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Improved impact assessment of micropollutants release from WWTP

Short communication

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Highlights:

- Machine learning models were used to estimate missing characterization factors (CF).
- This allows complementing impact assessment of micropollutants release from WWTP.
- This impact resulted of a high-emitted mass or a high toxicological potential.

- 23 • It will help to select substances to work on for environmental restoration.
- 24 • It could be easily adapted to any other compartment or geographical context.

25

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27

28 **Abstract:**

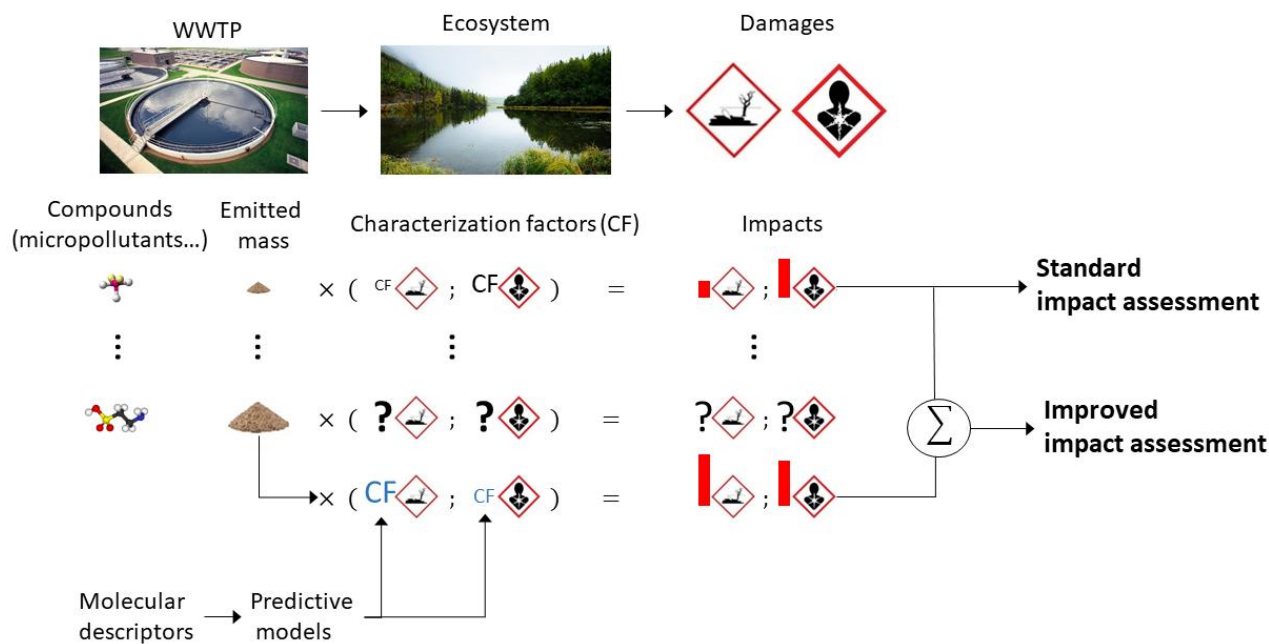
29 During wastewater treatment, incomplete elimination of micropollutants occurs..
30 Recently, the potential impacts of the release of some micropollutants at the scale of
31 France have been studied.. These impacts calculations were incomplete due to a
32 lack of characterization factors. In the present study, we used already developed
33 machine learning models to complement them. The conclusions were not modified
34 for the impact on aquatic environment, but were mitigated for the human health
35 impacts: the higher toxicological potential impact could be driven by a high-emitted
36 mass, and a high number of compounds could take a significant part of the overall
37 impact.

38

39

40

41 **Graphical Abstract:**



42

43 **Keywords:** characterization factors; (eco)-toxicity; continental freshwater; human
 44 health; Life Cycle Assessment; machine learning.

45

46 **1. Introduction**

47 For several years, the presence of organic micropollutants such as pharmaceuticals,
 48 pesticides, or Polycyclic Aromatic Hydrocarbons (PAH) in the effluents of wastewater
 49 treatment plants (WWTP) is ubiquitous and has raised increasing concerns. More
 50 than thousands of active substances are identified in wastewater and their treatment
 51 within the plants remains incomplete (Addamo et al., 2005; Aemig et al., 2021). In
 52 parallel, with increasingly accurate and efficient analytical technologies, more and
 53 more compounds are detected at low concentrations (ng.L^{-1} to $\mu\text{g.L}^{-1}$) in rivers,
 54 groundwater, surface water, and drinking water (Bayer et al., 2014). Incomplete
 55 removal and release of micropollutants into the aquatic environment represents a
 56 potential danger to human health and to the aquatic environment of continental

57 freshwater. The identification and quantification of the potential impact of toxic
58 substances induce the development of new sustainable process technologies of
59 targeted substances and represent a great challenge for the safety of aquatic
60 ecosystems (Rosenbaum et al., 2008; Zhu et al., 2015).

