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1 **Levels and trends of synthetic musks in marine bivalves from French coastal areas**

2

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9

10 **Abstract**

11 The levels and trends of four bioaccumulative synthetic musks (galaxolide - HHCB, tonalide -

12 AHTN, musk xylene - MX and musk ketone - MK) were investigated in filter-feeding

13 bivalves collected yearly since 2010 at sites of contrasted pressure along the French coasts.

14 Quantification rates were high for all 4 compounds (85-99%), indicating their geographical

15 and temporal extensive occurrence in the French coastal environment. The polycyclic musks

16 HHCB and AHTN prevailed, with median concentrations of 2.27 ng g⁻¹ dw and of 0.724 ng g⁻¹

17 ¹ dw, whilst nitromusks were found 1 to 2 orders of magnitude lower. These levels were in the

18 high range of those encountered for various other CEC families at the same sites and

19 comparable to those from other locations on European coasts. Unlike for the other musks, the

20 accumulation of HHCB was evidenced to be species-specific, with significantly lower levels

21 found in oysters in comparison with mussels, possibly suggesting a higher metabolization in

22 oysters. Geographical differences in musk distribution highlighted the sites under strong

23 anthropogenic pressures and these differences were found to be consistent between years. The

24 HHCB / AHTN ratio proved to be discriminant to explain the relative occurrence of

25 polycyclic musks. The 8-year time series showed that only the now-banned compound MX

26 displayed a significant decrease in most sites, whilst stable concentrations of the other musks
27 suggested consistency in their usage over the last decade. These results provide reference data
28 for future studies of the occurrence of personal care products on European coasts.

29

30 **Highlights**

- 31 - Investigation of synthetic musks in bivalves from French coasts in 2010-2019
- 32 - Widespread occurrence of HHCB, AHTN, musk xylene and ketone
- 33 - Species-specific accumulation of HHCB, potentially related to metabolization
- 34 - Levels reflect urban pressure, notably in the Seine Bay
- 35 - Significantly decreasing temporal trend for musk xylene only

36

37 **Keywords:** coastal marine environment; bioaccumulation; shellfish; Personal Care Products
38 (PCPs); Galaxolide; Tonalide

39 **1. Introduction**

40 Synthetic musks are extensively used as fragrance additives in a wide range of scented
41 consumer goods, such as personal care (perfumes, soaps, deodorants, shampoo, etc.) and
42 household products (air fresheners, cleaning agents, detergents, etc.). Among the predominant
43 compounds in these products are polycyclic musks (galaxolide - HHCB and tonalide -
44 AHTN), macrocyclic musks and nitromusks (musk ketone - MK and musk xylene - MX)
45 (Nakata et al., 2015; Reiner and Kannan, 2006; Sanchez-Prado et al., 2011). Although in 2004
46 95% of the European market for all polycyclic and nitromusks was composed, in decreasing
47 tonnage, of HHCB, AHTN, MK and MX (OSPAR, 2008), the previously cited studies have
48 reported the growing use of the more degradable macrocyclic musks and the lower prevalence
49 of nitromusks in consumer products in the last 10-15 years. Very persistent, very
50 bioaccumulative (vPvB) and toxic, MX has been banned under the European REACH

51 regulation (Registration, Evaluation, Authorization and Restriction of Chemical substances)
52 since 2011 (European Commission, 2011). This compound has also been included in the List
53 of Chemicals for Priority Action of the Convention for the Protection of the Marine
54 Environment of the North-East Atlantic (OSPAR Convention) since 1998. Recent data have
55 established that the polycyclic musks HHCB and AHTN are produced or imported between
56 1,000 and 10,000 tons per year in the EU and the nitro-musk ketone (MK) between 100 and
57 1,000 t y⁻¹ (ECHA, 2020). HHCB and AHTN are recognized as priority substances by the
58 Norman network (<https://www.norman-network.net/?q=node/19>) and HHCB belongs to the
59 Howard and Muir's list of high-priority pollutants regarding persistence and bioaccumulation
60 potential (Howard and Muir, 2010).

61 Reflecting their use, synthetic musks enter the aquatic environment mainly via effluents from
62 waste water treatment plants (WWTPs, Homem et al., 2015), a different pathway to most
63 persistent organic pollutants (POPs, Melymuk et al., 2014). Synthetic musks have
64 subsequently been found in coastal waters and sediments receiving anthropogenic inputs
65 (Aminot et al., 2019; Lee et al., 2014; Sumner et al., 2010). Further volatilization
66 (McDonough et al., 2016) and direct release to ambient air from urban areas (Weinberg et al.,
67 2011; Wong et al., 2019) cause atmospheric contamination. If the potential for long-range
68 transport is debated (Wong et al., 2019 and references herein), synthetic musks have been
69 detected in polar environments (Xie et al., 2007) and in alpine locations (Ferrario et al., 2017),
70 suggesting dry/wet deposition as a possible secondary source of oceanic contamination.

71 Due to their lipophilic character (log K_{ow} 4-6), these substances tend to accumulate in marine
72 biota (Liu et al., 2020), and bivalves in particular (Nakata et al., 2012; Picot Groz et al.,
73 2014).

74 Based on a rather low reported (eco)toxicity of most synthetic musks, several evaluations
75 have assumed that such compounds pose no risk to the marine environment (OSPAR, 2019)

76 despite their relatively high concentration levels (Casatta et al., 2015; Nakata et al., 2012).
77 The recent global concerns on endocrine disruption have prompted a new evaluation of
78 HHCB and AHTN within the European REACH framework as of 2020, whilst the possibility
79 for a systematic underestimation of their toxicity in laboratory conditions *in vivo* due to
80 inadequate experimental design for testing semi-volatile compounds was raised (Tumová et
81 al., 2019). Regardless of their toxicity, the authors share the opinion that the persistence of
82 contaminants in the environment is, by itself, a major cause of concern warranting further
83 research (Cousins et al., 2019).

84 Monitoring of bioaccumulative contaminants using filter-feeding shellfish as sentinel species
85 has long been a technique of choice for the determination of the levels and trends of POPs in
86 the marine environment, in particular within large scale “Mussel watch” programs
87 operated/conducted worldwide (Farrington et al., 2016). More recently, the inclusion of
88 Contaminants of Emerging Concern (CECs) alongside the well-established POPs allowed the
89 environmental evaluation in coastal ecosystems of various compounds such as non-PBDE
90 flame retardants (Isobe et al., 2012; Munsch et al., 2015), alkylphenols (Dodder et al., 2014),
91 PFASs (Munsch et al., 2019), or personal care products (Nakata et al., 2012). Regarding
92 synthetic musks, although a number of studies reported concentrations of synthetic musks in
93 coastal ecosystems, extended evaluations of spatial distribution and recent evaluations of their
94 temporal variabilities in the marine environment are lacking. In light of the above, this study
95 aims to investigate the levels, geographical distribution and inter-annual trends of 4 selected
96 synthetic musks in shellfish collected between 2010 and 2019 at 21 sites of contrasted
97 anthropogenic pressure along the French coastlines.

