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► To cite this version:

Rémi Servien, Coralie Leenknecht, Kevin Bonnot, Virginie Rossard, Eric Latrille, et al.. Machine learning to improve the impact assessment of micropollutants release from WWTP. 2021. hal-03346134v1

HAL Id: hal-03346134

<https://hal.science/hal-03346134v1>

Preprint submitted on 16 Sep 2021 (v1), last revised 6 Dec 2021 (v2)

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Machine learning to improve the impact assessment of micropollutants release from WWTP

Short communication

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Highlights:

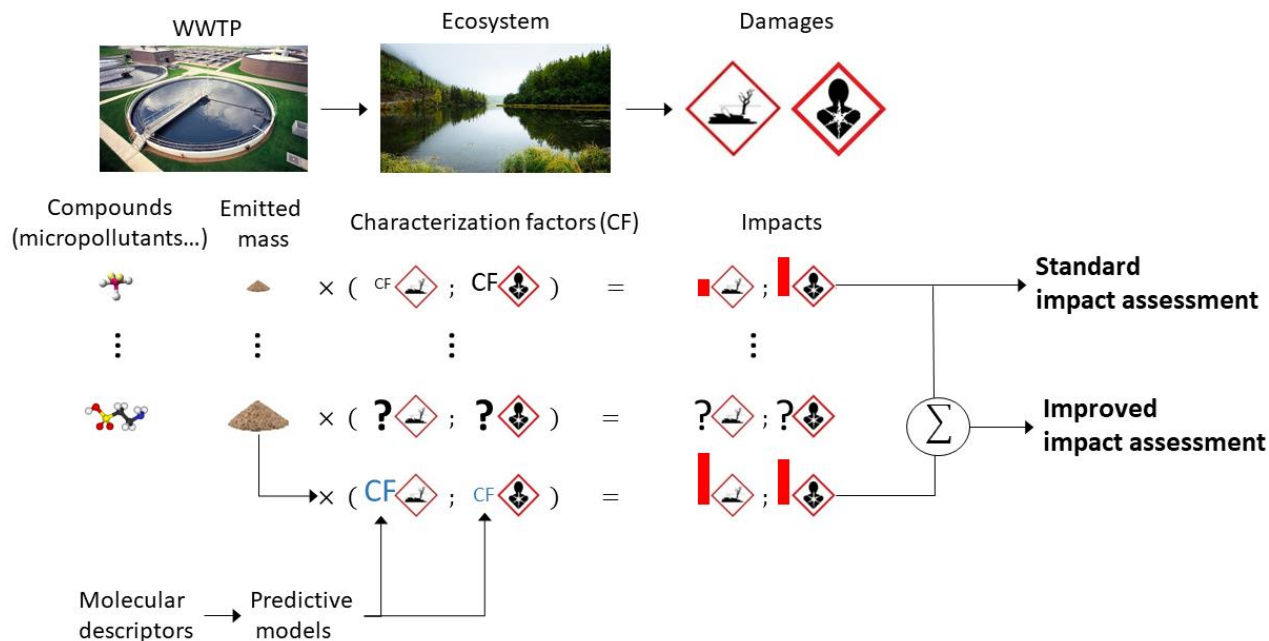
- Machine learning models were used to estimate missing characterization factors (CF).
- This allows complementing impact assessment of micropollutants release from WWTP.

- The human health impact was doubled by adding the compounds with predicted CF.
- This impact resulted of a high-emitted mass or a high toxicological potential.
- The impact on aquatic environment was nearly unchanged.

Abstract:

The emission of micropollutants by human activities represents a potential threat to human and ecosystems health. During wastewater treatment, incomplete elimination of these substances occurs. Indeed, effluents released to the environment still contain a non-negligible part of these micropollutants. Recently, the potential impacts on human health and aquatic environment of the release of some organic and inorganic micropollutants at the scale of France have been studied. The high impacts were mainly due to the (eco)-toxicological potential of a few numbers of compounds, not to their mass emitted in the environment. Furthermore, the impact was estimated for less than 1/3 of the initial list of organic substances due to a lack of concentration and toxicological data in the literature. In the present study, we used already developed machine learning models to complement these impact calculations. The conclusions were not modified for the impact on aquatic environment, but were different for the human health impacts: the higher toxicological potential impact could be driven by a high-emitted mass, and a high number of compounds could take a significant part of the overall impact.