61 Recently, Aemig et al. (2021) identified 261 organic micropollutants in the effluents of
62 French WWTP. The toxicological and ecotoxicological impacts of 94 and 88
63 micropollutants, respectively, were quantified by multiplying the emitted mass of the
64 compound in the total volume of effluents from French WWTPs by their
65 characterization factors (Lindim et al., 2019). Characterization factors (CF) are used
66 in the Life Cycle Assessment (LCA) framework to represent the fate, the exposure,
67 the toxicity, and the ecotoxicity of compounds, addressing human toxicity and
68 freshwater ecotoxicity (Hauschild and Huijbregts, 2015). Results showed that a
69 molecule can be highly toxic for the aquatic environment without necessarily being
70 toxic for human health, and vice versa. Moreover, a high concentration does not
71 necessarily lead to a high impact, and in the same way, a molecule with a low
72 concentration can lead to a significant impact. As stated by Oldenkamp et al. (2018),
73 the CF seemed to be the most important variable to explain the potential impact of a
74 substance because the differences in terms of CF were more important than in terms
75 of mass. The authors also pointed out that there was a significant lack of toxicological
76 and ecotoxicological CF for many substances to draw conclusions. Up to now, if a CF
77 is missing for any substance, the potential impact of these substances could not be
78 estimated (*i.e.* is set equal to zero) leading to an underestimation of the potential
79 overall impacts.

80 Recently, machine learning algorithms have been used to predict hazardous
81 concentration 50% (HC50) based on 14 physicochemical characteristics (Hou et al.,

82 2020a) or on 691 more various variables (Hou et al., 2020b). Nevertheless, their
83 input variables need some experiments and could be difficult to collect. This problem
84 was tackled by Song et al. (2021) who predicted Lethal Concentration 50 (LC50)
85 based on 2000 easy-to-obtain molecular descriptors. The TEST software (U.S. EPA,
86 2020) also performs predictions of LC50, among other environmental parameters,
87 based on molecular descriptors. But their output variables are not directly the CFs
88 that are closer to the endpoints (DALY and PDF) than the HC50 or the LC50 (i.e. the
89 acute aquatic toxicity experimental threshold). More recently, Servien et al. (2021)
90 developed a modeling method based on machine learning approaches and 40 easy-
91 to-obtain molecular descriptors. This approach allowed the prediction of toxicological
92 and ecotoxicological CF in continental freshwater with an acceptable margin of error.
93 Applying these models to estimate the missing CF could bring the assessment of the
94 overall potential impacts closer to reality.

95 The objective of this study was thus to predict missing toxicological and
96 ecotoxicological factors using the machine learning models developed by Servien et
97 al. (2021). This allowed a completed assessment of the overall potential impacts (on
98 human health and on aquatic environment) of 153 organic micropollutants in
99 continental freshwater at the scale of France.

100

101 **2. Materials and Methods**

102 **2.1 Molecules**

103 Aemig et al. (2021) identified 261 organic micropollutants (released by WWTP)
104 representing a potential danger to human health and aquatic environment in
105 continental freshwater. These molecules came from (i) the Waste Framework
106 Directive (WFD, Directive 2008/105/CE), (ii) the RSDE national action for survey and

107 reduction of hazardous substances in water (INERIS, 2016), and (iii) the AMPERES
108 French project in which micropollutants (registered in the WFD and pharmaceuticals)
109 were analyzed in influents and effluents of 15 WWTP (Martin Ruel et al., 2012).
110 Among these 261 organic micropollutants, the emitted mass of 153 was estimated
111 with 90% of the measured data above the limit of quantification. The impacts of these
112 153 compounds, whose names are gathered in Table S1, are assessed in this work.

