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► To cite this version:

Rémi Servien, Kevin Bonnot, Eric Latrille, Arnaud Hélias, Dominique Patureau. Consideration of unmeasured micropollutants released from WWTP for potential impact estimations. *Science of the Total Environment*, 2023, pp.166313. 10.1016/j.scitotenv.2023.166313 . hal-03952680v3

HAL Id: hal-03952680

<https://hal.science/hal-03952680v3>

Submitted on 21 Aug 2023

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1 **Consideration of unmeasured micropollutants**

2 **released from WWTP for potential impact**

3 **estimations**

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14
15 **Abstract:** During wastewater treatment, micropollutants are only partly eliminated and
16 may present a risk for human health and aquatic ecosystems. The potential impacts
17 these substances may have are currently underestimated due to the lack in available
18 concentrations that lie below the limit of quantification (LOQ) for an important set of
19 micropollutants. Here, the potential impacts due to 261 organic micropollutants on
20 human health and aquatic environments were investigated at the scale of France. Even
21 with concentrations below the LOQ, certain micropollutants were found to have a

22 significant potential impact. For unmeasured concentrations, a global concentration
23 distribution built from several datasets with different LOQ was used. By disregarding
24 the unmeasured micropollutants, the potential impacts have been underestimated by
25 more than 300% on both human health and aquatic environments. Certain substances,
26 such as hydrazine, endrin, or 2,3,7,8-TetraCDD, could lead to very strong potential
27 impacts, even with unmeasured concentration levels. Moreover, the usual convention
28 of LOQ/2 to replace unmeasured concentrations also appeared to overestimate the
29 potential impact. The present work can be adapted to any other compartment or
30 geographical context.

31

32 **Keywords:** characterization factors; limit of quantification; (eco)-toxicity; continental
33 freshwater; human health; Life Cycle Assessment.

34

35 **Highlights:**

- 36 • Potential impacts for micropollutants with concentrations below LOQ are
37 derived.
- 38 • Some micropollutants can have a significant impact with an unmeasured
39 concentration.
- 40 • Ignoring the unmeasured substances leads to a strong underestimation of the
41 impacts.
- 42 • This could contribute to the prioritization of unmeasured micropollutants.
- 43 • The more robust value to impute the missing concentrations seems to be
44 LOQ/3.

45

46 **1. Introduction**

47 Thanks to the implementation of the Water Framework Directive (Directive
48 2008/105/CE, 2008), many European countries have launched organic micropollutant
49 monitoring campaigns, either in the effluents of urban and industrial wastewater
50 treatment plants (WWTP) or in the receiving rivers. Indeed, many articles refer to the
51 quantification of thousands of compounds including pharmaceutical products,
52 hormones, pesticides, hydrocarbons, and solvents in treated wastewater, thus
53 indicating the incomplete removal capacity of conventional treatments (Addamo et al.,
54 2005; Bisognin et al., 2021; Yao et al., 2021).

55 Furthermore, thanks to increasingly accurate and efficient analytical technologies
56 more and more low concentration compounds can be detected (from ng.L^{-1} to $\mu\text{g.L}^{-1}$)
57 in rivers, groundwater, surface water, and drinking water (Bayer et al., 2014; Kiefer et
58 al., 2019; Muter et al., 2020; Postigo et al., 2021). The incomplete removal and release
59 of micropollutants into aquatic environments lead to a potential danger for human
60 health and the aquatic environments of continental freshwater systems. To ensure the
61 identification and quantification of the potential impacts of toxic substances, the
62 development of novel sustainable process technologies for targeted substances has
63 become crucial. This ambitious challenge would thus contribute to the safety of aquatic
64 ecosystems (Rosenbaum et al., 2007; Zhu et al., 2015).

65 Recently, Aemig et al. (2021) identified 261 organic micropollutants in the effluents of
66 French WWTP. The toxicological and ecotoxicological potential impacts of 94 and 88
67 micropollutants respectively, were quantified by multiplying the emitted mass of the
68 compound in the total volume of effluents from French WWTPs by their
69 characterization factors (CFs) (Fantke et al., 2018) as is usually carried out in Life
70 Cycle Assessment (LCA) frameworks. Some compounds could not be assessed
71 because they had no known concentration or because their CFs were unavailable.

72 Servien et al. (2022a) developed a method based on machine learning approaches
73 and 40 easy-to-obtain molecular descriptors to predict missing CFs. Thanks to this
74 model, toxicological and ecotoxicological CFs in continental freshwater could be
75 predicted, within an acceptable margin of error. An upgraded assessment could then
76 be made for the overall potential impacts (on human health and aquatic environments)
77 of 153 organic micropollutants in continental freshwaters at the scale of France. As
78 usually observed (Marlatt et al., 2022), results demonstrated that a molecule could be
79 highly hazardous for aquatic environments without necessarily representing an issue
80 for human health, and *vice versa*. Moreover, a high potential impact could be driven by
81 a high CF, a high mass, or a combination of both. As machine learning models now
82 allow for the prediction of the CF of any new compound, the missing concentrations
83 represent the only obstacle for a complete potential impact estimation. Nevertheless,
84 building models based on easy-to-obtain inputs does not seem to be easily attainable
85 for compounds with missing concentrations and the lack of data for some
86 micropollutants has currently become an acknowledged issue (Leenhardt et al., 2022).
87 Cantoni et al. (2020) tackled this problem by comparing several statistical methods to
88 estimate concentrations below the LOQ. Their work is promising but was limited to a
89 small number of micropollutants and could not be applied to compounds with no value
90 above the LOQ. By omitting to consider micropollutants with a high number of
91 concentrations below the LOQ within the potential impact estimations, their potential
92 impact would be equivalent to zero, which obviously implies a strong underestimation
93 of the potential impacts. Consequently, the objective of this work was to investigate the
94 potential impacts of micropollutants for which no measured concentrations were
95 available or for which more than 90% of the measurements were below the limit of
96 quantification (LOQ) threshold, including those with no measurement greater than the

97 LOQ. Considering those unmeasured micropollutants in the potential impact
98 assessment is the major novelty of this study as they are usually not taken into account
99 whatever their CFs. In this aim, an estimation procedure was developed and is detailed
100 in the following section. A complete assessment of the individual potential impacts (on
101 human health and aquatic environments) can thus be made for each organic
102 micropollutant of interest in continental freshwaters at the scale of France.

103

104

105 **2. Materials and Methods**

106 **2.1 Molecules**

107 Aemig et al. (2021) identified 261 organic micropollutants that present a potential
108 danger for human health and aquatic environments in continental freshwaters. The
109 choice for these molecules was initiated by (i) the Water Framework Directive (WFD,
110 Directive 2008/105/CE, 2008), (ii) the national action for the survey and reduction of
111 hazardous substances in water (called RSDE) (INERIS, 2016), and (iii) the AMPERES
112 French project in which micropollutants (registered in the WFD and pharmaceuticals)
113 were analysed in influents and effluents of 15 WWTP (Martin Ruel et al., 2016). Among
114 these 261 organic micropollutants, 153 emitted compounds were estimated from at
115 least ten measuring sites and from 90% of the measured data above the limit of
116 quantification. The potential impacts of these 153 compounds were assessed by
117 Aemig et al. (2021) for those present in the USEtox[®] database (Rosenbaum et al.,
118 2007) and by Servien et al. (2022a) for the compounds that are not present in this latter
119 database.

