environment) has been conducted using databases, books, websites specialized on pesticides, and lists of priority substances in the field of water from European directives (**Table 1**). Three criteria were selected for prioritization of molecules; they are detailed below.

Table 1. Criteria, subcriteria and sources used for substance hierarchization

Criteria	Sub criteria	Sources
USE	Authorization in France Sales data from 2008 to 2016 Type of use	E-phy (ANSES, France) National database of sales data (BNV-D) (2008-2016) Phytosanitary index ACTA 1984, 2005, 2008, 2015

TOXICITY	Molecule carcinogenic, mutagenic, reprotoxic (CMR) ADI (acceptable daily intake mg/kg/d) LD50 rat (lethal dose, mg/kg) Endocrine disruptor	Pesticides properties database (University of Hertfordshire, UK) Classification of carcinogenic substances by the International Agency for Research on Cancer (IARC) EC Regulation n°1272/2008 Environment Protection Agency, endocrine disruption screening program for the 21st century
ENVIRONMENTAL FATE	Log K_{ow} K_{oc} (mL/g) DT50 (days) Solubility (mg/L) Hydrolysis (days) Photolysis (days)	Pesticides properties database (University of Hertfordshire, UK) Portal of chemical substances (INERIS, France) Agritox, pesticides (ANSES, France)

The choice of each parameter and the way it has been evaluated was broadly based on recommendations from INERIS (*Institut national de l'environnement industriel et des risques*) (Dulio and Andres, 2012) and NORMAN network (NORMAN, Dulio and von der Ohe, 2013). The way a score was attributed depended on the parameter considered. A binary "yes/no" approach was used for four parameters: ED effects, CMR effects, authorization of a molecule, and type of use. In the latter case, for which several "yes" answers were possible, the score was incremented with the number of "yes". The main difference with aforementioned approaches concerns the scoring of other parameters. Regarding PNEC for instance, previous approaches used to give a grade between 0 and 1, on the basis of the PNEC value when known (PNEC ≤ 0,1 µg/l: 1; PNEC ≤ 1 µg/l: 0.75; PNEC ≤ 10 µg/l: 0.5; PNEC ≤ 100 µg/l: 0.25; PNEC > 100 µg/l: 0). A default value of 0.25 was given when PNEC was not available. In the present work, criteria were given a numeric value when possible and the corresponding scores were calculated by dividing each value by the maximum one. This approach has been chosen in order to accentuate the differences between low PNEC molecules and high PNEC molecules in the prioritization process (here again, a default value of 0.25 was given when PNEC was not available). Score trees summarizing how each criterion was determined are displayed in the supplementary data file SD2.

First criterion: use

The use criterion was declined in three subcriteria:

(i) Authorization of use in France in 2017. This information is available on the E-PHY website (ANSES, 2017). In 2017, 100 molecules from the starting list were prohibited, 46 were still allowed. A molecule has been given a score of 1 if it is allowed and 0.25 otherwise. A zero score was not attributed to prohibited molecules since these molecules can be quantified in water resources due to their persistence in the environment.

(ii) Average sales BNV-D data from 2008 to 2016. BNV-D is a database created in 2009, following the introduction of fees for diffuse pollution; it references the annual sales data for phytosanitary products declared by distributors (BNV-D, 2016; http://www.data.eaufrance.fr/). In France, used quantities range from 1 kg for fipronil to 3,320,347 kg for mancozebe. A score of zero was attributed to molecules banned before 2008 (86 molecules), for which no sales data could be found since sales declarations were not done at that time. A score between 0 and 1 was attributed to remaining molecules according to their average volume of use between 2008 and 2016. If a molecule has been banned during this period only the available data are averaged. The final score is calculated by dividing each values by the maximum value of the sales quantities. Mancozebe, fosetyl and prosulfocarb constitute the top 3 best-selling active substances with a score of 1; 0.6 and 0.5 respectively. Followed by toclofos-methyl and metiram with a score of 0.3 and 0.4. For the remaining molecules, scores are below 0.1. This criterion highlight mainly 5 molecules used in wide quantities compared to the others but it is well completed by the next criterion which reflect the degree of use.

