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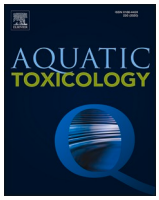

Long-term exposure to sediment-associated antidepressants impacts life-history traits in an estuarine deposit-feeding worm

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ABSTRACT

Hydrophobic pollutants, such as the antidepressant sertraline (SER), tend to sorb to particles in the water column and subsequently accumulate in the sediment. Long-term exposure to these pollutants may significantly affect sediment-dwelling organisms' fitness and behavior. To address this knowledge gap, we investigated the impact of chronic exposure to a range of environmentally relevant and higher concentrations of sediment-associated SER on the deposit-feeding polychaete *Capitella teleta*. Since certain antidepressants can function as neurotoxic chemicals and endocrine disruptors on non-target species, we examined feeding rate and burrowing behavior in adult worms after 23 days of exposure (Experiment 1), and key life-history traits in juvenile worms during 35 days of exposure (Experiment 2) to sediment-associated SER (0.33 - 100 μg/g dw sediment). SER did not affect survival but reduced maturation and time to first reproduction: 37%, 50%, and 29% of the worms exposed respectively to SER 0.33, 3.3 and 33 μg/g reached maturation on day 21, whereas worms in the other treatments did not mature (0%; control) or reached a lower maturation degree (6%; 100 μg/g). Although not statistically significant, growth, feeding, and burrowing manifested non-monotonic trends: at environmentally relevant SER concentrations adults increased feeding and extended time to fully burrow into the sediment, and juveniles increased growth, whereas high concentrations had an inhibitory or no effect. Reproductive endpoints appeared most sensitive to chronic SER exposure. Even at low environmental concentrations, antidepressants can cause sublethal effects in non-target species, potentially affecting population dynamics and ecosystem functioning. Further research is key to fully understanding the ecological impact of hydrophobic chemicals in natural environments.

1. Introduction

The consumption of antidepressants has increased over the past decades, and in Europe, it has more than doubled between 2000 and 2019 (OECD, Health at a Glance 2021). New pharmaceuticals are continuously produced with a more specific mode of action and softer side effects (Jayampathi et al., 2019). Indeed, the most widely prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), which act on the serotonin receptor 5-TH, inhibiting serotonin reuptake from the synaptic cleft and healing depression and anxiety disorders symptoms (Chu A., Wadhwa R., 2022). Among all the new-generation SSRIs, sertraline is one of the most efficacious and with lesser side effects, thus it is among the most frequently prescribed (Luo et al., 2020). SER's hepatic metabolism is its main elimination route, with multiple cytochrome P450 (CYP) isoforms biotransforming the parent compound to its N-Desmethyl-sertraline (DMS) metabolite, also called norsertraline (norSER) (DeVane et al., 2002). When patients consume these drugs, their metabolites and a percentage of the parent compound are excreted, e.g. via the urine, thus ending in wastewater treatment plants via the down-the-drain pathway (Sehonova et al., 2018a). Wastewater treatment plants' efficiency in reducing pharmaceuticals is very low, thus drugs are released via wastewater treatment plants' effluents into the aquatic environment (Van Dijk et al., 2023). The continuous release creates a pseudo-steady state for pharmaceuticals in the receiving waters (Wilkinson et al., 2022). In wastewater effluents and surface riverine waters, SER concentrations are found in the range of ng L^{-1} in Spain (1.06 – 144.87 ng L^{-1}) (Fernandes et al., 2021) and in the United States (0.84 – 37.5 ng L^{-1}) (Schultz et al., 2010) and up to 1 μg L^{-1} in some wastewater treatment plants effluents in the USA (Arnnok et al., 2017). SER was reported in the ng g^{-1} range in sediment in Spain (1.15 – 119.28 ng g^{-1}) and in sludge in the UK (1138 ng g^{-1}) (Fernandes et al., 2021). An extensive sampling campaign collected and analyzed surface

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water and sediment samples to detect pharmaceuticals in various freshwater systems suspected to receive considerable amounts of contamination from the local population and livestock farming in Spain. The authors reported notable levels of psychoactive drugs in the sediment, and SER was detected at concentrations of 12.1 ng g^{-1} (Osorio et al., 2016). Antidepressants constant flux not only makes them pseudo-persistent in the environment but also leads to their detection across the globe. An extensive global study was carried out and reported by Wilkinson et al., (2022), to measure the presence of various kinds of active pharmaceutical ingredients (APIs) in 258 rivers across Africa, Antarctica, Asia, Europe, North America, Oceania, and South America. In this comprehensive sampling campaign, different SSRIs in the range of ng L^{-1} were detected, with citalopram, venlafaxine, and desvenlafaxine found in almost all continents besides Antarctica. Despite the well-documented widespread presence of SSRIs in the environment, the knowledge of the fate and distribution of antidepressants in various environmental compartments is still limited (Schultz and Furlong, 2008). This knowledge gap hinders a comprehensive understanding of the fate and impacts of SSRIs.

Even if the concentrations detected in the environment are at the ng g^{-1} level, the continuous release and increase in pharmaceutical consumption and their incomplete removal in wastewater treatment plants, suggest that environmental concentrations will increase over time and potentially harm the local fauna in the long term. Indeed, the occurrence of antidepressant residues in surface waters has already been shown to affect non-target organisms' behavior, reproduction, development, and survival, even at low environmental concentrations (in the ng L^{-1} - µg L^{-1} range) (Melchor-Martínez et al., 2021; Sehonova et al., 2018b). Another consequence of antidepressants' environmental presence is that these chemicals bioaccumulate in the tissues of various organisms. For example, fluoxetine and sertraline were the main antidepressants detected in the fish *Catostomus commersonii* brain tissues (up to 1.65 and 4.24 ng/g respectively) (Schultz et al., 2010), and fish exposed to wastewater treatment plants effluents in Montreal bioaccumulated SSRIs, and especially SER and norSER were found in the brook trout *Salvelinus fontinalis* liver and muscle tissues (0.04 - 10.3 ng g^{-1}) (Lajeunesse et al., 2011). As extensively reviewed by Bacqué-Cazenave et al., (2020), 5-HT neuromodulatory functions are evolutionarily conserved across invertebrates and vertebrates. Therefore, not surprisingly multiple studies on both invertebrates and vertebrates have shown that SSRIs can induce adverse effects such as altering foraging behavior (Méndez et al., 2013), inducing endocrine disruption (Lopes et al., 2020), and altering growth (Yang et al., 2014).