120

121 **2.2 Characterization factors**

122 Among the remaining 108 compounds, 58 have a CF for ecotoxicological potential
123 impacts (CF_{ET}) and 43 a CF for human potential impacts (CF_{HT}) in the USEtox[®]
124 database version 2.12 with a default landscape (to remain consistent with Servien et
125 al. (2022a,b)). USEtox[®] is an international consensus for characterizing the human and
126 ecotoxicological potential impacts of chemicals (UNEP-SETAC, 2019). It was
127 developed by the life cycle initiative under the United Nations Environmental
128 Programme (UNEP) and the Society for Environmental Toxicology and Chemistry
129 (SETAC) (Henderson et al., 2011) to produce a transparent and unanimous
130 characterization model. Within a single characterization factor, this model assembles
131 the chemical fate, exposure and effect for each of the several thousands of organic
132 and inorganic compounds. While the structure of the USEtox[®] multimedia model is
133 always the same, the CF of a molecule can be established using numerous
134 physicochemical parameters (such as solubility, hydrophobicity, degradability) and
135 detailed toxicological and ecotoxicological data must be provided. In detail, CFs were
136 calculated in the USEtox database via the following formula: $CF = FF \times XF \times EF$. FF
137 was the fate factor indicating the residence time in the environment and was estimated
138 with physicochemical properties for organic micropollutants or speciation for inorganic
139 micropollutants. XF was the exposure factor i.e. the fraction of micropollutants in the
140 environment that was available for organisms. EF was the effect factor corresponding
141 to the effect on the aquatic environment (considering three trophic levels) or the effect
142 on Human health. For human toxicity CFs, USEtox calculated the intake fraction (iF)
143 i.e. the amount of micropollutants absorbed through air, water, and food after release
144 into the freshwater compartment. iF was equal to $XF \times FF$. LCA tool was preferred to
145 approaches such as Toxic Unit or Risk Quotient because both the potential impacts of

146 each micropollutant and the overall potential impact of the mixture had to be
147 estimated.

148 The remaining CFs were computed using machine learning models developed by
149 Servien et al. (2022a). These models predict ecotoxicological or toxicological
150 characterization factors using 40 selected easy-to-obtain molecular descriptors (see
151 the list in Table S1). For further details concerning the choice and calculation of these
152 descriptors, the reader can refer to Servien et al. (2014). These models are based on
153 a comparison between different linear or non-linear (machine learning) models and,
154 according to a cluster-then-predict approach, could be either global or local. The
155 modelled CFs were compared to USEtox[®] database values. The differences between
156 the modelled CFs and the USEtox[®] CFs were minor, therefore the models were
157 considered to be applicable. The best approaches were then selected for each cluster
158 and each characterization factor. To apply the cluster-then-predict approaches, the
159 cluster of each new compound needed to be estimated using a supervised clustering
160 approach based on clusters previously obtained by Servien et al. (2022a). This was
161 applied using the well-known k-nearest neighbour approach through the *knn* function
162 of the R package *class* (Ripley, 1996). The models selected by Servien et al. (2022a)
163 were then applied without any modification, with the assumption that they had been
164 previously tested on a large diversity of molecules covering the diversity of the
165 compounds assessed in the present study. These previous tests have proven the
166 reliability of the models to predict the CFs missing in USEtox[®].

167 It is noteworthy that the tributylstannanylium (CAS 36643-28-4) contains an atom of
168 tin. Consequently, its molecular descriptors, thus its CFs, cannot be computed by the
169 above-mentioned methods. In addition, chloroalkanes C10-13 (CAS 85535-84-8) were

170 also excluded, since they compose a mixture of different molecular structures that can
171 lead to varying molecular descriptors and CFs.

172 The 106 corresponding characterization factors have been compiled in Table S2. A
173 schematic of the whole study is summarized in Figure S1, available in the
174 Supplementary Material.

175

176

177

178 **2.3 Quantification of significant potential impacts**

179 The annual volume of water effluent released into the environment by WWTP in France
180 was estimated to be 5.10^9 m³ (Aemig et al., 2021). This volume was computed by
181 multiplying the daily flow arriving at the WWTP by 365 days, and by assuming that it
182 was equal to the effluent. The emitted mass of micropollutants was calculated by
183 multiplying each concentration of micropollutants, when available, by the volume of the
184 effluent. The concentrations and masses were obtained from the Supplementary
185 Material in Aemig et al. (2021) and are compiled in Table S3. Total potential impacts
186 on human health and aquatic environments in continental freshwaters were quantified
187 by summing the potential impacts of all the compounds, as is usually performed in LCA
188 (Heijungs and Suh, 2002).

189 As explained above, insufficient data were available for the remaining 106
190 micropollutants in order to correctly estimate their concentrations. Therefore, the risk
191 threshold concentration for these compounds was calculated to reach 1% of the total
192 sum of potential impacts obtained previously for the 153 micropollutants considered in
193 Servien et al. (2022b). Note that this 1% threshold is obviously arbitrary and fully
194 depends upon the compound selection that was performed in the study. Nevertheless,

195 this methodology could easily be adapted to any chosen threshold, any selection of
196 compounds (even containing transformation products), and any compartment of
197 interest. It could also be applied to other endpoints that are based on measured
198 concentrations such as risk quotients. When the LOQ of a micropollutant was available,
199 this risk threshold concentration was also expressed in terms of the percentage of the
200 LOQ to be comparable among different micropollutants. For 42 compounds, no data
201 (no measurements or LOQ) were available, resulting in the expression of the risk
202 threshold concentration in $\mu\text{g}\cdot\text{L}^{-1}$. Obviously, since the potential impacts are linearly
203 related to the estimated concentration, a measured concentration defined by the risk
204 threshold concentration multiplied by a constant k would lead to corresponding
205 potential impacts defined by $k\%$ of the total sum of the previously calculated potential
206 impacts.