98 **2. Materials and methods**

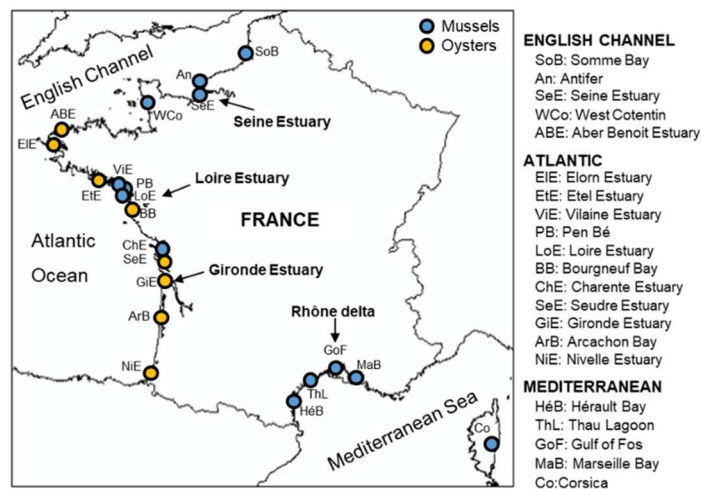
99 *2.1 Chemicals and reagents*

100 All chemicals were carefully-selected to satisfy trace analysis requirements. Picograde®
101 solvents (dichloromethane - DCM, *n*-hexane, isooctane, methanol, ethyl acetate) were
102 purchased from Promochem (Germany) or LGC Standards (France). Bio-Bead S-X3
103 polystyrene gel beads (200–400 Mesh) were supplied by Bio-Rad Laboratories Inc. (USA).
104 Silica gel (100–200 Mesh), aluminium oxide (90 standardized), Florisil (60–200 Mesh) were
105 supplied respectively by Sigma Aldrich (Germany), Merck (Germany) and Fluka (Germany).
106 Musk standards were purchased from LGC Standards (France): 1,3,4,7,8-hexahydro-
107 4,6,6,7,8,8-hexamethylcyclopenta-(γ)-2-benzopyran (HHCB, 51% purity and 73% purity in
108 2019); 4-aceto-3,5-dimethyl-2,6-dinitrotert-butylbenzene (MK, 98%); 7-acetyl-1,1,3,4,4,6-
109 hexamethyl-1,2,3,4-tetrahydronaphthalene (AHTN, 98.5%) and 2,4,6 -trinitro-1,3-dimethyl-5-
110 tert-butylbenzene (MX, 99.5%). Standard purity was accounted for in the preparation of the
111 parent solutions. Regarding HHCB low purity, a higher grade (Dr. Ehrenstorfer, 73 %) was
112 used in 2019. Consistent response coefficients and accurate measurements of our in-house QC
113 material confirmed the suitability of all HHCB standards used. Deuterated-musk xylene (MX-
114 d15, chemical purity 96.8% - LGC Standards, France) was used as internal standard and *d*10-
115 Phenanthrene (Phe-d10, 98% - CIL, USA) or *d*9-musk xylene (MX-d9, 98% - CIL, USA)
116 were used as an injection standard. Deuterated-AHTN (AHTN-d3, LGC Standards, France)
117 was tested for use as a potential internal standard but D-H exchange occurring during the
118 preparation protocol caused an unacceptable increase of AHTN levels in procedural blanks, in
119 agreement with previous reports (Bester, 2009).

120 2.2 Sampling strategy

121 The mussel (*Mytilus spp*) and oyster (*Crassostrea gigas*) samples used for our study were
122 collected annually in autumn (out of spawning season) in 2010 and from 2013 to 2019 at the
123 same selected locations in the English Channel, Atlantic and along Mediterranean coasts, as

124 shown in Figure 1. These locations cover main estuaries and deltas (Seine, Loire, Gironde,
 125 Rhône), together with smaller tributaries and various locations away from direct sources.
 126 The shellfish were collected and handled in accordance with international guidelines for the
 127 monitoring of contaminants in biota (OSPAR, 2018), as previously described (Munschy et al.,
 128 2019). Briefly, all samples were collected in the same manner and at the same time of year
 129 (from late November to early December); each individual had spent at least 6 months *in situ*
 130 beforehand. Each composite sample consisted of at least 50 ± 5 mussels of similar size (30–
 131 60 mm shell length) or 10 ± 1 oysters (90–140 mm shell length). All samples were
 132 systematically depurated in settled water from the site for 24 h, shelled, homogenized (whole
 133 soft body) and stored at $-20\text{ }^{\circ}\text{C}$ prior to freeze-drying (dry weights provided in Table S1). The
 134 dried samples were stored in a cool, dry, dark place until further analysis.



135
 136 **Figure 1.** Sampling sites for bivalves collected in 2010 and from 2013 to 2019 from the
 137 English Channel, Atlantic and Mediterranean coasts

138 *2.3 Sample preparation and analysis*

139 The entire sample preparation and subsequent analyses were performed in clean laboratories,
 140 under a low-dust atmosphere and positive pressure (ISO 8 class according to NF EN ISO

141 14644). Between 2 and 5 grams of freeze-dried bivalve sample were spiked with the internal
142 standard MX-d15 and extracted by Accelerated Solvent Extraction (ASE, Dionex) using
143 DCM/*n*-hexane (50:50, v:v). The extracts were cleaned on a gel permeation chromatography
144 glass column (460 mm × 26 mm) filled with styrene–divinylbenzene (65 g of Bio-beads SX3)
145 and eluted with DCM (185 mL first discarded, followed by 65 mL of the analyte elution
146 fraction). Purification was further performed on both florisil and silica/alumina columns
147 eluted respectively with *n*-hexane/ethyl acetate (95:5, v:v) and *n*-hexane/DCM (60:40, v:v).
148 After concentration in isooctane, the extracts were spiked with the injection standards Phe-
149 d10 (samples from 2010-2017) or the more-closely related MX-d9 (2018-2019).

