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Catchment-scale rapid transfer of livestock pharmaceuticals under Mediterranean climate

Nico Hachgenei¹, Nicolas Robinet², Christine Baduel¹, Guillaume Nord¹, Lorenzo Spadini¹, Jean M.F. Martins¹, Céline Duwig¹

¹Univ. Grenoble Alpes, CNRS, INRAE, IRD, Grenoble INP, IGE, Grenoble, France

²UMR CNRS 5194 Pacte, Université Grenoble Alpes, Cermosem, 1064 chemin du Pradel, 07170 Mirabel, France

Correspondence to: Nico Hachgenei (nico.hachgenei@univ-grenoble-alpes.fr)

Highlights 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point), separate submission

- 1/3 of the farmers in the catchment were interviewed on pharmaceutical use
- Pharmaceutical stream concentrations measured on high frequency during flood events
- Targeted veterinary pharmaceuticals not detectable in surface water during low flow
- Peak concentrations are found for short duration during flood events
- Mediterranean climate represents an elevated risk of stream contamination

Keywords (6 max)

Contaminants of Emerging Concern (CEC), rapid transfer, hydrology, animal husbandry

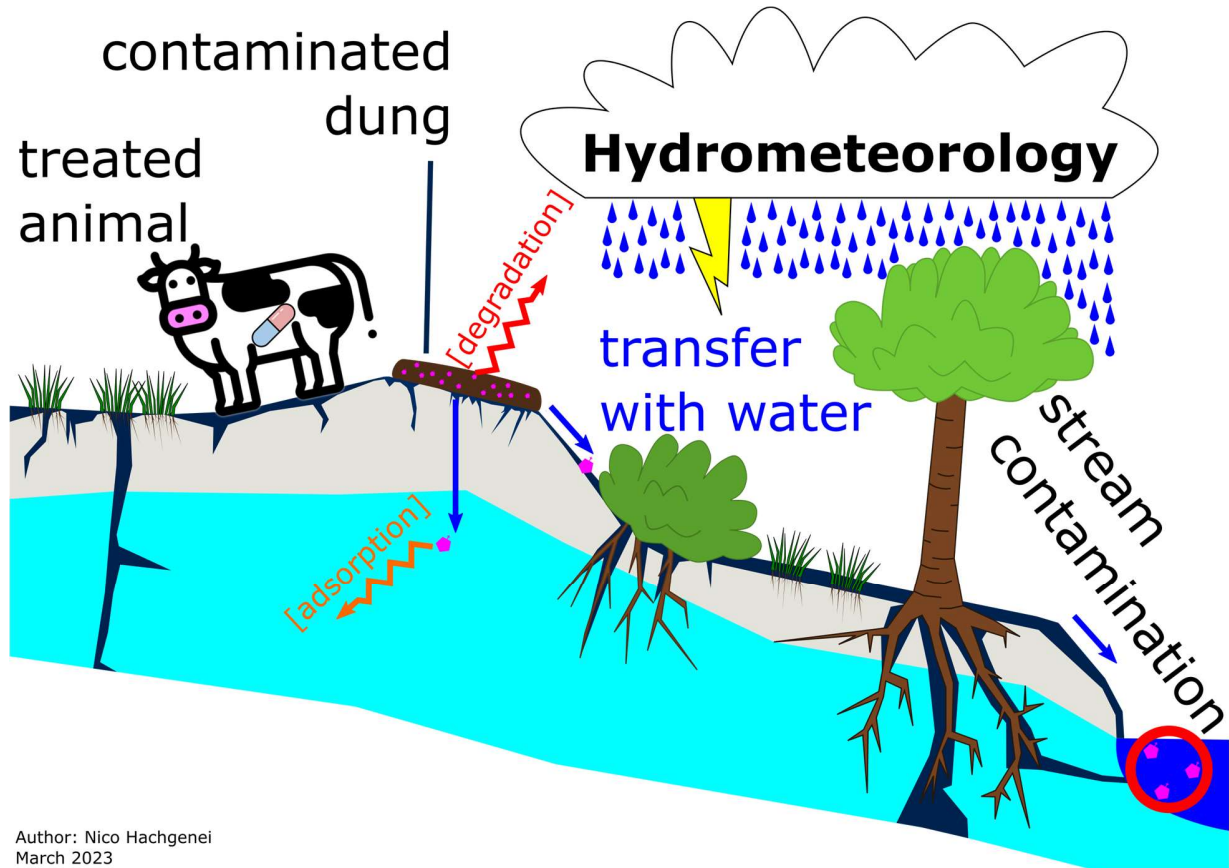
Abstract (300 words max)

Various pharmaceuticals are essential for livestock farming but some are highly toxic to aquatic life if they reach surface water bodies. Mediterranean Climate is characterized by a dry summer followed by intense autumn storms. We studied the effect of these climatic conditions on the risk of pharmaceutical residues transfer to streams at the catchment-scale. The pharmaceuticals used routinely in the study area, as well as their application frequency and season, were identified through interviews with livestock farmers. As a proof of concept, a selection of three veterinary pharmaceuticals (Fenbendazole (FBZ), Mebendazole (MBZ) and Ivermectin (IVM)) was chosen as model chemicals based on their relatively high usage, their specificity to represent different types of livestock (swine, sheep and cattle), and their ability to be analyzed using the same analytical method. Stream water was analyzed during low flow and on high frequency (up to 3 h⁻¹) during floods.

The selected veterinary pharmaceuticals were not detected during low flow, but FBZ and MBZ reached high concentrations for short periods during floods. Due to the event-driven nature of their transfer, a significant load of veterinary pharmaceuticals can reach the river and lead to a temporary but significant degradation of water quality (e.g. for FBZ, the water concentration reached up to 355 times the

35 predicted no effect concentration (PNEC)). This indicates that special care should be taken to avoid
36 keeping freshly treated livestock on pastures that become hydrologically connected under wet
37 conditions. In addition, it suggests that low-frequency monitoring is not sufficient to detect those high
38 concentration levels that exist during very short durations.