207

208 **2.4 Estimation of values below the LOQ**

209

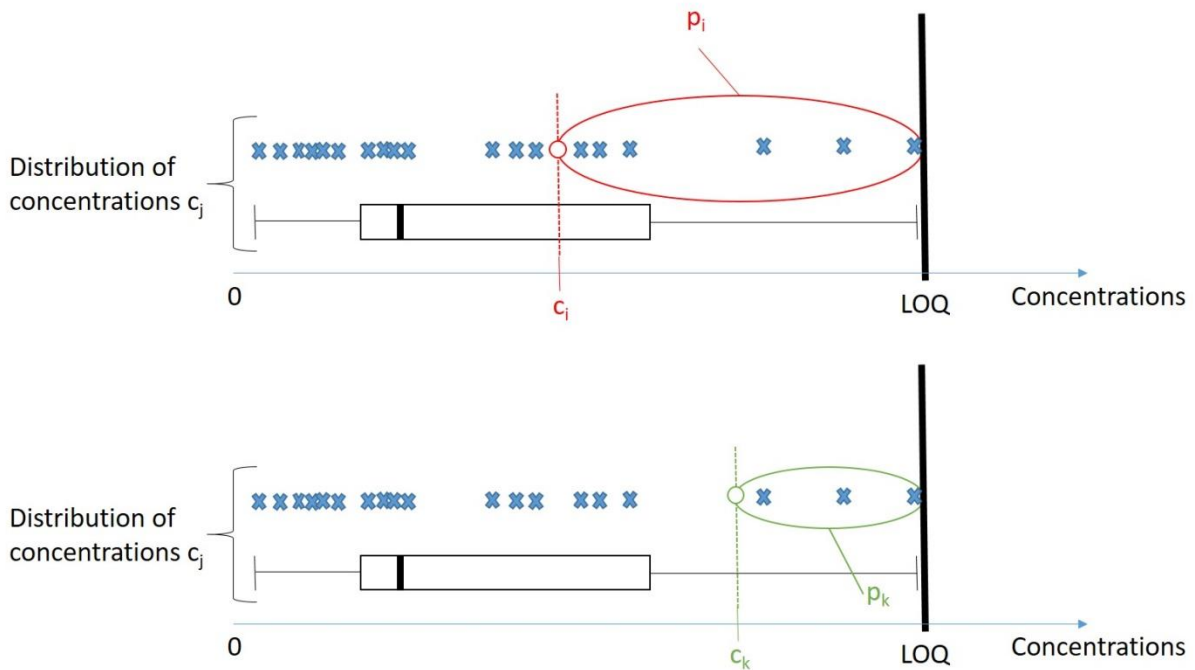
210 According to Table S3, for these 106 micropollutants, a very high amount (more than
211 90%) of the values were below the LOQ of the corresponding study. As usually applied
212 in environmental studies, data values lower than the LOQ are usually estimated as half
213 the quantification limit (INERIS, 2016). This very strong assumption could have a major
214 impact on the estimated concentration (and thus the potential impact) when there are
215 many concentrations below LOQ. It would be advantageous to test this strong
216 assumption.

217 In the RSDE samples, as the compounds are measured using routine methods, most
218 of the LOQ are quite high. This is not always the case for the other sources of quantified
219 concentrations. Therefore, certain concentration values that lie below the LOQ of the

220 main dataset of the study, i.e. the RSDE LOQ, were obtained from other sources.
221 These values relative to the RSDE LOQ for all compounds could then be scaled in
222 order to have a sufficient number of measured concentrations lying below the RSDE
223 LOQ. This provided a dataset of 141 samples with concentrations denoted $(c_j)_{1 \leq j \leq 141}$
224 issued from 25 different compounds. The distribution of these samples was then used
225 for computing the probability that the risk threshold concentration c_i of compound i had
226 been reached in case of quantification below the LOQ. This probability p_i was
227 computed as the number of measurements above the corresponding risk threshold
228 concentration c_i divided by the total number of measurements (i.e. 141): $p_i =$
229 $\frac{\sum_{j=1}^{141} \mathbb{1}(c_i < c_j)}{141}$ and is detailed in the following Figure 1. In other terms, when the risk
230 threshold concentration c_i is close to the LOQ, the probability to get a value above c_i
231 is low.

232

233



234

235 **Figure 1:** Summary of the computation of the probability to reach a risk threshold
 236 concentration. The RSDE LOQ is represented by a large black line whereas the
 237 distribution of concentrations $(c_j)_{1 \leq j \leq 141}$ provided by other sources is represented by
 238 blue crosses and their corresponding boxplot. On the top subfigure, a risk threshold
 239 concentration c_i is estimated for a new compound i this results in the corresponding
 240 p_i , calculated by counting all concentrations $c_j > c_i$. On the bottom subfigure, another
 241 risk threshold concentration c_k is estimated for another compound k , with $c_k > c_i$.
 242 Obviously, the probability p_k that the risk threshold concentration for the compound k
 243 would be attained is below p_i .

244

245 Note that if a sample that was not obtained from RSDE has a measured concentration
 246 lower than its LOQ (and, thus, lower than the RSDE LOQ), it would not be taken into
 247 account. Therefore the final distribution will probably be only slightly overestimated.
 248 Indeed, if these unknown measurements relying on different relative LOQ values were

249 taken into account, they would add many uncertainties to the following LOQ distribution
250 calculations.

251

252 **2.5 Calculation of the total potential impacts**

253

254 As usually performed in LCA, the total potential impacts on human health and aquatic
255 environments in continental freshwaters were quantified by summing the potential
256 impacts of all the compounds. Human potential impact is expressed in DALY
257 representing the number of negatively impacted human years, and the ecotoxicological
258 potential impact is expressed in PDF representing the potential fraction of disappeared
259 species. In order to compute these potential impacts, values below the LOQ were
260 imputed by the median values below the LOQ for all compounds (see Figure 2), namely
261 $LOQ/3$. For compounds without a LOQ, the median value of the LOQ, namely 0.05
262 $\mu\text{g.L}^{-1}$, was used.

