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

4  
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13 **Abstract**

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

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

37 **Keywords:** pesticides; prioritization; metabolites; water resources; toxicity; environmental  
38 fate

39

## 40 **Introduction**

41 France is one of the most pesticide-consuming countries in Europe with more than 68.000  
42 tons in 2015 according to the national database of phytosanitary product sales (BNV-D,  
43 2015). Fungicides (46%) and herbicides (41%), are still intensely used in the agricultural  
44 sector for the control of pests and weeds or for curative purpose regarding plant diseases  
45 (BNV-D, 2016). Phenomena of runoff, leaching and spray drift result in the dispersion of  
46 pesticides from the intended target areas and lead to a global contamination of the different  
47 environment compartments: air, soil and water (Biodegradation of Pesticides, 2011; Pollutants  
48 in Buildings, Water and Living Organisms, 2015). Generally speaking, the environmental fate  
49 of these substances (persistence, mobility or degradation both in resources and treatments  
50 plants) (Farré et al., 2008; Li et al., 2016) and their toxicity towards human and animals  
51 (Burden et al., 2016; Hamadache et al., 2016; Mekonen et al., 2016; Morrissey et al., 2015)  
52 are a major concern. On September the 1<sup>st</sup> 2018, neonicotinoids were banned from the French  
53 market (Law, 2016, Article 125), after they had been assumed responsible for the decline of  
54 honeybees (Goulson, 2013; Bonmatin et al., 2015). Many studies have reported the  
55 occurrence of pesticides and their degradation products particularly in surface and ground  
56 waters (Gervais et al., 2008; Lapworth et al., 2015; Lopez et al., 2015). These substances have  
57 also been detected in raw water, along drinking water treatment plants (DWTPs), where they  
58 are not always fully removed by the conventional treatment processes, and in treated water  
59 used for human consumption. (Guillon et al., 2018; Klarich et al., 2017). According to the  
60 Regulation 1107/2009 (EC, 2009) a metabolite means any degradation products of an active  
61 substance, safener or synergist, formed either in organisms (biotic reactions such as  
62 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 organophosphate  
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

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

107 In 2015, the French Ministry of Health requested ANSES (French Agency for Food,  
108 Environmental and Occupational Health & Safety) to define evaluation criterion of relevance  
109 of metabolites in water intended for human consumption in order to manage non-compliances  
110 at national level. On January the 30<sup>th</sup> 2019, the final evaluation was released ([ANSES, 2019](#))  
111 allowing to evaluate metabolites relevance with a decisional tree based on (i) pesticidal  
112 activity, (ii) toxicological criterion (genotoxicity, carcinogenesis, reprotoxicity and endocrine  
113 disrupting character) and potential of transformation in DWTP into a dangerous product for  
114 human health. This evaluation is applicable to all metabolites, even those with very few  
115 toxicological data available and required extensive literature research. In absence of data for  
116 the pesticidal activity and genotoxicity of the metabolites, it is considered relevant by default.  
117 In absence of data for the other toxicological criterion, toxicity of parent molecule of the  
118 metabolites is considered to determine its relevance. Consequently, a metabolite is considered  
119 relevant for water intended to human consumption if it could cause (itself or its  
120 transformation products) a health risk unacceptable to the consumer and if it has a pesticidal  
121 activity similar to the parent molecule; limits values similar to those mentioned in Directive  
122 98/83/EC are then applicable. On the contrary, a metabolite classified as non-relevant by  
123 ANSES methodology have a unique limit value sets at 0.9 µg/L. This value was defined  
124 according to TTC approach (Threshold of Toxicological Concern; [EFSA and WHO, 2016](#)).  
125 The final method was applied to 8 metabolites, 5 of them were classified as non-relevant and  
126 methodology will be used to others molecules to complete their evaluation. ANSES approach  
127 is intended to help the health authority to manage situations where regulatory quality limits  
128 are exceeded but it does not provide a national indicative list of metabolites to be monitored  
129 as part of the sanitary control.

