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1 **Assessment of dietary Selenium and its role in Mercury fate in cultured fish**
2 **rainbow trout with two sustainable aquafeeds**

3 **Claudia Marchán-Moreno^a, Silvia Queipo-Abad^a, Warren T. Corns^c, Maite Bueno^a,**
4 **Florence Pannier^a, David Amouroux^a, Stéphanie Fontagné-Dicharry^b, Zoyne Pedrero^{a*}**

5 ^a Université de Pau et des Pays de l'Adour, E2S UPPA, CNRS, IPREM, Institut des Sciences
6 Analytiques et de Physico-chimie pour l'Environnement et les Matériaux, Pau, France.

7 ^b Université de Pau et des Pays de l'Adour, INRAE, NUMEA, 64310, Saint-Pée-Sur-Nivelle,
8 France.

9 ^c PS Analytical, Arthur House, Crayfields Industrial Estate, Main Road, Orpington, Kent BR5 3HP,
10 UK

11 ***Corresponding author:** zoyne.pedrerozayas@univ-pau.fr

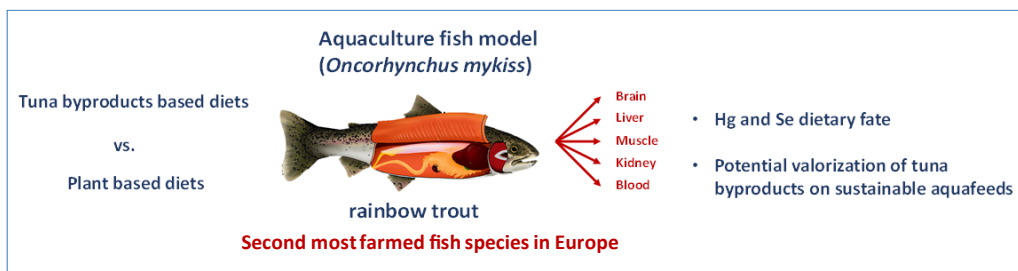
12 **Abstract**

13 This study enhances the current limited understanding of the interaction between mercury (Hg)
14 and selenium (Se) species in fish. Rainbow trout (*Oncorhynchus mykiss*), a model aquaculture fish,
15 was exposed to Hg and Se species through controlled dietary conditions. Over a 6-month feeding
16 trial, the impact of dietary Se on Hg bioaccumulation in fish, including flesh, brain, and liver, was
17 tracked. Twelve dietary conditions were tested, including plant-based diets (0.25 µgSe g⁻¹) and
18 tuna byproduct diets (0.25 µgHg g⁻¹, 8.0 µgSe g⁻¹) enriched with methylmercury and/or Se as
19 selenite or selenomethionine. The tuna byproduct diet resulted in lower Hg levels than the plant-
20 based diets, with muscle Hg content below the European Commission's safe threshold. This study
21 highlights the significant impact of specific Se compounds in the diet, particularly from tuna-based
22 aquafeed, on Hg bioaccumulation. These promising results provide a strong recommendation for
23 future use of fisheries byproducts in sustainable aquafeeds.

24 **Keywords:** methylmercury, tuna byproducts, aquaculture, selenoneine, biota, rainbow trout
25

26 **Synopsis:** The interactions between Hg and Se species in biota are not completely understood yet.
27 This work discusses the fate of dietary Se species and their effect on Hg bioaccumulation in
28 rainbow trout, an aquaculture model fish.
29

30 **Abstract art**



31

32

33 **1. Introduction**

34 The main source of human intake of mercury (Hg) is via the consumption of fish and seafood
35 products (Córdoba-Tovar et al., 2022). Mercury is considered to be one of the top ten chemicals
36 of major public health concerns by the World Health Organization (WHO, 2021). In fish and
37 seafood, Hg is principally found as methylmercury (MeHg) (Lavoie et al., 2013; Wu & Zhang,
38 2023). MeHg levels are biomagnified through the trophic chain, resulting in serious social,
39 environmental, and human health effects. The U.S. Food and Drug Agency (U.S. FDA) have
40 established a MeHg limit in fish of $1 \mu\text{gMeHg g}^{-1}$ wet weight (ww) (U.S. FDA, 2022). A more
41 restrictive criterion has been set by the European Commission, which depends on the species of
42 fish and in this case, it is defined as total Hg (EU, 2022). This maximum level varies from 0.30
43 $\mu\text{gHg g}^{-1}$ ww for fish/seafood species with a low content of Hg, such as the muscle of rainbow
44 trout, to $1.0 \mu\text{gHg g}^{-1}$ ww in the muscle of fish/seafood species with a high content of Hg such as
45 shark, swordfish, and tuna. For some other fishery products and crustaceans, the maximum level
46 is set at $0.5 \mu\text{gHg g}^{-1}$ ww.

47 More advanced toxicity assessment criteria have been proposed in which consider not only the
48 MeHg level but also the selenium (Se) content (Plessl et al., 2019; Ralston et al., 2016). These
49 approaches rely on the potential antagonistic effect of Se against Hg toxicity in animals (Raymond
50 & Ralston, 2004). Mercury detoxification pathways involving the formation of tiemannite (HgSe)
51 a bioinert compound have been proposed and this species has been found in several organs of
52 vertebrates thereby supporting this theory (Lailson-Brito et al., 2012; Manceau et al., 2021). The
53 key role of Se species in this detoxification process is widely acknowledged but not fully
54 understood.

55 Aquaculture fish production has become an alternative industry to wild capture of fish for
56 providing seafood products. It plays a crucial role in global food security with production rates
57 growing at 7.5% per year since 1970 (FAO, 2020). Aquaculture management is currently facing
58 one of the world's greatest challenges. By 2050, more than 9 billion people will need reliable food
59 supplies in a context of climate change, economic and financial uncertainty, and growing
60 competition for natural resources. The UN Member States implemented the 2030 Agenda for
61 Sustainable Development to set aims for the contribution and conduct of fisheries and aquaculture
62 towards food security and nutrition.

63 Plant-based and fish byproducts diets appear as more cost-effective and ecofriendly aquafeed
64 solutions compared with traditional fishmeal diets from dedicated over fishing (FAO, 2022). The
65 preferred alternative protein sources for replacing fishmeal in aquaculture feeds are plant-based
66 proteins (Hasan & Tan, 2020). Some of the challenges and limitations on the use of plant-based
67 diets are their amino acid, fatty acid, and mineral profiles, as well as their mycotoxin contents
68 which can affect the growth and health status of fish (Hasan & Tan, 2020). However, several
69 studies have already proved that aquaculture fish growth and performance are not affected with
70 plant-based diets and adequate micronutrient supplementation (Fontagné-Dicharry et al., 2015).
71 Fish byproducts represent up to 70% of processed fish and constitute a collection of fish parts such
72 as heads, viscera, skin, bones, and scales, which were usually discarded as waste (Coppola et al.,
73 2021). These non-commercialized parts of large wild fish represent a significant source of
74 nutrients, rich in minerals and amino acids, and sustainable alternative ingredients for aquafeeds
75 (Kim et al., 2019). Catches of tuna and tuna-like species increase over the years, reaching their
76 highest levels in 2019 at about 8.2 million tons (FAO, 2022). The tuna canning industry discards
77 around 65% of byproducts, which represents a precious protein source for sustainable aquafeeds
78 production. Nevertheless, the principal disadvantage of the use of tuna byproducts-based diets is
79 their potential high content of heavy metals, such as mercury and cadmium (Kim et al., 2019).