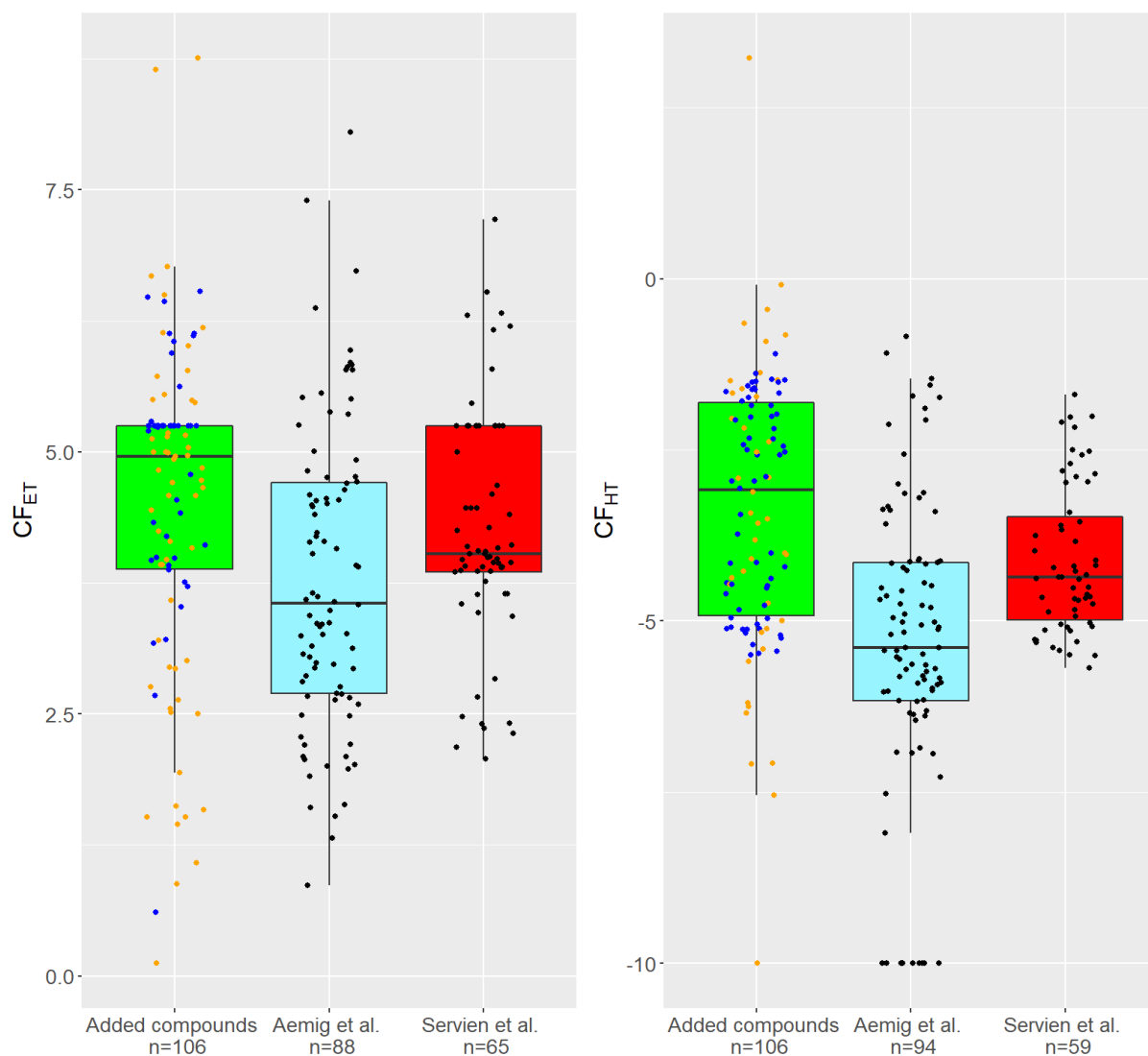
263

264 **3. Results and discussion**

265 **3.1 Global analysis of characterization factors**

266 Regarding the CFs, the different values were reported in the boxplots of Figure 2
267 below. As usual, the CFs are log-transformed with the addition of $1\text{e-}10$ for the CF_{HT}
268 in order to avoid a computational issue with $\log_{10}(0)$. $1\text{e-}10$ was chosen to be less than
269 the minimum of the USEtox[®] database ($5\text{e-}9$).

270



271

272

273

274 **Figure 2.** Comparison between the CF_{HT} and CF_{ET} (both in \log_{10} scales), for the
 275 previously investigated and for the added compounds. For the added compounds, the
 276 CFs in orange originated from USEtox[®] whereas those in blue were computed using
 277 Servien et al. (2022a).

278

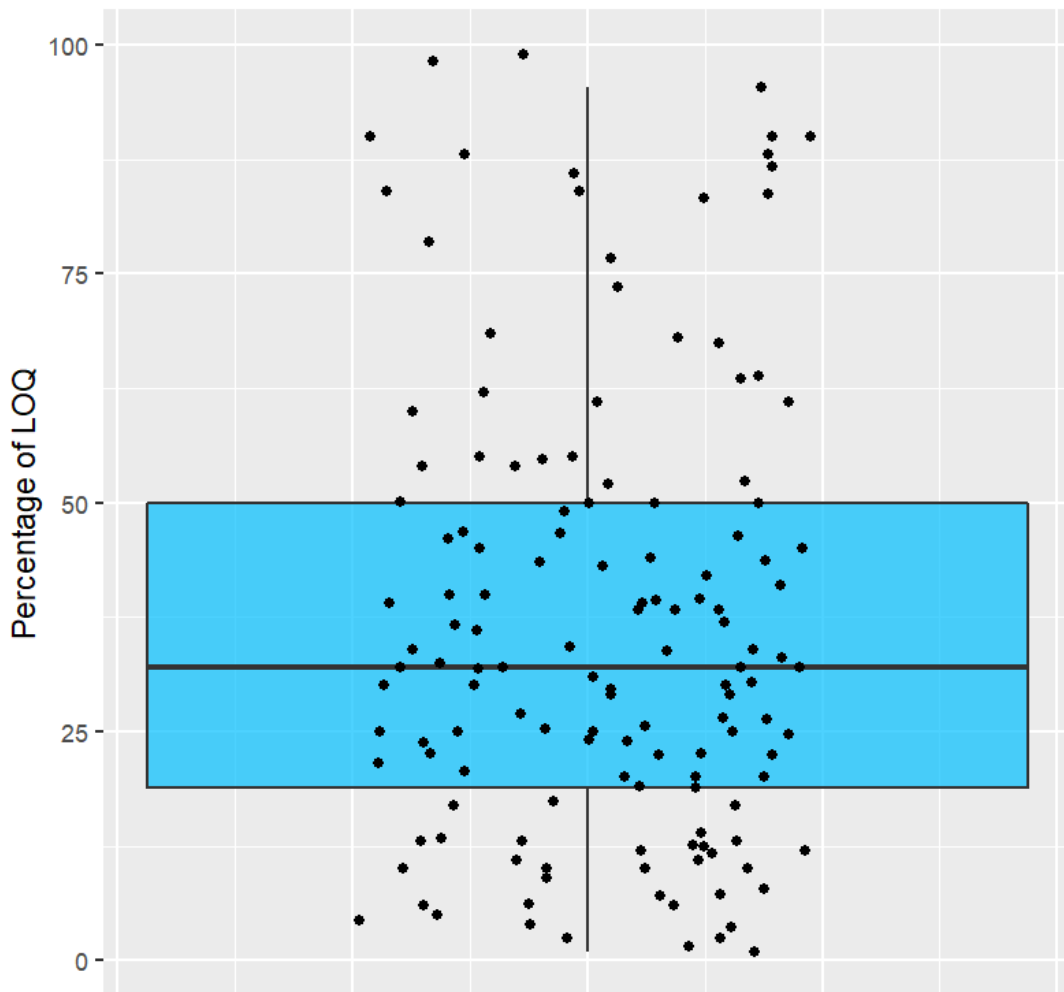
279 Figure 2 points out that the added compounds globally presented a higher CF than
 280 those already included in previous studies. More specifically, for the CF_{HT} and CF_{ET} ,

281 the maximum, the 1st and 3rd quartile, the median and the mean of the added
282 compounds lay above those of the previously studied compounds. However, there
283 were also very low CF values that were significantly lower than those from previous
284 studies. All the descriptive values are provided in Table S4. Extremely high values
285 were also observed for certain compounds already included in USEtox[®]. For the CF_{ET},
286 these two strong values concerned the 1,2,3,7,8-PentaCDD (CAS 40321-76-4) and
287 the 2,3,7,8-TetraCDF (CAS 51207-31-9) from the polychlorodibenzodioxin/furane
288 family. Their extreme values could lead to significant potential impacts if their
289 concentrations were not too low. For the CF_{HT}, the extreme value concerns the 2,3,7,8-
290 TetraCDD (CAS 1746-01-6). This is the only value within the whole USEtox[®] database
291 that is log-positive for this variable. Nevertheless, the estimation of the available CF_{HT}
292 in the environmental footprint database (Fazio et al., 2018) also seems to corroborate
293 this very high value. This dioxin is a well-studied and recognized endocrine disrupter
294 presenting a highest affinity for the aryl hydrocarbon receptor (AhR), a cytosolic protein
295 present in most vertebrate tissues, that mediates the toxic and biological effects of
296 such compounds (Van den Berg et al., 2006). Its very high CF_{ET} and CF_{HT} are related
297 to its high endocrine-disrupting potency. If this compound were not considered, five
298 others present a CF_{HT} above the maximal value already included in previous studies.
299 These compounds are all pesticides: chlordane (CAS 57-74-9), 1,1-bis(4-
300 Chlorophenyl)-2,2-Dichloroethane (CAS 72-54-8), dieldrin (CAS 60-57-1), heptachlor
301 epoxide (CAS 1024-57-3) and toxaphene (CAS 8001-35-2).