46 **Graphical Abstract:**



47

48 **Keywords:** characterization factors, toxicity, ecotoxicity, continental freshwater,

49 human health, Life Cycle Assessment, molecular descriptors.

50

51 **1. Introduction**

52 For several years, the presence of organic micropollutants such as pharmaceuticals,

53 pesticides, or Polycyclic Aromatic Hydrocarbons (PAH) in the effluents of wastewater

54 treatment plants (WWTP) is ubiquitous and has raised increasing concerns. More than

55 thousands of active substances are identified in wastewater and their treatment within

56 the plants remains incomplete (Addamo et al., 2005; Aemig et al., 2021). In parallel,

57 with increasingly accurate and efficient analytical technologies, more and more

58 compounds are detected at low concentrations (ng.L^{-1} to $\mu\text{g.L}^{-1}$) in rivers, groundwater,

59 surface water, and drinking water (Bayer et al., 2014). Incomplete removal and release

60 of micropollutants into the aquatic environment represents a potential danger to human

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

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

Recently, Servien et al. (2021) developed a modeling method based on machine learning approaches and 40 easy-to-obtain molecular descriptors. This approach

allowed the prediction of toxicological and ecotoxicological CF in continental freshwater with an acceptable margin of error. Applying these models to estimate the missing CF could bring the assessment of the overall potential impacts closer to reality. The objective of this study was thus to predict missing toxicological and ecotoxicological factors using the machine learning models developed by Servien et al. (2021). This allowed a completed assessment of the overall potential impacts (on human health and on aquatic environment) of 153 organic micropollutants in continental freshwater at the scale of France.

2. Materials and Methods

2.1 Molecules

Aemig et al. (2021) identified 261 organic micropollutants (released by WWTP) representing a potential danger to human health and aquatic environment in continental freshwater. These molecules came from (i) the Waste Framework Directive (WFD, Directive 2008/105/CE), (ii) the RSDE national action for survey and reduction of hazardous substances in water (INERIS, 2016), and (iii) the AMPERES French project in which micropollutants (registered in the WFD and pharmaceuticals) were analyzed in influents and effluents of 15 WWTP (Martin Ruel et al., 2012). Among these 261 organic micropollutants, the emitted mass of 153 was estimated with 90% of the measured data above the limit of quantification. The impacts of these 153 compounds, whose names are gathered in Table S1, are assessed in this work.

2.2 Characterization factors

Among the 153 micropollutants, Aemig et al. (2021) identified 88 compounds with characterization factors for aquatic environment (CF_{ET}) and 94 compounds with

characterization factors for human health (CF_{HT}) for emissions in continental freshwater in the USEtox[®] (Rosenbaum et al., 2008) database, version 2.12. USEtox[®] is an international consensual for characterizing human and ecotoxicological impacts of chemicals (UNEP-SETAC, 2019). To perform the calculation of the impacts of the 153 compounds, we computed 65 missing ecotoxicological characterization factors and 59 missing toxicological characterization factors, using the machine learning models developed by Servien et al. (2021). These models predict ecotoxicological or toxicological characterization factors using 40 selected easy-to-obtain molecular descriptors, provided in Table S2. For more details on the choice of these descriptors, the interested reader is referred to Servien et al. (2014). These models are based on a comparison between global and cluster-then-predict approaches with partial least squares, support vector machines, and random forest. The best approaches were then selected for each cluster and each characterization factor. To apply the cluster-then-predict approaches, the cluster of each new compound needs to be estimated using a supervised clustering approach based on the clusters already obtained in Servien et al. (2021). So, the cluster of each compound was estimated using the well-known k-nearest neighbor approach through the *knn* function of the R package *class* (Ripley, 1996). Then, the models selected in Servien et al. (2021) were applied without any modification, assuming they had been previously tested on a large diversity of molecules covering the diversity of the compounds assessed in the present study.

2.3 Calculation of molecular descriptors

CHEM-3D of ChemOffice Ultra 12.0 (2017) molecular modeling software was used to build three-dimensional chemical structures (3D-structures) in order to calculate the quantum-chemical molecular descriptors (see Table S2). The Excel function of

ChemOffice was then used to calculate the molecular weights and the Connolly surface areas. Finally, the constitutional (except the molecular weight) and the topological descriptors were calculated with Dragon 7.0 (2017).