80 Interestingly, tuna byproducts contain relatively high Se concentration levels (range 0.7-7.9 μgSe
81 g^{-1} ww) (Donnarumma et al., 2021). Many of the current works on Hg toxicity in marine organisms
82 include Se:Hg molar ratios as a valuable toxicology variable (Plessl et al., 2019; Ruelas-Inzunza
83 et al., 2020), and these publications advise further investigation on the interaction between Hg and
84 Se, for understanding Hg metabolic pathways (Albuquerque et al., 2020).

85 Despite a large number of studies focusing on the effect of Se on Hg bioaccumulation, they are
86 principally exclusively limited to the muscle (Amlund et al., 2015; Ribeiro et al., 2022). However,
87 the understanding of such complex interactions in biota requires the analyses of other tissues,
88 providing information about their fate in the whole organism. In addition, Se speciation in fish is
89 still not fully understood. Selenoneine, a Se analogue of ergothioneine, was recently identified and
90 therefore its presence and effect on Hg has not been considered (Achouba et al., 2019; El Hanafi
91 et al., 2022; Ribeiro et al., 2022) despite its large presence in aquatic ecosystems.

92 The present work aims to advance the current limited understanding of the Hg and Se (species)
93 interaction in fish through dietary exposure. A model aquaculture fish, rainbow trout
94 (*Oncorhynchus mykiss*) was dietarily exposed to Hg and Se species under controlled conditions.
95 The dietary Se effect on Hg bioaccumulation in flesh, and other key organs like brain and liver
96 were studied. Mercury and Se species were kinetically tracked during a 6-month feeding trial,
97 where fish were exposed to plant and tuna byproducts-based diets. The reported outcomes of this
98 work could help the aquaculture industry in setting new guidelines for aquaculture feeding
99 practices to avoid fish contamination with toxic forms of Hg and to ensure proper bio assimilation
100 of its antagonist Se species. In addition, this study constitutes a solid basis for the evaluation of
101 tuna byproducts as an alternative protein source for the development of sustainable aquafeeds.

102 **2. Materials and Methods**

103 **2.1 Feeding trial with rainbow trout juveniles**

104 The feeding and sample collection was performed at the French National Research Institute for
105 Agriculture Food and Environment (INRAE). All experimental procedures complied with the
106 European Directive 010/63/EU for the protection of animals used for scientific purposes, and the
107 French Decree no. 2013-118 for animal experimentation (project agreement number:
108 APAFIS#27846-2020102812241350v2). Rainbow trout juveniles (mean initial body weight: $26 \pm$
109 1 g) were fed with Se and Hg supplemented experimental diets for 24 weeks. Fish were hand-fed
110 twice a day in the morning and afternoon to apparent visual satiation (*i.e.*, feed distributed until
111 the fish stop displaying active feeding). The experimental feeds consisted of 6 plant-based diets
112 and 6 tuna meal-based diets (Table S1), with different dietary Se and Hg species and concentrations
113 (Table 1). The two control diets (PC, TC) with basal content of Se and Hg, were supplemented
114 with $1.5 \mu\text{gSe g}^{-1}$ ww either in the form of sodium selenite (Se(IV)) (PI, TI) or as L-

115 selenomethionine (SeMet) (from Excellent Selenium 4000, Orffa, Breda, The Netherlands) (PO,
 116 TO), or with 2.0 $\mu\text{gHg g}^{-1}$ in the form of methylmercury(II) chloride (Sigma-Aldrich, Saint-
 117 Quentin-Fallavier, France) (PH, TH). For each control diet, a combination of both Se, either
 118 inorganic or organic, and Hg supplementation was also included. Liver, kidney, muscle, brain, and
 119 blood tissues of rainbow trout juveniles were collected after 7, 21, 84, and 168 days of feeding
 120 trial. Tissue samples were immediately frozen in liquid nitrogen and stored at $-80\text{ }^{\circ}\text{C}$ for further
 121 analyses. Three tissue replicates from three different individuals were lyophilized and stored at
 122 room temperature for determination of Se and Hg. A comprehensive description of the feeding
 123 trial setting is presented elsewhere (Bidon et al., 2023).

124 **Table 1** Dietary Se and Hg concentrations in the plant-based and tuna meal-based diets (in $\mu\text{g g}^{-1}$ ww,
 125 uncertainty represents the standard deviation of 3 sample replicates).

Diets	ID	Plant-based diets		ID	Tuna meal-based diets	
		$\mu\text{gSe g}^{-1}$	$\mu\text{gHg g}^{-1}$		$\mu\text{gSe g}^{-1}$	$\mu\text{gHg g}^{-1}$
Control	PC	0.25 ± 0.02	< LOD ^a	TC	8.0 ± 0.3	0.25 ± 0.02
Se(IV)	PI	3.5 ± 0.2	< LOD	TI	10.3 ± 0.7	0.19 ± 0.04
SeMet	PO	2.3 ± 0.1	< LOD	TO	10.6 ± 1.5	0.21 ± 0.02
MeHg	PH	0.28 ± 0.01	2.6 ± 0.2	TH	7.8 ± 0.3	2.13 ± 0.05
Se(IV) + MeHg	PHI	2.3 ± 0.1	2.5 ± 0.1	THI	11.2 ± 1.7	2.2 ± 0.1
SeMet + MeHg	PHO	2.2 ± 0.1	2.4 ± 0.2^b	THO	10.3 ± 1.1	2.0 ± 0.1

126
 127 ^a LOD: Limit of detection

128 ^b Standard deviation of only two samples

129 2.2 Se and Hg quantification

130 Freeze-dried and homogenized rainbow trout tissues (0.02 - 0.2 g) were pre-digested overnight at
 131 room temperature with concentrated HNO_3 (0.5-5 mL) using a sample to acid ratio of 1:25 in a
 132 borosilicate-glass tube covered with Teflon caps. Total digestion was performed in a single-
 133 reaction chamber system (UltraWAVE, Milestone Srl, Italy) following the procedure described in
 134 Table S2. The resulting sample digests were diluted in 2% (v/v) HNO_3 and 5% (v/v) HCl for
 135 analyses of Se and Hg, respectively.