150 The instrumental analyses for samples from 2010 to 2016 were performed on an Agilent 7890
151 gas chromatograph coupled to an Agilent 5975 mass spectrometer (GC/MS) equipped with an
152 EI and NCI sources, and from 2017 onwards using a Agilent A7890 coupled to a Waters
153 Xevo TQ-S micro triple quadrupole mass spectrometer (GC-MS/MS) equipped with an
154 APGC source (APCI). The configuration was as follows: HHCB EI or APGC, AHTN EI or
155 APGC, MX NCI, MK NCI or APGC. Ions were monitored by single ion monitoring (single
156 MS) or multiple reaction monitoring (tandem MS). The GC was fitted with a DB-5 MS
157 capillary column (40 m × 0.18 mm × 0.18 μm) with helium as the carrier gas (0.8 mL min⁻¹ in
158 GC-MS and 1.5 mL min⁻¹ in GC-MS/MS). Musks were separated in a 42 min (GC/MS) or 34
159 min (GC-MS/MS) temperature gradient from 110 °C to 320 °C, with an inlet temperature of
160 280 °C. Relative response factors of target analytes relative to internal standard (MX-d15)
161 were calculated from a 7-point calibration curve for quantification. MX-d15 recovery was
162 calculated against the injection standard (Phe-d10 or MX-d9).

163 QA/QC is provided in supplementary information (QA/QC section, Fig S1 and Fig S2).

164 *2.4 Statistical analysis*

165 Statistical analyses were performed using Addinsoft XLStat software. Spearman rank
166 correlations were applied (Spearman “ ρ ” coefficient). The non-parametric Mann–Whitney test
167 was used for comparison of two independent samples, with a significance level of 0.01. The
168 significance of the temporal trend was assessed using the non-parametric Mann-Kendall
169 statistical method, which assesses ranks across samples. Concentrations < LOQs (less than
170 15% of the samples, see detection frequencies in 3.1) were ignored in correlation analyses,
171 counted as zero in distribution profiles and given a value of LOQ/2 in temporal trend analysis.

172 **3. Results and discussion**

173 *3.1 Levels and profiles of synthetic musks*

174 Among the 125 samples analysed over the 9 year study, AHTN was quantified in 99%
175 (annual min-max 95-100%), MK in 92% (77-100%), MX in 89% (64-100) and HHCB in 85%
176 (73-100%) of the samples. The highest median concentrations were found for the polycyclic
177 musks HHCB at 2.27 ng g⁻¹ dw (min 0.131 – max 54.5 ng g⁻¹ dw) and AHTN at 0.724 ng g⁻¹
178 dw (min 0.146 – max 9.30 ng g⁻¹ dw). The nitro-aromatic musks MX and MK were found at
179 median concentrations of 0.032 ng g⁻¹ dw (min 0.009 – max 0.167 ng g⁻¹ dw) and 0.066 ng g⁻¹
180 dw (min 0.006 – max 1.47 ng g⁻¹ dw), respectively. These levels are consistent with their
181 usage in Europe, as MX use is now banned and MK is in a lower production/import tonnage
182 band (100-1 000 for MK vs 1 000-10 000 t y⁻¹ for HHCB and AHTN, ECHA, 2020).

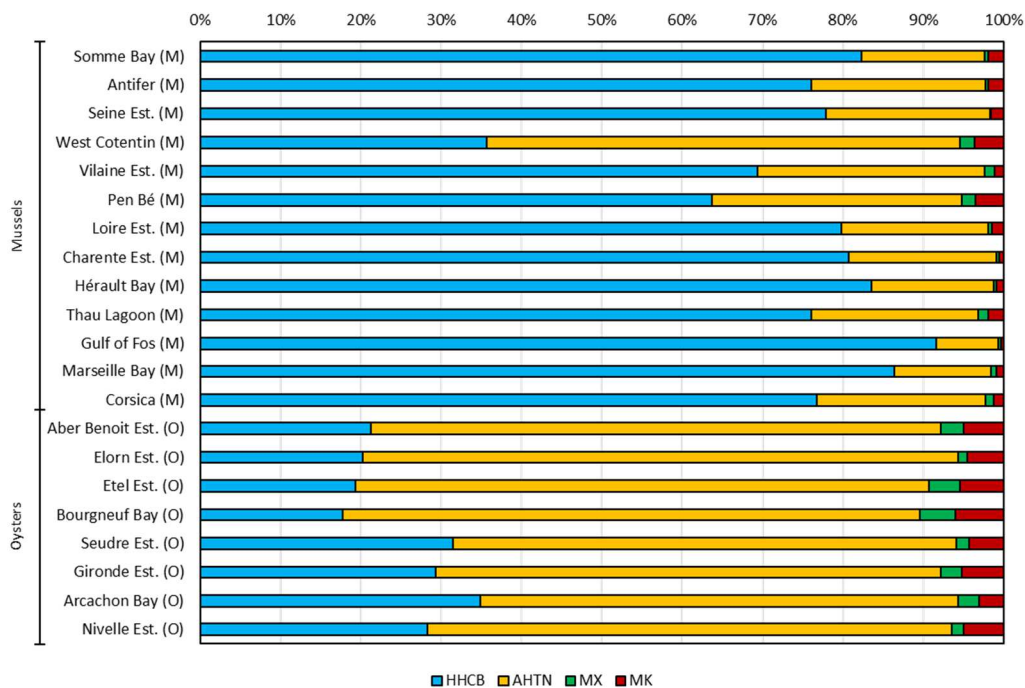
183 In comparison with other hydrophobic contaminants also analysed in the same samples,
184 synthetic musks were found to be the most abundant, with concentrations decreasing as
185 follows: in the ng g⁻¹ dw: polycyclic musks; in the hundreds of pg g⁻¹ dw: perfluorocarboxylic
186 acids (\sum C₉-C₁₄ PFCAs) > perfluorooctane sulfonate (PFOS) ~ polybrominated diphenyl
187 ethers (\sum 8 OSPAR PBDE congeners) > hexabromocyclododecane (HBCDD); in the tens of
188 pg g⁻¹: nitromusks and alternative brominated flame retardants (BTBPE, DBDPE) (for further

189 details, refer to (Munschy et al., 2019, 2015, 2013). Similar rankings between contaminant
190 families have been reported worldwide; however, co-analysis of synthetic musks and other
191 contaminants in bivalve biomonitoring programme has seldom been reported. In the Asia-
192 Pacific region, synthetic musk levels were also one to two orders of magnitude higher than
193 PBDEs (Nakata et al., 2012) and in clams of an Italian lagoon under influence of the Po
194 River, AHTN concentrations were ~100 times higher than PBDEs and ~10-100 times higher
195 than HBCDDs (Casatta et al., 2015). In light of these rankings, synthetic musks in the marine
196 environment should deserve a wider attention from the marine research community and in
197 marine biomonitoring programs.