2.4 Quantification of the potential impacts

The annual volume of water effluent released into the environment by WWTP was estimated to be 5.10^9 m^3 , in France (Aemig et al., 2021). This volume was determined by multiplying the daily flow arriving at the WWTP during 365 days, assuming that it was equal to the effluent. The emitted mass of micropollutants was estimated by multiplying each concentration of the 153 micropollutants by the volume of effluent. The mass was expressed in kilograms or tons of micropollutants discharged by the WWTP effluents in one year at the national scale. The concentrations and masses are those of the Supplemental Material of Aemig et al. (2021) and are gathered in Tables S1 and S3. Total impacts on human health and aquatic environment in continental freshwater were quantified by summing the impacts of all the compounds, as it is usually done in LCA (Heijungs and Suh, 2002). Human impact is expressed in DALY (Disability-Adjusted Life Years) representing the number of negatively impacted human years, and the ecotoxicological impact is expressed in PDF (Potentially Disappeared Fraction of species) representing the potential fraction of disappeared species.

3. Results and discussion

3.1 Global analysis

The addition of new molecules (+59 for human toxicity and +65 for ecotoxicity) more than doubled the total emitted mass (from 71.1 and 64.5 tons to 147.1 tons) of micropollutants released into freshwater in one year. We can notice in Table S1 that

161 valsartan (137862-53-4), dichloromethane (75-09-2), irbesartan (138402-11-6),
 162 ranitidine (66357-35-5), hydrochlorothiazide (58-93-5), and AMPA (1066-51-9)
 163 represent 51% of the total mass released, and less than 4% of the micropollutants
 164 identified.