136 Selenium was determined with an Agilent 7500 ICP-MS (Agilent Technologies, Tokyo, Japan)
 137 instrument equipped with an octopole collision/reaction cell following the parameter settings of
 138 Table S3. External calibration with sodium selenite (Se(IV)) standard solution (SCP SCIENCE,

139 France) was performed. Stock standard solutions containing 50 $\mu\text{gSe L}^{-1}$ were prepared in 4% (v/v)
140 HNO_3 and stored at -4°C . Working standard solutions were daily prepared by dilution in 2% (v/v)
141 HNO_3 . Milli-Q (ultrapure) water (18.2 $\text{M}\Omega\text{ cm}$, Millipore, Bedford, MA, USA) was used for all
142 dilution preparation. Trace Metal Grade conc. HNO_3 (67% w/w) and Instra-analysed grade conc.
143 HCl (36–38.5% w/w, J.T. Baker) acids, were purchased from Fisher Scientific, Illkirch, France.

144 Mercury quantification was performed by cold vapor - atomic fluorescence spectrometry (CV-
145 AFS) (10.025, P S Analytical, Kent, UK) by reduction with 3% (m/v) SnCl_2 (Scharlab, Barcelona,
146 Spain) in 10% (v/v) HCl as described elsewhere (Queipo-Abad et al., 2022). The quantification
147 was performed by external calibration.

148 Detection limits defined as three times the standard deviation on blank analyses (2% (v/v) HNO_3
149 for Se and 5% (v/v) HCl for Hg) were 0.08-0.7 ngSe g^{-1} and 0.06 ngHg g^{-1} for fish tissues (dry
150 weight). Measurement validation was performed by analysis of certified reference materials
151 (DOLT-5, ERM-CE101, BCR-464 and TORT-2) (Table S4).

152 **2.3 Statistical analyses**

153 Data are expressed as means of three sample replicates \pm standard deviation (SD). Unless
154 otherwise stated, the element concentration is presented as $\mu\text{g}(\text{Element})\text{ g}^{-1}$ of dry weight (dw)
155 sample. One-way ANOVA with post hoc Tukey's honestly significance test was used for the
156 comparison of Se and Hg concentration data. Statistical significance level was defined as $p < 0.05$
157 (95% confidence).

158 **2.4 Bioaccumulation rate**

159 Selenium and Hg bioaccumulation rate constant (k_{uptake} in day^{-1}) was calculated using a one
160 compartment first-order kinetic model (Equation (1)) (Wang & Tan, 2019).

$$\frac{[\text{Element}]_{\text{tissue}}}{[\text{Element}]_{\text{diet}}} = \frac{k_{\text{uptake}}}{k_{\text{elimination}}} \times (1 - e^{-(k_{\text{elimination}} \times t)}) \quad (1)$$

161
162 where $[\text{Element}]_{\text{tissue}}$ ($\mu\text{g}(\text{Element})\text{ g}^{-1}$) represents the mean values of concentration of the element
163 in tissues of three individuals at each sampling time (t, in days). Mass of Se and Hg in tissues were
164 independent of growth therefore element concentration values were used. $[\text{Element}]_{\text{diet}}$
165 ($\mu\text{g}(\text{Element})\text{ g}^{-1}$) is the average concentration of each element in each diet. k_{uptake} and $k_{\text{elimination}}$

166 (in day⁻¹) corresponds to the constant of uptake and elimination rate respectively. $k_{\text{elimination}}$ was
167 obtained from the slope of the kinetic model and used for calculation of k_{uptake} . Values represent
168 $k_{\text{uptake}} \pm$ standard error (95% confidence interval).

169 **3. Results and Discussion**

170 **3.1 Selenium bioaccumulation in rainbow trout organs**

171 **3.1.1 Plant-based diets exposure**

172 Control plant-based diets resulted in constant Se concentrations ($p > 0.05$) during the 6-month
173 feeding period in all tissues (Table S5). Fortification with Se (as Se(IV) or SeMet) led to an
174 increase of Se levels in all the organs. The biggest increase was observed in the liver of fish fed
175 with Se(IV) where final Se concentration was 65-fold higher than in the control group (Figure 1).
176 The final Se concentration in kidneys and blood was independent of the specific dietary Se species
177 (Figure 1). In contrast, the Se content in muscle and brain was 5- and 2-fold higher respectively
178 when fish were fed with SeMet than with inorganic Se, illustrating a Se species specific
179 bioaccumulation in the mentioned organs (discussion in section 3.3).

180 The Se bioaccumulation rate in kidneys was strongly dependent of the Se species dietarily
181 supplemented, contrasting with the rest of the organs where values were on the same range for
182 both Se sources (Table S6). In kidneys, SeMet enriched diets led to a higher Se bioaccumulation
183 rate than when fed with Se(IV). Meanwhile, the liver exhibited the highest bioaccumulation rate
184 (up to 10 times more than in the other tissues), independently of the supplemented Se species.

185 In general, the simultaneous dietary exposure of trout to MeHg and both Se species does not affect
186 the Se concentrations and bioaccumulation kinetics (Figure 1, Tables S5 and S6) previously
187 described. A singular trend is observed in the liver of fish simultaneously co-exposed to Se(IV)
188 and MeHg. Despite similar Se hepatic concentration profiles, at the end of the trial the Se levels
189 were 2-times higher when fish were exposed to Se(IV)+MeHg than exclusively to Se(IV)
190 (discussion in section 3.3).

191 **3.1.2 Tuna meal-based diets exposure**

192 Dietary exposure to the control tuna meal-based diets (TC, Table 1) resulted in the increase of Se
193 levels in all the rainbow trout tissues. It should be highlighted that the Se basal level on the tuna
194 byproduct-based diet was $7.9 \mu\text{gSe g}^{-1}$ ww. Liver exhibited the highest Se levels reaching $70 \mu\text{gSe}$

195 g⁻¹ dw when exposed to tuna-meal control diet (Figure 1). Muscle, kidney, brain, and blood Se
196 concentration values were not significantly different ($p > 0.05$) (Table S5).

197 The addition of Se(IV) to the tuna based aquafeeds did not significantly induce any variation on
198 the final Se concentration in comparison to the control group ($p > 0.05$). In contrast, SeMet-
199 enriched tuna aquafeeds induced higher Se levels in the muscle, brain, and blood tissues than in
200 the control tuna-based aquafeed group (Figure 1). The most important Se content raise was
201 observed in muscle, reaching Se levels 4-times higher than with TC and TI diets (Table S5).

202 Addition of MeHg in the absence of Se fortification (TH, Table 1) does not have any significant
203 effect on the Se bioaccumulation rates (Table S6), or on the Se biodistribution among the rainbow
204 trout tissues in comparison to fish fed with control diet TC ($p > 0.05$). However, the simultaneous
205 dietary supplementation of MeHg with Se(IV) (THI) led to some specific increases of final Se
206 hepatic levels in comparison to those obtained without MeHg dietary exposure (Figure 1, Table
207 S5) (discussion in section 3.3).