198 All sites and years confounded, all compounds (but HHCB with MX) were significantly
199 correlated (ρ between 0.42 and 0.87); however, the correlation appears altered by the high
200 values found in the Seine Estuary and Bay (details on the correlations are given in Table S2).
201 After exclusion of these strong outliers, no correlation was found between HHCB and any of
202 the other musks (ρ between 0.11 and 0.24) when both species were considered together.
203 However, when considered separately and without outliers, HHCB concentrations
204 significantly correlated with AHTN and MK ones in both mussels (AHTN $\rho = 0.59$, $n=62$;
205 MK $\rho = 0.47$, $n=56$) and oysters (AHTN $\rho = 0.64$, $n=28$; MK $\rho = 0.54$, $n=28$). AHTN, MX
206 and MK were significantly correlated regardless of the bivalve subset (ρ 0.37-0.88), with the
207 strongest correlation observed between AHTN and MK (ρ 0.75-0.88, $p < 0.01$). As HHCB,
208 AHTN and MK share a common wastewater-derived source (Homem et al., 2015), the weaker
209 correlations with HHCB would suggest a dissimilarity in its environmental behaviour (such as
210 persistence and bioaccumulation). However, the paucity of comparable data on the
211 environmental degradation of musks and the somewhat variable bioaccumulation factors
212 reported in the literature prevent further examination of this hypothesis.

213 In abiotic media from various locations worldwide, HHCB and AHTN are found to co-vary.
214 Examples where their concentrations are strongly correlated have been observed in water and
215 sediment samples from the Songhua River, China (Lu et al., 2015), in sewage and surface
216 water samples from South Korea (Lee et al., 2010) and in coastal waters from southern Spain
217 (Pintado-Herrera et al., 2020). These studies highlight similar sources and behaviours for
218 these two SMs. Further, these observations suggest that the lack of correlation we observed
219 when mussels and oysters were considered together does not reflect geographical
220 peculiarities, but rather points towards a species-specific pattern. The musk distribution
221 profiles (Figure 2) were indeed significantly distinct in the 8 sites sampled for oysters, with
222 HHCB composing 18-35% of the profiles, while the 13 mussel-monitored sites had a much
223 higher contribution of HHCB (64-92%, except for one site at 36%). When considering the
224 concentrations measured at all sites and years for mussels and oysters separately (Figure S3),
225 no significant differences in concentrations between species were observed for AHTN, MX
226 and MK, in contrast to HHCB concentrations in oysters, significantly lower (p-value <
227 0.0001) than in mussels by an average factor of 5. This difference cannot be attributed to a
228 specific matrix effect as good recoveries were obtained for both matrices on spiked controls
229 (see Fig S2). With comparable hydrophobicity (log K_{ow} of 5.3 and 5.4, (EU, 2008a, 2008b),
230 HHCB lower bioaccumulation in oysters compared with AHTN could relate to partial
231 metabolism of HHCB in this species. Supporting their use as bioindicators, the metabolic
232 capacities of bivalves are generally considered to be low (Beyer et al., 2017), and such
233 biotransformation of HHCB by bivalves has not been reported in the literature. Species-
234 specific accumulation patterns of musks have been observed in various freshwater fish
235 species, with more pronounced differences in HHCB accumulation compared with AHTN
236 (Gatermann et al., 2002). The authors attributed this result to varying metabolic capacities of
237 freshwater fish, in conjunction with the inherent stronger susceptibility of HHCB to undergo

238 metabolism. In another study on a marine fish of higher trophic level (sea bass -
 239 *Dicentrarchus labrax*), HHCb was also found to be actively metabolised (Fernandes et al.,
 240 2013). The presence of a stable transformation product of HHCb, HHCb-lactone, has been
 241 reported in biota (Lange et al., 2015; Trabalón et al., 2015), but its use as a tracer for
 242 metabolism warrants further research as it can also originate in the environment by chemical,
 243 photochemical and/or microbiological processes. In marine bivalves, similar bioaccumulation
 244 factors for HHCb and AHTN have been reported for Lokan clams (*Polymesoda expansa*) and
 245 Asian green mussels (*Perna viridis*) (Bayen et al., 2019). HHCb and AHTN were also found
 246 to correlate regardless of the species (*Perna viridis*, *Mytilus edulis*.) in the Asia-Pacific mussel
 247 watch (Nakata et al., 2012). Further research is needed to unambiguously attribute our
 248 observations to oyster-specific metabolism, and definitely exclude peculiar contamination
 249 profiles of certain bivalve collection sites.



251 Figure 2. Relative distribution of the musk concentrations in mussels (M) and oysters (O)
252 collected on the French coastlines in 2010-2019, using the site median concentrations (n = 4
253 to 8, depending on the site). Non-detects were attributed the value LOQ/2.

254 *3.2 Comparison with worldwide levels*

255 The musk contamination levels observed in this study were compared to those reported in the
256 literature in filter-feeding bivalves from other countries (Table 1). These should be considered
257 with caution due to differences in data calculation methods (dry, wet or lipid weight
258 calculation), or lack of information on sample preparation. In the absence of a depuration
259 phase after sampling, ingested particles could incorrectly contribute to body-burden
260 concentrations (Booij et al., 2002). Moreover, results are rarely associated with sampling
261 periods, despite the significant influence of bivalve sexual maturity (spawning season and
262 lipid content) on contamination by lipophilic organic contaminants. Considering the limited
263 amount of data available for synthetic musks in marine bivalves, concentrations reported prior
264 to our period of study were also included, but comparisons should be made with extra care
265 when dealing with contaminants known or expected to show temporal variations. The levels
266 we reported are similar to those reported in Europe, with a predominance of the polycyclic
267 musks HHCB and AHTN over the nitro-musks. The maximum levels observed are also
268 comparable to those reported for three sites located at the mouth of different rivers in southern
269 Europe in Italy, Spain, and Portugal (Cunha et al., 2015; Saraiva et al., 2016) or on touristic
270 areas of South Portugal (Castro et al., 2018; Picot Groz et al., 2014). In Northern Europe,
271 Rüdél et al. (2006) performed a retrospective analysis of mussel samples from the German
272 Environmental Specimen Bank (from 1986 to 2000). The levels determined for the North Sea,
273 ranging from 0.5–1.7 ng g⁻¹ ww for HHCB and 0.4–2.5 ng g⁻¹ ww for AHTN, compare to
274 those obtained in most of our samples, while far lower levels were reported in the Baltic Sea.
275 Somewhat higher results were reported outside of Europe, in Asia, Canada or along the

276 Pacific coast of the United States, but differences in fragrance uses and practises cannot be
277 excluded. In the late 1990's, significantly different levels of polycyclic vs nitro-musks
278 between Canadian and European biota were attributed to the highest use of nitro-musks in
279 products from North America compared with Western Europe (Gatermann et al., 1999). In
280 Korea, although musk consumption patterns differed (in 2006: HHCB, 88 t/year; MK, 20
281 t/year; MX, 0.5 t/year; AHTN, below 0.1 t/year), bivalve contamination profiles remain
282 comparable to those found elsewhere, a result attributable to the higher lipophilicity of AHTN
283 and the potential contribution of global atmospheric sources (Lee et al., 2010, 2014). In
284 between Asian countries, the bivalve contamination profiles were also found to differ, with
285 high AHTN levels (relative to HHCB's) found in the 7 studied Japanese *Mytilus edulis*
286 samples in comparison to those found in that same species and in *Perna viridis* in other Asian
287 countries (Nakata et al., 2012). All of the studies, however, show high discrepancies in the
288 contamination levels, with the influence of local point sources. On the Pacific coast of the
289 USA, Nakata et al. (2012) observed high HHCB contamination levels (1600 to 2200 ng g⁻¹
290 lw) in San Francisco Bay (SF ~9.7 million inhab.) while for all the other stations on the west
291 coast, the levels were lower than 200 ng g⁻¹ lw. Similar contrasted observations were made for
292 the various sites located in Hong Kong Bay (HK ~7.4 million inhab.), with the highest levels
293 found near the discharge point of treated wastewaters. The level of contamination appears
294 related to the size of the wastewater catchment area, and to the distance-driven dilution
295 between the sampling point and the urbanised contamination sources.