113

114 **2.2 Characterization factors**

115 Among the 153 micropollutants, Aemig et al. (2021) identified 88 compounds with
116 characterization factors for aquatic environment (CF_{ET}) and 94 compounds with
117 characterization factors for human health (CF_{HT}) for emissions in continental
118 freshwater. These impacts were complemented (for two molecules without CF_{ET} and
119 one without CF_{HT}) and updated using the USEtox[®] (Rosenbaum et al., 2008)
120 database, version 2.12 with a default landscape (to remain consistent with Servien et
121 al. (2021)). USEtox[®] is an international consensual for characterizing human and
122 ecotoxicological impacts of chemicals (UNEP-SETAC, 2019). It was developed by life
123 cycle initiative under the United Nations Environmental Programme (UNEP) and the
124 Society for Environmental Toxicology and Chemistry (SETAC) (Henderson et al.
125 2011) to produce a transparent and consensus characterization model. This model
126 gathers in one single characterization factor the chemical fate, the exposure, and the
127 effect for each of the several thousands of organic and inorganic compounds. If the
128 structure of the USEtox[®] multimedia model is always the same, to determine the CF
129 of a molecule, numerous physicochemical parameters (such as solubility,
130 hydrophobicity, degradability) and detailed toxicological and ecotoxicological data
131 must be provided. For example, EC50 values (i.e. the effective concentration at

132 which 50% of a population died) for at least three species from three different trophic
133 levels are required for the ecotoxicological effect factor.

134 To perform the calculation of the impacts of the 153 compounds, we computed 63
135 missing ecotoxicological characterization factors and 58 missing toxicological
136 characterization factors, using the machine learning models developed by Servien et
137 al. (2021). These models predict ecotoxicological or toxicological characterization
138 factors using 40 selected easy-to-obtain molecular descriptors, provided in Table S2.
139 For more details on the choice of these descriptors, the interested reader is referred
140 to Servien et al. (2014). These models are based on a comparison between global
141 and cluster-then-predict approaches with partial least squares, support vector
142 machines, and random forest. These models were compared to USEtox[®] database,
143 exhibited small differences, and were therefore considered to be comparable. The
144 best approaches were then selected for each cluster and each characterization
145 factor. To apply the cluster-then-predict approaches, the cluster of each new
146 compound needs to be estimated using a supervised clustering approach based on
147 the clusters already obtained in Servien et al. (2021). So, the cluster of each
148 compound was estimated using the well-known k-nearest neighbor approach through
149 the *knn* function of the R package *class* (Ripley, 1996). Then, the models selected in
150 Servien et al. (2021) were applied without any modification, assuming they had been
151 previously tested on a large diversity of molecules covering the diversity of the
152 compounds assessed in the present study. These previous tests have shown the
153 reliability of the models to predict CFs that are missing in USEtox[®].

154

155 **2.3 Calculation of molecular descriptors**

156 CHEM-3D of ChemOffice Ultra 12.0 (2017) molecular modeling software was used to
157 build three-dimensional chemical structures (3D-structures) in order to calculate the
158 quantum-chemical molecular descriptors (see Table S2). The Excel function of
159 ChemOffice was then used to calculate the molecular weights and the Connolly
160 surface areas. Finally, the constitutional (except the molecular weight) and the
161 topological descriptors were calculated with Dragon 7.0 (2017).

162

163 **2.4 Quantification of the potential impacts**

164 The annual volume of water effluent released into the environment by WWTP was
165 estimated to be 5.10^9 m³, in France (Aemig et al., 2021). This volume was
166 determined by multiplying the daily flow arriving at the WWTP during 365 days,
167 assuming that it was equal to the effluent. The emitted mass of micropollutants was
168 estimated by multiplying each concentration of the 153 micropollutants by the volume
169 of effluent. The mass was expressed in kilograms or tons of micropollutants
170 discharged by the WWTP effluents in one year at the national scale. The
171 concentrations and masses are those of the Supplemental Material of Aemig et al.
172 (2021) and are gathered in Tables S1 and S3. Total impacts on human health and
173 aquatic environment in continental freshwater were quantified by summing the
174 impacts of all the compounds, as it is usually done in LCA (Heijungs and Suh, 2002).
175 Human impact is expressed in DALY (Disability-Adjusted Life Years) representing the
176 number of negatively impacted human years, and the ecotoxicological impact is
177 expressed in PDF (Potentially Disappeared Fraction of species) representing the
178 potential fraction of disappeared species.

