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Insights on impact estimation of unmeasured micropollutants from WWTP release

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Abstract: During wastewater treatment, incomplete elimination of micropollutants occurs. These micropollutants are often incompletely eliminated and may pose a risk to human health and aquatic ecosystems. The potential impacts of these substances are underestimated due to the lack of available concentrations below the limit of quantifications (LOQ) for an important set of micropollutants. Here, we studied the potential impacts on human health and aquatic environment of the release of 261 organic micropollutants at the scale of France and we showed that, even with a concentration below the LOQ, some micropollutants could have a significant impact. For the unmeasured concentrations, a global concentration distribution built on several

24 datasets with different LOQ is used. Ignoring the unmeasured micropollutants led to
25 an underestimation of the impacts of more than 300% on both human health and
26 aquatic environment. Some substances, such as hydrazine, endrin, or 2,3,7,8-
27 TetraCDD, could lead to a very high impact even with an unmeasured concentration.
28 The usual convention of LOQ/2 for the unmeasured concentrations is also shown to
29 be an overestimation. This work can be adapted to any other compartment and any
30 other geographical context.

31

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

34

35 **Highlights:**

- 36 • Impacts for micropollutants with concentrations below LOQ are derived.
- 37 • Some micropollutants have a significant impact with an unmeasured
38 concentration.
- 39 • Ignoring these unmeasured substances leads to a strong underestimation of
40 the impacts.
- 41 • This could help to prioritization of unmeasured micropollutants.

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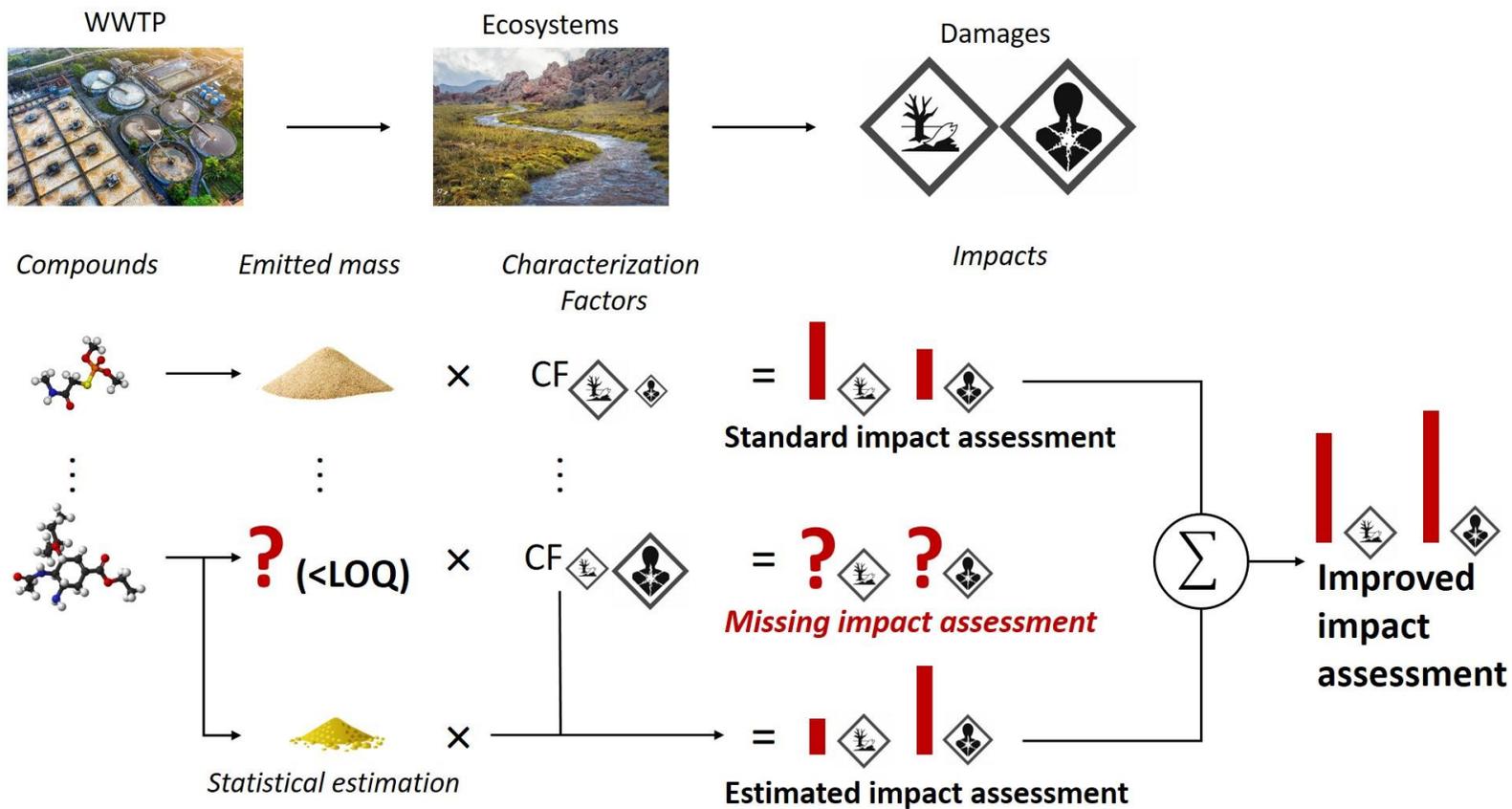
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49 **Graphical abstract**

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51

52 **1. Introduction**

53 Thanks to the implementation of the Water Framework Directive (Directive
54 2008/105/CE, 2008), many European countries have launched monitoring campaigns
55 for organic micropollutants either in the effluents of urban and industrial wastewater
56 treatment plants (WWTP) or in the receiving rivers. Indeed, many papers refer to the
57 quantification of thousands of compounds including pharmaceuticals, hormones,
58 pesticides, hydrocarbons, and solvents in treated wastewaters, underlying incomplete
59 removals of the conventional treatments (Addamo et al., 2005; Bisognin et al, 2021;
60 Yao et al., 2021).

61 Moreover, with increasingly accurate and efficient analytical technologies, more and
62 more compounds are detected at low concentrations (ng.L^{-1} to $\mu\text{g.L}^{-1}$) in rivers,
63 groundwater, surface water, and drinking water (Bayer et al., 2014; Kiefer et al., 2019;
64 Muter et al., 2020; Postigo et al., 2021). The incomplete removal and release of
65 micropollutants into the aquatic environment represent a potential danger to human
66 health and the aquatic environment of continental freshwater. The identification and
67 quantification of the potential impact of toxic substances induce the development of
68 new sustainable process technologies for targeted substances and represent a great
69 challenge to the safety of aquatic ecosystems (Rosenbaum et al., 2007; Zhu et al.,
70 2015).