296

297 Table 1. Musk concentrations (minimum - maximum and/or median/mean (\pm sd) in ng g⁻¹ dw)
298 in marine filter-feeding bivalves from various coastal locations (including this study,
299 concentrations <LOQ not considered). nd: not detected; na: not analysed.

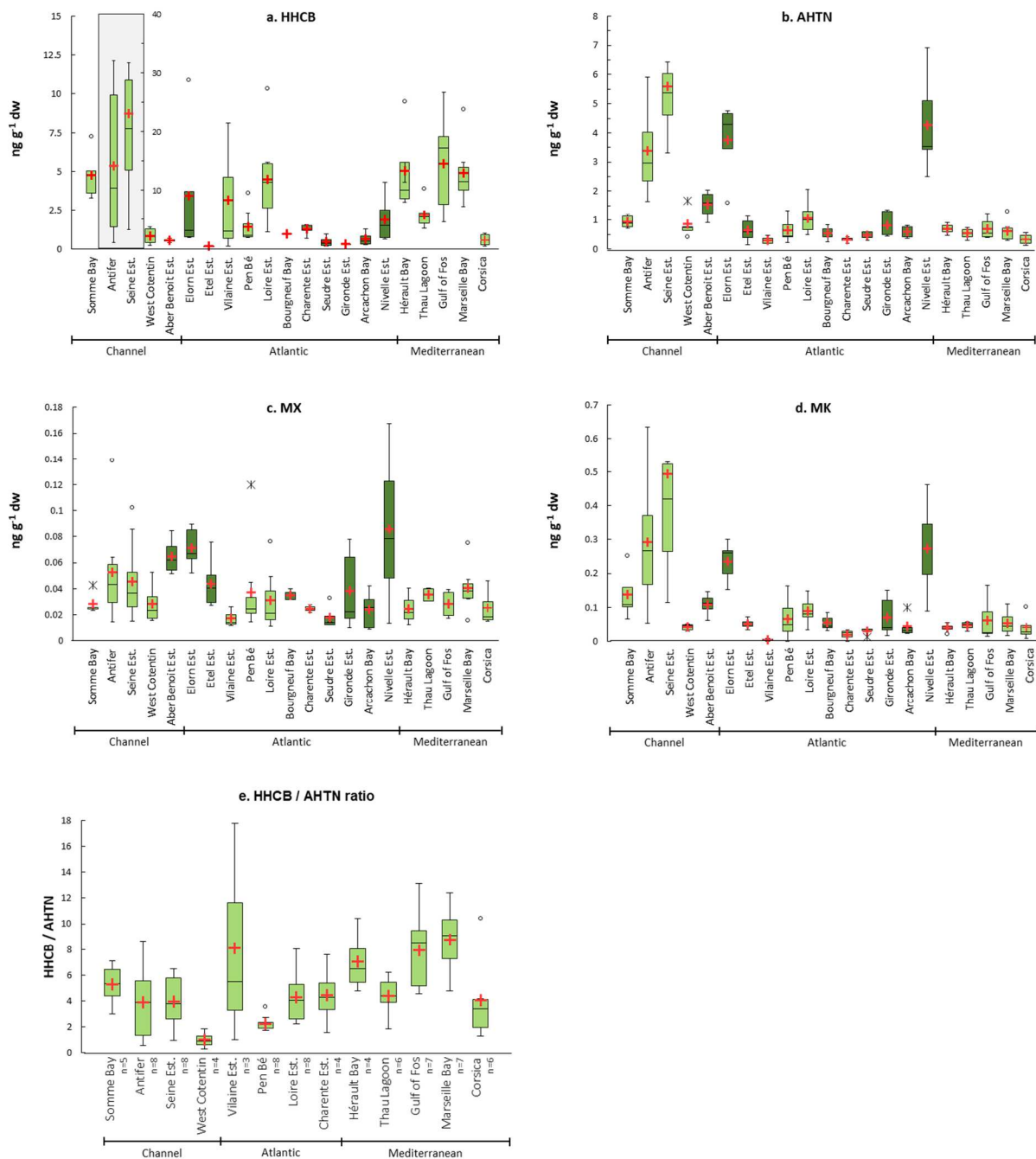
Year	Species	Concentration (min - max / median or mean) (ng g ⁻¹ dry weight*, wet weight# or lipid weight)				Reference	
		HHCb	AHTN	MX	MK		
France	2010-2019	<i>Crassostrea gigas</i> , <i>Mytilus spp.</i>	0.131 – 54.5 / 2.27*	0.146 – 9.30 / 0.724*	0.009 - 0.167 / 0.032*	0.006 - 1.47 / 0.066*	This study (dw)
	2010-2019		1.4 – 600 / 25.2	1.7 – 103 / 8.0	0.1 – 1.9 / 0.4	0.1 – 16.3 / 0.7	This study (lw)
Atlantic (La Rochelle)	2013	<i>Crassostrea gigas</i>	3.17 ± 0.01*	2.04 ± 0.01*	0.028 ± 0.001*	0.010 ± 0.001*	Saraiva et al., 2016
Atlantic (Arcachon)	2013	<i>Crassostrea gigas</i> , <i>Mytilus spp.</i>	<1.94*	2.14 ± 0.04*	<0.01*	<0.002*	Saraiva et al., 2016
Europe							
Portugal	2015	<i>Mytilus spp.</i>	nd- 159*	<10 - 31.7*	18.4*	nd	Castro. et al., 2018
Portugal, Aveiro lag.	2013	<i>Crassostrea gigas</i>	2.7*	3.1*	0.04*	<0.002*	Saraiva et al., 2016
Spain, Urdaibai	2013	<i>Crassostrea gigas</i>	4.3*	6.9*	<0.01*	0.009*	Saraiva et al., 2016
Italy, Pô delta	2013	<i>Mytilus spp.</i>	35*	13*	nd	nd	Cunha et al., 2015
Spain, Ebro delta	2013	<i>Mytilus spp.</i>	9*	7*	nd	nd	Cunha et al., 2015
Portugal, Tagus est.	2013	<i>Mytilus spp.</i>	13*	8*	nd	nd	Cunha et al., 2015
Spain, Tarragona	2013	<i>Mytilus galloprovincialis</i>	8.94*	5.65*	nd	nd	Vallecillos et al., 2015
Portugal, South	2011	<i>Mytilus galloprovincialis</i>	<0.5 - 11*	nd	na	<50*	Picot Groz et al. 2014
North Sea	1992-2000	<i>Mytilus edulis</i>	0.5 - 1.7#	0.4 – 1.7#	<0.1#	<0.1 – 0.26#	Rüdel et al., 2006
Baltic Sea	1992-2000	<i>Mytilus edulis</i>	<0.2 – 0.32#	<0.2 – 0.4#	<0.1#	<0.1#	Rüdel et al., 2006
Asia							
Singapore	2012-2013	<i>Perna viridis</i>	<17-250*	<10-30*	na	na	Bayen et al., 2019
Korea	2010	<i>Mytilus coruscus</i> , <i>Mytilus edulis</i> , <i>Crassostrea gigas</i>	56.2 - 1110	nd - 360	nd	2.36-	Lee et al., 2014
	2005	<i>Mytilus edulis</i>	nd - 14000	nd - 700	na	na	Nakata et al., 2012
Cambodia, Indonesia, Malaysia, Philippines, Vietnam	2003-2004	<i>Perna viridis</i>	nd - 5100	nd - 650	na	na	Nakata et al., 2012
China/Hong Kong	2004	<i>Mytilus edulis</i> , <i>Perna viridis</i>	nd - 2600	nd - 480	na	na	Nakata et al., 2012
Japan	2007	<i>Mytilus edulis</i>	nd - 7000	nd - 2500	na	na	Nakata et al., 2012
Canada							
Port Halifax	1997	<i>Mytilus edulis</i>	1650	<	<	2200	Gatermann et al., 1999
USA							
California, Oregon	2004-2005	<i>Mytilus spp.</i>	nd - 2200	na	na	na	Nakata et al., 2012
New Bedford (Massachusetts)	2005	<i>Mytilus edulis</i>	836	376	na	na	Subedi et al., 2014