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

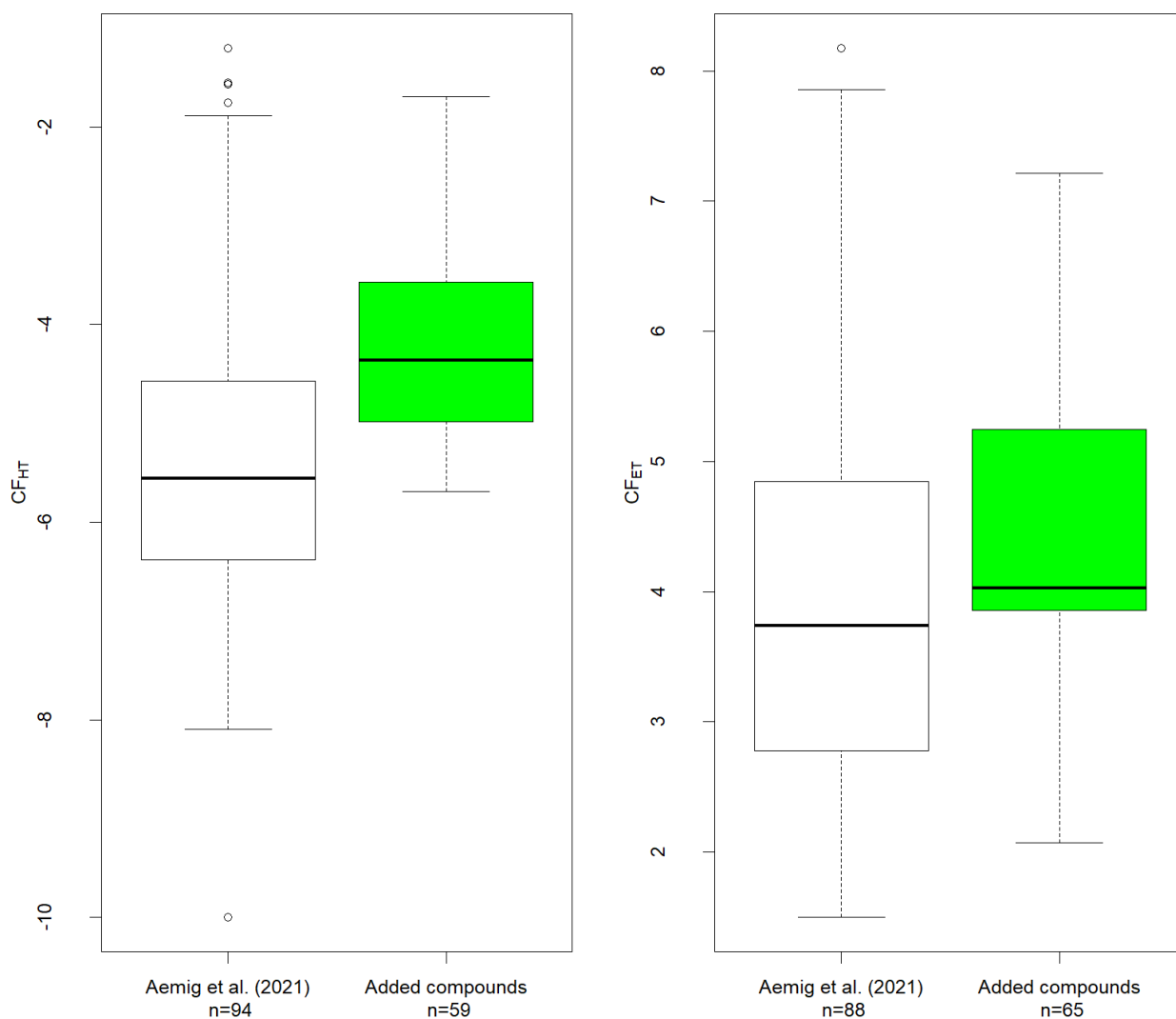


Figure 1. Comparison of the $\log_{10}(\text{CF}_{\text{HT}}+1\text{e-}10)$ and $\log_{10}(\text{CF}_{\text{ET}})$ for the compounds taken into account in Aemig et al. (2021) and the added compounds for which the CFs are calculated using the models in Servien et al. (2021).

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

In more details, for the CF_{HT} (resp. CF_{ET}), the \log_{10} median of the value of the study of Aemig et al. (2021) is 1.2 \log_{10} (resp. 0.3 \log_{10}) smaller than that of the added compounds. For the CF_{HT} , the minimum, the first and third quartiles, the mean, and the median values of Aemig et al. (2021) are all more than 1 \log_{10} smaller than those of the added compounds. The differences are smaller for the CF_{ET} , around 0.5 \log_{10} . But, for both CF, the maxima were higher in the Aemig et al. (2021) study. All these descriptive values are given in Table S4.

3.2 Impact on the aquatic environment

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

- 99% of the impact is now induced by 24 molecules and 21% of the total mass,
- the 10 molecules with the highest impact represent nearly 98% of the impact and 6% of the total mass (Table 1),
- among the 10 most impactful, three were different from the previous study
- the total impact has increased by only 4%.

195

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

CAS Number	Name	Impact (%)	Emitted mass (%)	Emitted mass (kg)	CF _{ET} (PDF/kg)	PDF
52315-07-8	Cypermethrin	79.21	0.47	696.3	7.17E+07	4.99E+10
37680-73-2	PCB 101	11.15	0.03	47.1	1.49E+08	7.03E+09
50-28-2	17- β -estradiol	2.28	0.01	9.6	1.50E+08	1.44E+09
<u>154-21-2</u>	<u>Lincomycin</u>	1.43	0.31	450.0	2.00E+06	9.01E+08
26787-78-0	Amoxicillin	1.09	0.07	100.0	6.87E+06	6.87E+08
<u>42399-41-7</u>	<u>Diltiazem</u>	0.91	0.02	35.0	1.64E+07	5.75E+08
74070-46-5	Aclonifen	0.52	0.44	653.5	5.00E+05	3.27E+08
3194-55-6	1,2,5,6,9,10-hexabromocyclododecan	0.44	0.20	296.2	9.27E+05	2.75E+08
<u>58-93-5</u>	<u>Hydrochlorothiazide</u>	0.32	4.64	6822.0	2.91E+04	1.99E+08
188425-85-6	Boscalid	0.31	0.22	320.8	6.06E+05	1.95E+08
Total		97.65	6.41	-	-	-

198

199 According to Aemig et al. (2021), cypermethrin accounted for 82% of the total impact.
 200 In this work, the addition of the 65 compounds slightly decreased this percentage to
 201 79%. If cypermethrin is not taken into account in the calculation of the total impact, the
 202 first nine most impactful compounds represent 90% of the total impact and 6% of the
 203 total emitted mass, highlighting that the total impact is due to only a small number of
 204 molecules and a small amount of the total mass. The three molecules added in the top