71 Recently, Aemig et al. (2021) identified 261 organic micropollutants in the effluents of
72 French WWTP. The toxicological and ecotoxicological impacts of 94 and 88
73 micropollutants, respectively, were quantified by multiplying the emitted mass of the
74 compound in the total volume of effluents from French WWTPs by their
75 characterization factors (CFs) (Fantke et al., 2018) as usually done in the Life Cycle
76 Assessment (LCA) framework. Some compounds cannot be assessed because they

77 have no known concentration or their CFs were not available. Then, Servien et al.
78 (2022a) developed a modeling method based on machine learning approaches and 40
79 easy-to-obtain molecular descriptors to predict missing CFs. This model allowed the
80 prediction of toxicological and ecotoxicological CFs in continental freshwater with an
81 acceptable margin of error. This allowed an upgraded assessment of the overall
82 potential impacts (on human health and aquatic environment) of 153 organic
83 micropollutants in continental freshwater at the scale of France. As usually observed
84 (Marlatt et al., 2022), results showed that a molecule can be highly hazardous for the
85 aquatic environment without necessarily being an issue for human health, and vice
86 versa. Moreover, a high impact could be driven by a high CF, a high mass, or a
87 combination of both. As the machine learning models allow a CF prediction for any
88 new compound, the missing concentrations are the only burden that prevents a
89 complete impact estimation. Nevertheless, building models based on easy-to-obtain
90 inputs seem not easily attainable for missing concentrations and the lack of data for
91 some micropollutants is nowadays a known problem (Leenhardt et al., 2022). Cantoni
92 et al. (2020) tackle this problem by comparing several statistical methods to estimate
93 concentrations below the LOQ. Their work is promising but is limited to a small number
94 of micropollutants and cannot be applied to compounds with no value above the LOQ.
95 Not considering the micropollutants with a high number of concentrations below the
96 LOQ in the impact estimations is equivalent to estimating that they have an impact
97 equal to zero, which obviously leads to a strong underestimation of the potential
98 impacts. So, the objective of this paper was to study the potential impacts of the
99 micropollutants for which we do not have measured concentrations or for which more
100 than 90% of the measurements are below the limit of quantification (LOQ) threshold,
101 including those with no measurement above the LOQ. For this, we develop an

102 estimation procedure detailed in the following Section. This allowed a complete
103 assessment of the individual potential impacts (on human health and aquatic
104 environment) of each of the organic micropollutants of interest in continental freshwater
105 at the scale of France.

106

107

108 **2. Materials and Methods**

109 **2.1 Molecules**

110 Aemig et al. (2021) identified 261 organic micropollutants representing a potential
111 danger to human health and aquatic environment in continental freshwater. These
112 molecules came from (i) the Water Framework Directive (WFD, Directive 2008/105/CE,
113 2008), (ii) the national action for the survey and reduction of hazardous substances in
114 water (called RSDE) (INERIS, 2016), and (iii) the AMPERES French project in which
115 micropollutants (registered in the WFD and pharmaceuticals) were analyzed in
116 influents and effluents of 15 WWTP (Martin Ruel et al., 2016). Among these 261
117 organic micropollutants, the emitted mass of 153 was estimated with at least 10 sites
118 of measures and 90% of the measured data above the limit of quantification. The
119 impacts of these 153 compounds were assessed by Aemig et al. (2021) for those
120 present in the USEtox[®] database (Rosenbaum et al., 2007) and by Servien et al.
121 (2022a) for those who are not in this database.

122

123 **2.2 Characterization factors**

124 Among the remaining 108 compounds, 58 have a CF for ecotoxicological impacts
125 (CF_{ET}) and 43 a CF for human ones (CF_{HT}) in the USEtox[®] database version 2.12 with
126 a default landscape (to remain consistent with Servien et al. (2022a,b)). USEtox[®] is an

127 international consensual for characterizing human and ecotoxicological impacts of
128 chemicals (UNEP-SETAC, 2019). It was developed by the life cycle initiative under the
129 United Nations Environmental Programme (UNEP) and the Society for Environmental
130 Toxicology and Chemistry (SETAC) (Henderson et al., 2011) to produce a transparent
131 and consensus characterization model. This model gathers in one single
132 characterization factor the chemical fate, the exposure, and the effect for each of the
133 several thousands of organic and inorganic compounds. If the structure of the
134 USEtox® multimedia model is always the same, to determine the CF of a molecule,
135 numerous physicochemical parameters (such as solubility, hydrophobicity,
136 degradability) and detailed toxicological and ecotoxicological data must be provided.
137 In details, CFs were calculated in the USEtox database through the following formula:
138 $CF = FF \times XF \times EF$. FF was the fate factor indicating the residence time in the
139 environment and was estimated with physicochemical properties for organic
140 micropollutants or speciation for inorganic micropollutants. XF was the exposure factor
141 i.e. the fraction of micropollutants in the environment that was available for organisms.
142 EF was the effect factor corresponding to the effect on the aquatic environment
143 (considering three trophic levels) or the effect on Human health. For Human toxicity
144 CFs, USEtox calculated the intake fraction (iF) i.e. the amount of micropollutants
145 absorbed through air, water, and food after emission in the freshwater compartment.
146 iF was equal to $XF \times FF$. LCA tool was preferred to approaches such as Toxic Unit or
147 Risk Quotient as we wanted to estimate the potential impacts of each micropollutant
148 and the overall impact of the mixture.

149 The remaining CFs were computed using the machine learning models developed by
150 Servien et al. (2022a). These models predict ecotoxicological or toxicological
151 characterization factors using 40 selected easy-to-obtain molecular descriptors (see

152 the list in Table S1). For more details on the choice and the calculation of these
153 descriptors, the interested reader is referred to Servien et al. (2014). These models
154 are based on a comparison between different linear or non-linear (machine learning)
155 models and could be global or local using a cluster-then-predict approach. The
156 modeled CFs were compared to USEtox[®] database, the differences between the
157 modeled CFs and the USEtox[®] ones were small, and the models were therefore
158 considered to be applicable. The best approaches were then selected for each cluster
159 and each characterization factor. To apply the cluster-then-predict approaches, the
160 cluster of each new compound needs to be estimated using a supervised clustering
161 approach based on the clusters already obtained in Servien et al. (2022a) which was
162 performed using the well-known k-nearest neighbor approach through the *knn* function
163 of the R package *class* (Ripley, 1996). Then, the models selected by Servien et al.
164 (2022a) were applied without any modification, assuming they had been previously
165 tested on a large diversity of molecules covering the diversity of the compounds
166 assessed in the present study. These previous tests have shown the reliability of the
167 models to predict CFs that are missing in USEtox[®].