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

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

## 163 **Methodology**

### 164 *Context and objectives of the prioritization method*

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

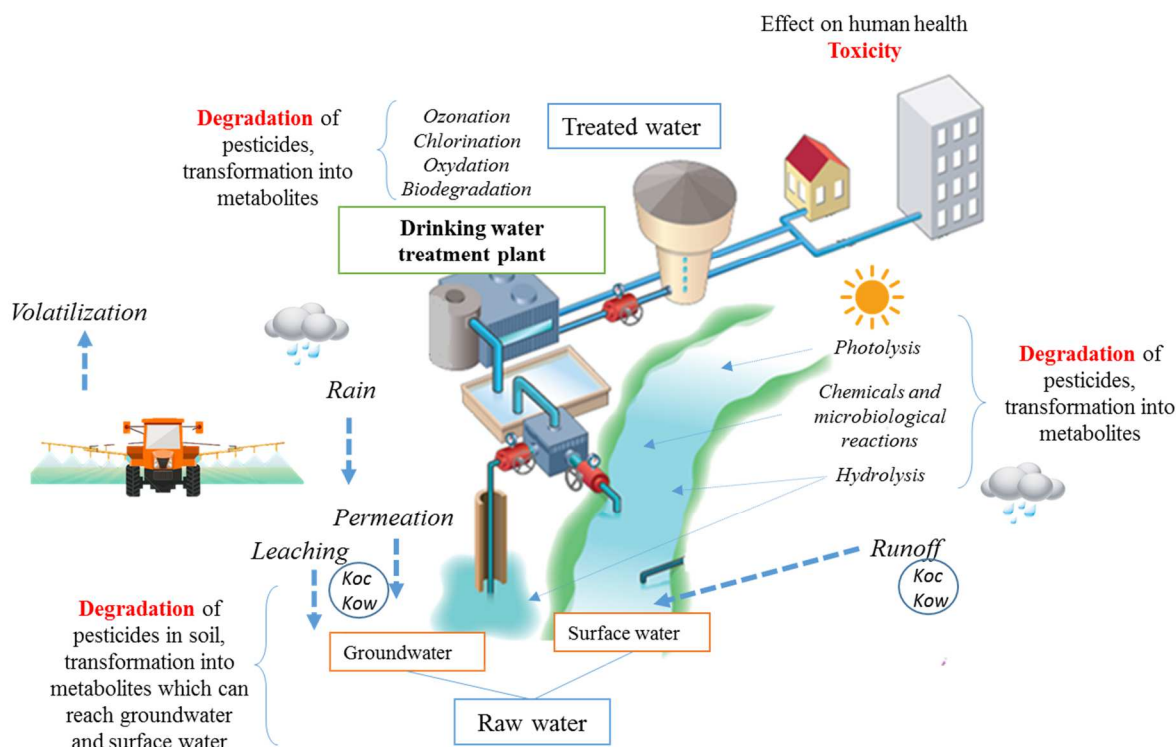
181 **(i)** The quantity of active substances sold and used in France. The assumption is that intensive  
182 use of pesticides increases contamination of water resources and exposure of humans. In such  
183 a way, Dabrowski et al. removed pesticides used in small quantities (< 1000 kg/an) from their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

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

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

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

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



204  
 205 **Fig. 1.** Fate of pesticides in drinking water resources and drinking water treatment plants  
 206



207 ***Building of the starting list***

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

221 ***Definition of criteria and scores***

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

227 **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

<b>TOXICITY</b>	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 21 <sup>st</sup> century
<b>ENVIRONMENTAL FATE</b>	Log K <sub>ow</sub> K <sub>oc</sub> (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)

228

229 The choice of each parameter and the way it has been evaluated was broadly based on  
230 recommendations from INERIS (*Institut national de l'environnement industriel et des risques*)  
231 (Dulio and Andres, 2012) and NORMAN network (NORMAN, Dulio and von der Ohe,  
232 2013). The way a score was attributed depended on the parameter considered. A binary  
233 “yes/no” approach was used for four parameters: ED effects, CMR effects, authorization of a  
234 molecule, and type of use. In the latter case, for which several “yes” answers were possible,  
235 the score was incremented with the number of “yes”. The main difference with  
236 aforementioned approaches concerns the scoring of other parameters. Regarding PNEC for  
237 instance, previous approaches used to give a grade between 0 and 1, on the basis of the PNEC  
238 value when known (PNEC ≤ 0,1 µg/l: 1; PNEC ≤ 1 µg/l: 0.75; PNEC ≤ 10 µg/l: 0.5; PNEC ≤  
239 100 µg/l: 0.25; PNEC > 100 µg/l: 0). A default value of 0.25 was given when PNEC was not  
240 available. In the present work, criteria were given a numeric value when possible and the  
241 corresponding scores were calculated by dividing each value by the maximum one. This  
242 approach has been chosen in order to accentuate the differences between low PNEC  
243 molecules and high PNEC molecules in the prioritization process (here again, a default value  
244 of 0.25 was given when PNEC was not available). Score trees summarizing how each  
245 criterion was determined are displayed in the supplementary data file SD2.