179

180 **3. Results and discussion**

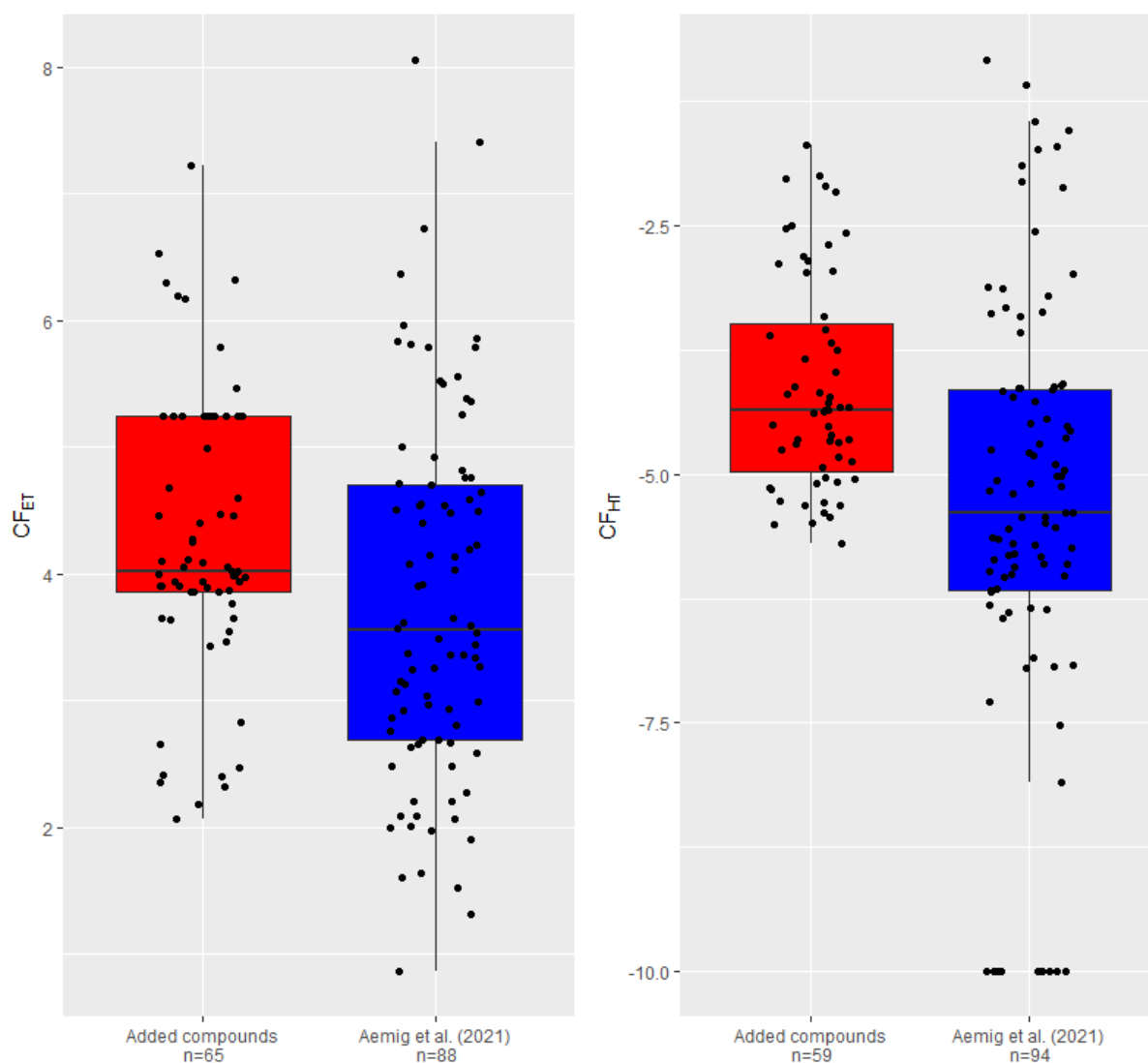
181 **3.1 Global analysis**

182 The addition of new molecules (+59 for human toxicity and +65 for ecotoxicity) more
183 than doubled the total emitted mass (from 71.1 and 64.5 tons to 147.1 tons) of
184 micropollutants released into freshwater in one year. We can notice in Table S1 that
185 valsartan (137862-53-4), dichloromethane (75-09-2), irbesartan (138402-11-6),
186 ranitidine (66357-35-5), hydrochlorothiazide (58-93-5), and AMPA (1066-51-9)
187 represent 51% of the total mass released, and less than 4% of the micropollutants
188 identified.

189 Regarding the CFs, the different values are reported in the boxplots of Figure 1. As
190 usual, the CFs are log-transformed with the addition of $1e-10$ for the CF_{HT} to avoid a
191 computational problem with $\log_{10}(0)$. $1e-10$ has been chosen to be below the
192 minimum of the USEtox database ($5e-9$).