205 ten are pharmaceuticals: one antibiotic (lincomycin from the lincosamide class), one
206 calcium channel blocker (diltiazem), and one diuretic usually used in combination with
207 irbesartan for the treatment of hypertensive disease (hydrochlorothiazide). For the
208 latter, the released mass is quite high, representing near 5% of the total mass, but its
209 low CF led to a net contribution to the impact of only 0.3%. As the most impactful
210 compounds represent only a very small percentage of the total mass, the impact is
211 mainly due to their high ecotoxicological value, given by the CF_{ET} . According to Figure
212 1, it can be expected that the addition of a set of compounds with higher CF_{ET} would
213 increase a lot the global impacts. However, these impacts are mainly due to extreme
214 values of CF_{ET} that are not present in our new set of compounds, as shown in Figure
215 2. We could also see that some added compounds have a high mass but a too low
216 CF_{ET} to have a significant effect on the overall impact.

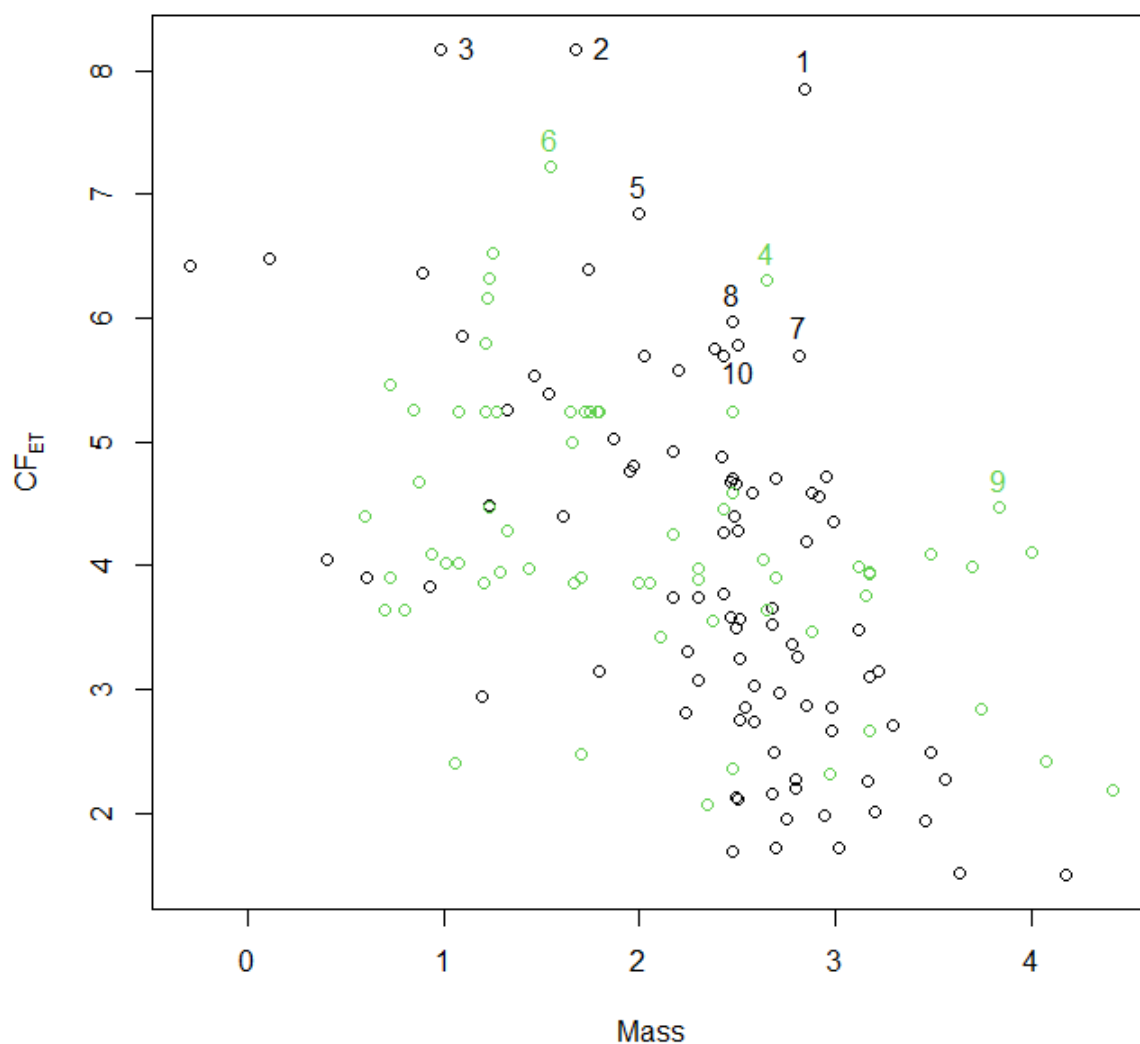


Figure 2 – CF_{ET} of the 153 studied compounds as a function of the emitted mass (both in log scale). Compounds of Aemig et al. (2021) are in black, the new ones are in green. The numbers represent the 10 most impactful compounds, in decreasing order (*i.e.* the same order as Table 1).

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

3.2 Impact on Human health

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

- 94% of the impact is now induced by 26 molecules and 41% of the total mass,