168 Note that the tributylstannanylium (CAS 36643-28-4) contains an atom of tin and, as
169 consequence, its molecular descriptors cannot be computed by the above-mentioned
170 methods and, thus, its CFs. In addition, chloroalkanes C10-13 (CAS 85535-84-8) is a
171 mix of different molecular structures that can lead to different molecular descriptors
172 and CFs and was also excluded.

173 The 106 corresponding characterization factors are gathered in Table S2. The scheme
174 of the whole study is summarized in Figure S1 available in Supplementary Material.

175

176 **2.3 Quantification of significative potential impacts**

177 The annual volume of water effluent released into the environment by WWTP was
178 estimated to be 5.10^9 m^3 , in France (Aemig et al., 2021). This volume was determined
179 by multiplying the daily flow arriving at the WWTP for 365 days, assuming that it was
180 equal to the effluent. The emitted mass of micropollutants was estimated by multiplying
181 each concentration of the micropollutants, when available, by the volume of the
182 effluent. The concentrations and masses are those of the Supplemental Material of
183 Aemig et al. (2021) and are gathered in Table S3. Total impacts on human health and
184 aquatic environment in continental freshwater were quantified by summing the impacts
185 of all the compounds, as is usually done in LCA (Heijungs and Suh, 2002).

186 As explained above, the remaining 106 micropollutants are those for which not enough
187 data were available to correctly estimate the concentration. So, for these compounds,
188 we calculate the risk threshold concentration to reach 1% of the total sum of impacts
189 calculated previously for the 153 micropollutants presented in Servien et al. (2022b).
190 Note that this 1% threshold is obviously arbitrary and fully depends on the compound
191 selection that is taken into account in the study. Nevertheless, this methodology could
192 easily be adapted to any chosen threshold, any selection of compounds (even
193 containing transformation products), and any compartment of interest. It could also be
194 used for other endpoints that are based on measured concentrations such as risk
195 quotients. When the LOQ of a micropollutant was available, this risk threshold
196 concentration was also expressed in the percentage of the LOQ to be comparable
197 among different micropollutants. For 42 compounds, no data (measurements and
198 LOQ) were available so this risk threshold concentration was only expressed in $\mu\text{g.L}^{-1}$.
199 Obviously, as the potential impacts are linearly related to the estimated
200 concentration, if a measured concentration is the risk threshold concentration

201 multiplied by a constant k , the corresponding impacts will be $k\%$ of the total sum of
202 impacts calculated previously.

203

204 **2.4 Estimation of values below the LOQ**

205

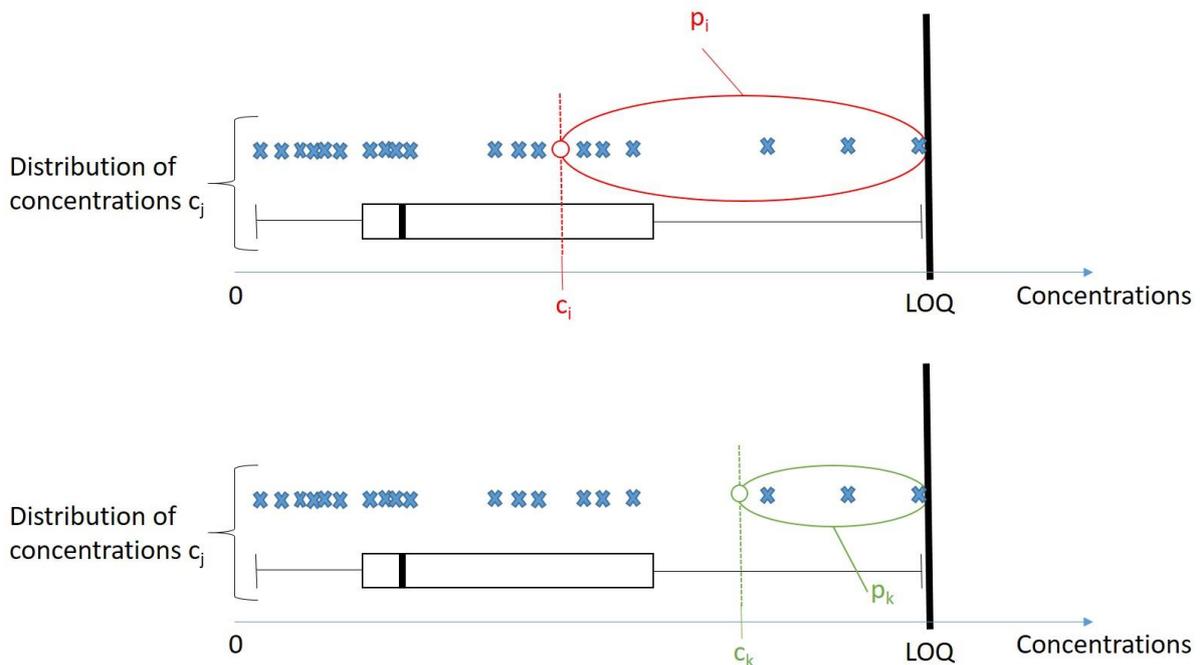
206 For these 106 micropollutants, according to Table S3, a very high number (more than
207 90%) of the values are below the LOQ of the corresponding study. Data inferior to LOQ
208 are usually estimated at half of the quantification limit as usually applied in
209 environmental studies (INERIS, 2016). This assumption is a very strong one that could
210 have a major impact on the estimated concentration (and thus the potential impact)
211 when there are a lot of concentrations below LOQ. Testing this strong assumption
212 could be of great help.