(iii) The type of use in France, which is divided into five main categories according to phytosanitary indexes: field crops, viticulture, arboriculture, gardening and any other use (roads or public open spaces, for example). The first three are agricultural uses and represent 70% of the total consumption in France. Gardening represents the domestic use of pesticides. Four phytosanitary indexes dating from 1984, 2005, 2008, and 2015 (ACTA, Dubois et al., 1984; Couteux and Lejeune, 2005 and 2008; Baudet and Meunier, 2015) were consulted to cover a broad period and thus take into account the oldest active substances. A molecule used in a single domain was attributed a score of 0.2 while a molecule used in two domains had a score of 0.4 and so on (increments of 0.2), up to a maximum of 1.0 for a compound used in the five categories.

A use criterion score was obtained combining these three subcriteria according to **Eq. 1**; it highlights the most widely sold and therefore the most used pesticides, but also those used on several types of crops that are likely to be found in different resources.

$$use\ score = (authorization\ score + sales\ score + mode\ of\ use\ score)/3 \qquad (Eq.\ 1)$$

Second criterion: toxicity

The toxicity criterion was declined in four subcriteria:

(i) The carcinogenic, mutagenic, reprotoxic (CMR) character of molecules. This information is extracted from the annex VI of regulation EC 1272/2008 on the classification, labeling and packaging of substances and mixtures (EC, 2008). Another data source provided by the International Agency for Research on Cancer (WHO, 1965) can be consulted but information found is less broad. 26 molecules classified in categories 1A (CMR effect proven for humans), 1B (presumed), or 2 (CMR effect suspected) are considered in the prioritization methodology. Only five molecules are classified in the group 1B (parathion, benomyl, carbendazim, thiacloprid and tetrachlorvinphos. A molecule classified CMR 1A, 1B or 2 (proven, presumed or suspected) was given a score of 1, otherwise (no data or no classification in 1A, 1B, 2) 0.25. The choice to give a non-zero score for non-CMR molecules or in the absence of data has been made to avoid oversights of molecules that could be one day C or M or R.

(ii) The acceptable daily intake (ADI). ADI refers to the amount of substance that may be ingested daily by the consumer throughout his or her life, with no adverse effect on health (ANSES, 2012). The lower this dose, the more toxic the molecule. Two databases were consulted: Agritox (ANSES, 2012), created in 1986 by INRA (National Institute of Agronomic Research) and the Pesticides Properties Database (PPDB, 2017). For this subcriterion, a score of 0 was given when no data was available (case of 42 substances) waiting for the re-evaluation of literature data to complete data gaps and thus a possible ranking modification. A score between 0 and 1 was assigned to the other molecules. The maximum value of 1 was attributed to the substance with the lowest ADI value (dichlorvos, which has been banned since 2008 in France). By dividing each ADI value by the maximum ADI value and then subtract by 1 a decreasing score is obtained.

(iii) The lethal dose 50 (LD50). The LD50 value corresponds to the quantity of an active substance, administered at one time, which causes the death of 50% of a group of test animals. The LD50 is a way of measuring the short-term toxic potential (acute toxicity) of an active substance (ANSES, 2012). Acute toxicity data were found for all molecules in PPDB (PPDB, 2017). Scores between 0 and 1 were attributed, inversely proportional to the LD50 value for rat. A score of 1 was assigned to the molecule with the lowest LD50 value (aldicarb). Intermediate values are obtained using the same calculation method as the one described for the ADI. Molecules that exert the lowest short-term toxic effects are benomyl, fenoxycarb and carbendazim (LD50 of 10,000 mg/kg), they were given a value of 0.