302

303 **3.2 Estimation of concentrations below the LOQ**

304 The following Figure 3 illustrates the distribution of the measured concentrations from
305 other sources and that lie below the RSDE LOQ.



306

307 **Figure 3:** Boxplot of the 141 measured concentrations below the RSDE LOQ on
 308 another dataset with lower LOQ (expressed in % of the RSDE LOQ).

309 The median (as well as the mean) value of this distribution seems to be close to $LOQ/3$,
 310 and not $LOQ/2$ as generally used in calculations when data are below the LOQ.
 311 Furthermore, since the concentration values below the smaller LOQ were not taken
 312 into account, $LOQ/3$ might even probably be an overestimation, when faced with a
 313 value below LOQ in the RSDE dataset. This is also confirmed by the conclusions of
 314 Cantoni et al. (2020) where the LOQ and $LOQ/2$ are found to be overestimations.

315

316 **3.3 Potential impact on the aquatic environment**

317 For the aquatic environment, all the 64 risk threshold concentrations that could be
 318 expressed in percentages of LOQ have been compiled in Table S5 and the smallest
 319 (i.e. below the LOQ) are reported in Table 1. These 64 compounds remain after the 42
 320 compounds with no data at all are subtracted from the 106 that do not have sufficient
 321 data for deriving an above-mentioned concentration.

322 **Table 1** – Estimation of the concentrations needed to reach 1% of the sum of the
 323 potential impacts on ecotoxicity, when the risk threshold concentration is below the
 324 RSDE LOQ. Computed using the distribution of subsection 3.2, it represents the
 325 assumption that a measurement below the LOQ is above the risk threshold
 326 concentration. The results for all compounds are compiled in Table S5.

CAS number	Name	Risk threshold concentration ($\mu\text{g}\cdot\text{L}^{-1}$)	Risk threshold concentration (% of RSDE LOQ)	Probability
302-01-2	Hydrazine	4.0E+00	4%	0.96
72-20-8	Endrin	1.0E-02	19%	0.75
143-50-0	Chlordecone	9.0E-02	46%	0.29
2921-88-2	Chlorpyrifos	2.0E-02	88%	0.04

327

328 There are only 4 compounds for which a concentration below the LOQ might still cause
 329 a significant potential impact on ecotoxicity and for 2 of them, the risk threshold
 330 concentration also lies below LOQ/3. For the 60 other compounds, the risk threshold
 331 concentration being above the LOQ and the measured concentration being frequently
 332 below, their contribution to the environmental potential impact could be considered as
 333 very low. For hydrazine, a very small concentration of only 4% of the RSDE LOQ, with
 334 a high probability of occurrence, would lead to a significant potential impact. Hydrazine
 335 and its derivatives are widely used compounds in chemical industries and
 336 pharmaceuticals (propellant, blowing agent, pesticide, antituberculosis, etc.). It is a
 337 very small molecule (32 g/mol), very soluble and volatile. No bioconcentration factor
 338 (BCF) has been found in the literature, nor degradation half-life (DT50). It was

339 classified by US EPA as a human carcinogen (group B2): an intermediate inhalation
340 minimal risk level of 4 µg/L was calculated and a minimum limit for cancer was fixed at
341 10 µg/L (Qi et al., 2020). The risk threshold concentration was found to be 4 µg/L and
342 is largely below the RSDE LOQ, which is very high (100 µg/L) by comparison to that
343 of endrin (0.052 µg/L) as well as RSDE LOQ of other compounds. However, very
344 recent papers refer to the development of spectroscopic methods and sensors to
345 analyse hydrazine in environmental samples including water up to pico-molar levels
346 (0.03 to 3.2 µg/L, Arulraj et al., 2015; Qi et al., 2020). Yet, no data have been provided
347 in real water samples.

348 Due to their hydrophobicity, the three pesticides are usually quantified in solid matrices
349 such as soil, sediment, and biota. However, concentrations of endrin have also been
350 reported in river water between 0.17 and 484 ng/L (Matsumo et al., 2009) and
351 concentrations of chlorpyrifos between 1 and 32 ng/L (Wan et al., 2021). Their
352 presence in such an environment is mainly due to their use in agriculture. They are
353 also targeted by the WFD. The Environmental Quality Standard (EQS) (yearly average
354 value) for the sum of the 4 cyclodiene pesticides in the WFD (aldrin, isodrin, endrin,
355 dieldrin) is 10 ng/L (inner surface water) and 5 ng/L (other water). For chlorpyrifos, the
356 EQS is 30 ng/L. The three calculated risk threshold concentrations to reach 1% of the
357 sum of the potential impacts lie within the same range as these environmental and
358 regulatory values.

359 The compounds lacking information on LOQ are gathered in the following Table 2.

360

361 **Table 2.** Risk threshold concentrations for each compound to reach 1% of the sum of
362 the potential impacts on ecotoxicity. The compounds in this table do not have any
363 measurement or LOQ.