39 **Graphical Abstract**



Author: Nico Hachgenei
March 2023

40
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42

43 **1 Introduction**

44 Il faut absolument citer :

45 Wilkinson, J.L. et al. (2022) Pharmaceutical pollution of the world's rivers. Proceedings of the National
46 Academy of Sciences of the United States of America. e2113947119. ISSN 1091-6490.
47 Doi.org/10.1073/pnas.2113947119

48 Food production in modern societies relies on the use of various drugs in order to prevent diseases. The
49 French agency for the control of veterinary medicines currently lists 887 active substances authorized in
50 veterinary medicine (Répertoire des Spécialités Pharmaceutiques). In addition to the important role that
51 drugs play in maintaining our standard of living, there are significant adverse effects on ecosystems and
52 human health. Drugs designed to kill or inhibit pathogenic bacteria and parasites can induce resistances

53 in populations of target organisms (Ventola, 2015; Roca et al., 2015; Spellberg et al., 2008) or impact
54 beneficial organisms (Lumaret et al., 2007; Halley et al., 1989b).

55 Globally, urban wastewater discharges are the major source of residues of pharmaceutical products in
56 the environment (aus der Beek et al., 2016). Many studies focus on these human sources, often in
57 urbanized catchments (Lecompte et al., 2016; Moreau-Guigon et al., 2011). After human consumption,
58 part of the pharmaceutically active compound (PhAC) and / or its metabolites is excreted into
59 wastewater, that is treated or released directly to natural streams. Conventional wastewater treatment
60 plants (WWTPs), when installed, have a mixed performance in removing PhACs. High concentrations in
61 untreated wastewater or low removal efficiency of WWTPs can lead to a significant release of PhACs into
62 streams and rivers (Kim et al., 2018). Other, locally important sources include manufacturing, hospitals,
63 animal husbandry and aquaculture. Urban wastewater, hospitals and manufacturing industry are point
64 sources, while livestock farming is a diffuse source. Treated livestock may excrete residues of PhACs
65 directly onto pastures when grazing or PhACs may be applied to crop fields with manure application.
66 Depending on their physico-chemical properties, these chemicals may be transformed by radiation or
67 microorganisms (photodegradation or biodegradation), adsorbed to soil minerals and organic matter and
68 / or transferred to other environmental compartments with water flow (Kim et al., 2018; Kümmerer,
69 2008). These processes are controlled by multiple factors ranging from the molecular scale (e.g. mineral
70 and organic matter composition, pH, redox potential) to the hillslope and catchment scales (water flow
71 paths) and can vary over time (e.g. season, cloud coverage, temperature, hydrologic conditions)
72 (Kümmerer, 2008).

73 The parent compound as well as transformation products can be toxic to non-targeted organisms. This
74 toxicity can vary by several orders of magnitudes for the same molecule depending on the
75 environmental compartment and the present species. Veterinary pharmaceutical residues can for
76 example inhibit the degradation of contaminated dung by affecting dung degrading insects (Römbke et
77 al., 2010), contribute to the spread of resistances in pathogenic bacteria (Grenni et al., 2018) or kill
78 aquatic organisms (Garric et al., 2007; Halley et al., 1989b).

79 It is difficult to assess the actual impact for the receiving ecosystem due to the complex chemical
80 mixture, the uncertainties about their environmental behavior, the lack of knowledge about their
81 potential interactions and the heterogeneity of environmental systems (Kümmerer, 2008; Cleuvers,
82 2004; Li and Lin, 2015). With water as the vector, the environmental transfer of veterinary
83 pharmaceuticals is governed by water flow paths and transit times, in particular the existence of
84 preferential flow (Jarvis, 2007; Singh and Stenger, 2018). At the catchment-scale, the importance of
85 preferential flow paths and their impact on contaminant mobility is still an important research topic
86 today (Beven and Germann, 2013; Glaser et al., 2019). May be add a sentence on how molecules are
87 authorized or not depending on their characteristics

88 Several authors have investigated the occurrence of different classes of PhACs in streams and rivers in
89 various regions of the world. Some molecules are specific to human or veterinary medicine, while others
90 are used in both. Despite a focus of most studies on human-use molecules, veterinary PhAC residues
91 have been detected in natural waters worldwide at concentrations ranging from less than one ng L^{-1} to
92 several hundred $\mu\text{g L}^{-1}$ or more in rare cases (Obimakinde et al., 2017; Charuaud et al., 2019b; Wei et al.,
93 2011; Zhou et al., 2013). Most of these studies have focused on antibiotics. Charuaud et al. (2019a)
94 conducted a review on the use and occurrence of veterinary pharmaceutical residues in environmental

95 and tap water. They considered a total of 38 studies that analyzed 64 different veterinary PhACs. Most of
96 the analyzed molecules were antibiotics and only few antiparasitics were searched for. While antibiotics
97 were analyzed in up to 1219 samples, the antiparasitic PhACs were analyzed in only 11 to 27 samples.
98 This clearly indicates a lack of studies investigating antiparasitic PhACs in environmental waters,
99 compared to antibiotics.

100 Studies on the fate and transfer of PhACs in catchments and rivers under Mediterranean climate are
101 scarce. Mediterranean climate is characterized by dry summers and intense rainfall in autumn, regularly
102 producing flash floods (see section 2.1). Some studies investigated the occurrence of PhACs in
103 Mediterranean catchments with dynamic hydrometeorology (Mandaric et al., 2019; Palma et al., 2020;
104 Osorio et al., 2014). They generally searched for human use PhACs and found that the main source were
105 WWTPs. During floods, a dilution of PhAC concentration was observed in most cases. This would indicate
106 a relatively constant input of PhACs from WWTPs that is diluted by the additional water. Osorio et al.
107 (2014) found three molecules with the opposite pattern (an increase in concentration during flood
108 events) or a mixed pattern, all of which are also used in veterinary medicine. This increase in
109 concentration during flood events was also observed for other molecules from diffuse sources such as
110 pesticides (León et al., 2017). Castaño-Ortiz et al. (2023) found an increase in concentration of mainly
111 human use PhACs in a Mediterranean lagoon following flash floods. They explain this observation by
112 sewer overflows and mobilization from agricultural soils that had been irrigated with treated
113 wastewater.

114 Due to a lack of studies focusing on the diffuse entry of veterinary PhACs from agricultural sources under
115 Mediterranean climate, there are still many unknowns about the extent to which these elevated
116 dynamics affect the transfer patterns of veterinary PhAC residues from agricultural soils into streams.
117 Under these conditions, flow paths and transit times can change completely within minutes. While rapid
118 overland and subsurface storm flow occur, long-term equilibrium sorption and degradation processes
119 may be of negligible importance for the transfer to streams and for the mobility of the studied
120 compounds. Little is known about the ability of these conditions to load streams with significant
121 amounts of PhACs from extensive livestock farming, despite the hydrophobicity of some of the most used
122 molecules in the catchment (see Table 3) and thus impact riverine ecosystems.