208 The simultaneous diet supplementation with MeHg and both Se species led to a different kinetic
209 trend of the Se content in brain compared to the trend when dietary MeHg was absent. Specifically,
210 in the absence of dietary MeHg, SeMet and Se(IV) enriched diets lead to a maximum Se level at
211 84 days followed either by a 45% decrease or by a plateau, respectively (Figure 1). The decrease
212 of brain Se concentration from 84 to 168 days when fish were fed with SeMet-tuna aquafeeds was
213 not observed when MeHg was simultaneously added with this Se-amino acid. In this case, the Se
214 content in brain remains constant during the last 3 months of the feeding trial. With Se(IV)-tuna
215 aquafeeds, the co-addition of MeHg results in the continuous increase of the Se content in brain
216 after 84 days, to reach similar concentration levels compared to fish fed with MeHg+SeMet-tuna
217 based diet. Interestingly, the addition of MeHg to the control tuna-based diet does not affect the
218 Se content found in brain (Table S5). The high standard deviation on Se- k_{uptake} values (Table S6)
219 hampers a complete comparison of the different dietary conditions.

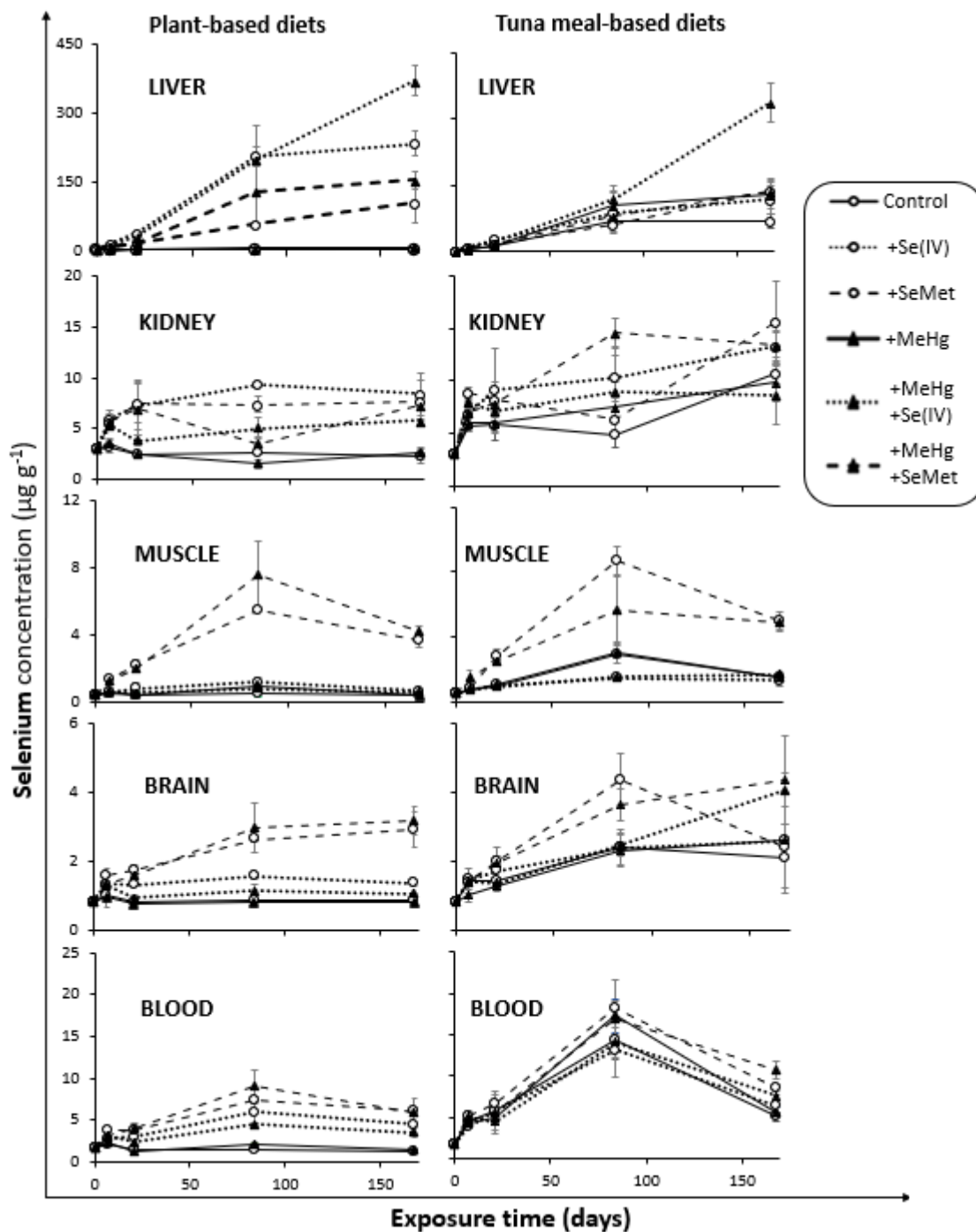


Figure 1 Selenium bioaccumulation in fish tissues after 0, 7, 21, 84 and 168 days of feeding trial with plant and tuna meal-based diets with (triangles) and without Hg (circles) and two Se species supplementation. Control and only MeHg-spiked diets are represented by continuous lines, while dotted and discontinuous lines correspond to the addition of Se(IV), and SeMet respectively. Selenium concentrations corresponds to the mean value \pm SD (dw) of 3 samples replicates.

221 **3.2 Mercury bioaccumulation in rainbow trout organs**

222 **3.2.1 Plant-based diets exposure**

223 Feeding with plant-based diets fortified with $2.5 \mu\text{gMeHg g}^{-1}$ ww with or without simultaneous Se
224 addition, gradually increased Hg levels in all tissues of rainbow trout except liver and kidney
225 (Figure 2A). Blood exhibited the highest Hg content in comparison to the rest of tissues, reaching
226 more than $20 \mu\text{gHg g}^{-1}$ dw (Figure 2A, Table S5). In all tissues, irrespective of the dietary
227 conditions, the increase of Hg concentration was much higher during the first 21 days compared
228 to the following weeks, in agreement with previous studies (Amlund et al., 2015; Vieira et al.,
229 2021). The specific trend observed during the initial Hg dietary exposure (first 21 days) may likely
230 be followed by detoxification strategies, leading to a less pronounced Hg bioaccumulation after
231 the 21-day period.

232 The Hg concentration in kidneys, muscle, and brain was not affected by co-supplementation with
233 either Se-species. Meanwhile Hg levels in kidneys remained constant from 21 exposure days, Hg
234 content in brain and muscle increased until the end of the trial. Supplementation with Se(IV) and
235 SeMet reduced Hg levels in this organ by 84 and 62%, respectively (Table S5). Despite the
236 observed decrease, the final Hg hepatic concentrations reached similar values with or without a Se
237 supplemented diet (Figure 2A, Table S5).