CAS number	Name	Risk threshold concentration ($\mu\text{g}\cdot\text{L}^{-1}$)
40321-76-4	1,2,3,7,8-P5CDD	9.62E-05
51207-31-9	2,3,7,8-T4CDF	1.23E-04
1746-01-6	2,3,7,8-T4CDD	1.16E-02
57653-85-7	1,2,3,6,7,8-H6CDD	3.61E-02
72-54-8	DDD 44'	4.04E-02
28159-98-0	Cybutryne	5.31E-02
72-55-9	DDE 44'	1.56E-01
19408-74-3	1,2,3,7,8,9-H6CDD	3.08E-01
39227-28-6	1,2,3,4,7,8-H6CDD	3.08E-01
57117-44-9	1,2,3,6,7,8-H6CDF	3.08E-01
70648-26-9	1,2,3,4,7,8-H6CDF	3.08E-01
72918-21-9	1,2,3,7,8,9-H6CDF	3.08E-01
57117-41-6	1,2,3,7,8-P5CDF	3.09E-01
3268-87-9	1,2,3,4,6,7,8,9-O8CDD	3.10E-01
35822-46-9	1,2,3,4,6,7,8-H7CDD	3.10E-01
39001-02-0	1,2,3,4,6,7,8,9-O8CDF	3.10E-01
446255-20-5	Heptabromodiphenylethers	3.10E-01
55673-89-7	1,2,3,4,7,8,9-H7CDF	3.10E-01
57117-31-4	2,3,4,7,8-P5CDF	3.10E-01
60851-34-5	2,3,4,6,7,8-H6CDF	3.10E-01
67562-39-4	1,2,3,4,6,7,8-H7CDF	3.10E-01
789-02-6	DDT 24'	5.58E-01
2032-65-7	Methiocarb	6.08E-01
25167-83-3	Tetrachlorophenols	6.50E-01
131860-33-8	Azoxystrobin	1.43E+00
139968-49-3	Metaflumizone	1.59E+00
118-79-6	2,4,6-tribromophenol	1.98E+00
564-25-0	Doxycycline	2.11E+00
153719-23-4	Thiamethoxam	2.61E+00
111988-49-9	Thiacloprid	4.24E+00
2303-17-5	Triallate	5.88E+00
21312-10-7	Acetyl sulfamethoxazole	6.67E+00
5466-77-3	Octinoxate	7.36E+00
615-58-7	2,4-dibromophenol	9.62E+00
135410-20-7	Acetamiprid	1.05E+01
210880-92-5	Clothianidin	1.65E+01
14297-93-9	4-epi-chlortetracycline	3.37E+01
25167-80-0	Monochlorophenol	3.67E+01
25167-82-2	Trichlorophenols	5.41E+01
128-37-0	Butylhydroxytoluene	6.19E+01
57-62-5	Chlortetracycline	1.27E+02
95-56-7	2-bromophenol	1.55E+02

365 For these compounds, only the risk threshold concentration with the usual unit ($\mu\text{g}\cdot\text{L}^{-1}$)
366 is available. Although this leads to results that are more challenging to interpret, 2
367 compounds from the dioxin/furane family (1,2,3,7,8-PentaCDD and 2,3,7,8-TetraCDF)
368 with concentrations above 0.01 and 0.1 $\text{ng}\cdot\text{L}^{-1}$ respectively, are found to be sufficient
369 for a significant potential impact to occur. The 15 other congeners of this family have
370 risk threshold concentrations between 11 and 310 ng/L . These compounds, produced
371 during waste incineration, and chemical manufacturing, are classified as very
372 hydrophobic and persistent compounds, and accumulate in environmental
373 compartments such as soil, and sediment as well as in biota (Srogi, 2008). For
374 example, Villanneau et al (2011) found soil concentrations of 23.8 $\text{ng I-TEQ}/\text{kgDM}$ for
375 the $\sum 17$ PCDD/F. The regulatory limit in meats for the sum of dioxin and furan is 1 to
376 5 $\text{ng I-TEQ} / \text{kg}$ of fat. In such organic and fat matrices, low concentrations can be
377 observed, although the probability to find such low concentrations in water matrices
378 may be very low. Dioxins and furans are also on the list of priority substances of the
379 WFD but no EQS for water is provided. Only EQS for biota is fixed at 6.5 $\text{ng}/\text{kg DW}$ (I-
380 TEQ for 7 PCDD+10 PCDF+12 PCB). Such low concentrations could probably be
381 reached locally (see Lu et al., 2016, for PCDD/F concentrations in raw and treated
382 drinking water and Ellis et al., 2008, for data on lake Chelan).

383 DDD 44' and DDE 44' are transformation products of DDT that is not used anymore in
384 western countries since the 1990s. All congeners are hydrophobic and persistent
385 compounds with a tendency to accumulate in biota (Garrison et al., 2014). Total DDT,
386 including several DDT isomers, DDE, and DDD, is listed on the WFD with an EQS of
387 25 ng/L implying its monitoring by the French RSDE program.

388 Cybutryne is a biocide from the triazine family and is used mainly in anti-fouling paints
389 for the protection of boat hulls. It was included on the WFD priority list for monitoring

390 and control in 2012 with an EQS of 2.5 ng/L (yearly average) and a maximal admissible
391 concentration of 16 ng/L. In Switzerland, Ollers et al. (2001) have quantified cybutryne
392 in effluents at very low frequencies around 15 ng/l, which is below the calculated risk
393 threshold concentration (53 ng/L).

394 At the bottom of Table 2, the listed compounds present high-risk threshold
395 concentrations ranging from 10 to 155 µg/L. As such, chlorophenols, present on EU
396 and US EPA priority lists, are widely used for dyestuff, pharmaceutical, and pesticide
397 synthesis and are also by-products of their degradation in the environment (Ganigar et
398 al., 2010). These compounds were mainly monitored in industrial wastewaters where
399 they are treated by biological and physicochemical processes before discharge into
400 the environment or domestic sewage; this could explain why no concentration of such
401 compounds was detected in the studied domestic effluents. Gao et al. (2008) have
402 quantified 2,4,6-trichlorophenol in 54.4 % of their river water samples (600 sites) at a
403 median value of 2 ng/L. These low measured values also suggest the existence of low
404 limits of quantification such as that provided by Suliman et al. (2006) around one µg/L
405 for TCP. These data suggest that it may not be realistic to obtain such a risk threshold
406 concentration in the effluent. To reinforce this idea, compounds like chlortetracycline
407 and its metabolite, 4-epi-chlortetracycline were investigated, since their risk threshold
408 concentrations reaching 1% of the total ecotoxicological potential impacts are
409 respectively 127 and 33 µg/L: these compounds were detected in the effluent of many
410 WWTP but at lower concentrations than the risk threshold one. For example, Li and
411 Zhang (2011) measured chlortetracycline levels around 24 and 33 ng/L in secondary
412 effluents of 2 WWTP in Hong Kong. Chlortetracycline concentrations in effluents of
413 American WWTPs (<8.1–60 ng L⁻¹) (Yang et al., 2005; Spongberg and Witter, 2008)
414 and Australian WWTPs (5–250 ng L⁻¹) (Watkinson et al., 2009) were also found.

415

416 3.4 Potential impact on human health

417 For human toxicity, all the 64 risk threshold concentrations that could be expressed in
418 percentages of LOQ are compiled in Table S6 and the smallest (i.e. below their LOQ)
419 are reported in the following Table 3.

420 **Table 3** – Estimation of the concentrations needed to reach 1% of the sum of the
421 potential impacts on human toxicity, when the risk threshold concentration is below the
422 RSDE LOQ. It is computed using the distribution of subsection 3.2 and is based on the
423 estimation that a measurement below the LOQ is above the risk threshold
424 concentration. With a probability equal to one, there is no measured value below this
425 percentage of LOQ. The results for all compounds are gathered in Table S6.