300

301 *3.3 Geographical distribution of concentrations*

302 HHCB, AHTN and MK highest levels were consistently found in mussels from the Seine
303 estuary and further along in the Bay, with median values of 20.5, 5.38 and 0.420 ng g⁻¹ dw,
304 respectively (Figure 3). This could obviously be attributed to the high anthropogenic pressure
305 in the Seine estuary catchment area, draining effluents from an estimated 17 million
306 inhabitants (around a quarter of the French population) and known to be a highly-impacted
307 estuary by various contaminants (Munsch et al., 2015; Tappin and Millward, 2015). In
308 relation with the aforementioned species-specific bioaccumulation, the geographical
309 differences in HHCB concentrations were considered for mussels and oysters separately.
310 Among mussel sites, the Loire estuary and the Mediterranean sites of the Gulf of Fos, the
311 Hérault, and Marseille Bays showed high median concentrations, between 3.82 and 6.52 ng g⁻¹
312 dw, albeit one order of magnitude below those found in the Seine estuary. Among oyster
313 sites, the Elorn and Nivelle estuaries showed the highest HHCB median concentrations (1.17
314 and 1.53 ng g⁻¹ dw, respectively). AHTN and MK showed a similar geographical distribution:
315 besides the Seine estuary and Bay, hot spots were identified in the Elorn and Nivelle estuaries
316 on the Atlantic coast, showing, on average, median concentrations 3 times the median values
317 found on this coast. If the Elorn estuary sampling site is located in the vicinity of the
318 discharge of a 170 000 population-equivalent WWTP, the Nivelle estuary has a rather limited
319 anticipated anthropogenic pressure, with a relatively low population on a small catchment
320 area, in particular when compared to the larger Loire or Gironde estuaries of the same coast.
321 Proximity of the sampling sites to local point sources such as urban effluent discharges
322 (Sumner et al., 2010) or landfills (Eggen et al., 2010), in combination with the local
323 hydrodynamics (mixing and dilution of such effluent plumes), could account for these
324 peculiarities. In contrast with the other musks, MX interannual median concentrations show

325 much more consistency between sites, including in the Seine estuary, with a relative
326 interquartile range between sites of 63%, while HHCB, AHTN and MK showed relative Inter-
327 Quartile Range (IQR) of 276% (both species together), 86%, and 166%, respectively. As MX
328 was banned from use in the EU in 2009-2011 (Abril, 2011), it is likely that its ubiquitous
329 presence in the marine environment results from older point source emissions, gradually
330 evened and distributed on the coast following various transport processes. For the same
331 reason, the existence of a remaining hotspot in the Nivelle estuary on the Atlantic coast
332 (highest median concentrations) is unlikely the result of a contemporary use of MX. Co-
333 occurring high levels of all musks at this site (including HHCB within the oyster subset,
334 Figure 3) tends to suggest that the aforementioned point source corresponds to old stocks, MX
335 high persistency (European Chemicals Agency, 2008) could cause its release in the
336 environment for a prolonged time.



337

338 Figure 3. a, b, c and d: Geographical distributions of musk concentrations ($\text{ng g}^{-1} \text{ dw}$)
 339 determined in bivalves (mussels light green, oysters dark green) collected on the French
 340 coasts between 2010 and 2019 ($n=1$ to 8). e: Distribution of the HHCB / AHTN ratio in
 341 mussels collected along French coasts between 2010 and 2019. Boxes are 1st quartile, median
 342 and 3rd quartile, the average is plotted with a red cross and the whiskers indicate min. and

343 max. values excluding outliers. Standard Outliers fall between 1.5*IQR (Inter-Quartile
344 Range) and 3.0*IQR outside of the IQR and are plotted with an open circle. Extreme Outliers
345 fall greater than 3.0*IQR outside the IQR and are plotted with an X. HHCB concentrations in
346 the Seine estuary and Bay are plotted on a distinct scale (see inset).