(iv) The endocrine disrupting character (ED). In 2012, EPA (Environmental Protection Agency) researchers have developed an Endocrine Disruptor Screening Program (EPA, 2012) to study ED effects. By definition, an endocrine disruptor is a substance or mixture that alters the functions of the endocrine system and thereby induces adverse effects on an intact organism, its offspring or within (sub) populations. By disrupting the endocrine system, these substances can alter different processes such as the production, use and storage of energy and more broadly the regulation of metabolism and development. Some of these substances may also have toxic effects on reproduction and affect fertility or development of the fetus (WHO, 2002). 31 molecules are listed as ED according to the EDSP developed by the EPA. 6 molecules (benomyl, phoxim, carbendazim, fenoxycarb, thiophanate-methyl, thiabendazole and thiacloprid) proven, presumed suspected to be CMR are also considered as endocrine disruptors. A molecule with ED effects was given a score of 1, otherwise (no data) 0.25. Similarly, as the CMR subcriteria, a score different of zero was attributed to molecules with no ED effects or no data released at the moment of the literature review.

The final toxicity score was calculated according to Eq. 2.

$$toxicity\ score = (CMR\ score + ADI\ score + DL50\ score + ED\ score)/4 \qquad (Eq.\ 2)$$

Third criterion: environmental fate

The environmental fate criterion is declined in six subcriteria for which data were all collected in the pesticides properties database (PPDB, 2017):

(i) The log Kow (octanol-water partition coefficient). It estimates the hydrophilic or lipophilic nature of a substance. It gives an overall estimation of the distribution of a compound in the

environment. Low values reflect high affinity for water. Data for log Kow were found for all molecules. A score of 1 was assigned to the lowest value; this score decreases as log Kow increases.

(ii) The organic carbon-water partition coefficient (Koc). It represents the retention potential of a substance on soil organic matter and estimates its mobility. For example, a molecule with a high Koc value will preferentially bind to the solid phase of soil and will reach water resources with greater difficulties. The most mobile molecule is methamidophos, which has been attributed a score of 1. Only 3 molecules for which there was no data available have a score of 0 (benthiavalicarb, propineb, nabam).

(iii) Solubility in water. The mobility of a pesticide is related to its solubility. The higher the solubility, the higher the score. The most water-soluble molecule is oxydemeton-methyl (score of 1). Intermediate score are obtained by dividing each value by the maximum one.

(iv) Half-life in soil ($DT50_{soil}$). This parameter expresses the potential for degradation of a substance and its rate of degradation in soil. DT50 is the time required for 50% of the mass of the substance to disappear from soil subsequently to transformations. Biological (biodegradation) and physicochemical processes (hydrolysis, photolysis, etc.) are the main degradation mechanisms. Fosetyl, mancozebe, malathion, azametiphos, benfuracarb, thiophanate-methyl, thiodicarb and fenamiphos degrade very quickly (in less than one day) in soil. The lower values lead to a score of 1; the score decreases as the persistency increases. For example, clothianidin, thiabendazole and isolan degrade very slowly in soil and therefore have a score close to zero. 11 molecules have a zero score because no data were found in the literature.

(v) Photolysis. The action of photolysis is evaluated by the degradation time of 50% of the active substance (DT50) in water under the effect of light. Propineb and clothianidin are the two compounds that degrade the fastest (≈ 3 h) under the influence of light and have therefore a score of 1. 53 molecules have a zero score because no data were found in the literature.

(vi) Hydrolysis. The action of hydrolysis is evaluated by the degradation time of 50% of the active substance in water. Formothion is the compound that hydrolyses the fastest (≈ 4 h) and has a score of 1 while furathiocarb and propham degrade very slowly (10,000 days or more)

and have thus a score of 0 and 0.13 respectively. 28 molecules have a zero score because no data were found in the literature.

To summarize, the fate in the environment score defined by **Eq. 3** prioritizes molecules based on their mobility and therefore their potential to reach water resources. It allows the selection of mobile, non-persistent molecules that degrade rapidly and potentially generate the most abundant metabolites. All subcriteria score excepted the solubility were calculated in a same approach by dividing each value by the maximum one and then subtract the result by 1 to attribute the higher score to low value. Molecules with no data have automatically a score of zero.

$$environ.\ fate\ score = (Log\ K_{ow} + K_{oc} + DT50 + solubility + hydrolysis + photolysis)/6 \qquad (Eq.\ 3)$$