193

194



195

196

197 **Figure 1.** Comparison of the $\log_{10}(CF_{HT}+1e-10)$ and $\log_{10}(CF_{ET})$ for the compounds
 198 taken into account in Aemig et al. (2021) and the added compounds for which the
 199 CFs are calculated using the models in Servien et al. (2021).

200

201 Figure 1 suggests that the added compounds have globally a higher CF than those of
 202 Aemig et al. (2021), but that the more extreme compounds, with the highest CF
 203 values, were already included in their study.

204 In more details, for the CF_{HT} (resp. CF_{ET}), the \log_{10} median of the value of the
 205 compounds of Aemig et al. (2021) is 1.1 \log_{10} (resp. 0.5 \log_{10}) smaller than that of the
 206 added compounds. For the CF_{HT} , the minimum, the first and third quartiles, the mean,
 207 and the median values of the compounds of Aemig et al. (2021) are all more than 0.7
 208 \log_{10} smaller than those of the added compounds. The differences are somewhat
 209 similar for the CF_{ET} . But, for both CF, the maxima were higher in the compounds of
 210 the study of Aemig et al. (2021). All these descriptive values are given in Table S4.

211

212 3.2 Impact on the aquatic environment

213 Aemig et al. (2021) showed that 99% of the total impact was induced by only 2% of
 214 the total emitted mass and 10 molecules. Thus, as a comparison with the addition of
 215 65 molecules:

- 216 • 99% of the impact is now induced by 38 molecules and 26% of the total mass,
- 217 • the 10 molecules with the highest impact represent 95% of the impact and 13%
 218 of the total mass (Table 1),
- 219 • among the 10 most impactful, four were different from the previous study
- 220 • the total impact has increased by only 10%.

221

222 **Table 1.** List of the 10 molecules with the highest aquatic environment impact. The
 223 underlined molecules were not taken into account in Aemig et al. (2021).

CAS Number	Name	Impact (%)	Emitted		CF_{ET} (PDF·m ³ ·d)	PDF
			mass (%)	mass (kg)		
52315-07-8	Cypermethrin	77,16	0,47	7,0E+02	2,5E+07	1,8E+10
50-28-2	17-beta-estradiol	4,76	0,01	9,6E+00	1,1E+08	1,1E+09

<u>154-21-2</u>	<u>Lincomycin</u>	3,97	0,31	4,5E+02	2,0E+06	9,0E+08
<u>42399-41-7</u>	<u>Diltiazem</u>	2,54	0,02	3,5E+01	1,6E+07	5,8E+08
26787-78-0	Amoxicillin	2,33	0,07	1,0E+02	5,3E+06	5,3E+08
	1,2,5,6,9,10-					
3194-55-6	Hexabromocyclododecane	1,21	0,20	3,0E+02	9,3E+05	2,7E+08
74070-46-5	Aclonifene	0,95	0,44	6,5E+02	3,3E+05	2,2E+08
<u>58-93-5</u>	<u>Hydrochlorothiazide</u>	0,88	4,64	6,8E+03	2,9E+04	2,0E+08
188425-85-6	Boscalid	0,86	0,22	3,2E+02	6,1E+05	1,9E+08
<u>66357-35-5</u>	<u>Ranitidine</u>	0,57	6,80	1,0E+04	1,3E+04	1,3E+08
Total		95.22	13.17	-	-	-

224

225 According to Aemig et al. (2021), cypermethrin accounted for 82% of the total impact.

226 In this work, the addition of the 65 compounds slightly decreased this percentage to

227 77%. If cypermethrin is not taken into account in the calculation of the total impact,

228 the first nine most impactful compounds represent 80% of the total impact and 13%

229 of the total emitted mass, highlighting that the total impact is due to only a small

230 number of molecules and a small amount of the total mass. The four molecules

231 added in the top ten are pharmaceuticals: one antibiotic (lincomycin from the

232 lincosamide class), one calcium channel blocker (diltiazem), one diuretic usually used

233 in combination with irbesartan for the treatment of hypertensive disease

234 (hydrochlorothiazide), and one acid-reflux treatment (ranitidine). For the two latter,

235 the released mass is quite high, representing near 12% of the total mass, but their

236 low CF led to a net contribution to the impact of less than 1%. As the most impactful

237 compounds (with impacts greater than 1%) represent only a very small percentage of

