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Occurrence of pharmaceuticals in muscle tissue of red drum (*Sciaenops ocellatus*) across subtropical estuaries: Comparison to blood plasma and implications for human exposure

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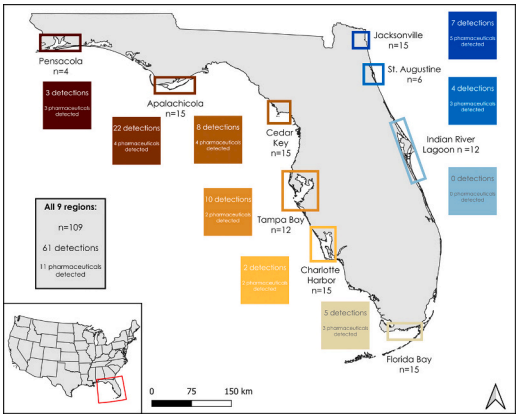
HIGHLIGHTS

- 11 different pharmaceuticals detected in a wild marine fish muscle across 9 estuaries
- Muscle tissue contained fewer pharmaceuticals and lower concentrations detected than plasma
- Number of detected pharmaceuticals was correlated between muscle and plasma
- Composition of detected pharmaceuticals differed between muscle and plasma
- High risk of human exposure via fish consumption but low risk of therapeutic effects

GRAPHICAL ABSTRACT



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ABSTRACT

Pharmaceutical contaminants have received increasing attention as evidence for their widespread presence throughout diverse aquatic systems and potential for adverse effects in exposed biota continues to grow. In addition to further documenting the extent of pharmaceutical exposure in wild fish species, particularly those in

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marine and estuarine systems, there is the need to understand the potential for effects in humans via consumption of contaminated seafood. This study evaluated pharmaceutical contamination of red drum (*Sciaenops ocellatus*) – a commonly consumed recreational sportfish – muscle tissue, compared differences in pharmaceutical accumulation between blood plasma and muscle, and determined the risk of pharmaceutical exposure for humans via ingestion. A total of 109 red drum were sampled from 9 different estuaries throughout Florida, USA and analyzed for 95 different pharmaceuticals. Among the 109 muscle samples, 42 fish (38.5 %) contained at least one pharmaceutical. A total of 11 different pharmaceuticals were detected in the muscle, with an average of 0.6 pharmaceuticals per sample. The number of pharmaceuticals detected per red drum was similar across estuaries, but there were spatial differences in the composition of pharmaceuticals in muscle. Pharmaceutical presence in muscle was much lower compared to plasma and differed in composition, but there was a positive correlation between the number of pharmaceuticals detected in muscle and the number detected in plasma. Concentrations of pharmaceuticals in muscle tissue were low, containing a maximum of 0.002 % of a recommended daily dose per serving. Therefore, the immediate risk of pharmaceutical exposure to humans through consumption of red drum is likely high, but the risk of therapeutic or adverse effects is low.

1. Introduction

Pharmaceutical pollution has increasingly been recognized as an emerging contaminant of concern to aquatic ecosystems (Wilkinson et al., 2022). Because of the conservation of target receptors across phylogeny and effectiveness at low concentrations, pharmaceuticals may make wildlife susceptible to potential physiological and behavioral effects (Mezzelani et al., 2018). Pharmaceuticals enter the environment through effluent of wastewater treatment facilities and septic systems, livestock runoff, pharmaceutical production, and improper disposal of unwanted or expired medications (Madikizela et al., 2020). The consistent discharge and chemical properties of pharmaceuticals can lead to their pseudo persistence in the environment (Bu et al., 2016). Because of this pseudo persistence, aquatic organisms are at a prolonged and spatially extensive risk of exposure to pharmaceutical pollution (Fahlman et al., 2018).

Pharmaceuticals accumulate to varying degrees in tissues throughout an organism due to tissue-specific uptake (Liu et al., 2021). Differences in routes of elimination, rate of metabolism, and the target tissue/receptor of the pharmaceutical, which are all related to pharmaceutical design, can lead to variability in tissue specific pharmaceutical accumulation (Grabicova et al., 2014; Liu et al., 2021). These mechanisms can lead to variation in the concentration or absence of pharmaceuticals in specific tissues (e.g., different composition and concentration of pharmaceuticals in plasma vs. muscle tissue) (Grabicova et al., 2014; Heynen et al., 2016; Cerveny et al., 2021). For example, exposure of Nile tilapia (*Oreochromis niloticus*) to six common pharmaceuticals showed different bioaccumulation across 11 tissues investigated for each pharmaceutical, and was likely related to ease of ionization and therapeutic target of pharmaceuticals (Liu et al., 2021).

The fate of pharmaceuticals can both influence the physiological and behavioral effects on the individual and how the pharmaceutical is transferred to other organisms (e.g., humans) (Srain et al., 2021; Adeleye et al., 2022; Matthee et al., 2023). The risk of adverse effects in exposed fish can vary depending on the tissue in which it accumulates (Lin et al., 2022). For example, when accumulating in the brain, neuroactive pharmaceuticals can alter neurotransmitter levels and ultimately lead to behavioral changes in fish, more so than when accumulating in other tissues (Brodin et al., 2013; Hellström et al., 2016; David et al., 2018). Pharmaceuticals that accumulate in muscle would be a greater risk to human health, since this tissue is typically consumed by humans compared to other tissues (Bobrowska-Korczak et al., 2021; Mello et al., 2022). Therefore, understanding the fate of pharmaceuticals is crucial to understanding the potential risk of the pharmaceuticals to the focal organism and via trophic transfer (i.e., consumption).