213 In the RSDE samples, the compounds are measured using routine methods so most
214 of the LOQ are pretty high. This is not always the case for the other sources of
215 quantified concentrations. So, we have some concentrations that came from other
216 sources and that are below the LOQ of the main dataset of the study, the RSDE one.
217 We could then scale these values relative to the RSDE LOQ for all compounds to have
218 a sufficient number of concentrations measured but below the RSDE LOQ. This gives
219 a dataset of 141 samples with concentrations denoted $(c_j)_{1 \leq j \leq 141}$ coming from 25
220 different compounds. The distribution of these samples is then used to compute the
221 probability that the risk threshold concentration c_i of compound i has been reached in
222 case of quantification below the LOQ. This probability p_i is computed as the number
223 of measurements above the corresponding risk threshold concentration c_i divided by
224 the total number of measurements (i.e. 141): $p_i = \frac{\sum_{j=1}^{141} \mathbb{1}(c_i < c_j)}{141}$ and is detailed in the

225 following Figure 1. In other terms, when the risk threshold concentration c_i is near the
 226 LOQ, the probability to get a value above c_i is low.

227

228



229

230 **Figure 1:** Summary of the computation of the probability to reach a risk threshold
 231 concentration. The RSDE LOQ is represented by a large black line whereas the
 232 distribution of concentrations $(c_j)_{1 \leq j \leq 141}$ that came from other sources are represented
 233 here by some blue crosses and its corresponding boxplot. On the top subfigure, a risk
 234 threshold concentration c_i is estimated for a new compound i , this results in the
 235 corresponding p_i , calculated by counting all the concentrations $c_j > c_i$. Then, on the
 236 bottom subfigure, another risk threshold concentration c_k is estimated for another
 237 compound k with $c_k > c_i$. Obviously, the probability p_k that the risk threshold
 238 concentration for the compound k will be attained is below p_i .

239

240 Note that if a sample that doesn't come from RSDE has a measured concentration
241 lower than its LOQ (and, thus, lower than the RSDE LOQ) it won't be taken into
242 account, so the final distribution will probably be a little overestimated. Indeed, taking
243 into account these unknown measurements relying on different relative LOQ values
244 would bring a lot of uncertainties in the below LOQ distribution calculations.

245

246 **2.5 Calculation of the total impacts**

247

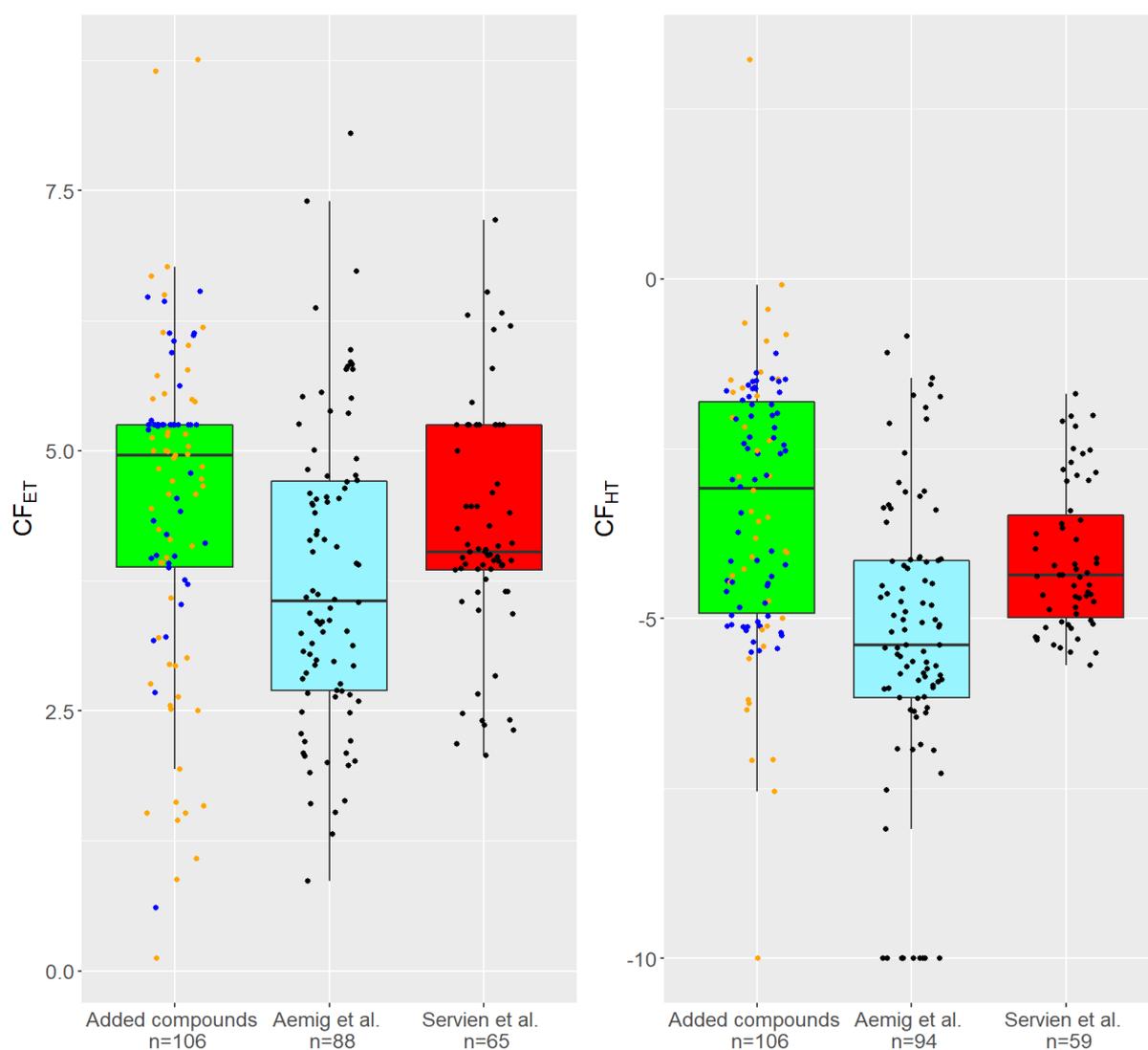
248 As usually done in LCA, the total impacts on human health and aquatic environment
249 in continental freshwater were quantified by summing the impacts of all the
250 compounds. Human impact is expressed in DALY representing the number of
251 negatively impacted human years, and the ecotoxicological impact is expressed in
252 PDF representing the potential fraction of disappeared species. To compute these
253 impacts, we impute values below the LOQ by the median values below the LOQ for all
254 the compounds (see Figure 2), namely LOQ/3. For the compounds without a LOQ, the
255 median value of the LOQ, namely $0.05 \mu\text{g.L}^{-1}$, was used.