Pesticides prioritization

Hierarchization of the starting list was carried out thanks to scores ranging from 0 to 1 (number of points attributed to a substance) applied to subcriteria of the three selected categories: use, toxicity and environmental fate. For each substance, the final score was calculated according to equation **Eq. 4**. It is fully assumed by the authors to give equal weight to each criteria considering that there is no reason to emphasis one parameter in the present work.

$$Final\ Score = (use\ score + toxicity\ score + environmental\ fate\ score)/3 \qquad (Eq.\ 4)$$

Results and discussion

The hierarchization method described above was applied to 146 pesticides from carbamates, organophosphorus, phenylpyrazoles and neonicotinoids families. By combining use, toxicity and environmental fate scores, all these molecules were evaluated and obtained a final score between 0 and 1. As previously mentioned, the strategic choice implemented to satisfy the objectives of this project was to equally weight the 3 criteria given that there was no reason to give more weight to one parameter than to another. A final list of 50 molecules (**Table 2**) was considered (4 neonicotinoids, 1 phenylpyrazole, 24 carbamates and 21 organophosphorus compounds). Metabolites corresponding to the prioritized pesticides were then selected. More

than 160 metabolites have been reported in the literature for this set of 50 molecules; 8 pesticides among those prioritized have zero metabolites identified. The absence of metabolites does not imply exclusion of the final list because new metabolites may be discovered in a near future. An analytical standard - necessary to develop analytical methods to conduct monitoring programs - is available for only 72 metabolites. This lack of analytical standard led to the removal of 45% of metabolites. As a result, 72 metabolites were identified considering data relative to parent molecules. The final list is given in the supplementary data file SD3.

The 50 compounds reported in **Table 2** represent 78% of the total amount of pesticides used at a national scale (total quantity of 11,507,842 kg). Among them, 16 molecules are currently banned from the French market. Monocrotophos is the oldest banned molecule (2003) while the most recent one is carbendazim (2009). In terms of toxicity, 70% of the CMR-classified compounds and 61% of the ED-classified molecules (corresponding to 26 and 31 compounds, respectively) are included in the final top 50. Molecules can have both CMR and ED effects (case of benomyl, carbendazim, phoxim, fenoxycarb, thiabendazole, thiacloprid and thiophanate-methyl) that attest of a high potential of toxicity. Among them, only phoxim is excluded from the top 50 list because it is rarely used and slightly soluble in water. LD50 and ADI were chosen to measure short-term and long-term toxicity; 29% of most acute toxic molecules and 35% of most chronic one are included in final top 50. In terms of environmental fate, all characteristics such as persistence, mobility and degradation are represented in the final top 50 list. Scores attributed for degradation potential (hydrolysis, photolysis and $DT50_{soil}$) are usually related to low persistence in the environment, which suggests potential formation of abundant metabolites. These previous criterions were selected in accordance with the initial objective of the present work, more focused on metabolites than on parent molecules Nevertheless, it must be kept in mind that in some cases fast degradation of the parent molecule can lead to fast mineralization thus reducing metabolite abundance. A pesticide can also be a metabolite of another pesticide as it is the case for methomyl and carbendazim, prioritized at 8^{th} and 48^{th} ranks, which are metabolites of thiodicarb and benomyl/thiophanate-methyl, respectively. Some other pesticides/metabolites such as methamidophos, omethoate, clothianidin and dichlorvos were not prioritized due to their final ranking as parent molecules but as metabolites. Metabolites appear in common for several parent molecules: 3-aminophenol (formetanate and phenmedipham), carbendazim (benomyl and thiophanate-methyl), phtalic acid (phosmet and carbaryl), methylamine (carbaryl and acetamiprid), 6-chloro-nicotinic acid (acetamiprid and imidacloprid). It is to be remarked in a

more general way that special attention should be paid on metabolites with several origins. Most of the time, the metabolite will be prioritized if at least one of the parent molecules has been retained by the prioritization process. However, one could imagine a case where none of the parent pesticides has been retained, for instance because they were individually detected in small amounts so they obtained a very low score regarding use, but the metabolite would deserve to be selected because the high transformation rate of parents into it and/or its specific toxicity make it more concerning. Such a case is not so likely but cannot be fully discarded. It is important to notice that mancozebe, thiram, maneb, ziram and fosetyl exist as strong complexes with various metal ions, often under polymeric forms, which makes them difficult to analyze directly because of their instability in aqueous solution and their limited solubility in most organic solvents (Kakitani et al., 2017). These compounds are thus rarely included in multi-residue analytical methods and were excluded from our top 50.