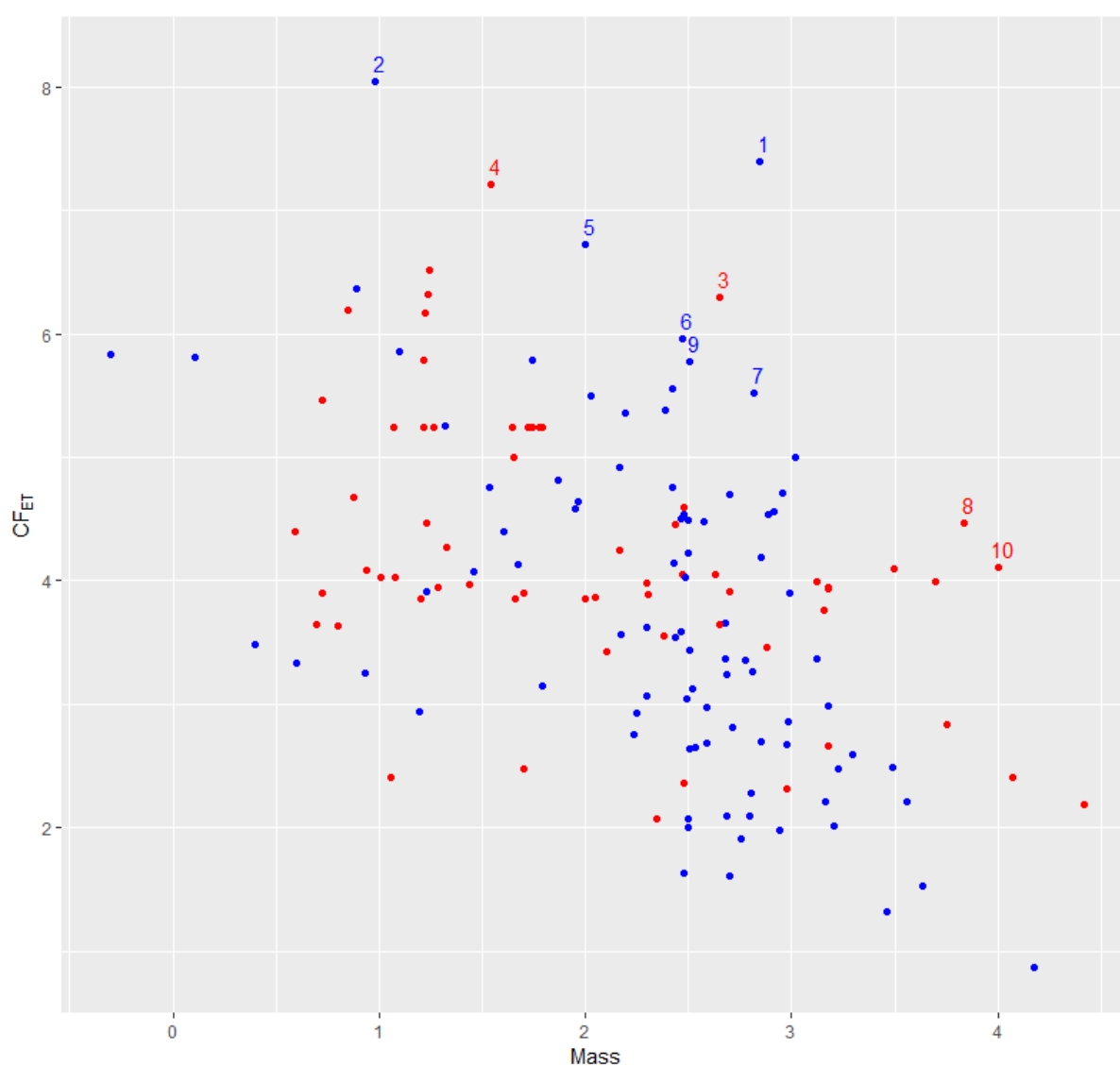
238 the total mass, the impact is mainly due to their high ecotoxicological value, given by

239 the CF_{ET} . According to Figure 1, it can be expected that the addition of a set of

240 compounds with higher CF_{ET} would increase a lot the global impacts. However, these
241 impacts are mainly due to extreme values of CF_{ET} that are not present in our new set
242 of compounds, as shown in Figure 2. We could also see that some added
243 compounds have a high mass but a too low CF_{ET} to have a significant effect on the
244 overall impact.

245

246



247

248 **Figure 2** – CF_{ET} of the 153 studied compounds as a function of the emitted mass
249 (both in log scale). Compounds of Aemig et al. (2021) are in blue, the new ones are

250 in red. The numbers represent the 10 most impactful compounds, in decreasing order
251 (*i.e.* the same order as Table 1).