246 ***First criterion: use***

247 The use criterion was declined in three subcriteria:

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

253 (ii) Average sales BNV-D data from 2008 to 2016. BNV-D is a database created in 2009,  
254 following the introduction of fees for diffuse pollution; it references the annual sales data for  
255 phytosanitary products declared by distributors ([BNV-D, 2016](#);  
256 <http://www.data.eaufrance.fr/>). In France, used quantities range from 1 kg for fipronil to  
257 3,320,347 kg for mancozebe. A score of zero was attributed to molecules banned before 2008  
258 (86 molecules), for which no sales data could be found since sales declarations were not done  
259 at that time. A score between 0 and 1 was attributed to remaining molecules according to their  
260 average volume of use between 2008 and 2016. If a molecule has been banned during this  
261 period only the available data are averaged. The final score is calculated by dividing each  
262 values by the maximum value of the sales quantities. Mancozebe, fosetyl and prosulfocarb  
263 constitute the top 3 best-selling active substances with a score of 1; 0.6 and 0.5 respectively.  
264 Followed by toclofos-methyl and metiram with a score of 0.3 and 0.4. For the remaining  
265 molecules, scores are below 0.1. This criterion highlight mainly 5 molecules used in wide  
266 quantities compared to the others but it is well completed by the next criterion which reflect  
267 the degree of use.

268 (iii) The type of use in France, which is divided into five main categories according to  
269 phytosanitary indexes: field crops, viticulture, arboriculture, gardening and any other use  
270 (roads or public open spaces, for example). The first three are agricultural uses and represent  
271 70% of the total consumption in France. Gardening represents the domestic use of pesticides.  
272 Four phytosanitary indexes dating from 1984, 2005, 2008, and 2015 ([ACTA, Dubois et al.,](#)  
273 [1984](#); [Couteux and Lejeune, 2005 and 2008](#); [Baudet and Meunier, 2015](#)) were consulted to  
274 cover a broad period and thus take into account the oldest active substances. A molecule used  
275 in a single domain was attributed a score of 0.2 while a molecule used in two domains had a  
276 score of 0.4 and so on (increments of 0.2), up to a maximum of 1.0 for a compound used in  
277 the five categories.

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

$$281 \quad \text{use score} = (\text{authorization score} + \text{sales score} + \text{mode of use score})/3 \quad (\text{Eq. 1})$$

## 282 ***Second criterion: toxicity***

283 The toxicity criterion was declined in four subcriteria:

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

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

307 (iii) The lethal dose 50 (LD50). The LD50 value corresponds to the quantity of an active  
308 substance, administered at one time, which causes the death of 50% of a group of test animals.  
309 The LD50 is a way of measuring the short-term toxic potential (acute toxicity) of an active  
310 substance (ANSES, 2012). Acute toxicity data were found for all molecules in PPDB (PPDB,  
311 2017). Scores between 0 and 1 were attributed, inversely proportional to the LD50 value for  
312 rat. A score of 1 was assigned to the molecule with the lowest LD50 value (aldicarb).  
313 Intermediate values are obtained using the same calculation method as the one described for  
314 the ADI. Molecules that exert the lowest short-term toxic effects are benomyl, fenoxycarb and  
315 carbendazim (LD50 of 10,000 mg/kg), they were given a value of 0.