Consequently, 72 metabolites were prioritized considering the data relative to parent molecules; they might be monitored in raw water and along drinking water treatments plants. Most of them have never been included in any monitoring program in France. Indeed, in 2016, only 14 metabolites, common with our final list were monitored in raw water and only 6 were quantified at least once (methomyl, carbofuran, hydroxy-carbofuran, carbendazim, omethoate, fipronil sulfide) (SISE-EAUX, 2016).

Table 2. Final priority ranking of pesticides based on their use, toxicity and environmental fate

Parent compound	Rank	Final score	Number of metabolites[a]	Parent compound	Rank	Final score	Number of metabolites
Mancozebe[b]	**1**	0.8090	0	Fenoxycarb	**26**	0.6387	0
Thiacloprid	**2**	0.7573	2	Monocrotophos	**27**	0.6353	0
Thiram[b]	**3**	0.7362	0	Diazinon	**28**	0.6332	1
Carbetamide	**4**	0.7249	1	Etofenprox	**29**	0.6281	1
Chlorpyrifos-ethyl	**5**	0.7230	2	Thiabendazole	**30**	0.6277	2
Indoxacarb	**6**	0.7013	2	Benomyl	**31**	0.6267	2
Mevinphos	**7**	0.6913	0	Chlorpropham	**32**	0.6261	1
Methomyl	**8**	0.6842	1	Desmedipham	**33**	0.6261	1
Thiophanate-methyl	**9**	0.6825	1	Parathion	**34**	0.6165	1
Formetanate	**10**	0.6773	2	Acephate	**35**	0.6137	1
Acetamiprid	**11**	0.6772	5	Phosphamidon	**36**	0.6086	0
Pirimifos-methyl	**12**	0.6717	0	Oxamyl	**37**	0.6069	1

Maneb	**13**	0.6692	0	Phosmet	**38**	0.6054	5
Thiametoxam	**14**	0.6688	2	Carbofuran	**39**	0.6048	3
Malathion	**15**	0.6688	2	Ethoprophos	**40**	0.6007	0
Imidacloprid	**16**	0.6632	4	Phenmedipham	**41**	0.6002	3
Prosulfocarb	**17**	0.6579	1	Oxydementon-methyl	**42**	0.5947	4
Diethofencarb	**18**	0.6569	1	Triallate	**43**	0.5945	0
Ziram[b]	**19**	0.6482	0	Thiodicarb	**44**	0.5910	1
Carbaryl	**20**	0.6479	4	Fosetyl[b]	**45**	0.5881	0
Pirimicarb	**21**	0.6470	4	Azinphos-methyl	**46**	0.5881	0
Chlorpyrifos-methyl	**22**	0.6464	1	Fipronil	**47**	0.5865	3
Phosalone	**23**	0.6446	1	Carbendazim	**48**	0.5854	1
Dimethoate	**24**	0.6434	1	Methiocarb	**49**	0.5849	4
Trichlorfon	**25**	0.6417	3	Fenitrothion	**50**	0.5843	3

[a] Number of metabolites identified with an analytical standard

[b] Molecules with analytical difficulties

Fig. 2 shows the influence of the three criteria in the top 10 final ranking. The 1st rank of mancozeb was clearly influenced by its use score (score of 1); indeed, it is a molecule widespread in many crops: 2,351,509 kg of mancozeb were sold in 2016 in metropolitain France. The second ranked molecule, thiacloprid, is clearly highly ranked due to its toxicity score (score value of 1) like chlorpyrifos ethyl and indoxacarb. For thiram and carbetamide, the three criteria have equally contributed to the final score. Mevinphos is largely influenced by both toxicity and environmental fate criteria. The three last molecules from top 10 are ranked according to their environmental fate score. In a general way, it can be concluded for these ten molecules that all criteria significantly contribute to the final ranking.