238 Mercury bioaccumulation rates mostly exhibited large standard deviations (higher than calculated
239 k_{uptake} values), probably due to the low concentration in the tissues or to the scattered time evolution.
240 Therefore, not all conditions/organs could be compared. However, $\text{Hg-}k_{\text{uptake}}$ was around 3-fold
241 higher in blood and kidney in comparison to muscle and brain tissues (Table S6). The same trend
242 of bioaccumulation rate was observed independently in the presence of dietary SeMet.

243 **3.2.2 Tuna meal-based diets exposure**

244 Dietary exposure to the natural Hg content in tuna byproducts (Figure 2C), resulted in an
245 enhancement of Hg levels in most tissues, reaching the highest content ($0.73 \pm 0.04 \mu\text{gHg g}^{-1}$ dw)
246 in the kidney at the end of the trial (Table S5). Mercury bioaccumulation rates among organs of
247 trout exposed to Hg originated from tuna byproducts exhibited the following trend: $\text{Hg-}k_{\text{uptake}}$ in
248 blood > kidney > brain, which could be attributed to the metabolic fate of Hg. Although these
249 pathways are yet to be fully characterized, it is acknowledged that ingested MeHg is primarily
250 transported from the blood to target organs potentially involved in Hg detoxification processes (Li

251 et al., 2022; Pedrero Zayas et al., 2014) such as the liver and kidneys (Feng et al., 2015; Queipo-
252 Abad et al., 2022; Renedo et al., 2021). The lowest Hg-uptake value in the brain could be
253 understood as a protective mechanism against the neurotoxicity of this element. The tracking of
254 Hg kinetics through isotopic analyses in different animal species, including fish and seabirds,
255 supports these hypotheses (Feng et al., 2015; Queipo-Abad et al., 2022; Renedo et al., 2021).

256 In respect of the kinetic profile of Hg levels in kidneys and muscle, a plateau was observed from
257 21 to 84 days of exposure and the final values were 4-fold higher than at the beginning of the
258 experiment. Meanwhile in liver, blood and brain, the Hg content increased during the first 21 days
259 of exposure, followed by a noticeable depletion at 168 days (Figure 2C). This Hg depletion with
260 time represented a reduction of 47 and 69% the Hg concentration in blood and brain respectively,
261 reaching the Hg values on these organs at initial time.

262 The Hg concentrations in the muscle were reduced from $0.59 \pm 0.07 \mu\text{g g}^{-1} \text{ dw}$ with the control
263 diet to 0.45 ± 0.03 and $0.38 \pm 0.02 \mu\text{g g}^{-1} \text{ dw}$ with SeMet and Se(IV) fortified tuna aquafeeds
264 respectively (Table S5, Figure 2C). The 6-month dietary exposure to tuna meal-based diets
265 (without MeHg supplementation) resulted in muscle Hg concentrations from 0.11 to $0.17 \mu\text{gHg g}^{-1}$
266 (ww), which was below the limit for human consumption ($0.3 \mu\text{gHg g}^{-1} \text{ ww}$) (EU, 2022). The
267 dietary supplementation with SeMet reduced by 44% the Hg bioaccumulation rate in blood, in
268 comparison with the control tuna group of animals (Table S6).

269 The addition of MeHg to the tuna meal aquafeeds (TH, THI, THO, Figure 2B) resulted in an almost
270 linear increase of Hg levels in all tissues in comparison with the control group (TC, Figure 2C).
271 Among organs, liver and brain showed the highest increases (Table S5). The tuna meal-diet co-
272 supplementation with MeHg and Se species did not induce any significant changes ($p > 0.05$) in
273 most of the final Hg concentrations in comparison with MeHg single addition (Figure 2C). Hepatic
274 Hg levels were slightly higher exclusively when Se(IV) was added to MeHg supplemented tuna
275 diet. Among tissues, Hg bioaccumulation rate values were higher in blood under the three dietary
276 conditions (MeHg, MeHg+Se(IV) and MeHg+SeMet) (Table S6), meanwhile Hg- k_{uptake} in blood
277 of fish exposed to MeHg with and without SeMet was identical. Hg bioaccumulation rate in trout
278 co-exposed to MeHg+Se(IV) was reduced by 40%.