Humans have the potential to be exposed to pharmaceuticals via consumption of organisms containing pharmaceuticals. Hao et al. (2021) examined the bioavailability of pharmaceuticals commonly found in fish from a fish market, finding that 26 % - 100 % of pharmaceuticals are bioavailable, demonstrating the potential for transfer to humans via ingestion. Previous studies examining human pharmaceutical exposure via seafood consumption have shown that humans are exposed to pharmaceuticals by consuming fish and mollusks, yet the immediate and acute risk is negligible (Liu et al., 2017; Omar et al., 2019; Ismail et al., 2021; Mello et al., 2022). While risk to adults has been deemed safe in several studies, research points to higher risk for certain age groups, such as toddlers (children 2–5 years old), if they consume seafood frequently (Martínez-Morcillo et al., 2020; Wang et al., 2023). Martínez-Morcillo et al. (2020) studied the risk from exposure to 27 pharmaceuticals in several seafood species (3 bivalves, 1 cephalopod, 2 crustaceans, and 1 fish) and reported a health risk for toddlers from an antidepressant (citalopram), and an anxiolytic (alprazolam). Wang et al. (2023) examined exposure risk to 21 antibiotics in a range of seafood species in the South China Sea (6 fishes, 4 crustaceans, and 5 bivalve species), and found a significant risk to toddlers from exposure to erythromycin, an antibiotic used to treat respiratory, skin, and other bacterial infections. Additionally, the effects of continuous chronic exposure to pharmaceuticals at low doses from seafood consumption, and other pathways, over the course of a human's lifetime are completely unknown and should not be disregarded as a potential human health risk (Klatte et al., 2017).

In this study, we investigated the concentration of 95 common pharmaceuticals in the muscle tissue of red drum (*Sciaenops ocellatus*) across 9 subtropical estuaries. We had 3 objectives: 1) Determine the prevalence of pharmaceuticals in muscle tissue of red drum, 2) Compare pharmaceuticals in muscle tissue to those in plasma, and 3) Quantify the risk of pharmaceutical exposure for humans consuming red drum. Recent studies have documented widespread exposure of pharmaceuticals in the plasma of recreational fish species in subtropical and tropical coastal habitats across Florida and the Caribbean basin (Castillo et al., 2024b, 2024a). We hypothesized that pharmaceuticals in muscle tissue are found across all estuaries sampled but at lower numbers and concentrations than in plasma and that the risk to humans via consumption would be low.

2. Methods

2.1. Study species

Red drum (*Sciaenops ocellatus*) are a common temperate estuarine species that use various habitat types, such as seagrass flats, muddy and sandy bottoms, oyster reefs, and spring-fed creeks (Murphy and Taylor, 1990; Kenworthy et al., 2018). This species shows high site fidelity, typically remaining in the same estuary from recruitment until maturity (Kenworthy et al., 2018; Lowerre-Barbieri et al., 2019). The diet of red drum mainly consists of benthic invertebrates (e.g., penaeid shrimp, blue crab, mud crab) and benthic fishes (e.g., toadfish; Malinowski et al., 2019). This type of diet places them at an elevated risk of pharmaceutical exposure since benthic invertebrates tend to have higher levels of pharmaceuticals (Miller et al., 2021). Additionally, red drum are an

important recreational and food fishery species, thus a potential source of contaminants to humans via their consumption (Adams and Onorato, 2005). The combination of inshore habitat use (in the vicinity of urbanized areas and potential pollution sources), high site fidelity, invertebrate diet, and their popularity as both a recreational and food fishery make it an ideal species for contaminant studies.

2.2. Sample collection

Red drum were collected from 9 estuaries around Florida using standard hook and line between June and September 2022 (Fig. 1, Table 1). These 9 estuaries were chosen to quantify the spatial variation of pharmaceutical prevalence in red drum muscle in Florida. On average, angling time was <5 min and often it took <1 min to capture red drum once hooked. All red drum were sampled from shallow, nearshore seagrass, open sand-mud bottom, and mangrove habitats (<10 m to a maximum of 30 km from a shoreline with human presence and potential pharmaceutical exposure). Sampling occurred in the summer when water temperatures are near the upper range of their thermal tolerance (~ 34.5–37 °C, Procarione and King, 1993). We collected 15 individuals in all regions except three (St. Augustine, Indian River Lagoon, and Pensacola) where sampling was difficult likely due to habitat deterioration and high fishing pressure (Table 1).

Upon capture, fish were measured for standard length, total length, girth, and weight and photographed. Latitude and longitude were recorded for the collection location of each fish. A blood sample and muscle sample was taken for pharmaceutical analysis according to the method described in Rehage et al., (in review). Approximately 1 g of muscle tissue was collected from underneath the 5th dorsal spine and placed in a sterile transport vial (Caplugs Evergreen 7 mL, Evergreen Scientific, Buffalo, NY, USA). Blood samples were centrifuged for 15 min at 3500 rpm (E8 Portable Centrifuge, LW Scientific, Lawrenceville, GA, USA) until plasma was clear. Plasma was then aliquoted using sterile polyethylene transfer pipets (Corning Scientific™, Corning, NY, USA) and placed in 2 mL cryovials (Corning Scientific™, Corning, NY, USA). Post collection, muscle and plasma samples were covered in aluminum foil and stored on ice, and then placed in a − 20 °C freezer until they were shipped to Sweden (see below) for analysis within 3 months of collection. A total of 109 muscle samples (4 to 15 samples per estuary, Table 1) were collected from the 9 study focal estuaries. Samples were shipped in September 2022, and stored in a − 20 °C freezer until processing at the Department of Chemistry of Umeå University, Umeå, Sweden in December 2022.