316 (iv) The endocrine disrupting character (ED). In 2012, EPA (Environmental Protection  
317 Agency) researchers have developed an Endocrine Disruptor Screening Program (EPA, 2012)  
318 to study ED effects. By definition, an endocrine disruptor is a substance or mixture that alters  
319 the functions of the endocrine system and thereby induces adverse effects on an intact  
320 organism, its offspring or within (sub) populations. By disrupting the endocrine system, these  
321 substances can alter different processes such as the production, use and storage of energy and  
322 more broadly the regulation of metabolism and development. Some of these substances may  
323 also have toxic effects on reproduction and affect fertility or development of the fetus (WHO,  
324 2002). 31 molecules are listed as ED according to the EDSP developed by the EPA. 6  
325 molecules (benomyl, phoxim, carbendazim, fenoxycarb, thiophanate-methyl, thiabendazole  
326 and thiacloprid) proven, presumed suspected to be CMR are also considered as endocrine  
327 disruptors. A molecule with ED effects was given a score of 1, otherwise (no data) 0.25.  
328 Similarly, as the CMR subcriteria, a score different of zero was attributed to molecules with  
329 no ED effects or no data released at the moment of the literature review.

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

$$331 \quad \textit{toxicity score} = (\textit{CMR score} + \textit{ADI score} + \textit{DL50 score} + \textit{ED score})/4 \quad (\textit{Eq. 2})$$

### 332 ***Third criterion: environmental fate***

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

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

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

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

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

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

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

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

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

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

$$375 \quad \text{environ. fate score} = (\text{Log } K_{ow} + K_{oc} + \text{DT50} + \text{solubility} + \text{hydrolysis} + \text{photolysis})/6 \quad (\text{Eq. 3})$$

### 376 ***Pesticides prioritization***

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

$$383 \quad \text{Final Score} = (\text{use score} + \text{toxicity score} + \text{environmental fate score})/3 \quad (\text{Eq. 4})$$

384

## 385 **Results and discussion**

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

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

402 The 50 compounds reported in **Table 2** represent 78% of the total amount of pesticides used  
403 at a national scale (total quantity of 11,507,842 kg). Among them, 16 molecules are currently  
404 banned from the French market. Monocrotophos is the oldest banned molecule (2003) while  
405 the most recent one is carbendazim (2009). In terms of toxicity, 70% of the CMR-classified  
406 compounds and 61% of the ED-classified molecules (corresponding to 26 and 31 compounds,  
407 respectively) are included in the final top 50. Molecules can have both CMR and ED effects  
408 (case of benomyl, carbendazim, phoxim, fenoxycarb, thiabendazole, thiachloprid and  
409 thiophanate-methyl) that attest of a high potential of toxicity. Among them, only phoxim is  
410 excluded from the top 50 list because it is rarely used and slightly soluble in water. LD50 and  
411 ADI were chosen to measure short-term and long-term toxicity; 29% of most acute toxic  
412 molecules and 35% of most chronic one are included in final top 50. In terms of  
413 environmental fate, all characteristics such as persistence, mobility and degradation are  
414 represented in the final top 50 list. Scores attributed for degradation potential (hydrolysis,  
415 photolysis and DT50<sub>soil</sub>) are usually related to low persistence in the environment, which  
416 suggests potential formation of abundant metabolites. These previous criterions were selected  
417 in accordance with the initial objective of the present work, more focused on metabolites than  
418 on parent molecules Nevertheless, it must be kept in mind that in some cases fast degradation  
419 of the parent molecule can lead to fast mineralization thus reducing metabolite abundance. A  
420 pesticide can also be a metabolite of another pesticide as it is the case for methomyl and  
421 carbendazim, prioritized at 8<sup>th</sup> and 48<sup>th</sup> ranks, which are metabolites of thiodicarb and  
422 benomyl/thiophanate-methyl, respectively. Some other pesticides/metabolites such as  
423 methamidophos, omethoate, clothianidin and dichlorvos were not prioritized due to their final  
424 ranking as parent molecules but as metabolites. Metabolites appear in common for several  
425 parent molecules: 3-aminophenol (formetanate and phenmedipham), carbendazim (benomyl  
426 and thiophanate-methyl), phtalic acid (phosmet and carbaryl), methylamine (carbaryl and  
427 acetamiprid), 6-chloro-nicotinic acid (acetamiprid and imidacloprid). It is to be remarked in a