The fate of SSRIs in receiving waters depends on their physicochemical properties. Hydrophobic chemicals like SER (Log *Kow*: 5.3; Costa Junior et al., 2022), sorb to particles in the water column and subsequently accumulate in sediment (Park et al., 2018). Further, given its ionizable properties ($pK_a = 9.16$; Tihanyi et al., 2006), SER will tend to speciate towards its non-polar form in seawater, thus promoting an even faster distribution to sediment and accumulation in organisms' tissues after ingestion (Tihanyi et al., 2006). Thus, deposit-feeding organisms may be particularly exposed to these compounds via dietary uptake (i.e., following ingestion of sediment) (Selck and Forbes, 2018). However, the current peer-reviewed literature primarily addresses the pelagic compartment and examines short- and long-term effects of antidepressants on vertebrates (Aich et al., 2024; Fergusson et al., 2024; Martin et al., 2019b, 2019a; Thoré et al., 2021). This highlights the need for further studies focusing on the sediment compartment and the effects of chronic exposure to environmentally relevant concentrations of SSRIs on benthic invertebrates.

Among benthic invertebrates, deposit-feeders like the polychaete *Capitella teleta* are cosmopolitan worms inhabiting estuarine benthic sediment (Blake et al., 2009). The sediment bioturbation processes resulting from their activity are fundamental to oxygenating sediment and sustaining sediment microbiota communities (Seaver, 2016). Since *C. teleta* is an opportunistic polychaete, it is also considered a bioindicator of organically contaminated environments (Seaver, 2016). While feeding on sediment organic matter, this species may be exposed to hydrophobic organic contaminants, like the SSRI SER, through the diet. Therefore, it is a good model species to assess the effects of sediment-associated chemicals (Selck and Forbes, 2018). Previous research has shown that, like other annelids, *C. teleta* possesses neurons with a serotonin-like immunoreactivity (5HT-LIR) (Meyer et al., 2015). Similarly, other lophotrochozoan invertebrates, including molluscs, exhibit serotonin (5-HT) neurons in their central nervous system, which are comparable to those found in vertebrates (Gillette, 2006). As a consequence, exposure to SER may also have detrimental effects on these worms. *C. teleta* pelagic larvae can settle in the sediment and undergo metamorphosis within a day if the environmental conditions and substrate are favorable (Méndez et al., 2000). Juveniles kept in a laboratory normally reach maturity in the time of 33 days (Méndez et al., 2000), with males developing genital spines and females developing ovaries when sexually matured (S. D. Hill et al., 2018; Ramskov et al., 2009b). On average, It can take up to 50 days for the time to first reproduction to occur (Linke-Gamenick et al., 1999), during which females construct brooding tubes from sediment and mucus, where they lay their eggs (Hill et al., 2018).

Since SSRIs' are known to affect behavior and reproduction in both vertebrates and invertebrates, which can ultimately affect population dynamics, we conducted two chronic experiments to investigate the impact of environmentally realistic- and higher sediment-associated SER concentrations (0.33 - 100 µg/g dw sediment) on *C. teleta*. First, we assessed survival, burrowing behavior, and feeding rate in exposed adults. Then we explored sertraline effects on juveniles' survival, growth, time to maturation, development of reproductive organs, sex ratio, and time to first reproduction.

2. Materials and Methods

2.1. Chemicals

SER (Sertraline hydrochloride, CAS: 79559-97-0, purity ≥ 98%, Log *Kow* = 5.3) was purchased from Sigma-Aldrich (Flanders, New Jersey, USA). Stock solutions were made by dissolving SER in methanol and stored at -20°C.

2.2. Sediment Collection

Sediment was collected in Isefjorden, Munkholm, Denmark (55°40'30.04"N 11°48'17.7"Ø). The location was selected because it is located away from contaminated areas. Moreover, previous studies have shown the absence of pollutants, such as heavy metals and PAHs (Ramskov et al., 2009a). Recent studies have used this sediment for experimental purposes and have shown no disruptive effects in the control condition, suggesting that there has been no recent unwanted contamination of the sediment in the area (Chan et al., 2024; Sandgaard et al., 2023; Thit et al., 2020). The upper layer of sediment was scraped off and sieved to < 1000 µm at the collection site, to avoid macrofauna. Then sediment was treated as described in (Grønlund et al., 2023). Briefly, sediment was sieved with seawater to < 63 µm grain size and left to settle for 48 hours. Overlying water was replaced with fresh seawater. After 48h, water was removed, and sediment was homogenized, collected in smaller containers, and frozen (-20°C) until use (i.e., for the rearing of cultures or for experiments). Then, the sediment was defrosted for 24 hours at room temperature, homogenized with an immersion hand blender, and rinsed twice with filtered seawater.

2.3. Capitella teleta Cultures

C. teleta adult worms can have average body volumes ranging from a few mm^3 (even 2-3) up to 20 mm^3 (Ramskov et al., 2009a; Sandgaard et al., 2023) Stock cultures were reared in plastic laboratory aquaria and

kept in a light-dark photoperiod (300 lux) that was set to 8:16h and kept at room temperature (21 ± 1°C) in thawed natural sieved (< 125 μm) sediment and filtered natural seawater (< 0.2 μm; 31‰ salinity (S); pH 7.88), hereafter referred to as seawater. Aeriation was delivered through air stones connected to air pumps. Cultures were fed weekly with a spoon of newly defrost natural < 63 μm sediment (grain size with the highest organic matter content which favors growth).