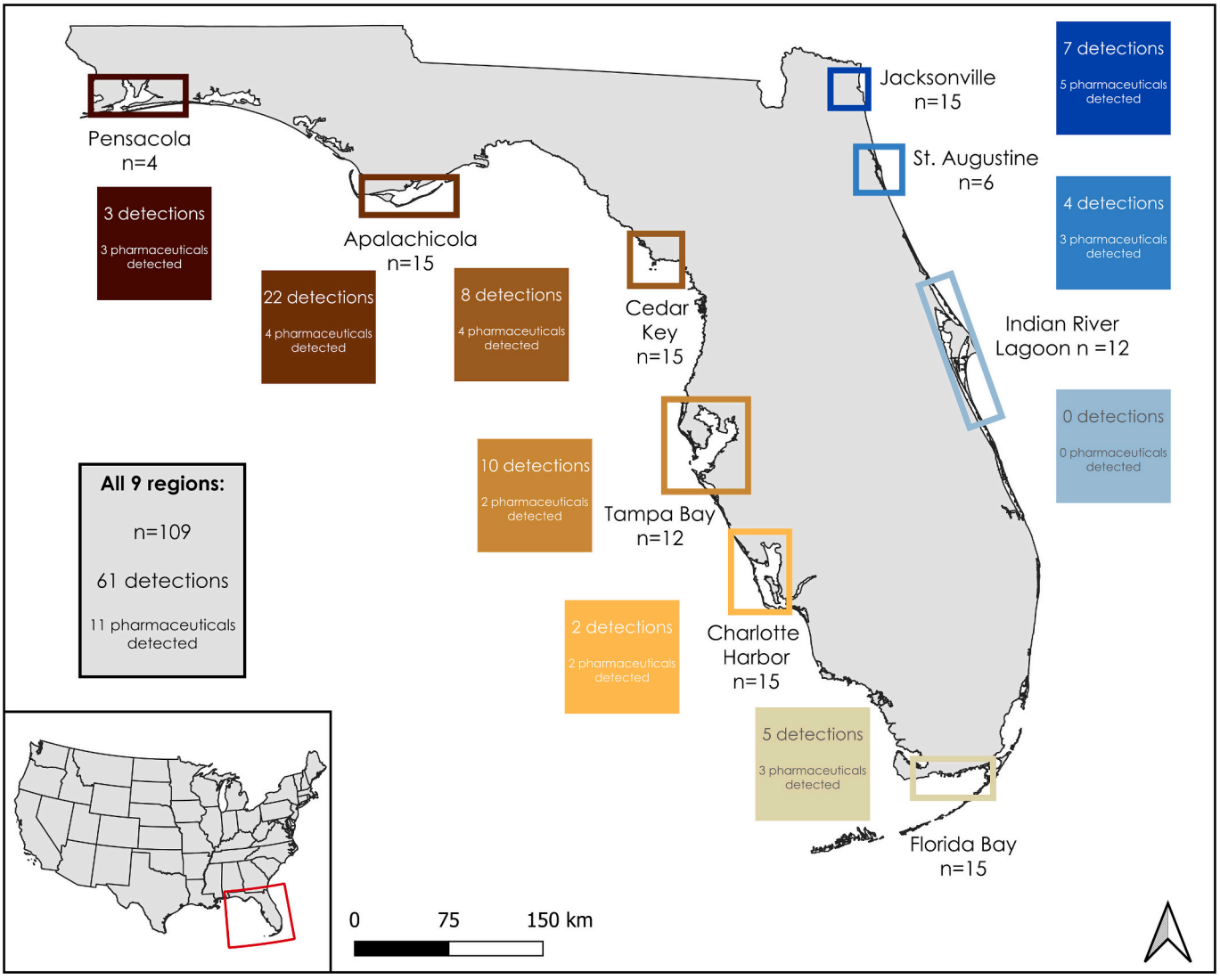

Fig. 1. Map of sampling locations with the number of fish sampled, number of detections within muscle tissue, and the total number of unique pharmaceuticals detected within each estuary.

Table 1
Size, date range, and number collected for red drum at each of the Estuaries sampled.

Estuary	Estuary size (km^2)	Nearest county population size	Collection date range	Red drum collected	Mean length (cm)	Minimum length (cm)	Maximum length (cm)	Mean weight (g)
Jacksonville	186.2	995,567 (Duval)	7/17/22–8/12/22	15	57.4	45.5	81	1905.3
St. Augustine	310.6	273,425 (St. Johns)	8/23/22–8/25/22	6	49.2	45	52	1105
Indian River Lagoon	914.3	606,612 (Brevard)	6/28/22–8/31/22	12	51.7	37.5	63.5	1656
Florida Bay	2198.9	82,874 (Monroe)	6/08/22–6/23/22	15	62.6	45.5	68.5	2302
Charlotte Harbor	699.3	186,847 (Charlotte)	8/8/22–8/10/22	15	62.1	54	74.5	2270
Tampa Bay	1036	1,459,762 (Hillsborough)	8/18/22–8/21/22	12	65.6	54	90	2959
Cedar Key	359.2	42,915 (Levy)	8/15/22–8/16/22	15	56.2	47	67	1649.3
Apalachicola	549.1	12,451 (Franklin)	7/12/22–7/13/22	15	53.6	46	68	1432
Pensacola	373	321,905 (Escambia)	9/01/22–9/03/22	4	55.4	46.5	70.5	1665

2.3. Target pharmaceuticals, standards, and analytical methods

A total of 95 pharmaceuticals were included in the analysis (Table S1) and target analyte selection was based on detectability and predicted ability to bioaccumulate in fish (Fick et al., 2010). A summary of analytical procedures is provided here, and additional details are provided in Grabic et al. (2012), Lindberg et al. (2014), and Sedvall et al. (2022).

All pharmaceutical standards were of analytical grade (>98 %). LC-MS/MS grade methanol (Merck, Darmstadt, Germany) and in-house prepared ultrapure water (Mili-Q Advantage system, Millipore, Billerica, USA) were used as a mobile phases during the analysis. Both mobile phases were acidified using formic acid (Sigma Aldrich, Steinheim, Germany) to 0.1 %.

Muscle samples were prepared according to the procedures described in detail previously (McCallum et al., 2019). In short, muscle samples underwent repeated solvent (acetonitrile) extraction, followed by evaporation of the supernatant, and its reconstitution (methanol), resulting in a 150 μL of final sample for analysis. Samples were spiked with the mixture containing 5 ng of each of 16 isotopically labeled internal standards before the extraction procedure. The concentrations of all pharmaceuticals quantified in muscle samples within this work are based on wet weight. A triple stage quadrupole mass spectrometer (TSQ Quantiva, Thermo Scientific, San Jose, CA) equipped with a heated-electrospray ionization (HESI) ion source was used for analysis of all samples. The instrument was coupled to an Accela LC pump (Thermo Fisher Scientific, San Jose, CA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland). A C18 phase Hypersil gold column (50 mm × 2.1 mm ID × 3 μm particles, Thermo Fisher Scientific, San Jose, CA, USA) with a guard column (2 mm, 2.1 mm, i.d. 5 μm particles) was used for liquid chromatography to separate the target analytes before mass spectrometry analysis.