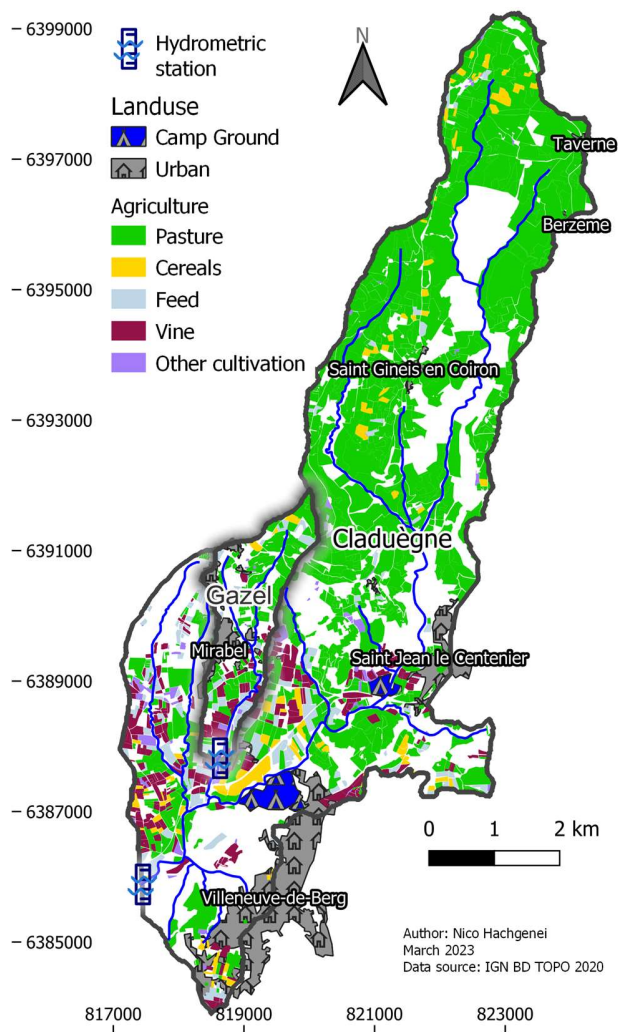
123 In order to investigate this question, veterinary pharmaceuticals used in a rural catchment under
124 Mediterranean climate are identified through interviews with livestock farmers. Then, their occurrence
125 and concentration in the stream are studied under different hydrologic conditions. Our objective is but
126 to identify the conditions that may lead veterinary PhAC to reach the streams in a backward approach
127 (starting from the stream as a receiving system), but not to investigate the fate of these molecules taking
128 into account all the processes that may occur (i.e. absorption, degradation and transfer).

129 2 Methods

130 The transfer dynamics of PhAC are studied in the Claduègne catchment (see section 2.1). We interviewed
131 farmers in the catchment in order to identify the veterinary PhAC that are routinely used and the
132 seasons and frequencies of treatment (section 2.2). We also collected stream water samples and
133 analyzed them for selected PhAC (see section 2.3).

134 2.1 Study site

135 The Claduègne mesoscale catchment (42 km²; Fig. 1) is located in the French Ardèche department and is
136 presented in detail by Nord et al. (2017). The northern, upstream half of the Claduègne catchment lies
137 on the Coiron basaltic plateau and the southern downstream part lies on sedimentary marly limestone
138 bedrock. The altitude ranges from 205 masl to 838 masl. The main land uses are pasture (46 %, mostly
139 for livestock), cultivated land (5.2 % vineyards, 2.8 % feed crops, 2.3 % cereals), small forests &
140 shrublands (most of the land not identified in Fig. 1) and villages. It shares significant parts of the five
141 communes of Mirabel, Saint-Gineys-en-Coiron, Berzème, Saint-Jean-le-Centenier and Villeneuve-de-
142 Berg. The site is characterized by its low population density (32.6, 8.5, 9.5, 52.0, and 117.9 inhabitants
143 per km² respectively for the communes listed above; calculated from INSEE (2017)), extensive agriculture
144 and natural vegetation.



145
146 *Figure 1: Land use in the Claduègne catchment. Agriculture is from RPG (Registre parcellaire graphique 2020). Coordinates are in*
147 *Lambert 93 [m], northing on Y, easting on X.*

148 The Claduègne catchment is exposed to Mediterranean climate, characterized by a strong seasonality
149 with a dry summer followed by an autumn with frequent intense storm events (Boudevillain et al., 2016,
150 2011; Nuissier et al., 2008) that regularly cause flash floods (Delrieu et al., 2005; Carrega, 2016). Annual

151 precipitation in the sedimentary part of the catchment is 1030mm (Huza et al., 2014). Streamflow
152 discharge follows the seasonality of precipitation, with some parts of the stream network being dry in
153 summer, the highest discharge values occurring in autumn and some flood events in spring. Between
154 2011 and 2020, 1/3 of the total streamflow volume left the catchment in only 1.4 % of the time.

155 The Claduègne catchment is instrumented with two hydrometric stations: one at the outlet on the main
156 catchment (CLA) and one at the outlet of the Gazel subcatchment (GAZ) with an area of 3.5 km² (see Fig.
157 1). Each measures water discharge (Q), electric conductivity (EC), turbidity (TU) and temperature (T) and
158 is equipped with an automated water sampler (see section 2.3). The Gazel catchment is mainly
159 agricultural (livestock, vineyards and cereals), and includes a phyto-WWTP that treats water from the
160 small village of Mirabel. The Claduègne catchment has a similar land use and additionally receives
161 treated wastewater from the town of Villeneuve-de-Berg, which includes a hospital and a large
162 campground (up to 2500 inhabitants in summer) with its own phyto-WWTP.

163 2.2 Interview methodology

164 We identified and contacted 33 livestock farmers within the catchment, 13 of whom agreed to
165 participate in semi-directive interviews. We interviewed 7 cattle, 2 swine, 1 goat, 1 sheep and 2 chicken
166 farmers from all parts of the catchment in 2018 and 2019. Their farmed fields inside the Claduègne
167 catchment add up to a total of 4.9 km² (about 12% of the catchment area). We obtained three complete
168 treatment schedules (2 cattle & 1 goat) that were used to verify the qualitative information given by the
169 farmers. The goal was to identify the PhACs systematically used (at least 30 % of the herd treated at least
170 once per year), the number of animals, the location of their plots, the seasons of application of
171 treatments and of grazing. The questionnaire is provided in the supplementary material. Due to large
172 uncertainties on the number of animals of each species in the catchment area and the distribution
173 between the different molecules, no estimate of the total use of each PhAC is presented in this study.