CAS number	Name	Risk threshold concentration ($\mu\text{g.L}^{-1}$)	Risk threshold concentration (% of RSDE LOQ)	Probability
302-01-2	Hydrazine	2.1E-01	0.2%	1
1024-57-3	Heptachlor epoxide	8.2E-05	0.4%	1
8001-35-2	Toxaphene	2.9E-04	0.6%	1
143-50-0	Chlordecone	1.6E-03	0.8%	1
60-57-1	Dieldrin	4.4E-04	0.9%	1
57-74-9	Chlordane	5.5E-04	2.8%	0.97
309-00-2	Aldrin	2.0E-03	4.0%	0.96
2385-85-5	Mirex	2.7E-03	5.4%	0.94
72-20-8	Endrin	3.5E-03	7.0%	0.91
62-53-3	Aniline	6.6E+00	13%	0.79
76-44-8	Heptachlor	3.1E-03	15%	0.77
50-29-3	DDT 44'	1.0E-02	20%	0.71
50-32-8	Benzo(a)pyrene	2.1E-03	21%	0.7
470-90-6	Chlorfenvinphos	2.3E-02	23%	0.67
67-56-1	Methanol	2.4E+03	24%	0.67
36483-60-0	Hexabromodiphenylethers	6.2E-03	31%	0.52
36355-01-8	Hexabromobiphenyl	6.9E-03	35%	0.44
75-01-4	Chloroethene	1.9E+00	38%	0.42
32536-52-0	Octabromodiphenylethers	2.5E-02	50%	0.26
120-12-7	Anthracene	2.3E-02	56%	0.18
39635-31-9	PCB 189	2.9E-03	59%	0.18
124495-18-7	Quinoxifen	6.0E-02	60%	0.18
118-74-1	Hexachlorobenzene	7.2E-03	72%	0.12

3424-82-6	DDE 24'	7.6E-02	76%	0.11
87-68-3	Hexachlorobutadiene	4.3E-01	86%	0.06
32774-16-6	PCB 169	4.7E-03	94%	0.02

426

427 If these results were compared with those from the previous subsection, more
428 compounds (26 against previously only 4) would be found to have a non-zero
429 probability to reach their risk threshold concentrations. For these 26 compounds, 16
430 present a risk threshold concentration below LOQ/3 which implies that they will have
431 an individual potential impact over 1% of the total sum of potential impacts if their
432 missing concentrations were replaced by the default value of LOQ/3. Among the four
433 previous compounds (hydrazine, endrin, chlordecone, chlorpyrifos) with a significant
434 ET potential impact, only chlorpyrifos is not present here. Many of these compounds
435 are pesticides, hydrocarbons, and fire retardants. They are persistent and hydrophobic
436 compounds that are usually quantified in soil, sediment, and biota and for which the
437 risk threshold concentration is between 10 $\mu\text{g.L}^{-1}$ (heptachlor epoxide) and 100 ng.L^{-1}
438 (hexachlorobutadiene). Smaller molecules, such as aniline, chloroethene, and
439 methanol, are used as solvents and intermediate chemicals for dye and
440 pharmaceutical industries and present higher risk threshold concentrations between
441 one $\mu\text{g.L}^{-1}$ and one mg.L^{-1} (methanol). These latter compounds are present in industrial
442 wastewater at very high concentrations but are quite efficiently degraded in WWTP
443 (Chaturvedi and Katoch, 2020), thus leading to low residual concentrations in urban
444 effluents. The compounds without any information on LOQ are compiled in Table 4.

445

446 **Table 4.** Risk threshold concentrations for each compound that reach 1% of the sum
447 of the HT potential impacts. The compounds in this table do not have any measurement
448 or LOQ.

CAS number	Name	Risk threshold concentration ($\mu\text{g.L}^{-1}$)
------------	------	---

1746-01-6	2,3,7,8-T4CDD	3.97E-08
72-54-8	DDD 44'	1.87E-04
39001-02-0	1,2,3,4,6,7,8,9-O8CDF	8.37E-04
3268-87-9	1,2,3,4,6,7,8,9-O8CDD	1.60E-03
55673-89-7	1,2,3,4,7,8,9-H7CDF	1.93E-03
35822-46-9	1,2,3,4,6,7,8-H7CDD	2.02E-03
67562-39-4	1,2,3,4,6,7,8-H7CDF	2.10E-03
57653-85-7	1,2,3,6,7,8-H6CDD	2.14E-03
39227-28-6	1,2,3,4,7,8-H6CDD	2.18E-03
72918-21-9	1,2,3,7,8,9-H6CDF	2.41E-03
19408-74-3	1,2,3,7,8,9-H6CDD	2.65E-03
70648-26-9	1,2,3,4,7,8-H6CDF	2.73E-03
57117-44-9	1,2,3,6,7,8-H6CDF	2.78E-03
57117-41-6	1,2,3,7,8-P5CDF	3.11E-03
60851-34-5	2,3,4,6,7,8-H6CDF	3.56E-03
57117-31-4	2,3,4,7,8-P5CDF	4.12E-03
40321-76-4	1,2,3,7,8-P5CDD	4.72E-03
51207-31-9	2,3,7,8-T4CDF	1.03E-02
446255-20-5	Heptabromodiphenylethers	1.45E-02
72-55-9	DDE 44'	1.59E-02
789-02-6	DDT 24'	2.09E-02
118-79-6	2,4,6-tribromophenol	3.53E-01
25167-83-3	Tetrachlorophenols	9.29E-01
131860-33-8	Azoxystrobin	9.47E-01
139968-49-3	Metaflumizone	1.08E+00
2303-17-5	Triallate	1.56E+00
564-25-0	Doxycycline	1.59E+00
615-58-7	2,4-dibromophenol	1.82E+00
14297-93-9	4-epi-chlortetracycline	1.92E+00
57-62-5	Chlortetracycline	2.05E+00
25167-82-2	Trichlorophenols	2.66E+00
28159-98-0	Cybutryne	8.56E+00
2032-65-7	Methiocarb	8.65E+00
95-56-7	2-bromophenol	8.79E+00
111988-49-9	Thiacloprid	9.89E+00
153719-23-4	Thiamethoxam	1.07E+01
210880-92-5	Clothianidin	1.17E+01
25167-80-0	Monochlorophenol	1.46E+01
128-37-0	Butylhydroxytoluene	1.70E+01
5466-77-3	Octinoxate	1.81E+01
135410-20-7	Acetamiprid	1.95E+01
21312-10-7	Acetyl sulfamethoxazole	2.05E+01

450 As described previously, the very high value of the CF_{HT} for the 2,3,7,8-TetraCDD
451 leads to a very low value for its risk threshold concentration. Many other compounds
452 of the same family only need around 1 ng.L^{-1} to produce significant potential impacts.
453 However, as already discussed for environmental potential impacts, such low
454 concentrations ought to be measured with a low probability in aqueous media. Other
455 compounds such as doxycycline, chlortetracycline, and acetyl sulfamethoxazole have
456 already been quantified in effluents of WWTP but at concentrations largely below the
457 calculated risk threshold concentrations (Verlicchi et al., 2012).

458

459 **3.5 Influence on the sum of the potential impacts**

460

461 According to all the assumptions previously made, the sum of the potential impacts of
462 the 106 micropollutants of this study were compared with the 153 of the Servien et al.
463 (2022b) study. For the environmental potential impacts, the sum of the potential
464 impacts of this study was nearly 4 fold higher than the previous one. This is illustrated
465 in the following Figure 4 where the environmental potential impacts of the 259
466 compounds are represented.