428 more general way that special attention should be paid on metabolites with several origins.  
 429 Most of the time, the metabolite will be prioritized if at least one of the parent molecules has  
 430 been retained by the prioritization process. However, one could imagine a case where none of  
 431 the parent pesticides has been retained, for instance because they were individually detected  
 432 in small amounts so they obtained a very low score regarding use, but the metabolite would  
 433 deserve to be selected because the high transformation rate of parents into it and/or its specific  
 434 toxicity make it more concerning. Such a case is not so likely but cannot be fully discarded. It  
 435 is important to notice that mancozebe, thiram, maneb, ziram and fosetyl exist as strong  
 436 complexes with various metal ions, often under polymeric forms, which makes them difficult  
 437 to analyze directly because of their instability in aqueous solution and their limited solubility  
 438 in most organic solvents (Kakitani et al., 2017). These compounds are thus rarely included in  
 439 multi-residue analytical methods and were excluded from our top 50.  
 440 Consequently, 72 metabolites were prioritized considering the data relative to parent  
 441 molecules; they might be monitored in raw water and along drinking water treatments plants.  
 442 Most of them have never been included in any monitoring program in France. Indeed, in  
 443 2016, only 14 metabolites, common with our final list were monitored in raw water and only  
 444 6 were quantified at least once (methomyl, carbofuran, hydroxy-carbofuran, carbendazim,  
 445 omethoate, fipronil sulfide) (SISE-EAUX, 2016).

446

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

Parent compound	Rank	Final score	Number of metabolites <sup>a</sup>	Parent compound	Rank	Final score	Number of metabolites
Mancozebe <sup>b</sup>	1	0.8090	0	Fenoxycarb	26	0.6387	0
Thiacloprid	2	0.7573	2	Monocrotophos	27	0.6353	0
Thiram <sup>b</sup>	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

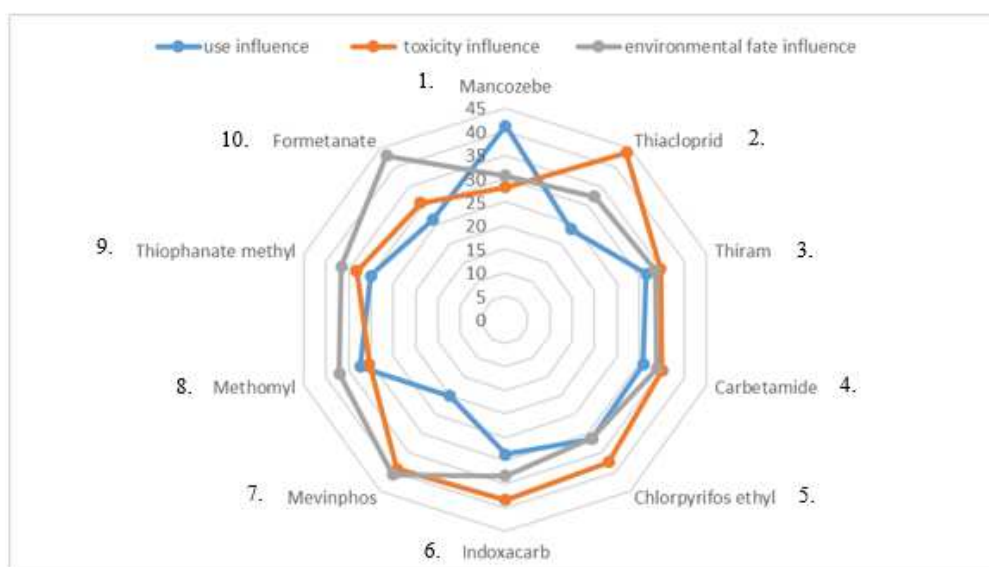
Maneb	<b>13</b>	0.6692	0	Phosmet	<b>38</b>	0.6054	5
Thiametoxam	<b>14</b>	0.6688	2	Carbofuran	<b>39</b>	0.6048	3
Malathion	<b>15</b>	0.6688	2	Ethoprophos	<b>40</b>	0.6007	0
Imidacloprid	<b>16</b>	0.6632	4	Phenmedipham	<b>41</b>	0.6002	3
Prosulfocarb	<b>17</b>	0.6579	1	Oxydementon-methyl	<b>42</b>	0.5947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

449 <sup>a</sup> Number of metabolites identified with an analytical standard

450 <sup>b</sup> Molecules with analytical difficulties

451

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



461

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

463

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

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

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

490

491 **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

492

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

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

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

513

## 514 **Conclusion**

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

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

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

537

538 **Appendix A. Supplementary data**

539

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

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

542 Supplementary data 3. Final list of prioritized metabolites

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

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

547

548

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