2.4. Quality assurance and quality control

Two MS/MS transitions were used for positive identifications of analytes with the criterion that the ratio between the transitions may not deviate more than ±30 % from the ratio in the corresponding calibration standard. Retention times for all analytes detected in muscle samples were within ±2.5 % of the retention time in the corresponding calibration standard. Precision, recovery, limit of quantification (LOQ), and measurement of blank samples were used as additional quality assurance/quality control measures for the analytical method used in this study.

Quantification of target compounds was carried out using the internal standard approach. Instrumental LOQs were derived from seven-point standard curve ranging from 0.01 to 50 ng/mL. Peak area corresponding to the lowest point of the standard curve that had a signal/noise ratio of at least 10 was then used for calculation of LOQs in individual samples. Precision was expressed as a relative standard deviation (RSD) of response factors calculated for each point of the standard curve from the peak areas of the target analytes and their corresponding internal standards. To assess recovery, muscle tissue from fish that had no pharmaceutical detected in the sample was used. Muscle tissue of these fish was fortified with the mixture of all target pharmaceutical surrogate standards at three concentration levels - 0.1, 1, and 5 ng $sample^{-1}$, each in five replicates, and extracted using the same protocol as for the other samples. The information about the performance of analytical method including the precision, LOQs, and recoveries for individual compounds is presented in Table S3. Processing blanks were prepared daily following the extraction protocol.

2.5. Risk of human exposure

In order to quantify the risk of human exposure, we calculated the dosage per serving for each pharmaceutical detected (Fehrenbach et al., 2022). We calculated this dosage per serving using the following formula:

$$\frac{\text{Dosage}}{\text{serving}} = \text{Conc}_{\text{max}} * \frac{g_{\text{serving}}}{\text{DD}}$$

where $Conc_{max}$ is the maximum concentration of a pharmaceutical found in the muscle in ng/g, $g_{serving}$ is the grams per serving of red drum, and *DD* is the daily dose of the pharmaceutical in ng. For $g_{serving}$, we used 226.8 g (8 oz). Daily dose (DD) is the average prescribed daily dose of a pharmaceutical in ng. DD data for each pharmaceutical was obtained from the WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/). In essence, this calculation provides the proportion of a daily dose of a pharmaceutical that a human receives when consuming an 8 oz. filet of fish. We also calculated the number of servings it would take to receive a single dose of the pharmaceutical by taking the inverse of the dosage per serving ($1/\frac{Dosage}{serving}$).

2.6. Statistical analyses

Generalized Linear Models (GLMs) with a Poisson error distribution and a log link function were used to assess the influence of region (the 9 estuaries sampled) and fish total length on the number of

pharmaceuticals detected in red drum muscle. The full model was compared to each model with region only or total length only using the corrected Akaike information criterion (AICc). Models that fell within 4 AICc of the model with the lowest AICc were considered candidate top models, and the most parsimonious model was selected as the final model (Aho et al., 2014). The R package emmeans (Lenth, 2023) was used to conduct pairwise comparisons of model contrasts with the Hochberg method of *p*-value correction for significant main effects of the final model (Hochberg, 1988). A Pearson correlation was used to test for a relationship between the number of pharmaceuticals detected in red drum muscle and red drum plasma. All analyses were done in R v4.3.1 (R Core Team, 2023).

3. Results

3.1. Prevalence of pharmaceuticals of muscle tissue in different estuaries

Among the 109 fish sampled, 42 fish had pharmaceuticals in their muscle tissue (38.5 % of all red drum sampled), with a total of 61 pharmaceutical detections. If present, most fish had 1 pharmaceutical in their muscle tissue, with a maximum of 4 pharmaceuticals found in 1 red drum from Apalachicola. On average, 0.6 pharmaceuticals were detected per muscle sample. There were 11 pharmaceuticals detected across eight pharmaceutical classes (Table 2, Figs. 2–3). Tramadol (opioid pain killer) and flecainide (cardiovascular antiarrhythmic) were the most common pharmaceuticals detected and were each found in 16 fish (15 % of samples, Table 2). For tramadol, 15 of the 16 detections were in red drum collected in Apalachicola (1 in Jacksonville), while flecainide was detected in 3 regions (from highest to lowest): Tampa Bay, Apalachicola, and Jacksonville (Fig. 3). Haloperidol (psychoactive antipsychotic) and diphenhydramine (antihistamine) were the next most detected, found in 9 and 8 fish respectively, and both were detected in 5 estuaries each, although the identity of the estuaries varied (Fig. 3). Diclofenac (non-steroidal anti-inflammatory) and trimethoprim (antibiotic) were detected a total of 3 times across 3 and 2 regions, respectively. Ketoconazole (antifungal) had a single detection in 2 regions. Caffeine (psychoactive stimulant), glibenclamide (antidiabetic), paroxetine (psychoactive antidepressant), and sulfamethoxazole (antibiotic) were also detected, but were only found in a single red drum sample each.

Based on AICc and parsimony, the final model included region only, and the results of the GLM indicated that there was a significant difference in the number of pharmaceuticals detected across the 9 regions sampled ($F_{8,100} = 4.6, p = 0.0001$). Post-hoc pairwise comparison with a Hochberg adjustment revealed that Apalachicola and Charlotte Harbor were the only regions that differed significantly (Fig. 2). Apalachicola had the highest pharmaceutical presence in red drum muscle, with an average of 1.5 pharmaceuticals per fish. Every fish had at least one pharmaceutical detected (Fig. 2). All other regions averaged <1 pharmaceutical per fish. The 12 fish collected in the Indian River Lagoon had no pharmaceuticals detected (Fig. 3). Fish from Charlotte Harbor averaged 0.1 pharmaceuticals. There was no relationship between total length and the number of pharmaceuticals detected per fish in muscle tissue (GLM, z value = −1.1, $p = 0.27$).