2.4. Sediment Spiking with Sertraline and Analysis

Wet sediment was distributed among five 500 mL glass beakers. A subsample of sediment was used to measure the moisture content (MC: 75.35 ± 0.31 %, n=3; 24h at 105°C), and total organic matter (TOM: 13.84 ± 0.051%, n=3; weight loss on ignition 2h at 550°C). Sediment was divided into five beakers and spiked to the following sertraline nominal concentrations: 0 (control, Ctrl), 0.33, 3.3, 33, and 100 μg/g dry weight (dw) sediment. Sediment spiking was handled as described in Grønlund et al., (2023). More specifically, direct spiking was carried out by introducing 50 μL of sertraline stock solution with the pipette tip placed directly into the wet sediment. After spiking, the sediment was stirred with a spoon. The five beakers, covered with Parafilm, that had small holes for ventilation to ensure solvent evaporation, were placed on a shaking table set to 220-250 rpm. They were left in the dark at 21 ± 1°C for at least 24 hours, to let the solvent evaporate and to ensure homogenous spiking. Finally, the sediment was thoroughly blended using a metal spoon, and subsamples needed for each sampling day (around 30 g of wet sediment) were transferred to 50 mL plastic falcons and were kept at -20°C until use. Two aliquots of spiked sediment of each concentration for both studies were analyzed using the QuEChERS protocol adapted from Santos et al., (2016) to measure psychoactive pharmaceuticals in sediment. For this purpose, we employed the extraction kit – 15 mL CT (Quick, Easy, Cheap, Effective, Rugged, and Safe), purchased from Agilent Technologies. Briefly, sediment was freeze-dried (48h) with Alpha 2-4 LSCplus and then 0.3 g dried sediment of each treatment was placed in a 50-mL polypropylene tube and 10 mL of ultra-pure water was added and vortexed for 30 seconds. Then 15 mL of 2% ammonium hydroxide in acetonitrile was added and vortexed for 30 seconds. After vortexing, the QuEChERS salts were introduced and the tubes were vortexed again for 1 minute, and then centrifuged (4000 rpm) for 5 minutes. 12 mL of acetonitrile were transferred to a 15 mL dispersive SPE tube containing primary secondary amine (OSA) and magnesium sulfate ($MgSO_4$), and vortexed once more for 1 minute and centrifugated (4000 rpm for 5 minutes). At the end, 9 mL of extract was relocated to a glass tube, and a nitrogen flow was employed to evaporate the solvent liquid. The dry extract was then reconstituted with 500 of methanol μL. Finally, samples were analyzed with GC-MS using a DB5-MS capillary column (nominal length, diameter, and film thickness, respectively: 30 m; 250 μm; 0.25 μm, Agilent Technologies) for the separation of the compound to assess spiking efficiency and the actual sertraline concentrations in the sediment.

2.5. Estimation of Maximum Sorption Capacity (MSC) and Expected Environmental Concentrations in Sediment

The sorption capacity of antidepressants has been largely overlooked in scientific studies, highlighting a significant gap in current research (Costa Junior et al., 2022). Assuming that SER is mainly sorbed to the sediment organic matter fraction, we estimate the maximum sorption capacity (MSC) based on the few data present in recent literature, applying the following equation:

$$MSC = Koc * ws \quad \text{(I)}$$

(Moyo et al., 2014) where

Kd = organic carbon-water partition coefficient; *foc* = fraction of organic carbon in the sediment; *ws* = water solubility.

Coefficient of distribution (mL/g).

Using the following for SER: *Kd* = 9.6 mL/g; calculated in a recent study from Costa Junior et al., (2022) for freshwater systems. Considering that the water solubility for SER equals 3.8 mg/mL at room temperature (Abdkarimi and Haghtalab, 2021) and assuming OM to be a good proxy for the fraction of organic carbon in the sediment, we estimate SER MSC in the sediment to be 2.64 mg/g.

To our knowledge, no published concentrations of SER exist in marine water and sediment. Thus, we estimate the environmental sertraline sediment concentration by applying the equilibrium partitioning method (see Van Der Kooij et al., 1991):

$$Cs = \frac{Cw * Ksw}{r} = \frac{(Cw * (0.6 * Kow * foc))}{r} \quad \text{(II)}$$

Where *Cs* = concentration of SER we want to estimate in the sediment; *Ksw* = partitioning coefficient, which represents the distribution of a chemical when in equilibrium between the water and the sediment phase; *Kow* = *n*-octanol-water partition coefficient; *Foc* = fraction of organic carbon in the sediment; *r* = ratio of suspended matter: sediment, which is 2 for organic chemicals. We used the range of the (few) measured SER concentrations in river surface waters: 1.9 ng/L (Chen et al., 2022) to 1000 ng/L (Gornik et al., 2020), a sediment organic matter content between 1.5 % - 20% OM (Hussan et al., 2023) as a proxy for *foc*, and assuming equilibrium between water and sediment. The model estimates a sediment SER concentration between 0.004 and 31.8 μg/g dw sediment.

2.6. Experimental Design

2.6.1. Experiment 1: Chronic Exposure of Adults Capitella teleta to Sertraline

Adult worms were exposed in 20 mL glass vials with plastic lids with 5 g wet sediment (< 63 μm) and 15 mL of aerated seawater (see Graphics S1). Aeration was kept using air needles connected to aeration pumps. We included five SER treatments (0, 0.3, 3.3, 33, 100 μg/g dw sediment; n=3 replicates per treatment), to cover low environmental- and higher concentrations. A pilot experiment was performed to assess whether methanol impacted the worms. We did not observe negative effects in worms exposed to the solvent control sediment. One day before the experimental start, worms were randomly selected from the stock cultures (total: 150 worms), worm volume was measured (for details see section 2.7.1. "*Worm Body Volume (BV)*"), and worms were pooled into groups of 10 of similar size per replicate. The experiment started by introducing 10 adults in each vial. The set-up was checked weekly (salinity) and every other day for aeration and water level, and deionized water was added to compensate for evaporation, to keep a constant salinity throughout the exposure. At the end of the exposure (day 23) the overlying water was collected from each exposure vial and worms were sieved (100 μm) from the sediment and used for the burrowing test. Fecal pellets were collected by sieving them with an 80 μm metal sieve to measure the feeding rate. Worms underwent the burrowing test, and then washed with newly oxygenated seawater to remove excess mucus and stored in Eppendorf tubes (-80°C). Water, sediment, and fecal pellets were stored in falcon tubes (-20°C).