174 2.3 Water sampling

175 Stream water grab samples of approximately 300 mL were taken in different times during low water flow
176 conditions. In addition, samples were taken at high frequency (up to 2 h⁻¹) by automated samplers
177 (Teledyne ISCO 3700) at the outlets of the Gazel (GAZ) and Claduègne (CLA) catchments (Fig. 1) during
178 two flood events (November 2019 and June 2020). All water samples were taken using glass bottles
179 washed with a professional washing machine (Miele professional G 7883) and then decontaminated at
180 500°C for 3 h. The filtration apparatus (DURAN) and filters (GF/F Whatman) were also burnt at 500 °C.
181 After collection, the samples were returned to the laboratory in a cool box at low temperature (4 °C) and
182 filtered as soon as possible within 48 h max. The samples were then frozen at -20 °C until chemical
183 analysis. Samples were protected from light during transport, storage and preparation where possible by
184 using amber glass and aluminum foil.

185 2.4 Chemical analysis

186 High purity solvents (LC-MS grade) methanol and acetonitrile were purchased from Biosolve (France).
187 Formic acid (LC-MS grade) was purchased from LiChropur (Germany). Ultra-pure water was obtained
188 with a Veolia ELGA Purelab chorus system. Native and internal standards were purchased from Sigma-
189 Aldrich (USA), Fisher Scientific (Germany), AccuStandard (USA), Cayman Chemicals (USA), Dr.
190 Ehrenstorfer (Germany) and ITW Reagents (USA). Whatman Filters (GF/F) were purchased from Sigma-
191 Aldrich (China) and OASIS HLB cartridges (6 cc, 200 mg, 30 µm) from Waters (Ireland).

192 Prior to analysis, the samples were thawed slowly at 4 °C. For some samples, brownish residues had
193 precipitated, presumably organic residues, in which case an additional filtration step was performed.
194 The samples, duplicate samples, field blanks and procedural blanks were then spiked with two internal
195 standard mixtures (25 µL each; working solution at 500 ng mL⁻¹). The samples were enriched by solid
196 phase extraction on OASIS HLB cartridges (6 cc, 200 mg, 30 µm). The cartridges were first conditioned
197 with 6 mL MeOH followed by 6 mL of pure water. The samples were then loaded and passed through the
198 cartridges. Finally, the cartridges were dried under vacuum, and eluted using 6 mL of methanol into 15
199 mL polypropylene tubes.

200 The analytes were eluted using 6 mL of methanol. The eluates were blown down at 32 °C under a gentle
201 stream of nitrogen to 1 mL and then vortexed in order to recover potential residues on the tube walls. The
202 samples were further concentrated down to 150 µL and then reconstituted by adding 350 µL of pure water.

203 A portion of the water samples was analyzed for three of the most commonly used veterinary
204 pharmaceuticals (Fenbendazole (FBZ), Ivermectin (IVM) and Mebendazole (MBZ)), in addition to a list of
205 different molecules of various uses, a selection of which is presented in this article. FBZ, IVM and MBZ
206 were chosen based on their high use, representation of different species as well as their characteristics
207 allowing to include the in the existing method. The samples extracts were analyzed by ultra-performance
208 liquid chromatography (Exion-LC) coupled with tandem mass spectrometry (5500 QTRAP Sciex system).
209 The targeted chemicals were separated using a Phenomenex® Kinetic® Biphenyl column (100x2.1 mm
210 internal diameter, 2.6 µm particle size).

211 Briefly, MilliQ water and acetonitrile (each with 0.1 % formic acid) were used as mobile phases A and B
212 respectively. A linear gradient was run from 10 % B to 40 % B over 5 min, then from 40 % B to 100 % B over
213 5 min and then remained at 100 % B for 4 min. Finally, it returned to the initial conditions in 0.1 min,
214 followed by 3 min of equilibration. The flow rate was 0.5 mL min⁻¹, the column oven was held at 40 °C. An
215 injection volume of 6 µL was used. The ion source parameters were optimized to give the following final
216 conditions: ion spray voltage: 4500 V; temperature: 600 °C; curtain gas: 30 L min⁻¹ and GS1 and GS2 at 60.
217 High purity nitrogen was used as curtain gas and collision gas. The mass spectrometer was operated in
218 positive electrospray ionization mode and was used in scheduled multiple reaction monitoring mode.

219 Eight calibration standards were prepared at concentrations of 0, 0.5, 1, 2.5, 5, 10, 50, and 100 ppb. The
220 data obtained were processed using Sciex OS (Sciex) software. The Calibration curves were established
221 using a 1/x-weighted linear regression. The reported values are corrected for recovery of internal
222 standards (using mass-labeled standards). The instrumental limits of detection (LDs) and quantification
223 (LQs) were set at three and ten times the standard deviation of the lowest standard concentration,
224 respectively, with a signal to noise ratio greater than 10 after eight injections. Table 1 shows the
225 instrumental LQs, in ng mL⁻¹ of the concentrated extract as well as the average method LQs in ng L⁻¹ of
226 the original water samples.

227 *Table 1: Limits of quantification (LQ) of the analyzed pharmaceutically active compounds (PhAC) in the analyzed extract*
228 *(concentrated solution after solid phase extraction and evaporation; instrument LQ) and the initial environmental water sample*
229 *(method LQ).*

Molecule	Extract [ng mL ⁻¹]	Water [ng L ⁻¹]
Atenolol	0.2	0.41
Carbamazepine	0.5	1.02

Fenbendazole	0.08	0.16
Ivermectine	1	2.05
Mebendazole	0.1	0.20
Sulfamethoxazole	0.3	0.61
Trimethoprim	0.2	0.41