252 The detailed results for all the 153 compounds can be found in Table S1.

253

254

255 **3.2 Impact on Human health**

256 As for the aquatic environment, a very important part of the total impact (94%) was
257 induced by a very small percentage of the total emitted mass (4%) and a very few
258 numbers of molecules (only eight) (Aemig et al., 2021). Thus, as a comparison, with
259 the addition of the 59 new molecules:

- 260 • 94% of the impact is now induced by 20 molecules and 33% of the total mass,
- 261 • the eight molecules with the highest impact represent 82% of the impact and 27%
262 of the total mass (Table 2),
- 263 •
- 264 • the total impact has increased of 25%.

265

266 **Table 2.** List of the 10 molecules with the highest human health impact. The
267 underlined molecules were not taken into account in Aemig et al. (2021).

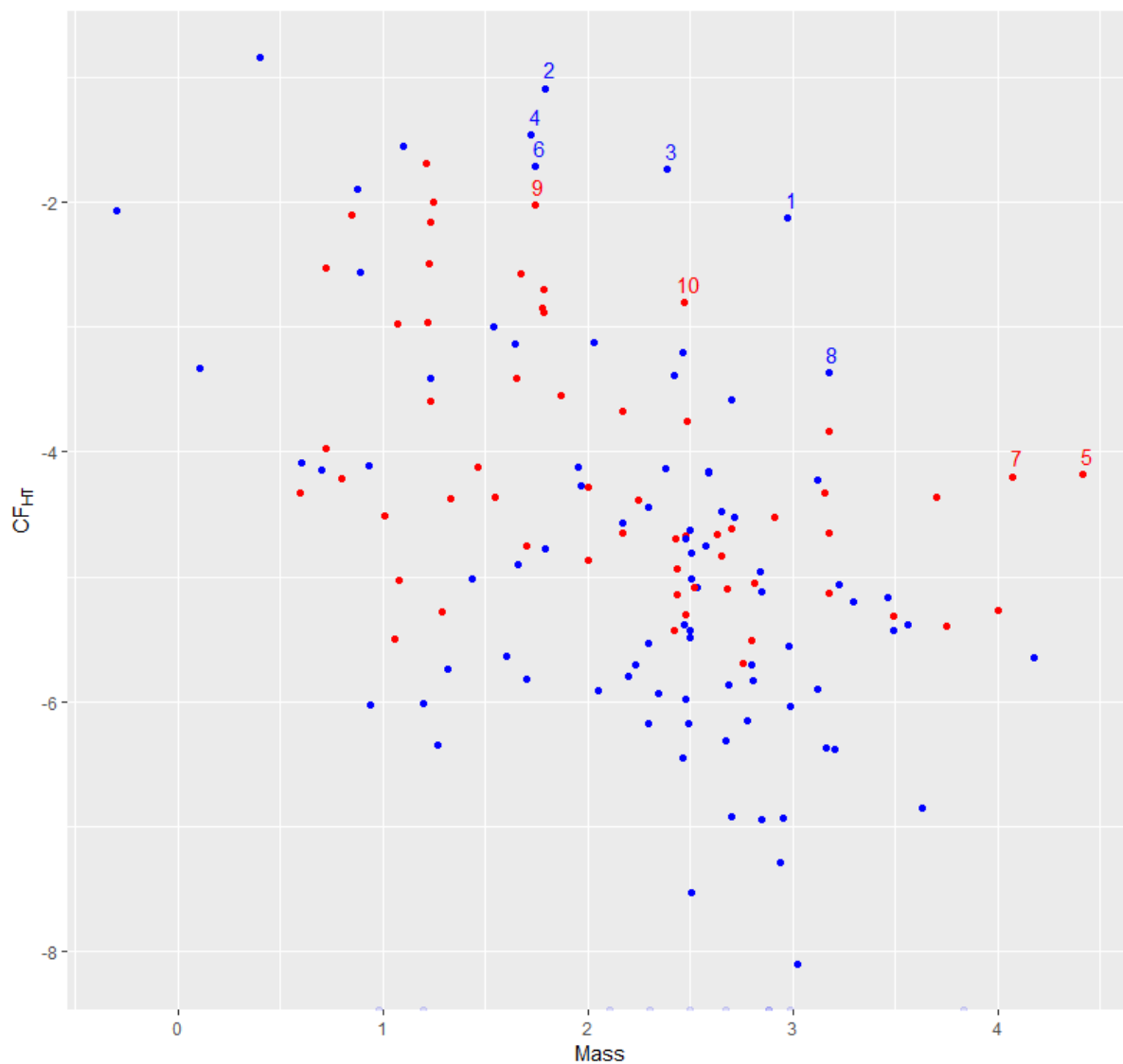
CAS Number	Name	Impact	Emitted	Emitted	CF _{HT} (DALY/kg)	DALY
		(%)	mass (%)	mass (kg)		
53-86-1	Indomethacin	25,77	0,64	9,4E+02	7,5E-03	7,06
205-99-2	Benzo(b)fluoranthene	18,34	0,04	6,2E+01	8,1E-02	5,02
115-32-2	Dicofol	16,33	0,17	2,4E+02	1,8E-02	4,47
207-08-9	Benzo(k)fluoranthene	6,67	0,04	5,3E+01	3,5E-02	1,83