347

348 *3.4 HHCB / AHTN diagnostic ratio*

349 As previously reported in the literature, the HHCB / AHTN concentration ratio can be used to
350 discriminate sources and environmental processes affecting polycyclic musk contamination in
351 the environment (Buerge et al., 2003; Xie et al., 2007). Considering the species-specific
352 accumulation previously discussed, this ratio was examined here for mussels only (Figure
353 3.e). The overall median ratio was 4.6, and spanned a large range from 0.3 to 17.8 (2.2-6.4;
354 1st-3rd quartile). Over half of the 13 sites sampled for mussels had a relatively high interannual
355 variability, i.e. over 50% (IQR). In the English Channel and Atlantic coastline, lower ratios
356 were observed for the coastal sites of West Cotentin (median 0.9) and Pen-Bé (median 1.9);
357 with both sites located further away from urban pressures when compared with more estuarine
358 sites (medians between 3.8 and 5.5). A similar observation can be made between the
359 Mediterranean sites, with lower ratios found in Thau lagoon (median 4.4) and Corsica
360 (median 3.4) compared to those of Hérault Bay (median 6.5), Gulf of Fos (median 8.6) and
361 Marseille Bay (median 9.1). The last three are under the influence of higher populated
362 watersheds (the Hérault river, the Rhone river and Marseille, the 2nd most populated city in
363 France).

364 To date, this ratio has mainly been used as a global marker of WWTP influence in surface
365 waters, although various processes have to be considered in order to fully interpret its
366 variation, leading to a broad range of values. In a Swiss lake, Buerge et al. (2003) found rather

367 constant ratios in WWTP effluents (2.6 ± 0.2), that increased with residence time in receiving
368 waters (from 3.3 ± 0.9 to 8.1 ± 1.4), an increase attributed to the highest photodegradability of
369 AHTN in water (HHCB having a 25-time longer phototransformation half-life). This was also
370 hypothesised in the lower Great Lakes (USA), where higher ratios were measured in the
371 dissolved phase further from sources (between 7-12, McDonough et al., 2016), but in apparent
372 contradiction with observations made in the UK, where ratios of 13-18 in effluents decreased
373 to 2.0-5.2 in the receiving coastal waters (Sumner et al., 2010). The authors attributed this
374 decrease to the higher degradability of HHCB, a hypothesis also supported by data from a
375 German river (ratio of 5.0 in waters downstream a WWTP discharge, decreasing to 3.8 along
376 the river, Lange et al., 2015). In South Korea, sewage effluents and their receiving surface
377 waters had comparable ratios of 4.08-5.42 (Lee et al., 2010), a similar observation made in the
378 Berlin region (2.87 in effluents, 2.77 in surface waters, Heberer, 2002) and in the Las Vegas
379 region (1.6 ± 0.3 in effluents, 1.9 ± 0.9 in lake, Osemwengie and Gerstenberger, 2004). There
380 is a general agreement on the finding of ratios close to 1 in air and background sites primarily
381 under influence of atmospheric depositions, where AHTN is more stable to atmospheric
382 oxidation processes (Lange et al., 2015; McDonough et al., 2016; Xie et al., 2007). When
383 comparing sediments and water, some authors have reported ratios closer to 1 in sediments,
384 primarily due to a stronger tendency of AHTN for sorption and/or a degradation of HHCB
385 into its lactone derivative in sediment (Bayen et al., 2019; Heberer, 2002; Lu et al., 2015).
386 Other studies measured an opposite trend, with no evident explanatory factor (Zhang et al.,
387 2020). In light of this literature, the geographical differences of the HHCB / AHTN ratio
388 determined in our study (i.e. higher ratios in areas under stronger anthropogenic pressure)
389 support a higher removal of HHCB with increasing distance from sources, and/or higher
390 inputs of AHTN through the relative higher contribution of atmospheric influence (both dry
391 and wet deposition). This is also in agreement with our understanding of the pressures

392 affecting these studied sites - a knowledge acquired through the long-term monitoring of
393 various hydrophobic contaminants (see Munsch et al., 2019, 2015, 2013). Interestingly,
394 when considered all sampling years, significantly higher values were found in the
395 Mediterranean sites compared to the English Channel and Atlantic coast sites, with average
396 values in the Mediterranean 1.8 and 1.6 times higher than in the English Channel and Atlantic
397 coast, respectively. In particular, the average ratios in Marseille Bay and the Gulf of Fos were
398 2.0 to 2.3 times higher than those in the Seine and Loire estuaries. Assuming likely
399 comparable sources in the Atlantic and Mediterranean shores (musk uses and effluent
400 composition), lower HHCB / AHTN ratios in the macrotidal Seine and Loire estuaries could
401 be attributed to a more pronounced degradation of HHCB due to the long residence time of
402 waters in such hydrosystems, and the high turbidity where particle-born bacteria promote
403 biodegradation of the less recalcitrant compounds (Aminot et al., 2018, 2016). Stronger
404 removal of AHTN through photolysis in the sunnier climate of the Mediterranean shore sites
405 could also account for the general observed trend.

406 *3.4 Temporal trends*

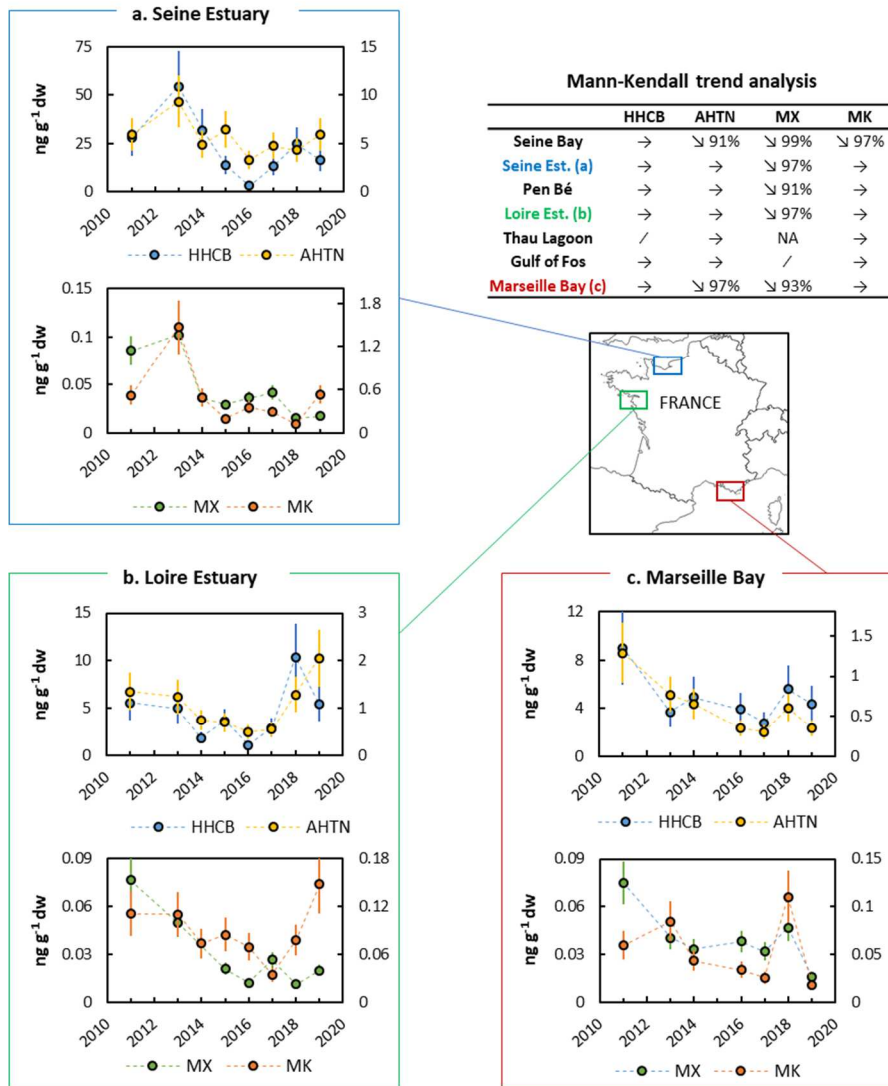
407 As datasets with a minimum of 4 time points have been recommended for trend evaluation,
408 and 7 for change point analysis (Land et al., 2018), our 8-year time series allows a robust
409 examination of the temporal trends of musks in the environment. Only the 7 sites for which a
410 maximum of 1 datapoint was missing (< LOQ) were selected for a monotonous trend analysis
411 using the Mann-Kendall non-parametric test (Figure 4).