256

257 **3. Results and discussion**

258 **3.1 Global analysis of characterization factors**

259 Regarding the CFs, the different values are reported in the boxplots of Figure 2 below.
260 As usual, the CFs are log-transformed with the addition of $1\text{e-}10$ for the CF_{HT} to avoid
261 a computational problem with $\log_{10}(0)$. $1\text{e-}10$ has been chosen to be below the
262 minimum of the USEtox® database ($5\text{e-}9$).



264

265

266

267 **Figure 2.** Comparison of the CF_{HT} and the CF_{ET} (both in \log_{10} scale) for the
268 compounds taken into account in previous studies and the added compounds. For the
269 added compounds, the CF in orange came from USEtox[®] whereas those in blue are
270 computed using Servien et al. (2022a).

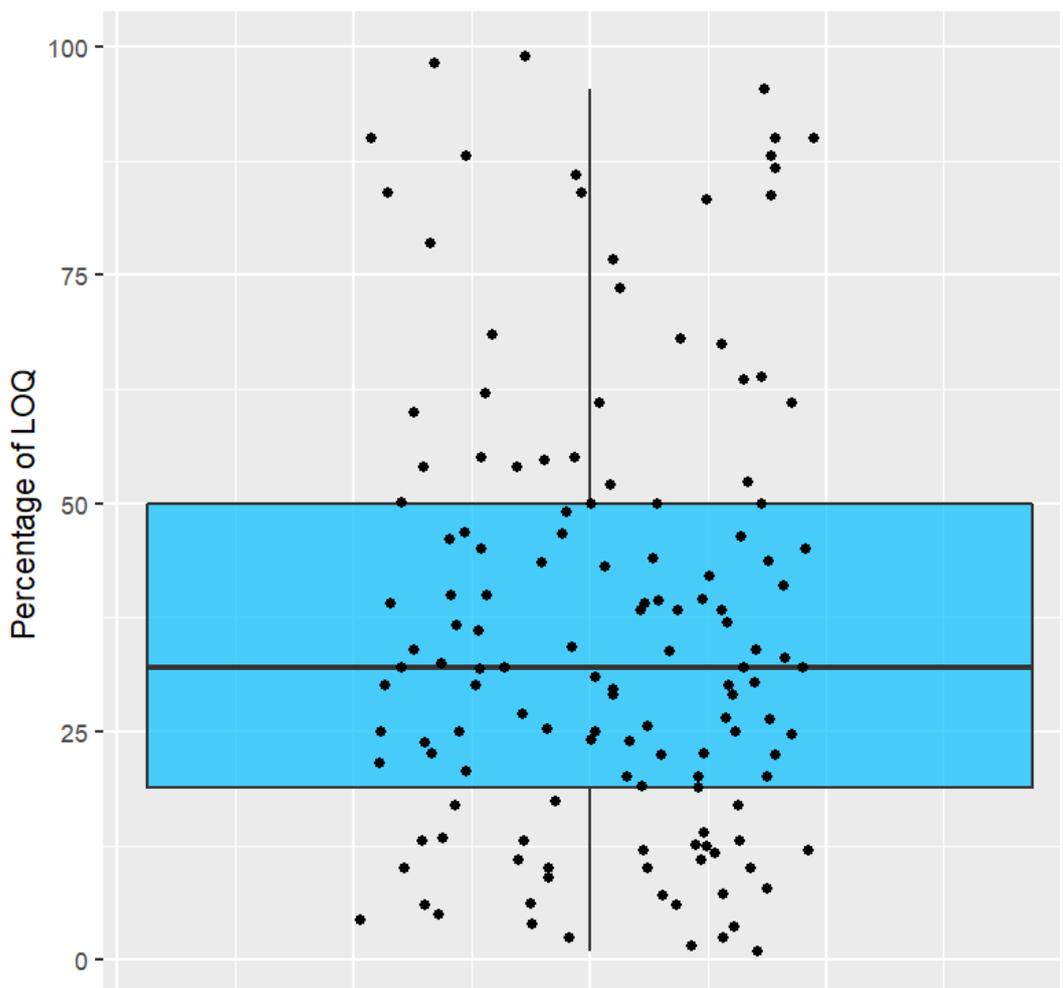
271

272 Figure 2 suggests that the added compounds have globally higher CF than already
273 included in the previous studies. In more detail, for the CF_{HT} and the CF_{ET} , the
274 maximum, the 1st and 3rd quartile, the median and the mean of the added compounds
275 are above those of the previous studies. But there are also very low CF values largely
276 below those of the previous study. All the descriptive values are given in Table S4. We
277 could also see that we have extremely high values for some compounds already
278 included in USEtox[®]. For the CF_{ET} , these two extreme values are for the 1,2,3,7,8-
279 PentaCDD (CAS 40321-76-4) and the 2,3,7,8-TetraCDF (CAS 51207-31-9) from the
280 polychlorodibenzodioxin/furane family. Their extreme values would lead to significant
281 impacts if their concentrations are not too low. For the CF_{HT} , the extreme value is for
282 the 2,3,7,8-TetraCDD (CAS 1746-01-6). This is the unique value of the whole USEtox[®]
283 database that is log-positive for this variable. Nevertheless, the estimation of the CF_{HT}
284 available in the environmental footprint database (Fazio et al., 2018) seems to
285 corroborate this very high value. This dioxin is a well-studied and recognized endocrine
286 disrupter presenting the highest affinity to the aryl hydrocarbon receptor (AhR), a
287 cytosolic protein present in most vertebrate tissues, that mediated the toxic and
288 biological effects of such compounds (Van den Berg et al., 2006). Its very high CF_{ET}
289 and CF_{HT} are linked to its high endocrine-disrupting potency. If we don't consider this
290 compound, five others have CF_{HT} above the maximal value already included in
291 previous studies. These compounds are all pesticides: chlordane (CAS 57-74-9), 1,1-
292 bis(4-Chlorophenyl)-2,2-Dichloroethane (CAS 72-54-8), dieldrin (CAS 60-57-1),
293 heptachlor epoxide (CAS 1024-57-3) and toxaphene (CAS 8001-35-2).

294

295 **3.2 Estimation of concentrations below the LOQ**

296 In the following Figure 3, the distribution of the concentrations measured on other
297 sources and that are below the RSDE LOQ is represented.



298
299 **Figure 3:** Boxplot of the 141 measured concentrations below the RSDE LOQ on
300 another dataset with lower LOQ (expressed in % of the RSDE LOQ).