230

231 3 Results

232 3.1 Veterinary pharmaceutical use in the Claduègne catchment

233 A main outcome of the interviews, consistent between the different farmers, is the generally very limited
 234 application of antibiotics in the context of extensive farming in the Claduègne catchment. The only
 235 species that is still relatively systematically treated with antibiotics is the goat (large-scale curative,
 236 approximately 50 % of the herd treated per year). For all other species, the use of antibiotics remains
 237 curative on a case-by-case basis with usually less than 5 % of the animals treated per year. This is also the
 238 case for anti-inflammatories. The other consistent finding is that, unlike antibiotics, antiparasitic drugs
 239 are used systematically for all species, in most cases with at least one preventive treatment of all
 240 individuals per year. They are used against parasitic worms, ticks and lice for example. These interviews
 241 permitted to identify the molecules most systematically used in the Claduègne catchment. A summary of
 242 the 14 molecules identified as systematically used is provided in Table 2 and their octanol-water
 243 partitioning coefficients (K_{ow}) and PNEC are shown in Table 3. Richard (2011) calculated PNECs from
 244 acute toxicity for 3 different aquatic species and we chose the lowest value for each molecule. The used
 245 toxicities were 72 h 50 % effect concentration (EC_{50}) for algal growth inhibition, 48 h EC_{50} for
 246 immobilization of *Daphnia magna* and 96 h 50 % lethal concentration (LC_{50}) for fish. The most toxic
 247 molecules all have a high K_{ow} . For the analyses, three of the systematically used antiparasitic molecules
 248 for three different species (FBZ, MBZ and IVM for swine, sheep and cattle respectively) were selected
 249 and added as target molecules to an existing analytical method. FBZ has the advantage of being used all
 250 year round, facilitating it's detection and interpretation.

251 *Table 2: List of pharmaceuticals systematically used in the Claduègne catchment by species with the main treatment season. AP:*
 252 *antiparasitic; AB: antibiotic; IVM: Ivermectin. The dose is given in mg per treatment per individual. It can vary depending on the*
 253 *weight of the animals and the way of administration. It is given for the most common way of administration and an average*
 254 *adult animal.*

Animal	type	Molecule	Season	comment	dose [mg]
Cattle	AP	Ivermectin	Mar-Apr	preventive, alternating	200
	AP	Clorsulon	Mar-Apr	in some IVM preparations	1300
	AP	Deltamethrin	Mar-Apr	preventive, alternating	500
Swine	AP	Fenbendazole	Apr / whole year	preventive	1200
Goat	AB	Benzylpenicillin	Nov, Jan-Mar	large-scale curative	2000
	AB	Dihydrostreptomycin	Nov, Jan-Mar	large-scale curative	2000
	AB	Nafcillin	Nov	large-scale curative	100
	AB	Praziquantel	Nov	large-scale curative	280
	AP	Oxfendazole	Dec	preventive	750
	AP	Eprinomectin	Spring	preventive	37
	AP	Ivermectin	Autumn	preventive	20
Chicken	AP	Levamisole	whole year	preventive	80

Sheep	AP	Moxidectin		preventive	15
	AP	Mebendazole	Jun-Jul (+ Autumn)	preventive	1125
	AP	Closantel	Jun-Jul (+ Autumn)	preventive	750
	AP	Ivermectin	Mar-Apr	preventive	10

255

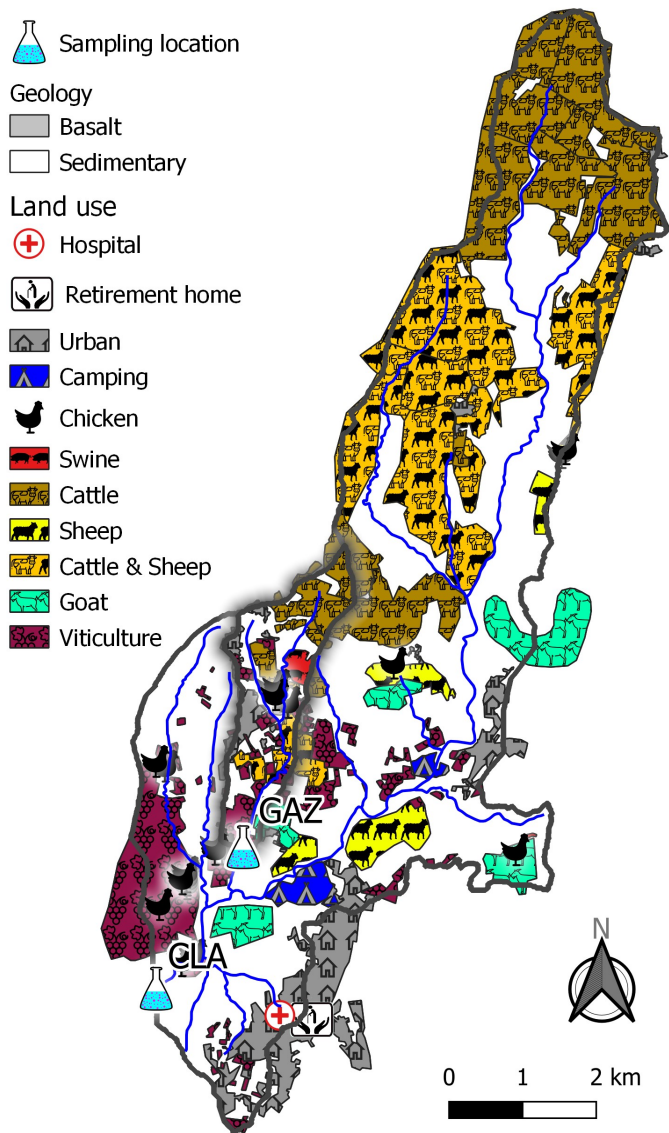
256 *Table 3: Hydrophobicity and predicted aquatic no effect concentration (PNEC) of the molecules systematically used in the*
 257 *catchment. PNECs are obtained from Richard (2011). The table shows the lowest acute PNEC between values for algal growth*
 258 *inhibition, Daphnia immobilization and fish toxicity. For the octanol-water partition coefficient $\log(K_{ow})$, experimental values*
 259 *were preferred to calculated values, when available. The column E/C indicates if $\log(K_{ow})$ values are experimental (E) or*
 260 *calculated (C).*

molecule	log(KOW)	source	E/C	PNEC water $\mu\text{g/l}$
Ivermectin	3.22	Halley, Nessel, et al. (1989)	E	0.000000025
Clorsulon	1.09	Grabowski et al. (2010)	C	356
Deltamethrin	5.43	Mestres & Mestres (1992)	E	
Fenbendazole	3.93	Mottier et al. (2003)	E	0.00008
Benzylpenicillin	1.83	Hansch et al. (1995)	E	
Dihydrostreptomycin	-9.05 ??	Grabowski et al. (2010)	C	
Nafcillin	3.3	Montoya-Rodríguez et al. (2020)	C	
Praziquantel	2.42	Grabowski et al. (2010)	C	5.23
Oxfendazole	2.03	Mottier et al. (2003)	E	0.52
Eprinomectin	5.4	Krogh et al. (2008)	E	0.00045
Levamisole	2.87	Grabowski et al. (2010)	C	32
Moxidectin	4.77	Krogh et al. (2008)	E	0.00003
Mebendazole	3.73	Mottier et al. (2003)	E	0.036
Closantel	8.11	Horvat et al. (2012)	C	32