2.6.2. Experiment 2: Chronic Exposure of Juveniles Capitella teleta to Sertraline

Following Ramskov et al., (2009), 10 brooding tubes were collected from the stock culture, each placed in a 3.5 cm plastic Petri dish with seawater, then located in a box covered with wet paper to reduce water evaporation (see Graphics S2). Water was renewed every other day to maintain oxygen levels. Brooding tubes were inspected daily until larvae were hatched. Before the experimental start, 20 mL glass vials with plastic lids were prepared with 5 g wet sediment (ca. 1 g dw sediment), and 15 mL of aerated seawater. SER concentrations were equal to Expt.1 (0 - 100 μg/g dw, n = 3). Hatched larvae were collected using a plastic pipette and transferred to newly prepared 3.5 cm plastic Petri dishes

containing a thin layer of un-contaminated sediment (< 63 μm). After 5 days, groups of 10 individuals were randomly sampled from different Petri dishes (i.e., different mothers) and placed in each exposure vial to start Expt.2. Salinity and water level were checked weekly and every second day, respectively, and deionized water was added in case of evaporation. Every 7 days, until all worms reached maturation (in detail in section 2.7.2. under "*Maturation*"), sediment was sieved to collect worms, which were then transferred to newly prepared glass vials containing freshly spiked sediment. At each census day, worms were inspected under the microscope to determine survival, individual worm body volume (BV), number of fully mature worms, sex ratio, and time to first appearance of brooding tubes. The experiment ended when all worms had reached maturation (35 days from Expt.2 start). The overlying water was collected, and worms were sieved from the sediment and stored as in Expt.1.

2.7. Endpoints

2.7.1. Experiment 1: Time to Fully Burrow and Feeding Rate

Survival - The number of living worms was counted at the experimental start and end (day 23).

Time to Fully Burrow. Right before ending Expt.1, 6-well multiwells were prepared with aerated seawater and uncontaminated sediment (3 g wet < 63 μm sediment per well). At the end of the 23 days of exposure, *C. teleta* were sieved from the set-up and placed (n=4) in separate wells. Time (sec) to fully burrow was recorded for individual worms. All worms fully burrowed within 700 seconds.

Worm Body Volume (BV) – Worm BV (mm^3) was measured to assess growth rate (GR). BV was estimated assuming the polychaetes are cylindrical following:

$$BV = \pi * A^2/4L \quad \text{(III)}$$

(Self and Jumars, 1978) where *A:* worm area (mm^2); *L:* worm length (mm). A and L were measured using pictures taken with a camera (Olympus UC90) under the microscope (Olympus SZX7) and then analyzed with ImageJ software.

Feeding Rate. C. teleta fecal pellets are bigger (> 90 μm; worms do not re-ingest fecal pellets) than the sediment grain size used in the experiment (< 63 μm). Since sediment primarily consists of inorganic grains (95%), the reduction in fecal pellet weight resulting from organic matter digestion is considered negligible. Thus, fecal pellet weight is regarded as a good estimate of the amount of sediment ingested by the worms (feeding rate) (Linton and Taghon, 2000). Fecal pellets were sieved from the sediment (80 μm sieve) at the experiment end (day 23) and washed with deionized water to remove salts before they were stored at -20°C until analysis. The fecal pellets were then dried (48h, 105°C) and weighed (mg dw). The total feeding per worm was calculated by dividing the total dry weight of fecal pellets produced over 23 days by the number of worms in each vial and the average worm BV (mm^3). The daily feeding rate was calculated as fecal pellets (mg of dw) produced per organism per day.

2.7.2. Experiment 2: Life History Traits

Survival - The number of living worms was counted on each census day (i.e., 7-day intervals) until all worms matured (see the section "*Maturation*" below for details). Survival was determined by comparing the number of living worms at the beginning and at the end of the experiment (day 35).

Worm body Volume (BV) – Worm BV (mm^3) was measured as described in Expt.1 (refer to section 2.7.1.).

Growth Rate (GR) – Worm growth over time tended to follow a sigmoidal shape (S-shape). The difference in worm growth was analyzed by fitting worm BV to 2 non-linear growth models (i.e., Gompertz (II); Logistic (III)):

$$Y = d * exp^{\left(-exp^{(-b*(X-e))}\right)} \quad \text{(IV)}$$

$$Y = \frac{d}{1 + \exp(-b(X-e))} \quad \text{(V)}$$

Where *Y:* worm BV over time, *d:* estimated maximum BV, *b:* the slope, and *e:* time at the inflection point where the S-curve shifts. Both models are robust and often used for predictions of animal and plant growth over time (Ridho et al., 2021).

Maturation – Worms' maturation stage was analyzed under the microscope every census day. The appearance of fully developed genital spines in males and eggs in females was used as a sign of maturation.

Reproduction – The time to the first appearance of brooding tubes and the number of brooding tubes were checked each census day.

Sex ratio – The total number of mature females, males, and hermaphrodites was noted to assess the ratio between sexes on each census day.