301 We could see that the median (and so is the mean) value of this distribution seems to
302 be close to $LOQ/3$, and not $LOQ/2$ as usually used for calculation when data are below
303 the LOQ. Furthermore, as the concentration values below the smaller LOQ are not
304 taken into account, even $LOQ/3$ is probably an overestimation, when faced with a
305 below LOQ value in the RSDE dataset. This is also confirmed by the conclusions of
306 Cantoni et al. (2020) where the LOQ and $LOQ/2$ are shown to be an overestimation.

307

308 3.3 Impact on the aquatic environment

309 For the aquatic environment, all the 64 risk threshold concentrations that could be
310 expressed in percentage of LOQ are gathered in Table S5 and the smallest (i.e. that
311 are below the LOQ) are reported in Table 1. These 64 compounds are the 106 without
312 enough data to derive a concentration mentioned above minus the 42 with no data at
313 all.

314 **Table 1** – Estimation of the concentrations needed to reach 1% of the sum of the
315 impacts on ecotoxicity, when the risk threshold concentration is below the RSDE LOQ.
316 It is computed using the distribution of subsection 3.2 and is the estimation that a
317 measurement below the LOQ is above the risk threshold concentration. The results for
318 all compounds are gathered 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 |

319

320 There are only 4 compounds for which a concentration below the LOQ could still cause
321 a significant impact on ecotoxicity and for 2 of them the risk threshold concentration is
322 also below LOQ/3. For the 60 other compounds, the risk threshold concentration being
323 above the LOQ and the measured one frequently below, their contribution to the
324 environmental impact could be considered as very low. For the hydrazine, a very small
325 concentration of only 4% of the RSDE LOQ, that have a high probability of occurrence,
326 will lead to a significant impact. Hydrazine and its derivatives are widely used
327 compounds in chemical industries and pharmaceuticals (propellant, blowing agent,

328 pesticide, antituberculosis...). It is a very small molecule (32 g/mol), very soluble and
329 volatile, no BCF is found in literature, nor DT50. It was classified by US EPA as a
330 human carcinogen (group B2): an intermediate inhalation minimal risk level of 4 µg/L
331 was calculated and a minimum limit for cancer was fixed at 10 µg/L (Qi et al., 2020).
332 The risk threshold concentration was found to be 4 µg/L and is largely below the RSDE
333 LOQ, which is very high (100 µg/L) by comparison to the one of endrin (0,052 µg/L)
334 and also other compounds. However, very recent papers refer to the development of
335 spectroscopic methods and sensors to analyze hydrazine in environmental samples
336 including water up to pico-molar level (0.03 to 3.2 µg/L, Arulraj et al., 2015; Qi et al.,
337 2020). However, no data are provided in real water samples.

338 For the three pesticides, due to their hydrophobicity, they are usually quantified in solid
339 matrices like soil, sediment, and biota. However, concentrations of endrin were
340 reported in river water between 0.17 and 484 ng/L (Matsumo et al., 2009) and
341 concentrations of chlorpyrifos between 1 and 32 ng/L (Wan et al., 2021). Their
342 presence in such an environment is mainly due to their use in agriculture. They are
343 also targeted by the WFD. The Environmental Quality Standard (yearly average value)
344 for the sum of the 4 cyclodiene pesticides in the WFD (aldrin, isodrin, endrin, dieldrin)
345 is 10 ng/L (inner water surface) and 5 ng/L (other water). For chlorpyrifos, the EQS is
346 30 ng/L. The three calculated risk threshold concentrations to reach 1% of the sum of
347 the impacts are in the same range as these environmental and regulatory values.

348 The compounds without any information on LOQ are gathered in the following Table
349 2.

350

351 **Table 2.** Risk threshold concentrations for each compound to reach 1% of the sum of
 352 the impacts on ecotoxicity. The compounds in this table are those without any measure
 353 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 |

354

355 For these compounds, only the risk threshold concentration in the usual unity ($\mu\text{g.L}^{-1}$)
356 is available. It leads to results that are more difficult to interpret but we could see that
357 there are 2 compounds from the dioxin/furane family (1,2,3,7,8-PentaCDD and 2,3,7,8-
358 TetraCDF) for which a concentration above 0,01 and 0,1 ng.L^{-1} will be enough to lead
359 to a significant impact. The 15 other congeners of this family present risk threshold
360 concentrations between 11 and 310 ng/L . These compounds, produced during waste
361 incineration, and chemical manufacturing, are classified as very hydrophobic and
362 persistent compounds, and accumulate in environmental compartments such as soil,
363 and sediment as well as in biota (Srogi, 2008). As an example, Villanneau et al (2011)
364 found soil concentrations of 23,8 ng I-TEQ/kgDM for the $\sum 17$ PCDD/F. The regulatory
365 limit in meats for the sum of dioxin and furan is 1 to 5 ng I-TEQ / kg of fat. In such
366 organic and fat matrices, low concentrations can be found, but the probability to find
367 such low concentrations in water matrices may be very low. Dioxins and furans are
368 also on the list of priority substances of the WFD but no EQS for water is provided only
369 EQS for the biota is fixed at 6,5 ng/kg DW (I-TEQ for 7 PCDD+10 PCDF+12 PCB).
370 Such low concentrations could probably be reached locally (see Lu et al., 2016, for
371 PCDD/F concentrations in raw and treated drinking water and Ellis et al., 2008, for data
372 on lake Chelan).

373 DDD 44' and DDE 44' are transformation products of DDT that is not more used in
374 western countries since the 1990s. All congeners are hydrophobic and persistent
375 compounds with accumulation in biota (Garrison et al., 2014). Total DDT, including
376 several DDT isomers, DDE, and DDD, is listed on the WFD with an EQS of 25 ng/L
377 implying its monitoring in the French RSDE program.

378 Cybutryne is a biocide from the triazine family and is used mainly in anti-fouling paints
379 for the protection of boat hulls. It was included on the WFD priority list for monitoring
380 and control in 2012 with an EQS of 2.5 ng/L (yearly average) and a maximal admissible
381 concentration of 16 ng/L. In Switzerland, Ollers et al. (2001) have quantified cybutryne
382 in effluent at very low frequencies around 15 ng/l, which is below the calculated risk
383 threshold concentration (53 ng/L).