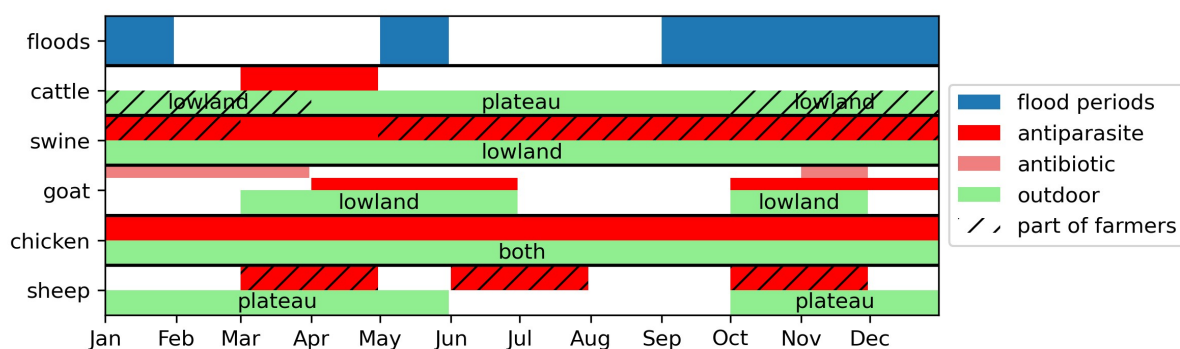
261

262 In addition to the drugs listed, hormones have been used in order to synchronize the reproduction cycles
 263 in some species. The mode of administration was not systematically inquired and in some cases there
 264 are different modes of administration for the same molecule. The practiced modes of administration
 265 included sub-cutaneous injection, oral administration and topical application. Figure 2 shows the spatial
 266 distribution of animal species within the Claduègne catchment. Main grazing periods and treatment
 267 seasons are summarized in Fig. 3. Goats are outdoor from March to June and October to November and
 268 are treated mainly in winter. While some farmers keep their cattle outside all year round (in the lower
 269 parts of the catchment in winter), most keep them indoor in winter. The exact grazing periods vary.
 270 Often the cows are brought indoor when autumn storms start. They are treated either in March, just
 271 before going outdoor or in autumn. Sheep are treated in summer and autumn. Most farmers keep their
 272 sheep outside all year round and move them to higher ground on the Coiron plateau in summer. Others
 273 keep them indoor during the warmer months (June - September). Chickens and swine are treated all year
 274 round with no dominant period. In the case of chickens, this is due to their life span, which is only 80
 275 days. This corresponds to about ten cycles per year as chickens are outside for half of their lifetime, in
 276 accordance to the rules of the "Label Rouge", a French food quality label from which most of the chicken
 277 farmers in the catchment benefit. For swine, the practice varies from farmer to farmer ranging from one
 278 treatment in spring to one every eight weeks, in case the animals stay in the catchment for only part of
 279 their life span. The timing of manure application (from periods when the animals stayed indoor) varied.

280 The period mentioned by most farmers is autumn, while all seasons were designated as periods of
281 manure application by the different farmers. In general, the farmers apply the manure to their own fields
282 (mostly cereals, feed crops or vineyards).



283
284 *Figure 2: Map of spatial distribution of animal husbandry par species in the Claduègne catchment. CLA and GAZ are the sampling*
285 *points at the two hydrometric stations.*

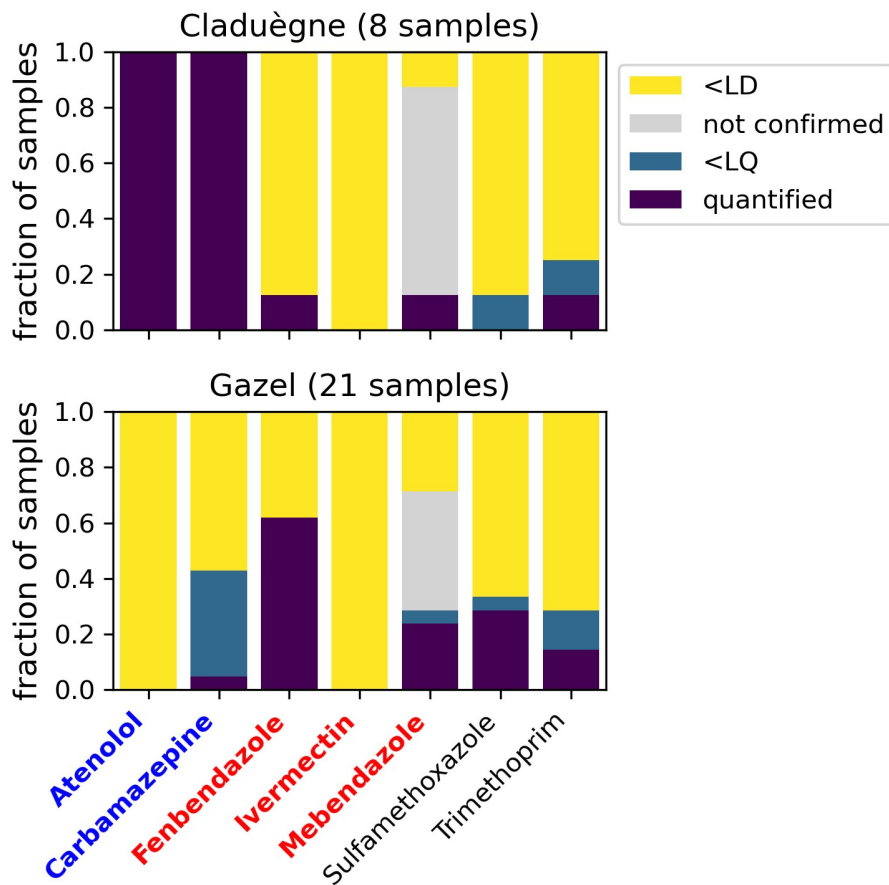


286

287 *Figure 3: Main periods of floods, treatments and grazing outdoors per species with grazing location (white text). Periods are*
 288 *approximate as they change between farmers and between the years. Hashed fill indicates contrasting practices between*
 289 *different farmers.*