- the eight molecules with the highest impact represent 70% of the impact and 27% of the total mass (Table 2),
- on the 20 molecules that are identified as the most impactful, 13 molecules were not incorporated in the previous study. This now represents 92% of the impact and 32% of the total mass,
- the total impact has nearly doubled.

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

CAS Number	Name	Impact (%)	Emitted mass (%)	Emitted mass (kg)	CF _{HT} (DALY/kg)	DALY
<u>137862-53-4</u>	<u>Valsartan</u>	14.959	17.7	26067.4	6.54E-05	1.71E+00
205-99-2	Benzo(b)fluoranthene	14.621	0.04	61.9	2.69E-02	1.67E+00
207-08-9	Benzo(k)fluoranthene	8.182	0.04	52.7	1.77E-02	9.33E-01
53-86-1	Indomethacin	7.581	0.64	940.2	9.19E-04	8.64E-01
115-32-2	Dicofol	6.847	0.17	243.8	3.20E-03	7.81E-01
<u>138402-11-6</u>	<u>Irbesartan</u>	6.600	8.05	11848.7	6.35E-05	7.52E-01
193-39-5	Indeno(1,2,3-cd)pyrene	6.283	0.04	55.5	1.29E-02	7.16E-01
<u>465-73-6</u>	<u>Isodrin</u>	4.526	0.04	54.9	9.41E-03	5.16E-01

<u>25637-99-4</u>	<u>1,3,5,7,9,11-</u> <u>Hexabromocyclododecane</u>	4.059	0.20	296.2	1.56E-03	4.63E-01
32534-81-9	Pentabromodiphenylethers	3.094	0.01	12.5	2.82E-02	3.53E-01
Total		76.75	26.9	-	-	-

240

241 The main conclusion of the study of Aemig et al. (2021) (only a small number of
242 molecules and a small percentage of the mass led to nearly all the impact) does not
243 stand anymore for the CF_{HT}. First, the high impact of the most impacting compound
244 (valsartan) is due to its very high emitted mass, nearly 18% of the total mass.
245 Depending on the compound, a high impact could be driven by a high mass, a high
246 CF_{HT}, or a combination of both (Figure 3).