3.2. Comparison of pharmaceuticals in muscle and plasma

Overall, there was a significant positive correlation ($r = 0.33, t = 3.6$, df = 107, $p = 0.0004$) between the number of pharmaceuticals detected in the muscle and the number detected in plasma (Fig. 4). Across all regions, only 11 out of 23 pharmaceuticals detected in plasma were found in muscle, highlighting potential chronic accumulation of these pharmaceuticals. Of the 11 pharmaceuticals detected in the muscle tissue, 5 were found in both muscle and plasma, while 6 were only found in the muscle tissue. The pharmaceuticals detected in muscle alone included haloperidol, trimethoprim, ketoconazole, glibenclamide, paroxetine, and sulfamethoxazole (Table 2). Examining the fate of pharmaceuticals within individual fish, only 3 of 5 pharmaceuticals detected in both muscle and plasma were found in both tissues within the same individual (Fig. 5). Diphenhydramine was detected in 8 fish, 4 of which it was detected in muscle only and 4 where it was detected in both the muscle and plasma. Tramadol and flecainide had the opposite pattern, with individual fish having detection in both muscle and plasma or plasma only. For most fish with a detection of tramadol (43/59) or flecainide (44/60), the pharmaceutical was detected in plasma only. Caffeine and diclofenac were either detected in the muscle or plasma only within an individual fish.

3.3. Risk of human exposure

Overall, the dosage per serving for red drum muscle was very low for all pharmaceuticals detected. Haloperidol was the pharmaceutical with the highest dosage per serving, with a value of 0.000021. In other words, consuming a 226.8 g (8 oz) filet of red drum would result in a human being exposed to 0.0021 % of the daily dosage for this pharmaceutical. At this concentration, to receive a full dose of this pharmaceutical, a human would need to consume 47,667 servings of red drum (Table 2). Caffeine was the second highest with a value of 0.000013 (or 0.0013 % of the daily dosage). All other pharmaceuticals were < 0.000001 of a dosage and would require >280,000 servings to receive one dose of either pharmaceutical.

4. Discussion

We investigated the prevalence of pharmaceuticals in red drum muscle tissue across 9 subtropical estuaries throughout Florida, USA and determined the potential for human exposure via ingestion. Of the 109 muscle samples, 42 fish (38.5 %) contained at least one pharmaceutical. We detected a total of 11 different pharmaceuticals in the muscle belonging to 8 therapeutic classes, with an average of 0.6 pharmaceuticals per sample. The number of pharmaceuticals detected per fish was

Table 2
Number and concentration of pharmaceuticals detected in red drum muscle tissue. Concentration range depicts minimum and maximum concentration. Daily dosage per serving is based on maximum concentration detected and 226.8 g (8 oz) serving size of red drum. Servings for 1 DD is the number of servings to receive 1 recommended daily dose of that pharmaceutical.

Pharmaceutical	Detections	Mean ± SD (ng/g)	Concentration range (ng/g)	Daily dosage per serving	Servings for 1 DD	Detected in Plasma
Flecainide	16	0.04 ± 0.02	0.02–0.09	0.0000001	9,798,158	Y
Tramadol	16	0.14 ± 0.05	0.07–0.27	0.0000002	4,899,079	Y
Haloperidol	9	0.15 ± 0.25	0.02–0.74	0.00002	47,667	N
Diphenhydramine	8	0.13 ± 0.14	0.02–0.42	0.0000005	2,099,605	Y
Diclofenac	3	0.61 ± 0.37	0.22–0.96	0.000002	459,289	Y
Trimethoprim	3	0.27 ± 0.10	0.16–0.36	0.0000002	4,899,079	N
Ketoconazole	2	0.16 ± 0.08	0.10–0.21	0.00000008	12,597,632	N
Caffeine	1	23	23	0.00001	76,681	Y
Glibenclamide	1	0.11	0.11	0.000004	280,584	N
Paroxetine	1	0.03	0.03	0.0000003	2,939,447	N
Sulfamethoxazole	1	0.29	0.29	0.00000003	30,408,076	N

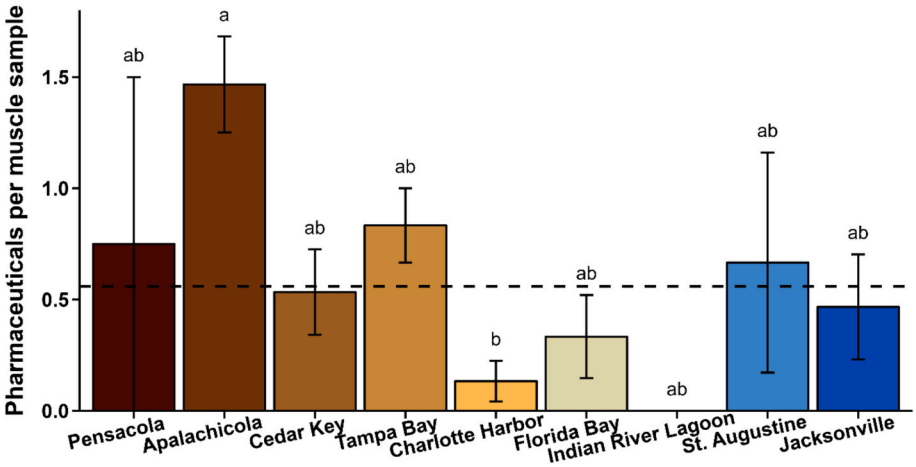

Fig. 2. Mean number of pharmaceuticals detected in muscle tissue per red drum across each region. Shown are means +/− standard errors. Regions in shades of brown are west coast estuaries, and regions in the east coast of Florida are in shades of blue (shades are darker northward). Dashed horizontal line is the mean number of pharmaceuticals detected per fish across all regions. Regions with different letters indicate significant groupings based on the results of GLM pairwise comparisons of model contrasts with the Hochberg method of p-value correction ($p < 0.05$).