290 3.2 Stream concentrations of pharmaceuticals

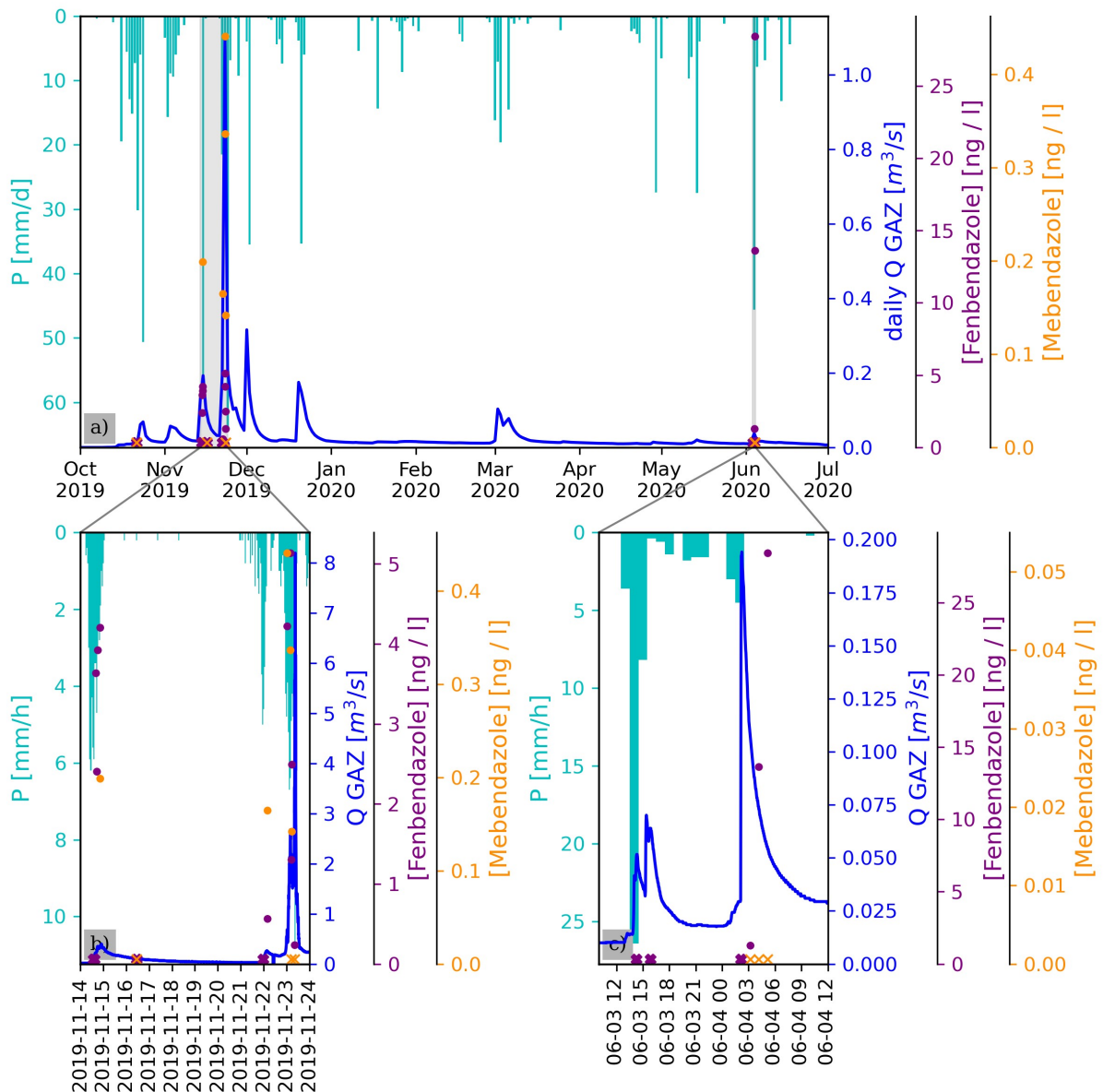
291 The concentrations of all analyzed molecules in all samples are provided in Hachgenei et al. (2023).
 292 Figure 4 presents the detection frequencies of a selection of human and veterinary PhACs at the outlets
 293 of the Claduègne and Gazel catchments (CLA and GAZ; Fig. 2). Atenolol is a beta-blocker and
 294 Carbamazepine is an anti-epileptic drug, both of human use only. FBZ, IVM and MBZ are antiparasitic
 295 drugs used routinely as a preventive measure in the catchment to treat swine, cattle and sheep
 296 respectively. Sulfamethoxazole (SMX) and Trimethoprim (TMP) are authorized for veterinary use, but
 297 were not reported to be used routinely by the farmers interviewed. Due to analytical interference on
 298 one transition, the quantification of MBZ could not be confirmed in some of the samples. All presented
 299 molecules were below the limit of detection in some samples. Atenolol and Carbamazepine were at
 300 quantifiable concentrations in all samples at the Claduègne outlet, ranging from 0.57 to 7.4 and from 3.8
 301 to 70.7 ng L⁻¹ respectively. At the Gazel outlet, Atenolol was never detected and Carbamazepine reached
 302 a maximum concentration of 0.10 ng L⁻¹. IVM was not detected in any of the samples. The maximum
 303 observed concentrations in CLA and GAZ respectively were the following (in ng L⁻¹): FBZ: 0.16, 28.4, MBZ:
 304 0.20, 0.44, SMX: <LD, 1.27, TMP: 0.36, 0.79. To summarize, the purely human PhAC were found in all
 305 samples from the Claduègne outlet, but rarely in the Gazel. The veterinary PhACs were found in some
 306 samples from both sites, but slightly more often and at higher concentrations in those from the Gazel.



307

308 *Figure 4: Detection frequencies of a selection of pharmaceutical products for human (blue) and mainly veterinary (red) use at the*
 309 *outlet of the Claduègne and Gazel catchment. Molecules written in black are authorized for veterinary use but were not*
 310 *systematically used by the interviewed farmers. <LD: below limit of detection, <LQ: detected but below the limit of quantification.*
 311 *Due to an interference on a Mebendazole transition, its quantification could not be confirmed in all samples.*

312 Fig. 5 shows the concentration evolution of FBZ and MBZ, the two PhAC systematically used by farmers
 313 in the catchment, at the Gazel outlet. FBZ was not detected in any sample outside of flood events, but its
 314 concentration spiked during the observed flood events, with a peak observed either before or after the
 315 peak stream flow. MBZ shows a very similar behavior, except that the highest concentration values are
 316 observed during the autumn flood and not in June as for FBZ.