2.8. Statistical analyses

GraphPad Prism 10.2.0 and R 4.2.1 were used for all statistical analyses. Feeding rate (Expt.1) and worm BV (Expt. 2) were analysed for normality (Shapiro-Wilk test). The feeding rate did not meet the assumption of normality, thus the Kruskal-Wallis non-parametric test was performed. Worm BV met the ANOVA assumption of normality and was analysed with repeated measures (RM) one-way analysis of variance (ANOVA). When ANOVA was significant, Tukey's post-hoc tests followed to assess differences among treatments. Maturation was examined with a two-way ANOVA testing multiple comparisons followed by a Tukey's post-hoc test to compare differences among treatments within each census day. Time to fully burrow (Expt.1) did not meet the ANOVA assumption of normality, thus the non-parametric Kruskal-Wallis test was performed. In Expt. 2, non-linear fits were made for both growth models (the Logistic and the Gompertz growth models) since the visual inspection of the BV measurements showed that *C. teleta* growth tended to follow a sigmoid curve. Confidence intervals (CIs) were employed to interpret whether the model-estimated parameters were statistically different (CIs not overlapping) or not (overlapping CIs) (Di Stefano, 2004). Maturation was analysed with Two-way ANOVA to investigate the influence of the treatment and the exposure time on the time worms took to develop matured sexual traits. Tukey's post hoc test followed, to highlight differences in the percentage of mature worms among treatments on each census day. Sex distribution was analysed with a Two-way ANOVA on the number of females found at each treatment over the exposure time and on the males' group separately, to assess the influence of time and concentration on the sex distribution. Tukey's multiple comparisons test was performed to compare the treatment effect on the sex distribution of females and males on each census day. Time of exposure and SER concentrations were defined as fixed effects. A significance level of $P = 0.05$ was used throughout.

3. Results

3.1. Both experiments: sediment concentration

The actual measured concentrations of SER in the sediment at the start of the experiment (d 0) were: 0.33 ± 0.02 μg/g, 1.10 ± 0.01 μg/g, 15.75 ± 0.02 μg/g, and 40.88 μg/g. In all the experiments, sediment was renewed every 7 days to keep a similar-to-constant exposure. Measured concentrations of SER after 7 days were: 0.31 ± 0.01 μg/g, 1.01 ± 0.28 μg/g, 5.54 ± 0.001 μg/g, and 37.23 μg/g (n = 2 except for the highest concentration related to the nominal concentration of 100 μg/g (n = 1; for both day 0 and day 7)) (Table 2). The results are presented as nominal concentrations throughout the manuscript.

3.2. Experiment 1: Chronic Exposure of Capitella teleta adults to Sertraline

3.2.1. Survival

Worm survival was high and randomly distributed among treatments (see Table S2).

3.2.2. Time to fully burrow

Although there was no difference among the different treatments (Kruskal-Wallis P value >> 0.05), we observed that worms exposed at the lowest SER concentration (0.33 μg/g dw) had a higher variation in burrowing time, and tended to burrow slower than worms in the Ctrl (Fig. 1a).

3.2.3. Feeding Rate

There was no significant impact of sediment-associated sertraline on worm feeding rate (Kruskal-Wallis P value >> 0.05) (Fig. 1b). However, the trend was that the feeding rate was higher for worms exposed to the three lowest concentrations of SER (0.33 - 33 μg/g dw) compared to the Ctrl, and feeding rates were similar between 100 μg/g dw and the Ctrl worms.

3.3. Experiment 2: Chronic Exposure of Capitella teleta Juveniles to Sertraline

3.3.1. Survival

Worm survival was high and randomly distributed among treatments (see Table S3).

3.3.2. Body Volume (BV) and Growth Rate (GR)

Worm BV of 5 days old worms was 0.0042 ± 0.0005 mm^3 (n = 20, Expt. 2), similar to BV measures of worms of the same age in other studies (Ramskov et al., 2009a; Sandgaard et al., 2023).

There was a general trend that worms exposed to intermediate concentrations (0.33, 3.3, 33 μg/g dw) grew faster compared to the Ctrl, and the highest concentration (100 μg/g dw) (Fig. 2a). Due to the high variability, both the Gompertz (Fig. 2b) and the Logistic (Fig. 2c) non-linear regression growth models showed overlapping confidence intervals (CIs) for all parameters (growth rate (b), the BV_{max} (d), and time to BV_{max} (e) (see SI Table S1). Nevertheless, a visual inspection of the curves (Fig.s 2a, 2b, 2c) and the estimated parameters (Table S1), suggest that the models adequately capture the dataset up to a concentration of 33 μg/g dw (Table S1).

3.3.3. Maturation

Time and SER interacted to impact time to maturation (Table 1). Maturation occurred faster (at day 21) in worms exposed to environmentally realistic concentrations of SER (0.33 – 3.3 μg/g dw; ANOVA P: 0.0137 and 0.0005, respectively), and between 67% and 87% of worms at environmentally realistic concentrations already matured at day 28 (SER 0.33, 3.3, and 33 μg/g dw; ANOVA P: all < 0.0001), while Ctrl worms took the longest to reach sexual maturity (i.e., 83% of worms were matured only at census day 35) (Fig. 3a). Worms exposed to the highest SER concentration (100 μg/g dw sediment) matured significantly later with only 40% of the worms matured at day 28 (ANOVA P-value: 0.0055, see SI Table S4) and 100% of the worms matured at day 35 (up to two weeks of delay) than worms exposed to the other lower SER. We did not observe abnormalities in either male or female reproductive organs.

3.3.4. Reproduction

The appearance of the first brooding tubes was noted on day 28 in worms exposed to the three lowest SER concentrations, which produced from 2 up to 4 brooding tubes. Worms exposed to 100 μg/g dw sediment did not produce brooding tubes until the last census day (d 35), when 7 brooding tubes were detected. The control worms did not reproduce within the experimental duration (until d 35) (Fig. 3b).

3.3.5. Sex ratio

All worms had matured at the end of the experiment (d 35) and no hermaphrodites were observed during the experiment. The distribution of matured worms in females and males differed significantly between Ctrl- and SER-exposed worms at experimental end (Tukey's multiple comparisons post-hoc test, P < 0.05; Fig. 4a, 4b, 4c), such that worms in Ctrl, had a significantly higher percentage of females and a lower number of males compared to exposed worms (all P: <0.0001) (see Table S5 and Figure S3 in SI).