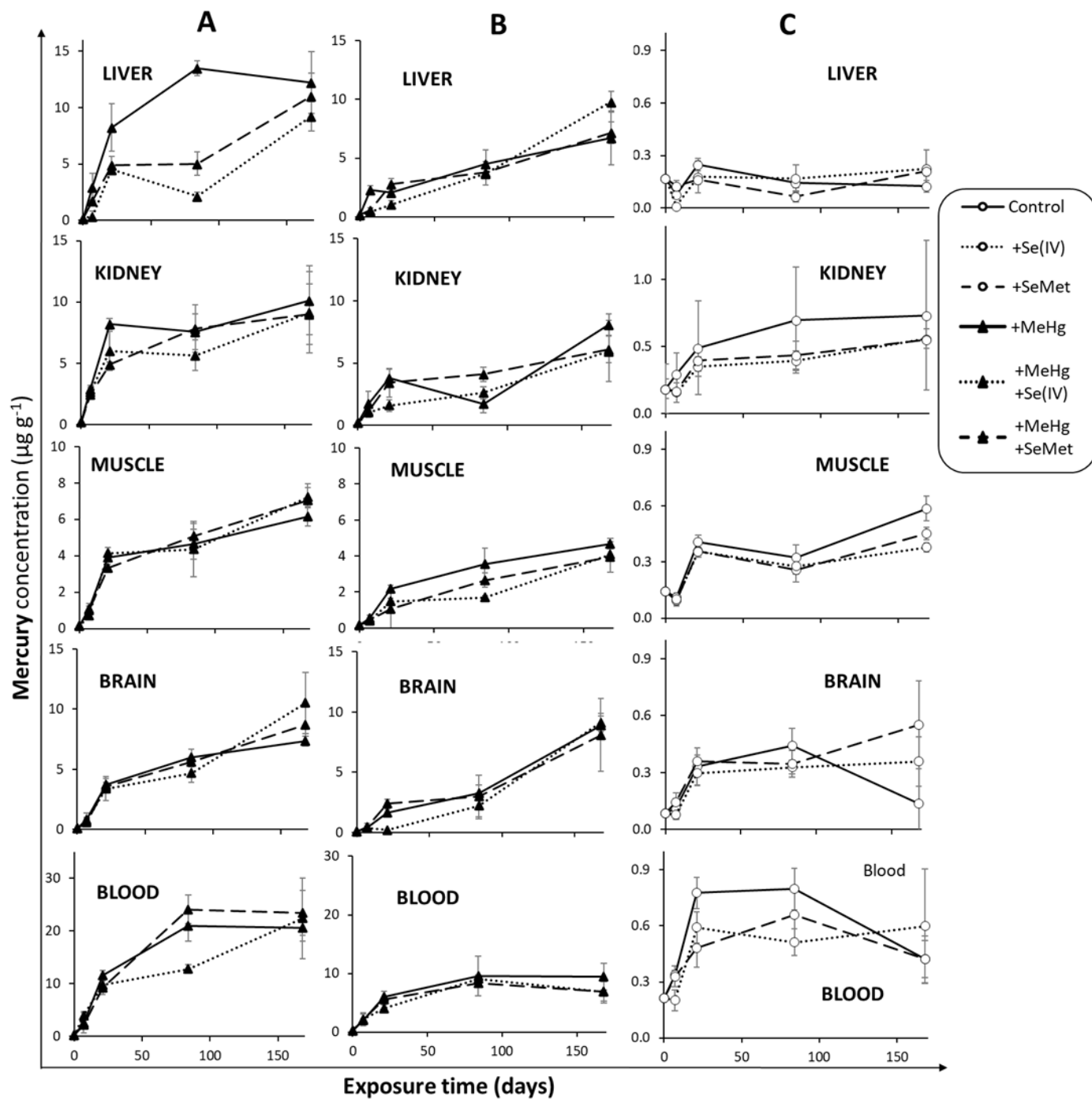


Figure 2 Mercury bioaccumulation in fish tissues after 0, 7, 21, 84 and 168 days of feeding trial with plant (A) and tuna meal-based diets with $2.5 \mu\text{gMeHg g}^{-1} \text{ ww}$ (B) and without (C) supplementation. Control and only MeHg-spiked diets are represented by continuous lines, while dotted and discontinuous lines correspond to the addition of Se(IV), and SeMet respectively. Hg concentrations corresponds to the mean value \pm SD (dw) of 3 samples replicates.

280 **3.3 Fate of dietary selenium in rainbow trout: plant vs. tuna-based aquafeeds**

281 This work compares for the first time the fate of Se in fish fed with plant and tuna-based diets.
282 Although both diets were fortified with the same amount of Se in the form of Se(IV) or SeMet, it
283 should be highlighted that Se level naturally present in the tuna based aquafeeds contributed to
284 80% of the total Se content in this diet. Therefore, fish fed with tuna based aquafeeds were exposed
285 to concentrations 5-times higher than those exposed to plant-based diets. The differences of final
286 Se concentrations in organs of fish fed with both Se supplemented diets were much lower than its
287 variation in basal diets (Table S5). These results suggest that the Se-species naturally present in
288 tuna meal-based diets might regulate the Se accumulation in the investigated rainbow trout tissues.
289 Selenoneine, a selenoamino acid reported for the first time in 2010 is considered to be a major Se
290 fraction in tuna (muscle, blood and other organs) (Yamashita et al., 2010, 2011, Tohfuku et al.,
291 2021). Therefore, its presence in the aquafeeds prepared from tuna byproducts is to be expected.
292 At the end of the feeding trial, the increase of Se concentrations in the fish fed with tuna basal diet
293 in comparison to plant basal diet and to the initial values, demonstrates the bioaccumulation of
294 naturally present Se in tuna-byproducts in all tissues except for the brain.

295 Selenium bioaccumulation in juvenile rainbow trout strongly depends on the Se species from
296 dietary sources and varies among organs. Dietary SeMet supplementation of both diets leads to
297 increased Se bioaccumulation specifically in muscle and to a lesser extent in the blood. The higher
298 capacity of SeMet, in comparison to Se(IV), to increase muscle Se levels was already reported in
299 rainbow trout broodstocks at lower supplementation levels (+ 0.3 $\mu\text{gSe g}^{-1}$ dw, Wischhusen et al.,
300 2019). At the fry stage, rainbow trout also exhibit higher whole-body Se level when exposed to
301 SeMet compared to Se(IV) (Fontagné-Dicharry et al., 2015, 2020; Godin et al., 2015). Considering
302 that the muscle represents about 75% of the whole-body, the higher Se increases could be related
303 to the enhanced dietary SeMet of Se in this specific organ.

304 Selenium bioaccumulation in blood of fish fed with tuna byproducts, with or without Se-
305 supplementation, exhibits a similar trend with maximum values measured at 84 days, followed by
306 a decrease by half at the end of the trial (Figure 1). Despite the much higher Se levels in tuna-
307 based diets in comparison to plant-based diets, both groups of fish exhibited similar Se blood
308 content. These specific results strongly suggest a blood regulation of the Se naturally present in
309 tuna.

310 As previously mentioned, selenoneine is expected to be one of the main Se species in tuna
311 byproducts. The trophic transfer of the mentioned Se-compound has been evoked (Achouba et al.,
312 2019; El Hanafi et al., 2022; Klein et al., 2011; Little et al., 2019). However, the fate and roles of
313 this compound has been scarcely investigated so far and are still not fully understood. Some studies
314 mentioned its potential impact on MeHg demethylation (Achouba et al., 2019; Little et al., 2019;
315 Queipo-Abad et al., 2022; Y. Yamashita et al., 2013) and protection of the nervous system (El
316 Hanafi et al., 2022). So far, the fate of dietary selenoneine in fish has only been exclusively
317 addressed in a 2 months feeding trial of juvenile amberjacks (Tohfuku et al., 2021). The juvenile
318 animals were dietarily exposed to selenoneine (purified from tuna blood) at two different levels
319 0.5 and 1 $\mu\text{gSe g}^{-1}$. Interestingly, at the end of the selenoneine feeding trial, a dose-dependence
320 was observed in Se bioaccumulation in blood. In contrast, final Se levels in muscle and
321 hepatopancreas were not significantly different despite the different selenoneine supplementation
322 doses, suggesting a regulation of this tuna Se-compound. In the current study, the observed trends
323 of Se bioaccumulation in several tissues of fish fed with tuna byproducts (Figure 1) are in good
324 agreement with these results using selenoneine-spiked aquafeeds (Tohfuku et al., 2021).

325 SeMet supplementation of plant based aquafeeds leads to higher Se concentrations in brain than
326 Se(IV) supplemented diets (Figure 1). This result is evidence of the preferential bioaccumulation
327 of dietary SeMet in this organ, in comparison to the inorganic Se form, which is in good agreement
328 with early studies (Salbe & Levander, 1990; Whanger, 2001). The reasons for the specific
329 enhancement of Se bioaccumulation in the brain of fish exposed to SeMet through their diet are
330 yet to be elucidated. Some current hypotheses are associated with compensating for a methionine
331 deficiency in the nervous system and/or the significant involvement of specific Se species in
332 neurological functions (Attaran et al., 2019; El Hanafi et al., 2022; Solovyev et al., 2021).
333 Interestingly, final Se concentrations in brain of fish exposed to tuna-based diets (without MeHg
334 exposure) was independent of the addition of SeMet and/or Se(IV). This is evidence that Se brain
335 bioaccumulation is dominated by the Se naturally present in tuna byproducts. A recent Se study
336 on the brains of seabirds (El Hanafi et al., 2022) revealed that this organ exhibited the highest
337 percentage of Se as selenoneine. Despite the role of this Se compound in biota being unknown, the
338 proposed trend supports the hypothesis of its key involvement in the nervous system.