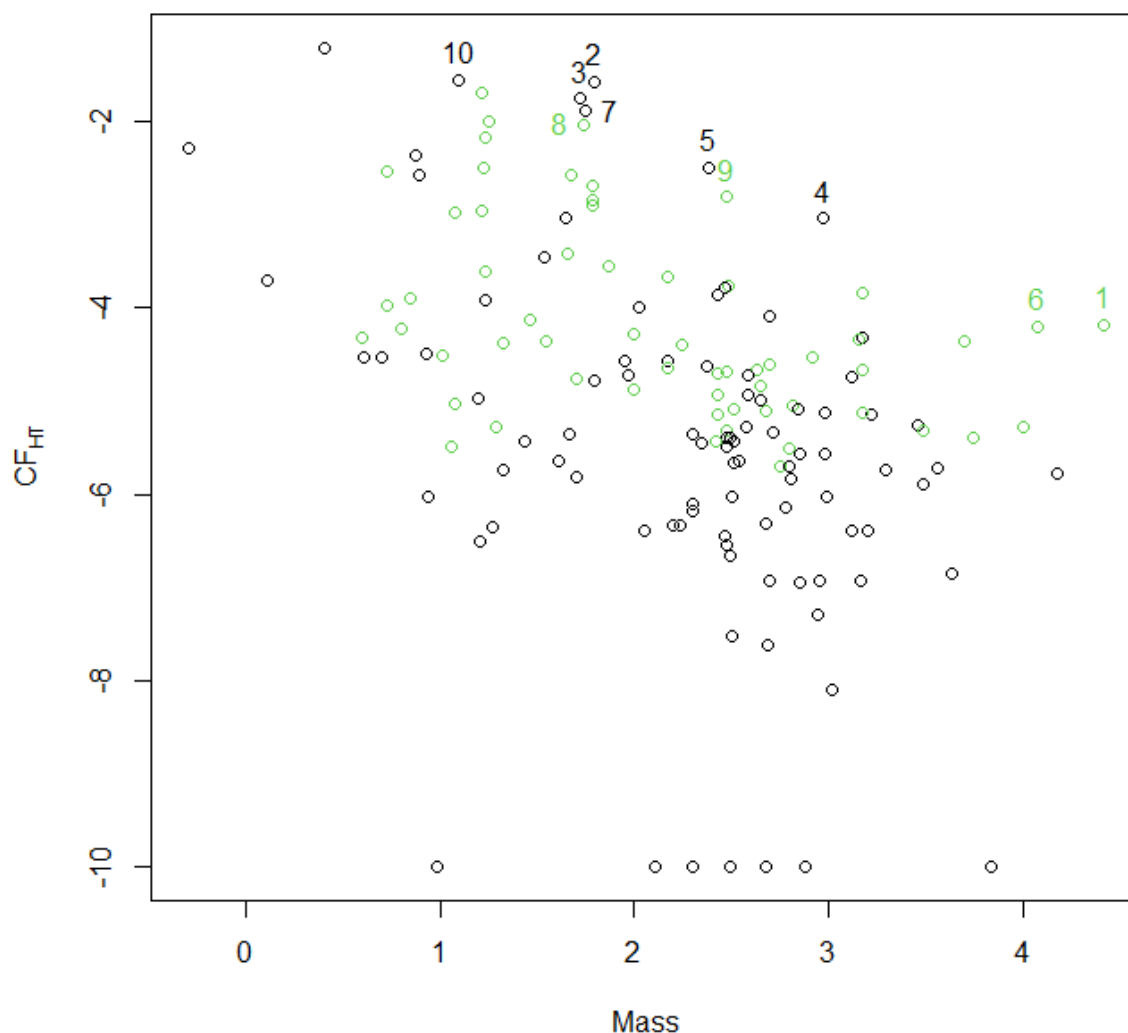


Figure 3 - CF_{HT} of the 153 compounds as a function of the emitted mass (both in log scale). Compounds of Aemig et al. (2021) are in black, the new ones are in green. The numbers represent the 10 most impactful compounds, in decreasing order (*i.e.* the same order as Table 2).

Second, the number of molecules needed to reach 94% of the total impact has been multiplied by more than three (8 to 26) highlighting a more equal distribution of the impacts among the compounds. In the ten most impactful molecules, six have been added by the present study. Among these six compounds, two are anti-hypertensive

drugs, valsartan, and irbesartan, which contributed to the impact (Table 2) thanks to their high masses released in the environment that could be linked to their high uses and low removal in WWTP (Boix et al., 2016). Two other molecules, the isodrin organochlorine insecticide (present in the WFD registered list with environmental quality standards and no more used in France) and the hexabromocyclododecane (HBCDD) flame retardant (included in the persistent mobile toxic (PBT) substances list of very high concern requiring authorization before use in EU and progressively banned since 2011(ECHA, 2008)) contributed to the impact because of their high toxicity, similarly to the first two PAHs (benzo(b)fluoranthene and benzo(k)fluoranthene) (Table 2).

Then, contrarily to the aquatic impacts, the total impact on human health has nearly doubled compared to the results of Aemig et al. (2021), leading to the conclusion that evaluating the human health impacts based only on the available CF_{HT} could provide very underestimated impacts (Table S3).

4 Conclusion

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

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

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