384 At the bottom of Table 2, the listed compounds present high-risk threshold
385 concentrations ranging from 10 to 155 µg/L. As such, chlorophenols, present on EU
386 and US EPA priority lists, are widely used for dyestuff, pharmaceutical, and pesticide
387 synthesis and are also by-products of their degradation in the environment (Ganigar et
388 al., 2010). These compounds were mainly monitored in industrial wastewaters where
389 they are treated by biological and physicochemical processes before discharge in the
390 environment or domestic sewage; this could explain why no concentration of such
391 compounds was found in the domestic effluent studied. Gao et al. (2008) have
392 quantified 2,4,6-trichlorophenol in 54.4 % of their river water samples (600 sites) at a
393 median value of 2 ng/L. These low measured values suggest also the existence of low
394 limit of quantifications as the one given by Suliman et al. (2006) around µg/L for TCP.
395 These data suggest that it may not be realistic to get such a risk threshold
396 concentration in the effluent. To reinforce this idea, we can have a look at compounds
397 like chlortetracycline and its metabolite, 4-epi-chlortetracycline, whose risk threshold
398 concentrations to reach 1% of the total ecotoxicological impact are respectively 127
399 and 33 µg/L: these compounds were found in the effluent of many WWTP but at lower
400 concentrations than the risk threshold one. For example, Li and Zhang (2011)
401 measured chlortetracycline levels around 24 and 33 ng/L in secondary effluents of 2
402 WWTP in Hong Kong. Chlortetracycline concentrations in effluents of American

403 WWTPs (<8.1–60 ng L⁻¹) (Yang et al., 2005; Spongberg and Witter, 2008) and
 404 Australian WWTPs (5–250 ng L⁻¹) (Watkinson et al., 2009) were also found.

405

406 3.4 Impact on human health

407 For human toxicity, all the 64 risk threshold concentrations that could be expressed in
 408 percentage of LOQ are gathered in Table S6 and the smallest (i.e. that are below their
 409 LOQ) are reported in the following Table 3.

410 **Table 3** – Estimation of the concentrations needed to reach 1% of the sum of the
 411 impacts on human toxicity, when the risk threshold concentration is below the RSDE
 412 LOQ. It is computed using the distribution of subsection 3.2 and is the estimation that
 413 a measurement below the LOQ is above the risk threshold concentration. When the
 414 probability is equal to one, it means that no measured value is below this percentage
 415 of LOQ. The results for all compounds are gathered in Table S6.

| CAS number | Name | Risk threshold concentration (µg.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 |

416

417 If we compare these results with those of the previous subsection we could see that
418 more compounds (26 whereas it was previously only 4) have a non-zero probability to
419 reach their risk threshold concentrations. On these 26 compounds, 16 have a risk
420 threshold concentration below LOQ/3 which implies that they will have an individual
421 impact over 1% of the total sum of impacts if we impute their missing concentrations
422 by the default value of LOQ/3. Among the four previous compounds (hydrazine,
423 endrin, chlordecone, chlorpyrifos) with a significant ET impact, only chlorpyrifos is not
424 present here. Many of these compounds are pesticides, hydrocarbons, and fire
425 retardants that are persistent and hydrophobic compounds usually quantified in soil,
426 sediment, and biota for which the risk threshold concentration is between 10 $\mu\text{g.L}^{-1}$
427 (heptachlor epoxide) and 100 ng.L^{-1} (hexachlorobutadiene). There are also smaller
428 molecules like aniline, chloroethene, and methanol, used as solvents and intermediate
429 chemicals for dye and pharmaceutical industries whose risk threshold concentrations
430 are higher between $\mu\text{g.L}^{-1}$ and mg.L^{-1} (methanol). These compounds are present in
431 industrial wastewater at very high concentrations and are quite well degraded in
432 WWTP (Chaturvedi and Katoch, 2020), suggesting low residual concentrations in
433 urban effluents. The compounds without any information on LOQ are gathered in Table
434 4.

435

436 **Table 4.** Risk threshold concentrations for each compound to reach 1% of the sum of
437 the HT impacts. The compounds in this table are those without any measure or LOQ.

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

439 As seen previously, the very high value for the CF_{HT} for the 2,3,7,8-TetraCDD lead to
440 a very low value for its risk threshold concentration. Many other compounds of the
441 same family only need around 1 ng.L^{-1} to have significant impacts. However, as already
442 discussed for environmental impact, such low concentration will be measured with low
443 probability in aqueous media. Other compounds such as doxycycline,
444 chlortetracycline, and acetyl sulfamethoxazole were already quantified in effluents of
445 WWTP but at concentrations largely below the calculated risk threshold concentrations
446 (Verlicchi et al., 2012).