339 Selenium bioaccumulates in the kidney irrespective of supplemented Se species in plant-based
340 diets (Figure 1), reaching in both cases to a concentration of $8 \pm 2 \mu\text{gSe g}^{-1} \text{ dw}$. The lack of
341 specificity (Se(IV)/SeMet) on Se bioaccumulation in this organ was already reported in Atlantic
342 salmon supplemented with such Se species for 64 days (Philip et al., 2020). In contrast, Se
343 bioaccumulation in this organ of individuals exposed to tuna (control and Se supplemented)
344 aquafeeds seems to be principally dominated by the Se naturally present in tuna byproducts.
345 Studies on Se bioaccumulation in the kidney of animals are scarce.

346 The liver exhibited the highest Se concentrations among all the investigated tissues. During the
347 first 84 days of exposure, the fish fed with tuna-based diets (supplemented with or without Se)
348 displayed similar Se bioaccumulation. This result strongly suggests that Se naturally present in
349 tuna byproducts is the primary source of the Se bioaccumulated in this organ. In the tuna control
350 group, from 84 days until the end of the trial, the Se values remained constant indicating a potential
351 saturation in the tissue (Figure 1) (Ribeiro et al., 2022). In contrast, during the second half of the
352 feeding trial (84-168 days), Se supplementation leads to an increase of Se bioaccumulation,
353 principally when added as SeMet. On the other hand, the liver of individuals exposed to Se-
354 enriched plant-based aquafeeds exhibited a contrasting kinetic trend. Dietary supplementation of
355 plant-based diets with Se(IV) led to the highest Se liver concentrations with a linear increase until
356 84 days, followed by a stabilization of the values probably due to the saturation of this organ. The
357 distinct bioaccumulation patterns of Se in the liver of fish exposed to SeMet and Se(IV) require
358 comprehensive Se speciation studies to unveil the resulting chemical form of Se in this crucial
359 organ. While the literature on Se speciation in the liver is still limited, some previous studies on
360 the liver of fish and marine mammals have identified the presence of Se nanoparticles, selenoneine,
361 and various Se proteins (Achouba et al., 2019; El Hanafi et al., 2022; Pedrero Zayas et al., 2014).
362 The specific Se species present in the liver of trout and its correlation with the dietary Se species
363 should be further investigated.

364 Dietary SeMet supplementation induced similar Se hepatic bioaccumulation for both diets. Hepatic
365 Se levels were thus higher in the fish exposed to Se(IV)-supplemented plant diet than tuna-based
366 aquafeeds despite the dietary Se content in the last one being 5-times higher. This specific result
367 is evidence that the regulation of natural Se present in tuna by the liver.

368 At lower supplementation levels ($0.3 \mu\text{gSe g}^{-1}$), hepatic Se content in juvenile and broodstock trout
369 reached similar levels for both Se dietary sources, SeMet and Se(IV) supplemented in plant-based
370 aquafeeds (Fontagné-Dicharry et al., 2020; Wischhusen et al., 2019). In contrast, in a 3-month
371 feeding trial with Atlantic salmon, a Se(IV) dietary dose of $15 \mu\text{g g}^{-1}$ ww led to a higher Se
372 bioaccumulation in this organ than the same dose of SeMet (Berntssen et al., 2017). The difference
373 on critical aspects like the exposure conditions (dietary Se levels, time, etc.), age, tissues samples,
374 and precise animal species of the previous studies makes it difficult to compare studies.

375 The dietary co-exposure of MeHg with Se species does not affect Se bioaccumulation trends
376 previously described in tissues except for liver. In both groups of trout, fed with plant and tuna-
377 based diets, the addition of MeHg exclusively affects the Se hepatic accumulation when
378 simultaneously administrated with Se(IV) (Figure 2). Final Se concentration was similar (around
379 $350 \mu\text{gSe g}^{-1}$ dw) when using both types of based diets, suggesting that it depends on the dietary
380 Se(IV) and not on the Se naturally present in the tuna aquafeeds.

381 **3.4 Effect of dietary selenium species on mercury bioaccumulation**

382 The effect of dietary SeMet and Se(IV) supplementation on the bioaccumulation of Hg was
383 investigated in a variety of organs and tissues (liver, kidney, muscle, brain, and blood) of rainbow
384 trout during this 6-month feeding trial. To the best of our knowledge, such relevant aspects are
385 until now under-investigated. Previous studies that focused on the potential effect of Se on Hg
386 bioaccumulation, relied on shorter-term observations of fish muscle (Amlund et al., 2015; Ribeiro
387 et al., 2022), which limited our understanding of its fate within the entire organism.

388 The primary effect observed corresponds to the divergence on Hg bioaccumulation in trout's fed
389 with plant or tuna byproducts aquafeeds. Apart from brain, Hg accumulation in individuals fed
390 with tuna byproducts were usually lower than in those fed with plant-based diets despite identical
391 dietary MeHg exposure levels in both MeHg-spiked aquafeeds (Figure 2A and B). Notably, the
392 most pronounced difference of Hg levels between the two categories of aquafeeds was observed
393 in blood. Fish exposed to tuna byproducts exhibit a Hg content 50% lower than those fed with
394 plants diets (Figure 2A and B). The observed trend in blood may be due to the reduced Hg
395 digestibility of the tuna byproducts used in the current study, which was approximately 30% lower
396 compared to plant-based diets (Bidon et al., 2023). The reduced bioaccumulation of Hg observed
397 in other fish organs when fed with tuna byproducts, compared to those fed with plant-based diets,

398 could be attributed to the mentioned pattern in blood tissues. It is acknowledged that Hg is
399 transported through the bloodstream to the rest of the internal organs (Li et al., 2022).

400 An alternative hypothesis concerning the decrease Hg bioaccumulation due to the naturally
401 occurring Se species in tuna byproducts, could involve an enhancement of Hg excretion by fish,
402 as a detoxification mechanism. This hypothesis is supported by the difference in Hg fecal content,
403 which is significantly higher in fish exposed to tuna-based diets than those fed with plant-based
404 ones (366 $\mu\text{g kg}^{-1}$ in TH, 96 $\mu\text{g kg}^{-1}$ in PH) reported Bidon et al. (2023). Naturally present seleno-
405 compounds in the tuna byproducts, accounting for 80% of total dietary Se, such as selenoneine
406 (M. Yamashita et al., 2013; Y. Yamashita & Yamashita, 2010), could play a key role in the
407 regulation of Hg in rainbow trout while masking the effects of supplemented Se species.