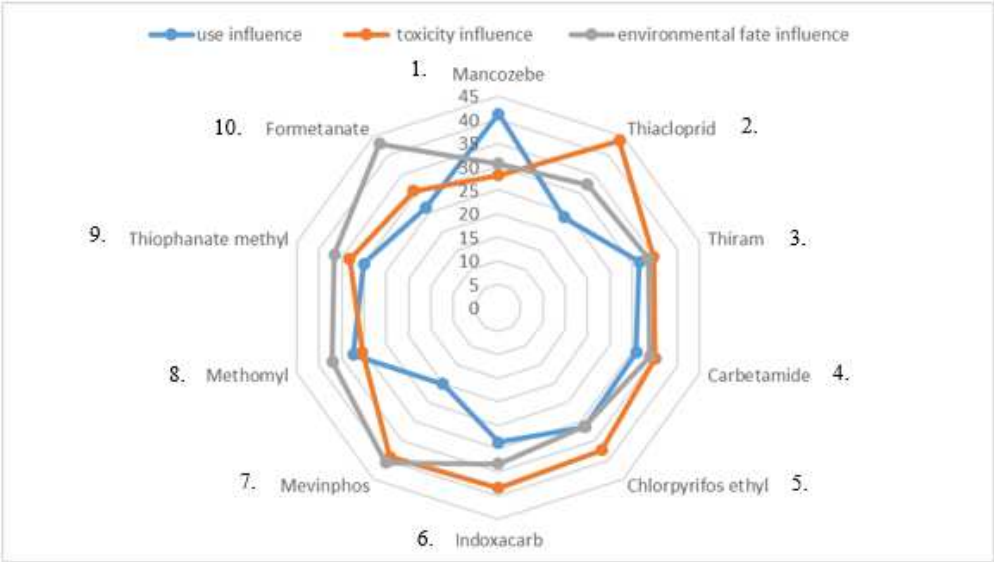


Fig. 2. Relative influences of each criteria on the top 10 compounds of the final list

A Principal Component Analysis (PCA) approach has been carried out to estimate how the use, toxicity and environmental fate criteria influence the final ranking of the 50 prioritized molecules and how each compound relates with others. Basic principles and results of the PCA are discussed in supplementary data file SD4. ~~This approach provides information on the parameters appearing as the most meaningful to describe the whole data set of 50 compounds. The 3 red axes represent the use, toxicity and environmental fate indexes. For a given molecule, closeness to a red axis indicates that its ranking has been mostly influenced by the corresponding index. A location between two axes means that the ranking of the pesticide was influenced by both corresponding indexes. The use index is strongly correlated with the 1st axis: molecules at the left extremity of this axis are those whose ranking is the most influenced by this index (fosetyl and mancozeb). Pesticides positioned in the opposite direction are those whose ranking is the less influenced by this criterion (monocrotofos, thiodicarb and phosphamidon). Similarly, pesticides in the top right quadrant are those whose ranking is the most influenced by environmental fate (acephate, oxydemeton methyl and oxamyl) while those towards the opposite direction correspond to compounds for which this criterion was not of major concern (chlorpyrifos ethyl and triallate).~~

Table 3 reports the top 10 list for each criterion used in the prioritization method. Only one pesticide (mevinphos) occurred in the top 10 for both criteria toxicity and environmental fate and is consequently ranked at the 7th place of the final list. Four molecules are absent from the

top 50 final list: terbufos, phorate, phoxim, and ferbam, which are ranked at the 63, 65, 67, and 88th places, respectively. Indeed, these molecules are no longer authorized in France, no data were found on their sales. Furthermore, they present low toxic potential (case of ferbam) or have little persistency in the environment (case of phoxim, phorate and terbufos). It is to be noticed that methamidophos and omethoate, which are not in the top 50 final list of pesticides, are nonetheless prioritized as metabolites of acephate and dimethoate (24th and 35th), respectively.