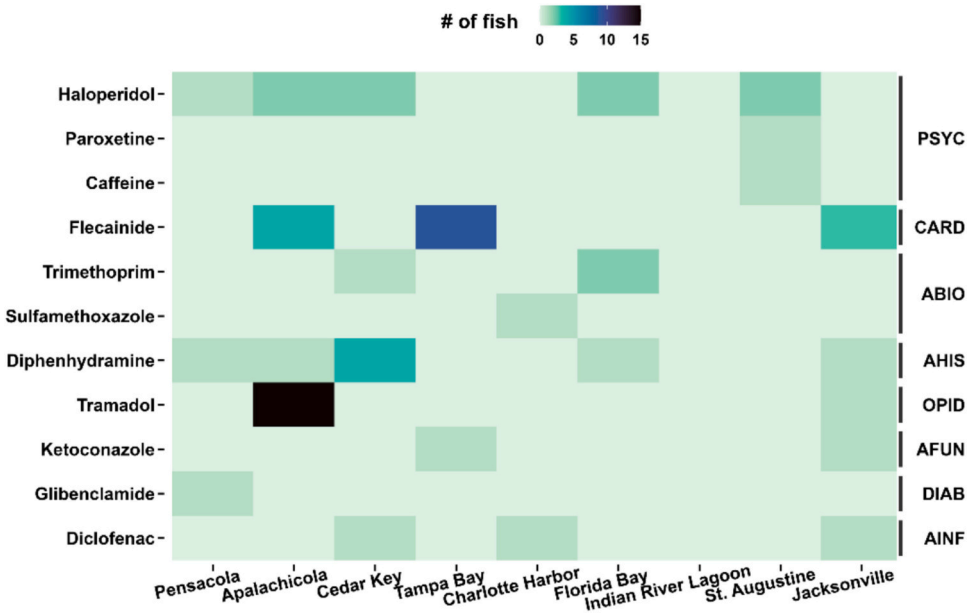

Fig. 3. Heat map of number of fish detected with each pharmaceutical in muscle tissue across each region. Abbreviation represents therapeutic class. PSYC = psychoactive, CARD = cardiovascular, ABIO = antibiotic, AHIS = antihistamine, OPID = opioid, AFUN = antifungal, DIAB = diabetic, ANIF = anti-inflammatory.

similar across space, but there were spatial differences in the composition of pharmaceuticals detected within muscle tissue. Pharmaceutical presence in muscle tissue was much lower than that in plasma (Rehage et al., in review), but there was a positive correlation between number of pharmaceuticals detected in muscle and the number detected in plasma. Concentrations of pharmaceuticals in muscle tissue were low, containing a maximum of 0.002 % of a recommended daily dose per serving. Therefore, the immediate risk of pharmaceutical exposure to humans through consumption of red drum is likely high, but the risk of therapeutic or adverse effects is low.

4.1. Prevalence of pharmaceuticals in muscle tissue

Even though Apalachicola and Charlotte Harbor differed in the number of detections from one another, all other estuary comparisons were not significant, indicating a general lack of spatial patterning in the number of pharmaceuticals that occur in muscle tissue across regions. However, there were differences in the composition of pharmaceuticals. Each region had 2–5 pharmaceuticals, but each region had a unique combination of the pharmaceuticals detected (Fig. 3). With the exception of paroxetine and caffeine, which were each only detected a single time in St. Augustine, each pharmaceutical displayed a unique spatial patterning. For example, tramadol, which was detected 16 times, was found in all 15 red drum from Apalachicola and a single fish in Jacksonville. The high detection numbers in Apalachicola suggest potential localized source of contamination. Haloperidol (9 detections) and diphenhydramine (8 detections) were detected across five regions. The spatial variation in pharmaceutical composition is likely related to both the sources of pharmaceuticals to the environment (wastewater treatment infrastructure, pharmaceuticals prescribed and taken by the population, and population density) and the fate and transport of pharmaceuticals within the environment (Durán-Álvarez et al., 2021; Bavumiragira et al., 2022). Other regional scale studies like our study have found spatial variation in pharmaceutical composition detected in