4. Discussion

After 7 days, the remaining concentration of sertraline in the sediment was between 35 and 93% across all treatments. Since the OM content of the current study is high (i.e., 13.8%), it is not likely that the sediment sorption capacity was reached. Indeed, given our estimations on the maximum sorption capacity (MSC), we do not expect sediment saturation was the reason behind the lower concentrations of SER left in the sediment, even for the highest SER (100 μg/g dw sediment). The lower concentrations of SER detected after 7 days may be related to many factors including 1) the worms' ability to biotransform SER as has

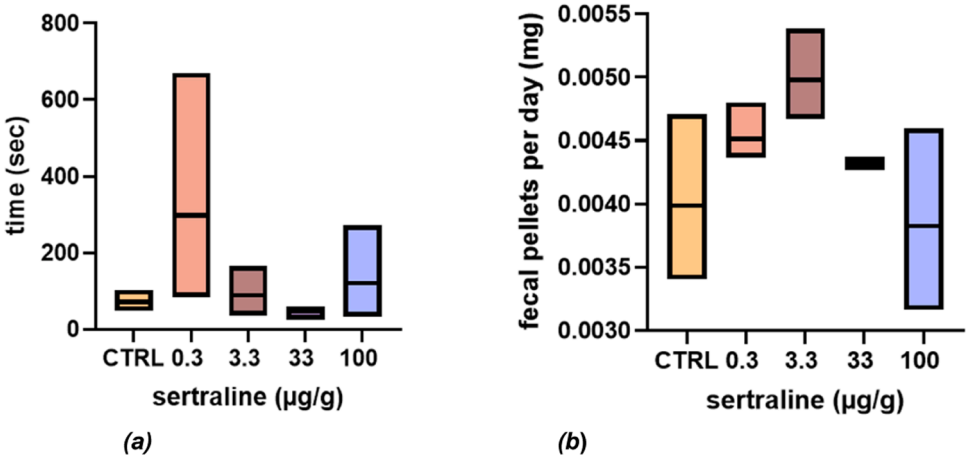

Fig. 1. Experiment 1 - *C. teleta* adults. (a) Time to fully burrow. *C. teleta* time to fully burrow in the sediment after exposure to different sertraline concentrations for 23 days (line at mean ± sd; n = 3). The was no significant difference among treatments (P value >> 0.05). **(b) Feeding rate.** *C. teleta* feeding rate during 23 days of exposure to varying concentrations of sertraline (line at mean ± sd; n = 3). The differences among treatments were not significant (P value >> 0.05).

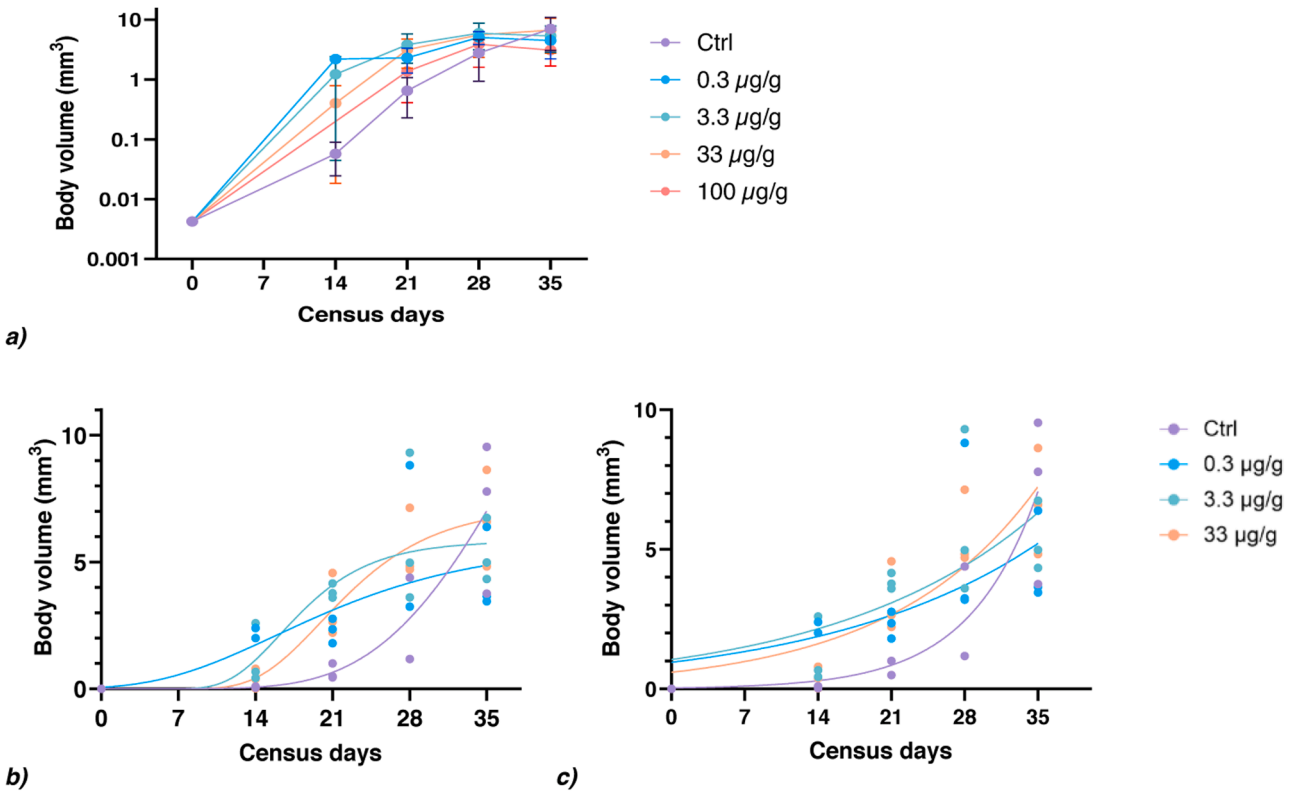

Fig. 2. Experiment 2 – *C. teleta* juveniles. (a) Growth. Ln-transformed body volume (mm^3) of *C. teleta* (mean ± sd; n=3) at different census days (D0, D14, D21, D28, D35) over a total of 35 days of exposure to different sertraline concentrations. Lines represent mean growth over time. **(b) Gompertz growth model.** Nonlinear fit for *C. teleta* growth over time up to concentration 33 μg/g (dots represent each replicate; n=3). **(c) Logistic growth model.** Nonlinear fit for *C. teleta* growth over time up to concentration 33 μg/g (dots represent each replicate; n=3).