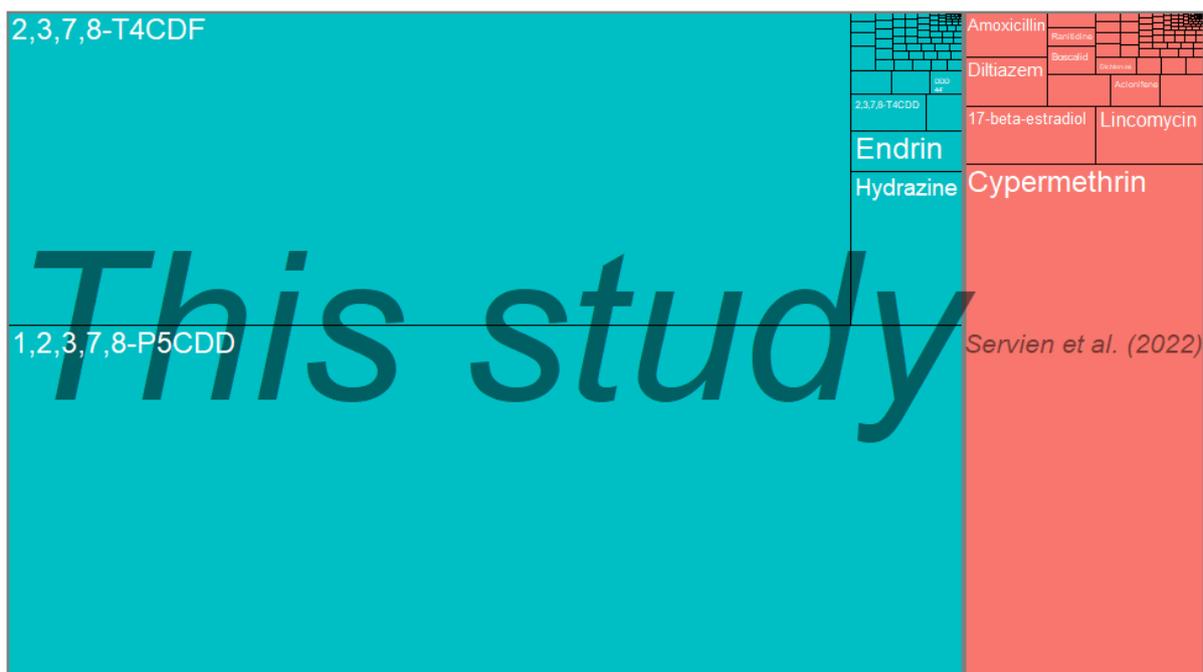
447

448 **3.5 Influence on the sum of the impacts**

449

450 According to all the assumptions made previously we were able to compare the sum
451 of the impacts of the 106 micropollutants of this study to the 153 of Servien et al.
452 (2022b). For the environmental impacts, the sum of the impacts of this study was nearly
453 4 times higher than the previous one. This could be seen in the following Figure 4
454 where the environmental impacts of the 259 compounds are represented.

455

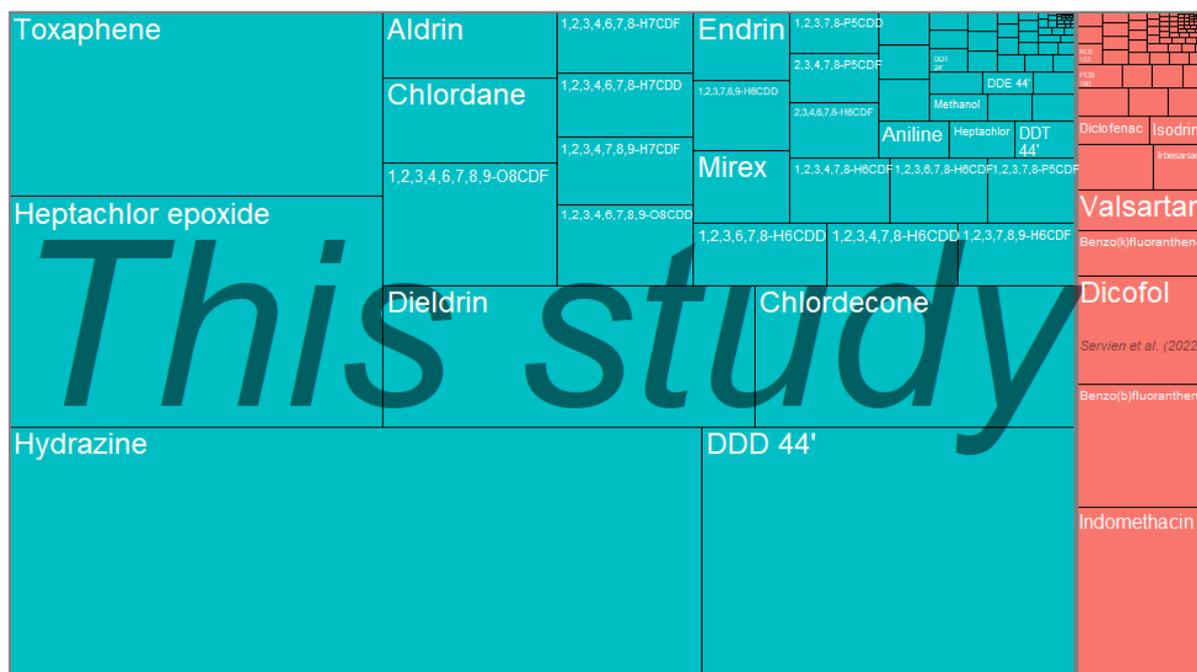


456

457 **Figure 4.** Graphical representation of the environmental impacts of the 259
 458 compounds studied in Servien et al. (2022b) (in red) and this study (in blue). Each
 459 compound has an estimated environmental impact proportional to its rectangular area.

460

461 For the impacts on human health, it was more than 8 times higher, even without taking
 462 into account the molecule 2,3,7,8-TetraCDD. This unique molecule has an impact of
 463 more than 500 000 higher than all the other ones, if we consider it, highlighting its very
 464 high potential impact, even at a very small concentration. The other impacts are
 465 represented in the following Figure 5.



466
 467 **Figure 5.** Graphical representation of the human impacts of the 258 compounds
 468 studied in Servien et al. (2022b) (in red) and this study (in blue). Note that the 2,3,7,8-
 469 T4CDD has been removed. Each compound has an estimated environmental impact
 470 proportional to its rectangular area.

471
 472 The choice of the imputation value for the measured concentrations below the LOQ is
 473 also crucial. Indeed, a choice of LOQ/2 instead of LOQ/3 would have led to an
 474 overestimation of 50.0% of the overall impacts on human health and 49.7% on
 475 environmental impacts.

476
 477 **4 Conclusion**

478 In a previous study, 261 organic micropollutants were selected to study their potential
 479 impacts on human health and aquatic environment in continental freshwater at the
 480 scale of France. However, the lack of data allows quantifying the impacts for only 1/3
 481 of these substances (88 for aquatic environment and 94 for human health). Using a

482 new modeling approach, we were then able to estimate the impact of 153 organic
483 micropollutants, *i.e.* for all with an estimated mass released in the environment
484 (Servien et al., 2022). The hundred remaining compounds without an accurate
485 concentration measure were not taken into account. It means that their impacts were
486 considered equal to zero, even if their characterization factors were high and could be
487 worrying. In this work, the potential impacts of all these compounds are considered.
488 We derive individual compound results, which could help to select substances in which
489 a special effort should be made on the tertiary treatments to implement in WWTP. It
490 was particularly possible to obtain a rough estimation of the probability that a
491 compound produces a non-negligible impact, even if a measured concentration is
492 below a LOQ. Obviously, due to the lack of concentration data, no precise results on
493 the total sum of the impacts could be obtained. Nevertheless, with some strong
494 assumptions, it was possible to conduct such a study and to show that ignoring
495 compounds with unmeasured concentrations could lead to strong underestimations of
496 total impacts. A future work could be to balance the individual impacts of these
497 compounds with a probability of occurrence or to take into account a cocktail effect,
498 which is not possible now in the LCA framework. Also, it has to be underlined that this
499 whole methodology (from the computation of missing CFs using machine learning
500 models to the individual compound impact estimations with missing concentrations)
501 can be adapted to any other compartment and any other geographical context, with
502 predictive models still to develop.

503

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