Table 3. Top 10 ranked pesticides for each criterion

Use score	Molecule	Final rank	Toxicity score	Molecule	Final rank	Environmental fate score	Molecule	Final rank
1.0000	Mancozeb	**1**	0.9978	Thiacloprid	**2**	0.8922	Acephate	**35**
0.8510	Fosetyl	**45**	0.9497	Phoxim	**67**	0.8770	Monocrotophos	**27**
0.7051	Prosulfocarb	**17**	0.8667	Thiabendazole	**30**	0.8769	Oxydementon-methyl	**42**
0.6989	Thiram	**3**	0.8124	Terbufos	**63**	0.8742	Formetanate	**10**
0.6804	Chlorpyrifos-ethyl	**5**	0.8124	Parathion	**34**	0.8449	Mevinphos	**7**
0.6743	Chlorpyrifos-methyl	**22**	0.8124	Phorate	**65**	0.7949	Oxamyl	**37**
0.6728	Carbetamide	**4**	0.8123	Mevinphos	**7**	0.7902	Ferbam	**88**
0.6689	Thiametoxam	**14**	0.8123	Phosphamidon	**36**	0.7816	Methamidophos	**77**
0.6673	Acetamiprid	**11**	0.8122	Carbofuran	**39**	0.7705	Omethoate	**61**
0.6667	Methomyl	**8**	0.8121	Monocrotophos	**27**	0.7685	Manebe	**18**

Graphical representations of the subcriteria contribution to the final top 10 ranking are given in the supplementary data file **SD5**. The left-hand radar in **SD5** shows the very high influence of sales data for mancozeb, fosetyl and prosulfocarb, the three of them representing 20% of the total sales data on the French market. For the other molecules, sales data score is very low. This subcriterion has an influence only on molecules used in high quantities in order to not penalize molecules banned before 2008 (63%) for which there are data gaps. Nevertheless, the use subcriteria balanced this lack of data and reflect the diversity of use of each molecule. 9 molecules are used in all the fields previously mentioned (agriculture and others) at the exception of prosulfocarb, and all molecules were authorized at the time this methodology was set up. The toxicity radar figure shows significant differences between each subcriterion.

All molecules have a high score for ADI and DL50 except phoxim and thiabendazole (for DL50) and ranking was mainly impacted by CMR and ED characters. The environmental fate radar shows lower scores for solubility (except for oxydemeton-methyl) and log Kow.

The limits of this methodology are mainly due to the lack of data for some subcriteria. For example, the use criterion scores range from 0.150 to 1. A very low score was attributed to molecules for which sales data were not available in the BNV-D database (63%), used for only one type of crops, or no longer authorized in France. However, some molecules in this case appear in the final top 50 list (mevinphos, trichlorfon, monocrotofos, parathion ethyl, acephate and phosphamidon) because of their toxicity and environmental fate. Indeed, **SD5** shows the very low influence of the sale subcriterion compared to other subcriteria.

Conclusion

The prioritization methodology presented in this paper is quite simple in its principle; input data for parent molecules are easily collected from online database and can be applied to all products used to protect crops. Nevertheless, there is still missing data for some subcriteria in our methodology, which could have an impact on some molecules for which research remains to be carry out. Scientific watch has to be done as often as possible in order to fill data gaps, update parent molecules starting list with potential new ones available on the market, update metabolites lists, and their standard availability to analyze them. Overall, the molecules ranking shows that the three criteria have a similar influence in the prioritization.

It is an innovative method to select metabolites of pesticides considering the ranking of parent molecules and extrapolating use, toxicity and environmental fate data. As a result, a ranking of metabolites from lowest to highest degree of concern was obtained. This study focused on the case of France but its application can be extended to European scale by considering the uses of pesticides that are specific to each country. It must be kept in mind that prioritization studies reflect the situation at the moment they are carried out and are doomed to become obsolete as the market of phytosanitary products constantly evolves. In the present case, we focused on four families for which toxicity is well recognized; they are still detected in waters but most of them are prohibited in many countries and new pesticides belonging to these chemical classes should not enter the market.