408 A singular similarity of Hg levels was found in the brain of both groups of trout fed with tuna
409 byproducts and plant-based diets (Figure 2, Table S5). Given the pronounced neurotoxicity of
410 MeHg, the regulation of Hg levels could be a result of the protective mechanisms taking place in
411 this organ (Li et al., 2022; Pan et al., 2022).

412 A lack of effect of Se supplementation in Hg accumulation levels has been previously described
413 in the testicles of male catfish (Ibrahim et al., 2019), internal organs of black seabreams (X. Wang
414 & Wang, 2017), liver of Atlantic cod (Olsvik et al., 2015), and also in model mice (Moniruzzaman
415 et al., 2021). The simultaneous diet supplementation with SeMet (5 $\mu\text{g g}^{-1}$ ww) and MeHg (0.2 μg
416 g^{-1} ww) was reported to not affect Hg concentration in rainbow trout flesh (Ribeiro et al., 2022).
417 Although Se might not always reduce Hg bioaccumulation, it could play a toxicity antagonist
418 effect. Se supplementation (0.1 $\mu\text{g g}^{-1}$ as Se(IV)) had a protective effect in the reproductive system
419 of a male catfish species after 30 days of exposure to sublethal Hg concentrations lower than 0.12
420 $\mu\text{g g}^{-1}$ (Ibrahim et al., 2019). Dietary SeMet and vitamin E supplementation, were positively
421 correlated with survival, growth, and weight gain of juvenile olive flounder exposed to induced
422 MeHg toxicity (20 $\mu\text{g g}^{-1}$ ww) (Moniruzzaman et al., 2017). In the current research, the dietary
423 inclusion of Se(IV) and SeMet led to enhanced growth performance and reduced inflammatory
424 effects, which were only evident when using MeHg-enriched aquafeed (Bidon et al., 2023).

425 It is important to highlight that Hg muscle levels in rainbow trout fed with tuna byproducts, without
426 Se supplementation, were below the threshold established for human consumption by the European

427 Commission (EU Marine Affairs and Fisheries Division) ($0.3 \mu\text{gHg g}^{-1} \text{ ww}$, EU, (2022)). Further
428 investigation is needed to identify Se, MeHg and Hg-Se-binding species. This research should
429 encompass both diets and tissues of farmed fish to enhance our understanding of the interactions
430 and metabolic pathways involving Se and Hg. Fish exposed to natural tuna byproducts resulted in
431 muscle Hg levels lower than the maximum recommended by food safety agencies such as the U.S.
432 Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), and
433 Se:Hg molar ratios higher than one. Several authors agree to include Se in the risk assessment
434 criterion for fish consumption, currently exclusively based on MeHg concentration (Ralston &
435 Raymond, 2018). An excess of molar Se in comparison to Hg (Se:Hg molar ratio >1) is usually
436 related with a Hg toxicity reduction (Zampetti & Brandt, 2023). The mentioned ratio in trout flesh
437 is much higher in fish fed with tuna byproducts than with plant based aquafeeds (Table S7).

438

439 **3.4.1 Environmental and socio-economic impact**

440 The rapid production growth of the aquaculture industry (FAO, 2020) in a global context of
441 population increase, climate change and growing competition for natural resources, leads to a
442 demand for new sustainable aquaculture strategies. Fish byproducts emerged as an ecofriendly
443 aquafeed alternative to the traditional fishmeal from dedicated over fishing (Hasan & Tan, 2020).
444 Nevertheless, one of the main limitations for its use is the Hg content in these raw products. Better
445 understanding of Hg and Se bioaccumulation in fish and their interaction could contribute to
446 answering currently unresolved questions of socioeconomic and health interest. The present work
447 provides necessary data for bridging this fundamental knowledge gap, which represents a necessity
448 for policy makers to establish more realistic scenarios to estimate human health risk and benefits
449 of seafood consumption. Natural tuna byproduct-based diets induced high Se:Hg molar ratios and
450 muscle Hg content lower than the maximum recommended by food safety agencies (EU, 2022;
451 U.S. FDA, 2022), which set the basis for the future use of these aquafeeds as an alternative protein
452 source for the development of sustainable aquafeeds.

453 **4. Conclusions**

454 This study sheds light on the kinetics of Hg and Se bioaccumulation in key organs/tissues of a
455 model aquaculture fish. The comprehensive investigation reveals the potential role of naturally
456 occurring basal Se (species) in tuna byproducts, effectively reducing Hg bioaccumulation.

457 Notably, in most organs, except for the brain, individuals fed with tuna byproducts exhibited lower
458 Hg accumulation compared to those on plant-based diets, despite both groups having identical
459 MeHg exposure levels in their diets. Fish exposed to natural tuna byproducts resulted in muscle
460 Hg levels lower than the maximum recommended by food safety agencies (0.3 $\mu\text{gHg g}^{-1}$ ww).
461 Furthermore, this work constitutes a pioneering investigation into Se bioaccumulation from tuna
462 byproduct-based aquafeeds. The resulting Se levels in fish fed Se-supplemented diets were
463 significantly lower than those in basal diets, indicating the potential regulation of Se species
464 naturally present in tuna meal-based diets within rainbow trout tissues.

465 Further studies, focusing on the kinetic fate of Hg and Se species through speciation and isotopic
466 analyses, constitute the main perspectives of this work to overcome current limitations in
467 understanding their interaction mechanisms.

468

469 **Credit authorship contribution statement:**

470 **Claudia Marchán-Moreno:** Data curation; Formal analysis; Writing - original draft, **Silvia**
471 **Queipo-Abad:** Data curation; Formal analysis, **Warren T. Corns:** Writing - review & editing;
472 Resources, **Maite Bueno:** Supervision; Validation; Writing - review & editing, **Florence**
473 **Pannier:** Writing - review & editing, **David Amouroux:** Supervision; Writing - review & editing,
474 **Stéphanie Fontagné-Dicharry:** Methodology; Resources; Supervision; Writing - review &
475 editing, **Zoyne Pedrero:** Funding acquisition; Supervision; Visualization; Writing - review &
476 editing.

477

478 **Supporting Information:** Additional experimental and results details, including methods
479 conditions and extensive data results (.docx).

480

481 **Ethics:**

482 The feeding trial with all-female diploid rainbow trout (*Oncorhynchus mykiss*) was conducted in
483 accordance with the European directive 2010/63/EU and the French decree n° 2013–118 on the
484 protection of animals used for scientific purposes. The protocol was approved by the Ethical

485 Committee C2EA-73 and the French Ministry of Higher Education and Research (reference
486 number APAFIS#27846–2020102812241350 v2). For sampling, fish were overnight starved
487 during 16 h, anaesthetized with benzocaine (30 mg/L) then killed with an overdose of benzocaine
488 (60 mg/L).

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