Table 1
Experiment 2 on *C. teleta* juveniles. Two-way ANOVA to highlight sertraline and exposure time influence on *Capitella teleta* time to maturation and sex distribution. Significant P values in gray cells (P = 0.05).

Two-way ANOVA	P value		
Factor	Maturation	Females (n)	Males (n)
Time x concentration	<0.0001	0.0725	0.5009
Time (census days)	<0.0001	<0.0001	0.0045
Sertraline concentration	<0.0001	<0.0001	0.0004

Table 2
Sediment concentrations. In the table are reported the nominal concentrations, the actual concentrations at day 0 and day 7 (μg/g), and the percentage (%) of sertraline left after 7 days.

Nominal concentrations (μg/g)	0	0.33	3.3	33	100
Actual concentrations Day 0 (μg/g)	0	0.33 ± 0.02	1.10 ± 0.01	15.75 ± 0.02	40.88
Actual concentrations Day 7 (μg/g)	0	0.31 ± 0.01	1.01 ± 0.28	5.54 ± 0.001	37.23
Sertraline left after 7 days (%)	0%	93.09%	91.82%	35%	91.07%

been observed for this species and other organic contaminants including PAHs (Selck et al., 2003) and fragrances (Dai et al., 2012), 2) microbial degradation (Zhang et al., 2020), or 3) the impact of salinity, which can influence sorption affinity, thus decreasing pharmaceuticals binding to sediment particles as suggested by (Sørensen et al., 2024). We speculate that an unexpected issue may have arisen with the nominal SER concentration of 33 μg/g, since only 5.54 μg/g of SER have been left after 7 days of exposure.

Moreover, based on our estimations on sertraline predicted concentrations in the sediment, we consider 0.3 μg/g, 1.1 μg/g, and 15.7 μg/g, (i.e., nominal: 0.33, 3.3, and 33 μg/g dw sediment) within ecologically relevant concentrations. Additionally, as SER consumption is continuous, and increasing, we expect that the sediment concentration will increase over time.

SSRIs are designed to inhibit the serotonin reuptake from the presynaptic cleft. Since it has been proven that both vertebrates and invertebrates share many similarities in monoaminergic signaling across neurons (Curran and Chalasani, 2012), SSRIs can also interfere with the nervous system of non-target organisms, exerting neurotoxic effects. Literature provides examples of SSRI effects on different behaviors, showing for instance that the antidepressants fluoxetine and venlafaxine decrease serotonin levels in the brain of hybrid striped bass fish, leading to an increased time to capture prey, with enhanced adverse effects when the chemicals are present at lower concentrations and in mixtures (Bisesi et al., 2016). Impairments in the serotonin signaling pathway have been linked to changes in the nematode *Caenorhabditis elegans*'s ability to avoid repellent chemicals and modulation of the aggressive behavior in *Drosophila melanogaster* flies (Curran and Chalasani, 2012). The capability of worms, like *C. teleta*, to quickly burrow into the sediment to escape predators and other external stressors may be impacted due to SER neurotoxicity (Sehonova et al., 2018a). Indeed, we found that adult worms exposed for 23 days to the lowest SER concentration (0.33 μg/g dw) showed a trend of increasing the time needed to burrow, a behavioral alteration that in nature could affect their ability to avoid environmental stressors (e.g., predators). On the contrary, the freshwater mussels *Lampsilis fasciola* exhibited an increased activity, covering greater distances in the aquaria, after chronic water exposure to fluoxetine (28 and 67d respectively) (Hazelton et al., 2014). The greater