This prioritization method allowed to identify 72 new metabolites that were mostly not monitored in 2016 (case of 80% of metabolites final list) despite their potential toxicity and high of presence in raw and treated water. As part of a research project to assess the occurrence and fate of these substances, an analytical methodology will be developed.

Appendix A. Supplementary data

Supplementary data 1. Summary of prioritization methodologies applied to various substances

Supplementary data 2. Score trees for use, toxicity and environmental fate criteria

Supplementary data 3. Final list of prioritized metabolites

Supplementary data 4. Influence of the use, toxicity and environmental fate criteria on ranking for the 50 prioritized molecules - the PCA approach

Supplementary data 5. Influence of subcriteria in the top 10 ranking of compounds: 1) Use, 2) Toxicity, 3) Environmental fate

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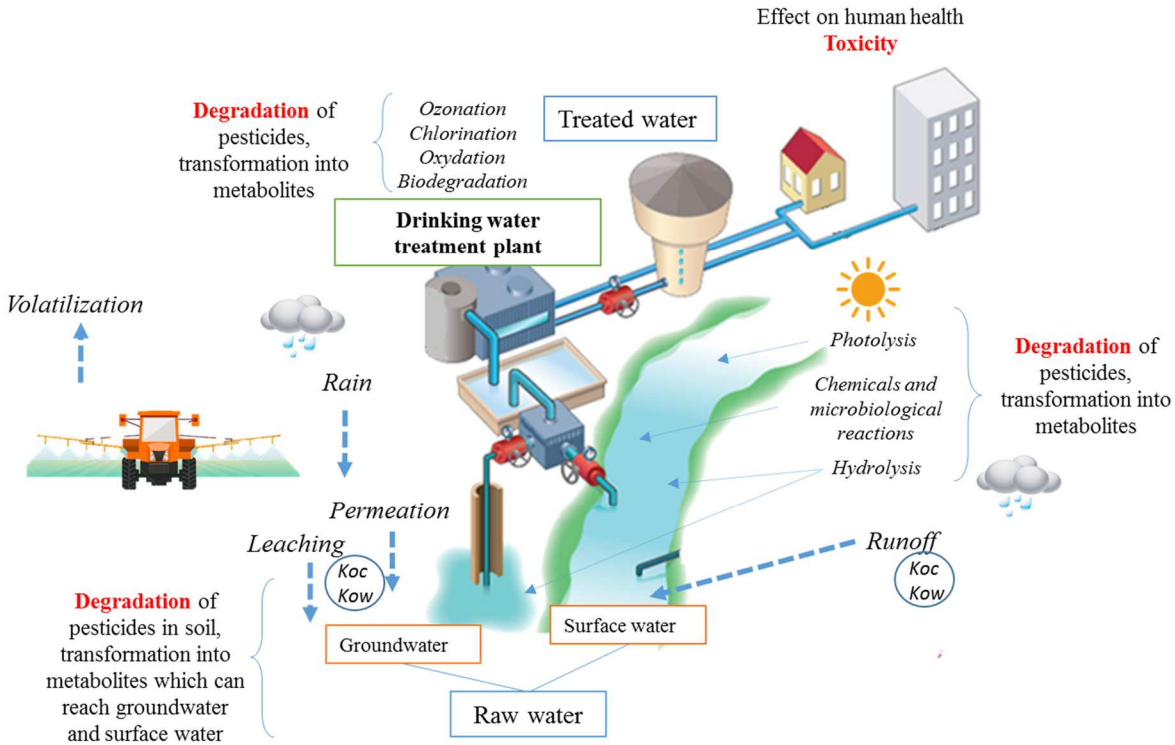
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Effect on human health
Toxicity
Degradation of pesticides, transformation into metabolites
Ozonation
Chlorination
Oxydation
Biodegradation
Treated water
Drinking water treatment plant
Volatilization
Rain
Photolysis
Chemicals and microbiological reactions
Hydrolysis
Degradation of pesticides, transformation into metabolites
Permeation
Leaching
Koc
Kow
Runoff
Koc
Kow
Degradation of pesticides in soil, transformation into metabolites which can reach groundwater and surface water
Groundwater
Surface water
Raw water