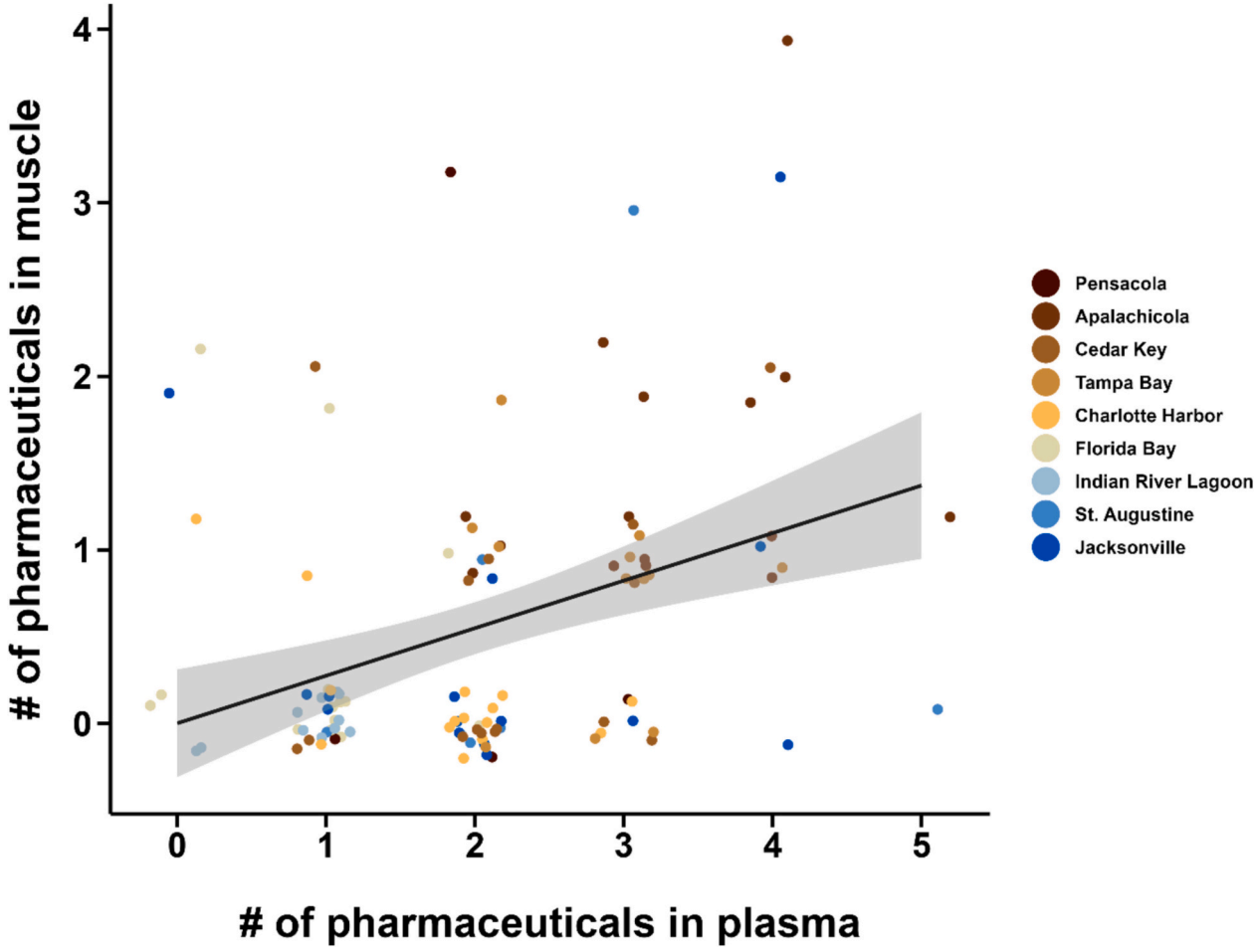

Fig. 4. Correlation (r = 0.33, t = 3.6, df = 107, $p = 0.0004$) between pharmaceuticals detected in red drum plasma (from Rehage et al., in review) and the number detected in the muscle. Data points are horizontally and vertically jittered for easier visualization.

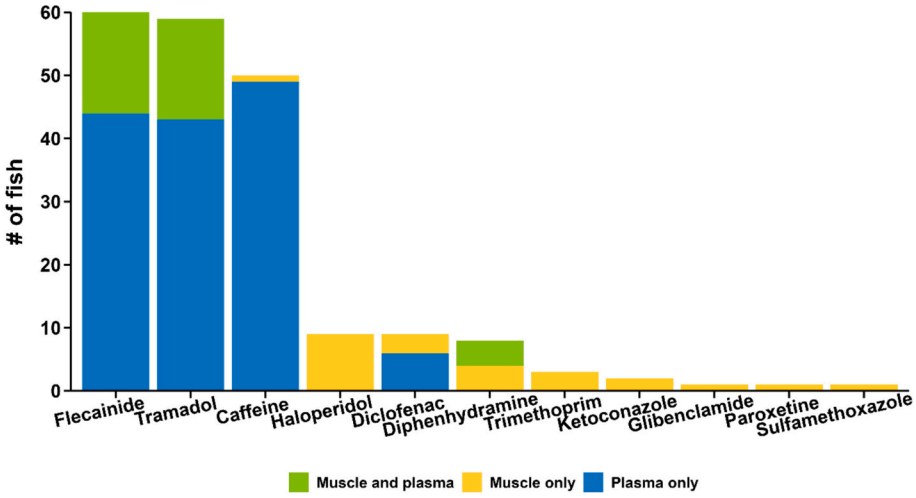

Fig. 5. Pharmaceutical detections by tissue (muscle and plasma, muscle only, or plasma only) for each individual red drum for the 11 pharmaceuticals detected in muscle tissue.

fish tissues (Castillo et al., 2024b, 2024a; Duarte et al., 2023).

Across Florida, there were 11 pharmaceuticals detected in muscle tissue, but <40 % of fish contained at least one pharmaceutical. Our results are similar to those in the Baltic Sea, which investigated 98 pharmaceuticals in fish muscle and also detected 11 pharmaceuticals at a similar occurrence rate in fish as in this study (Bobrowska-Korczak et al., 2021). In contrast, Duarte et al. (2023) tested for 33 neuroactive pharmaceuticals in fish from Portuguese estuaries and found 95 % of muscle samples contained at least one pharmaceutical. One limitation of our present study is that the 95 pharmaceuticals tested were selected

based on European consumption rates, probability of environmental exposure, and ability to accumulate in aquatic biota (Fick et al., 2010). Therefore, it is likely that this study represents a conservative estimate of pharmaceutical occurrence in red drum because of differences in pharmaceutical usage and prescriptions between the United States and Europe. Additionally, our pharmaceutical survey does not test for metabolites, which can also be detected in biota (Madikizela et al., 2020; Weng et al., 2023). It is also fair to note that the analytical method performance for three out of 11 detected pharmaceuticals was not excellent, and therefore slightly higher uncertainty can be expected in terms of exact concentrations measured for diphenhydramine, haloperidol (recovery <50 %), and tramadol (recovery >150 %). The low recovery obtained for haloperidol and diphenhydramine indicates that the real concentrations might be higher in the fish muscle (theoretically twice the amount detected), while opposite could be expected for tramadol which would occur at lower concentrations. However, given the fact that all three pharmaceuticals were detected at trace levels (average concentration bellow 0.2 ng/g), the impact of such uncertainty on the presented conclusions (e.g., related to implications for human exposure) is negligible.

4.2. Comparison of pharmaceuticals in muscle and plasma

Compared to plasma, pharmaceuticals in red drum muscle were detected in fewer fish and at lower concentrations (Rehage et al., in review). This is not unexpected as pharmaceuticals are typically found to be more prevalent and at higher concentrations in plasma than muscle tissue (Garcia et al., 2012; McCallum et al., 2017). Compared to other tissue types, muscle is routinely found to be the tissue with the lowest occurrence of pharmaceuticals in both lab (Heynen et al., 2016; McCallum et al., 2017) and field studies (Castillo et al., 2024c; Garcia et al., 2012; Tanoue et al., 2015). Despite the lower occurrence of pharmaceuticals in muscle, there was a positive correlation between the number of pharmaceuticals detected in muscle tissue with the number detected in plasma. Concentrations of pharmaceuticals in plasma are thought to be a good indicator of acute exposure (Garcia et al., 2012; Heynen et al., 2016), while other tissues, such as brain, liver, or muscle, could be indicating more chronic exposure (Castillo et al., 2024c). The positive correlation between plasma and muscle tissue suggests that fish with higher acute exposure are likely also experiencing higher chronic accumulation. Further research is needed to know if this pattern applies to other commercially important and vulnerable fish species.