<u>137862-53-4</u>	<u>Valsartan</u>	6,23	17,71	2,6E+04	6,5E-05	1,71
193-39-5	Indeno(1,2,3-cd)pyrene	3,94	0,04	5,5E+01	1,9E-02	1,08
<u>138402-11-6</u>	<u>Irbesartan</u>	2,75	8,05	1,2E+04	6,3E-05	0,75
15307-86-5	Diclofenac	2,33	1,01	1,5E+03	4,3E-04	0,64
<u>465-73-6</u>	<u>Isodrin</u>	1,88	0,04	5,5E+01	9,4E-03	0,52
	<u>1,3,5,7,9,11-</u>					
<u>25637-99-4</u>	<u>Hexabromocyclododecane</u>	1,69	0,20	3,0E+02	1,6E-03	0,46
Total		85.94	27.94			

268

269 The main conclusion of the study of Aemig et al. (2021) (only a small number of
270 molecules and a small percentage of the mass led to nearly all the impact) has now
271 to be seriously mitigated for the CF_{HT} . Depending on the compound, a high impact
272 (*i.e.* higher than 1%) could be driven by a high mass, a high CF_{HT} , or a combination
273 of both (Figure 3).

274



275
 276 **Figure 3** - CF_{HT} of the 153 compounds as a function of the emitted mass (both in log
 277 scale). Compounds of Aemig et al. (2021) are in red, the new ones are in blue. The
 278 numbers represent the 10 most impactful compounds, in decreasing order (*i.e.* the
 279 same order as Table 2). The transparent points at the bottom are the compounds
 280 with a CF_{HT} equal to zero.

281
 282 Second, the number of molecules needed to reach 94% of the total impact has been
 283 multiplied by more than two (8 to 20) highlighting a more equal distribution of the
 284 impacts among the compounds. In the ten most impactful molecules, four have been

285 added by the present study. Among these four compounds, two are anti-hypertensive
286 drugs, valsartan, and irbesartan, which contributed to the impact (Table 2) thanks to
287 their very high masses released in the environment that could be linked to their high
288 uses and low removal in WWTP (Boix et al., 2016). Two other molecules, the isodrin
289 organochlorine insecticide (present in the WFD registered list with environmental
290 quality standards and no more used in France) and the hexabromocyclododecane
291 (HBCDD) flame retardant (included in the persistent mobile toxic (PBT) substances
292 list of very high concern requiring authorization before use in EU and progressively
293 banned since 2011(ECHA, 2008)) contributed to the impact because of their high
294 toxicity, similarly to the first two PAHs (benzo(b)fluoranthene and
295 benzo(k)fluoranthene) (Table 2).

296 By conclusion, evaluating the human health impacts based only on the available
297 CF_{HT} could provide very uncompleted impacts (Table S3).

298

299 **4 Conclusion**

300 In a previous study, 261 organic micropollutants were selected to study their potential
301 impacts on human health and aquatic environment in continental freshwater at the
302 scale of France. However, the lack of data did not allow quantifying the impacts for
303 more than 1/3 of these substances (88 for aquatic environment and 94 for human
304 health). In this work, and using a new modeling approach, we were able to estimate
305 the impact of 153 organic micropollutants, *i.e.* for all with an estimated mass released
306 in the environment. These results could be used to select substances on which a
307 special effort should be made on the tertiary treatments to implement in WWTP. Also,
308 it has been shown that, depending on the substances, a high potential impact could
309 be due to a high emitted mass and/or a high characterization factor, especially for

310 human health. Using the machine learning models, any characterization factors can
311 be easily estimated from the 40 easy-to-obtain molecular descriptors. Therefore, to
312 estimate the impacts of 100% of the substances, the lack of data on the mass
313 emitted in the environment is now the only remaining limitation. It has to be
314 underlined that this whole methodology can be adapted to any other compartment
315 and any other geographical context, with predictive models still to develop.

316

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