317

318 *Figure 5: Temporal evolution of the dissolved concentrations of Fenbendazole and Mebendazole in water samples from the Gazel*
 319 *outlet, and of discharge (Q) and precipitation (P). The 'x' symbols at the bottom indicate analyzed samples without detectable*
 320 *concentration of the corresponding substance*

321 4 Discussion

322 We could show that even hydrophobic PhACs such as FBZ and MBZ were transferred to the stream
 323 during floods at significant concentrations. The maximum observed concentration of FBZ represents 355
 324 times its lowest PNEC for aquatic organisms (Richard, 2011). The observed concentrations of FBZ & MBZ
 325 peaking during flood events, while being below the LD the rest of the time, are in agreement with the
 326 initial hypothesis that these PhACs reach surface water only under wet conditions. During floods, large
 327 amounts of event water can reach the stream directly (Hachgenei et al., 2023b; Hachgenei, 2022). This
 328 event water can carry contaminants into the stream by overland flow, thus avoiding the “filtering” effect

329 of the soil. These flood events occur regularly in autumn and spring. The results suggest that
330 hydrometeorology is the determining factor for the risk of contaminants transfer to streams in this study
331 site under Mediterranean climate and that there is a particular risk of surface water contamination with
332 PhACs from diffuse agricultural sources during floods. This is in agreement with a previous study in the
333 Claduègne catchment (Martins et al., 2019), which analyzed different PhACs for mainly human use and
334 some pesticides. While it found a dilution pattern for human PhACs, an increase in the concentration of
335 most pesticides was observed during or at the end of floods, indicating that their diffuse sources are not
336 hydrologically connected to streams during low flow periods and get connected during flood events.

337 The fact that the highest concentration of MBZ was observed in November while the highest
338 concentration of FBZ was observed in early June can probably be explained by the treatment seasons.
339 Sheep are treated with MBZ in summer and autumn, while swine are treated with FBZ either all year
340 round every eight weeks, or once in spring.

341 It should be noted that only the dissolved fraction was analyzed. Due to the high octanol-water
342 partitioning coefficient K_{ow} of the three analyzed routinely used veterinary PhAC ($\log(K_{ow})$ of 3.2, 3.9 and
343 3.7 for IVM, FBZ and MBZ respectively (Halley et al., 1989a; Mottier et al., 2003)), it is expected that a
344 large part of the molecules is adsorbed onto particulate and dissolved organic matter (OM). This is
345 particularly true with regard to the precipitation of OM during frozen storage that made a second
346 filtration necessary. Therefore, the analyzed concentration may be an underestimate of the initial
347 dissolved concentration in the stream, which is probably lower than the total concentration (dissolved +
348 adsorbed on suspended solids). Cattle are only treated once a year and farmers alternate between IVM
349 and Deltamethrin, so it is most likely that due to the small number of floods analyzed, potential export of
350 IVM was not detected. Furthermore, IVM is very sensitive to photo-degradation which might take place
351 in the stream, but also during sample handling, even though protective measures had been taken (use of
352 aluminum foil or amber glass where possible). It should also be noted that the LQ for IVM is 10^5 times
353 the lowest aquatic PNEC (Richard, 2011). Therefore, the result does not mean that there is no risk for
354 aquatic organisms.

355 The compounds analyzed are excreted over several days (FBZ & MBZ; Gokbulut et al., 2006; J. M.
356 Lumaret, 1986) to several weeks (IVM; Herd et al., 1996) and tend to persist in dung and soil (Wohde et
357 al., 2016; Kreuzig et al., 2007; McKellar, 1997; Floate et al., 2005). Therefore, although the season of
358 treatment is important, the risk is not limited to the exact time of treatment, but more data covering all
359 seasons would be needed to draw conclusions on this. Therefore, during the days or weeks following
360 treatment, livestock should be kept on fields with low hydraulic connectivity and low risk of overland
361 flow formation (low slopes, conducting soils), even if no precipitation is expected in the following days.

362 Another important consequence is that the hydrometeorologic conditions should be taken into account
363 when defining a sampling strategy for monitoring these molecules, with emphasis on flood periods.
364 Otherwise, studies may miss the short periods during which almost all export takes place and therefore
365 wrongly conclude that there is no risk associated with these compounds. In addition, we argue that due
366 to the high number of authorized molecules (Répertoire des Spécialités Pharmaceutiques) and the low
367 number of systematically used molecules, it is essential to identify the molecules actually used in the
368 study site and to adapt the analytical methods in order to draw meaningful conclusions about the impact
369 of livestock farming on water quality. Without the interviews conducted in this study, the choice of
370 molecules to be analyzed would have been difficult and the interpretation less significant. The analytical

371 method is currently being extended to include most of the routinely used PhACs. In addition, it can now
372 also be used to analyze soils and sediment. These modifications will serve to continue studying the
373 transfer of PhAC in Mediterranean climate.

374 5 Conclusion

375 In the context of extensive agriculture on our study site, the use of antibiotics is currently low, whereas
376 antiparasitic drugs are systematically used. Current analytical methods still focus mainly on antibiotics.
377 We suggest to systematically include antiparasitic drugs in the analytical methods in all agricultural study
378 sites. In addition, we have been able to show that the transfer of residues of veterinary pharmaceuticals
379 is strongly dependent on hydrometeorology, with intense storms causing the highest export. This means
380 that the risk of these molecules reaching streams is higher in climatic conditions with intense storms, as
381 is the case in Mediterranean climate. Under these conditions, special care needs to be taken to avoid
382 hydrologically connected pastures after animal treatment. Furthermore, we emphasize that sampling
383 strategies for the monitoring of these compounds should cover a large range of conditions including high
384 frequency sampling during floods, in order to allow conclusions on their presence in streams. The
385 interviews with livestock farmers in this study allowed targeted analyses of the contaminants and linking
386 sources to stream concentrations in a meso-scale catchment with various livestock farms.

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390 Data availability

391 The full results of the chemical analyses are available under the following temporary link for review and
392 will get a DOI for publication:

393 [https://entrepot.recherche.data.gouv.fr/privateurl.xhtml?token=aceda4c-9325-4626-ae5c-](https://entrepot.recherche.data.gouv.fr/privateurl.xhtml?token=aceda4c-9325-4626-ae5c-a6401efbdc75)
394 [a6401efbdc75](https://entrepot.recherche.data.gouv.fr/privateurl.xhtml?token=aceda4c-9325-4626-ae5c-a6401efbdc75)

395

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