412 MX concentrations were found to be significantly decreasing in 5 sites (confidence factor
413 between 91 and 99%), whilst no trend could be fitted in the Gulf of Fos. The concentrations
414 measured at most sites over the first 2 years of monitoring were generally higher than the
415 following 6, and it is worth noting that all decreasing trends become stable if these first 2

416 years are not considered. With caution over these 2 years driving the trend, the results
417 observed for MX probably reflect the regulations on this chemical. MX is banned by EU since
418 2011, and its use was not approved by fragrance industrials since the late 2000's (Abril,
419 2011), but early substitutions started in the mid 1990's (Käfferlein and Angerer, 2001). MX
420 levels were found to decrease in human plasma collected in Germany between 1992 and 1998
421 (Käfferlein and Angerer, 2001) and in mother's milk in Sweden in the late 1990's (Lignell et
422 al., 2008), indicating that the use of MX declined prior to its ban. In freshwater biota (bream),
423 MX was found to decrease in Germany between 1993 and 1999 (Rüdel et al., 2006). Within
424 lake sediment cores, MX was also found to decrease in the last decades, but their large core
425 time resolution prevents the determination of a clear change point (Peck et al., 2006). The
426 absence of a contemporary use of MX is in agreement with its lower geographical variability
427 observed in our study. This indicates that, similarly to other regulated persistent compounds,
428 current MX concentrations most likely result from its high stability towards both abiotic (Gao
429 et al., 2019) and biotic degradation (Tas et al., 1997). Conversely, HHCb concentration trends
430 were found to be stable (or have no trend) in the 7 sites considered, as well as MK's and
431 AHTN's in 6 and 5 sites, respectively, for which the remaining sites were found to be
432 decreasing with a 91-97% confidence factor. The absence of significant time trends and the
433 existence of "hot spots" related to anthropogenic pressures indicate current use and
434 continuous inputs of these 3 contaminants. As a constant release of persistent compounds
435 should result in the increase of their environmental concentrations, the absence of an
436 increasing time-trend could suggest a better degradability of musks compared with other
437 POPs. Recent trend analysis of musks are relatively scarce in the literature and are somewhat
438 conflicting for polycyclic musks, potentially as a result of different practises and regulations
439 worldwide (see Gatermann et al., 1999, and Nakata et al., 2012). In the USA, *Mytilus edulis*
440 specimens collected between 1991 and 2005 in an urban tidal estuary showed significantly

441 decreasing concentrations for both HHCB and AHTN (Subedi et al., 2014), whilst lake
442 sediments concentrations revealed an opposite increasing trend over the investigated period
443 (1990-2003), showing correlation with production data (Peck et al., 2006). Similarly, in a
444 survey from the 1970's to 2005, HHCB concentrations in marine mammals have increased
445 significantly since the 1990s in Japanese waters (Nakata et al., 2007). A study on various
446 marine and freshwater organisms in Germany over the earlier 1986-2000 period only found
447 trace levels of musks in mussels, with no exploitable time trend, while HHCB and AHTN
448 levels showed decreasing levels in bream (*Abramis brama*) in the late 1990s, with AHTN
449 concentrations decreasing faster than HHCB's (Rüdel et al., 2006). In Sweden, AHTN was
450 found to decline significantly in mother's milk between 1996 and 2003 (Lignell et al., 2008),
451 whilst an increase of HHCB concentrations in sewage sludge was found between 2005 and
452 2015 and was attributed to increase in its use (Veenaas et al., 2018). On the other hand, time
453 trends of MK are lacking, except a decrease reported in bream in Germany in the mid-1990's
454 (Rüdel et al., 2006). This lack of information is probably caused by its trace-level
455 concentrations in the environment and by the assumption that nitro-musks have been entirely
456 substituted by polycyclic musks (Lange et al., 2015), dissuading its monitoring. However,
457 according to ECHA, MK is still produced/imported in EU between 100 – 1 000 tonnes per
458 annum (ECHA, 2020), consistent with our data indicating no decreasing trend over the 8
459 years investigated.

460



461

462 Figure 4. Temporal trends of the 4 musks in the sites with a minimum of 7 annual datapoints
 463 (6 in Mediterranean sites). Concentrations are given in a, b and c for 3 selected sites in ng g^{-1}
 464 dw. The left Y-axis are given for HHCB and MX, the right Y-axis for AHTN and MK. The
 465 trends and confidence factors of the Mann-Kendall statistic at all sites are provided in the
 466 table.

467

468 **4 Conclusion**

469 Our study has shown evidence of widespread contamination of coastal bivalves by synthetic
470 musks, with a predominance of polycyclic over nitro-musks. Contrary to AHTN, MK and
471 MX, significant differences of HHCB concentrations between mussel- and oyster-monitored
472 sites suggest its species-specific accumulation potentially related to metabolization, and
473 warrants further research. With wastewater as the major source of musks in the environment,
474 the geographical distributions observed reflected the urban pressure, with the Seine estuary
475 showing the highest concentrations of HHCB, AHTN and MK. Conversely, more consistent
476 concentrations of MX among the sites indicated background concentrations in agreement with
477 its restricted use and its persistence. In addition to be indicative of species-specific
478 bioaccumulation of HHCB, HHCB / AHTN ratio was proven to be a relevant marker of
479 sources and processes affecting their environmental occurrence levels. Our 8-year monitoring
480 afforded the evaluation of a robust time-trend and revealed a significant decrease for MX
481 only, when concentrations of HHCB, AHTN and MK remained stable. Without further
482 regulations or change in consumers' practices, synthetic musks are likely to remain
483 contaminants of concern in the near future They should receive a wider attention from the
484 marine research community and be included in marine biomonitoring programs.

485

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491

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