Among the 11 pharmaceuticals found in red drum muscle tissue, only five were also detected in red drum plasma. Tissue specific uptake of pharmaceuticals has also been shown in other fish species and is likely related to both species specific differences in metabolism (van den Berg et al., 2021; Brooks et al., 2023) and the chemical and physical properties of the specific compounds (Liu et al., 2021; Duarte et al., 2022). Interestingly, only three of the five pharmaceuticals found in both tissues were detected within both tissues in the same fish. Flecainide and tramadol (the two most common pharmaceuticals detected) were only detected in the muscle when they were also detected in the plasma. In contrast, diphenhydramine was detected in muscle tissue only and both tissues, but never in plasma alone. Caffeine and diclofenac were either detected in the muscle tissue or plasma, but not in both tissues in the same fish. These pharmaceuticals are from different therapeutic classes and have different spatial occurrence patterns, and the small number of pharmaceuticals detected across tissues makes it difficult to parse out within fish patterns of occurrence. Additionally, this could be an indication of fish movement leading to differential exposure in plasma (e.g., acute exposure) and muscle tissue (e.g., chronic exposure) due to a temporal effect (Heynen et al., 2016). Further investigation into what factors lead to these observed patterns is warranted.

4.3. Risk of human exposure

Overall, the risk of human exposure of pharmaceuticals at pharmacologically active concentrations from consuming red drum muscle is likely low. All pharmaceuticals detected would take at least 47,000 servings of red drum to receive a single daily recommend dose. Florida residents have higher rates of fish consumption (0.70 g/kg-day to 2.3 g/kg-day) compared to other US states (Moya et al., 2008), but given pharmaceutical concentrations found in this study, pharmacological effects in humans are unlikely. Unlike other contaminants, pharmaceuticals typically do not bio magnify, with lower trophic level consumers often having higher concentrations of pharmaceuticals than higher trophic levels (Gómez-Regalado et al., 2023). For example, mussel and snails had higher concentrations of pharmaceuticals compared to higher trophic level fish in Taihu Lake in China (Lagesson et al., 2016; Xie et al., 2017). Red drum are mid to upper trophic level consumers (Malinowski et al., 2019), and exposure via consumption of pharmaceuticals is lower compared to other contaminants (e.g., heavy metals). Eating lower on the trophic chain is typically a recommendation to avoid risk of contaminants (Has-Schön et al., 2006; Terra et al., 2008), but this may not be true for pharmaceuticals. Even with low concentrations found in this study, populations that consume higher amounts of fish or are more vulnerable (e.g., toddlers, pregnant woman, and the elderly) may face higher risks (Martínez-Morcillo et al., 2020; Wang et al., 2023). This is especially true for pharmaceuticals that have bioaccumulation potential (e.g., diclofenac) or those designed to have strong therapeutic effects (e.g., tramadol).

Although the risk of therapeutic and adverse effects of pharmaceuticals via red drum is likely low, it is not zero. The true risk of pharmaceutical exposure to humans is difficult to measure. People are exposed to pharmaceuticals via multiple pathways, such as drinking water (de Jesus Gaffney et al., 2015), vegetable consumption (Prosser and Sibley, 2015), and food animal (livestock) products (Baron et al., 2014). Therefore, the total exposure remains unknown, and red drum are likely one of many sources of exposure that could in combination lead to concentrations of concern in humans. For example, haloperidol, which was detected at the highest percentage of the recommended daily dosage, is active at low concentrations (Marcus et al., 2002; Dong et al., 2013), and has been shown to have negative effects on humans that unknowingly consume it over long periods of time (Gerace et al., 2012). Some of the red drum muscle samples contained multiple pharmaceuticals, which could expose humans to a mixture of pharmaceuticals. The resulting toxicity of these mixtures of pharmaceuticals has the potential to be more severe than isolated exposure to a single pharmaceutical (McGrane et al., 2022; Madikizela and Ncube, 2022). Further, pharmaceutical metabolites and transformational products have the potential to be more harmful than their parent compounds (Brezina et al., 2017). In addition, although consuming red drum likely poses only low acute risk of exposure, the effects of chronic low-level exposure of pharmaceuticals remains unknown and an important area of future study.

5. Conclusion

In this study, we investigated the distribution of pharmaceuticals in the muscle tissue of red drum across 9 subtropical estuaries. Compared to plasma, the detection frequency and total number of pharmaceuticals were lower in muscle tissue. There was a positive correlation between the number of pharmaceuticals detected in the plasma and muscle of individual fish, but the identity of pharmaceuticals was different between tissues. These results indicate that sampling plasma could be a good proxy for overall pharmaceutical exposure in muscle tissue, but to understand the risk of specific pharmaceuticals in muscle to humans (i.e., pharmaceutical risk via consumption), sampling and analyzing muscle is needed. These efforts could be informed by long-term monitoring (e.g., Water Framework Directive in Europe, National Mussel

Watch program in US) of pharmaceuticals. Concentrations of pharmaceuticals in muscle tissue were low, indicating a low acute risk of therapeutic effects in humans via red drum consumption, yet the prevalence of pharmaceuticals in muscle highlights the potentially high risk of exposure following ingestion. Thus, future research should investigate chronic low dosage exposure to pharmaceuticals and consider the additive exposure of multiple pathways.

CRediT authorship contribution statement

W. Ryan James: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nicholas A. Castillo:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andy Distrubell:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Shakira Trabelsi:** Writing – review & editing, Methodology, Conceptualization. **Rolando O. Santos:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Daniel Cerveny:** Writing – review & editing, Formal analysis. **Ryan J. Rezek:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Ross E. Boucek:** Writing – review & editing, Investigation, Conceptualization. **Aaron J. Adams:** Writing – review & editing, Conceptualization. **Jerker Fick:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Tomas Brodin:** Writing – review & editing, Methodology, Conceptualization. **Jennifer S. Rehage:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2025.179106.

Data availability

Data will be made available on request.

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