467



468

469 **Figure 4.** Graphical representation of the environmental potential impacts of the 259

470 compounds studied in Servien et al. (2022b) (in red) and in this study (in blue). Each

471 compound has an estimated environmental potential impact proportional to its

472 rectangular area.

473

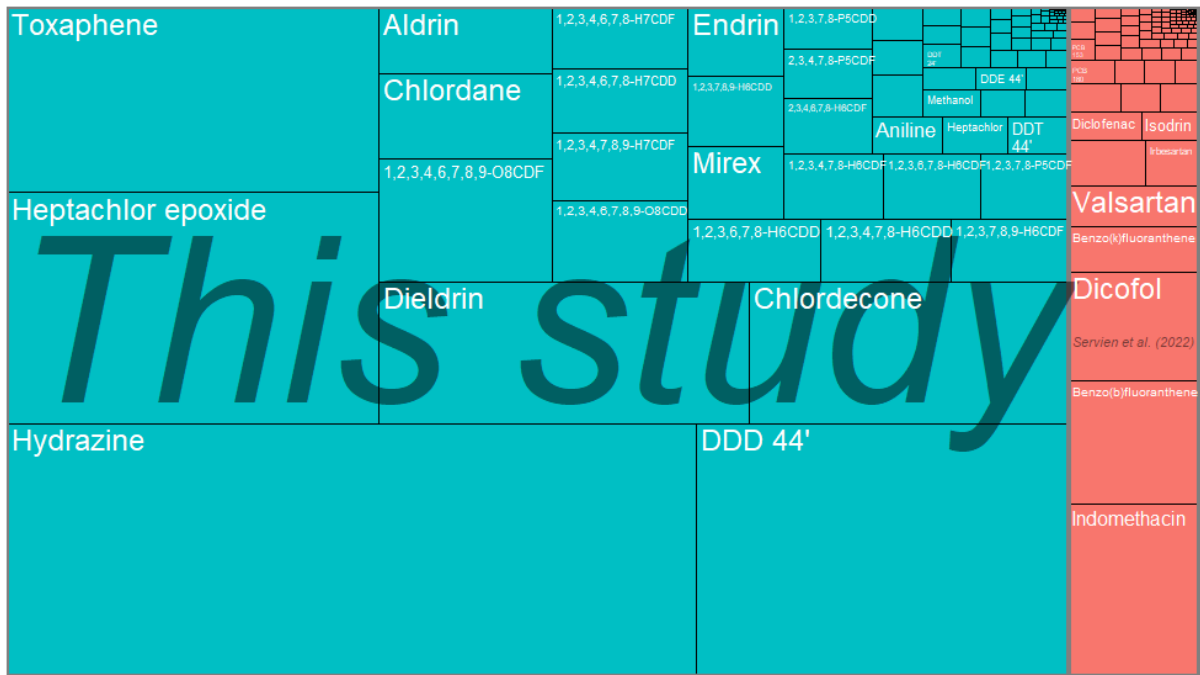
474 Concerning potential impacts on human health, they were more than 8 fold higher,

475 even without accounting for the 2,3,7,8-TetraCDD molecule. If it is considered, this

476 unique molecule presents a greater than 500 000 fold potential impact than all the

477 others, highlighting its very high potential potential impact, even at extremely low

478 concentrations. The other potential impacts are illustrated in the following Figure 5.



479

480 **Figure 5.** Graphical representation of the human potential impacts of the 258
 481 compounds studied in Servien et al. (2022b) (in red) and this study (in blue). Note that
 482 the 2,3,7,8-T4CDD has been removed. Each compound has an estimated
 483 environmental potential impact proportional to its rectangular area.

484

485 The choice of the imputation value for the measured concentrations below the LOQ is
 486 also crucial. Indeed, a choice of LOQ/2 instead of LOQ/3 could lead to an
 487 overestimation of 50.0% of the overall potential impacts on human health and 49.7%
 488 on environmental potential impacts.

489 The potential impact predictions provided by this approach could not be validated using
 490 a classical train and test approach. Nevertheless, the USEtox model is well-known and
 491 recommended approach (Frischknecht and Jolliet, 2019) with a known margin of error
 492 and the performances of the machine learning models (Servien et al. (2022)) have
 493 already been assessed. The choice of the median of the values below the LOQ to
 494 impute the missing concentrations leads us to LOQ/3 instead of LOQ/2 was made to
 495 have a robust estimation, as the median is known to be a robust indicator with a 50%

496 breakdown point. We hope that advances in measurement capabilities will enable
497 further lowering of the LOQ and, through this, help to enlighten the choice of using
498 LOQ/3.

499 **4 Conclusion**

500 In a previous study, 261 organic micropollutants were selected and their potential
501 impacts on human health and aquatic environments in continental freshwaters were
502 investigated at the scale of France. However, lack of data only allowed for the
503 quantification of the potential impacts for 1/3 of these substances (88 for aquatic
504 environments and 94 for human health). Using a new modelling approach, it became
505 possible to estimate the potential impact of 153 organic micropollutants, *i.e.* for all
506 associated with an estimated mass released into the environment (Servien et al.,
507 2022). The one hundred remaining compounds that did not have an accurate
508 concentration measurement were not taken into account. This implies that their
509 potential impacts were considered equal to zero, even though their characterization
510 factors were high and could be dangerous. In the present work, the potential impacts
511 of all these compounds have been considered. New individual compound results were
512 derived under this new framework, which could contribute to the selection of new
513 substances for which specific efforts should be made in tertiary treatments to be
514 implemented in WWTP. It was particularly possible to obtain a rough estimation of the
515 probability for a compound to produce a non-negligible potential impact, even though
516 the measured concentration lies below a LOQ. Obviously, due to the lack of
517 concentration data, no precise results on the total sum of the potential impacts could
518 be obtained. Nevertheless, given a few strong assumptions, such a study was made
519 possible. Results point out that by ignoring compounds with unmeasured
520 concentrations, significant underestimations of total potential impacts could be made.

521 The new estimation methodology defined in this study could help to estimate this
522 underestimation and to make her closer to the real one. Future investigations could
523 involve the balancing of the individual potential impacts of these compounds with a
524 probability of occurrence or the consideration of a cocktail effect, which is not currently
525 possible in the present-day LCA framework. Furthermore, it is noteworthy that this
526 entire methodology (from the computation of missing CFs using machine learning
527 models to the individual compound potential impact estimations with missing
528 concentrations) could be adapted to any other compartment and to any other
529 geographical context, with predictive models that are still to be developed.

530

531 **CRedit authorship contribution statement**

532 **Rémi Servien** : Conceptualization, Methodology, Software, Writing - original draft, and
533 Writing - review & editing. **Kevin Bonnot** : Software. **Eric Latrille** : Conceptualization.
534 **Arnaud Hélias** : Conceptualization and Writing - review & editing. **Dominique**
535 **Patureau** : Conceptualization and Writing - review & editing.

536

537 **Declaration of competing interest**

538 The authors declare that they have no known competing financial interests or personal
539 relationships that could have appeared to influence the work reported in this paper.

540

541 **Acknowledgments**

542 The authors would like to thank the anonymous referees for valuable comments that
543 improved the quality of the paper.

544

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