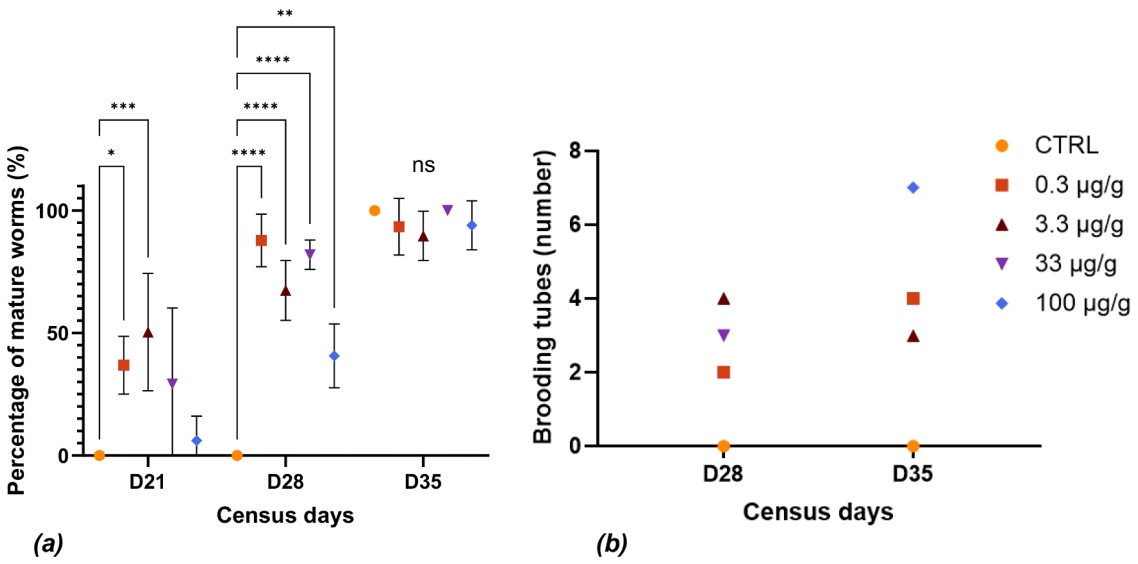

Fig. 3. Experiment 2 - *C. teleta* juveniles. (a) Maturation. *C. teleta* maturation (% mature worms) at each census day (D21, D28, D35), from the census day when sexual traits began to be visible (D21). Tukey's multiple comparisons test followed the Two-way ANOVA to show significant differences with the control within census days (* = $P \leq 0.05$; ** = $P \leq 0.01$; *** = $P \leq 0.0001$; **** = $P \leq 0.00001$). ns = not significant. **(b) Reproduction.** The cumulative number of brooding tubes produced within census day (D28 and D35) for each treatment (0, 0.3, 3.3, 33, and 100 µg/g dry weight of sediment), counted since the first brooding tube was observed on day 28 (D28).

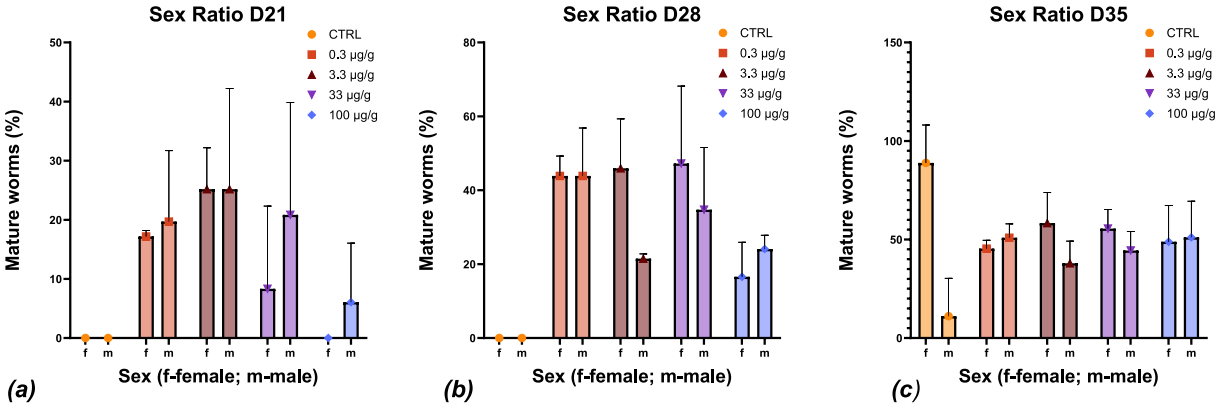

Fig. 4. Experiment 2 - *C. teleta* juveniles. Sex ratio expressed as the percentage of matured *C. teleta* related to the total number of worms at each census day: D21 **(a)**, D28 **(b)**, and D35 **(c)**. Ctrl worms had a significantly higher number of females and a lower number of males compared to exposed worms (Tukey's multiple comparison $P<0.001$; see Table S3 in Supplementary Information for more details).

activity resulted in the mussel's faster burrowing (Hazelton et al., 2014). However, additional studies are needed on a wider set of key behaviors to further analyse the extent to which the deposit feeder *C. teleta* manifests neurotoxicity due to SSRI exposure.

Sertraline inhibition of serotonin reuptake alters serotonin levels in vertebrates and invertebrates. We know that monoamines, like serotonin, regulate steroid hormone production and functionality, and energy balance, among their many other biological functions (Berger et al., 2009). Juveniles in the lowest SER concentrations (0.33 - 33 µg/g dw) tended to grow faster approaching more rapidly the steady state compared to polychaetes reared in uncontaminated sediment (Fig. 2a). This may be explained by an increase in feeding rate since adult worms seemed to increase feeding rate at the intermediate sertraline concentrations (Fig. 1b). Serotonin has been shown to inhibit feeding behavior, giving a sense of satiation in mammals, while studies on invertebrates have shown that serotonin enhances the feeding rate (Voigt and Fink, 2015). Even though the SSRI, fluoxetine, didn't affect *C. teleta* feeding activity when chronically exposed to sediment-associated fluoxetine (0, 0.001, 0.03, 0.3, and 3.3 µg/g dw sediment) (Méndez et al., 2013), our experiment showed that worms exposed to SER at environmentally realistic concentrations (0.33 - 33 µg/g dw) tended to have higher feeding rates and increased growth. At the same time, non-exposed worms and worms exposed to the highest SER concentration (100 µg/g dry wt) tended to exert a slower increase in body volume (BV) until day 28 (worms aged 33 d old), compared to worms in the intermediate concentrations. However, Ctrl worms had increased their BV faster on the last census day 35 (worms aged 40d old) compared to all *C. teleta* exposed to SER (0.33 - 100 µg/g dw). These trends were also reflected in the growth models (SI Table S1), although the high biological variance in BV, which has also been highlighted by other authors (Méndez et al., 2013; Ramskov et al., 2009a; Sandgaard et al., 2023), introduces uncertainty in the model estimates thus impairing the likelihood of detecting significant impacts. Increasing the number of replicates will likely improve model fitting. Both model parameter estimations showed a trend that *C. teleta* exposed at intermediate sertraline concentrations had a higher growth rate (GR) and reached their maximum body volume (BV_{max}) faster (time to BV_{max}) compared to control worms (Table S1). Both models estimated that the mean BV_{max} was highest in the Ctrl

compared to all other treatments. Focusing on the estimates from the Gompertz model, for example, BV_{max} (d) of worms reared in uncontaminated conditions was estimated to be around 35 mm^3 with a GR (b) of 0.064. At the same time, polychaetes exposed to the intermediate concentrations (SER: 0.33 - 33 μg/g dw) tended to have a higher GR ($0.095 \leq b \leq 0.218$), reaching their maximum BV faster ($16 \leq e \leq 20$ days) compared to the estimated time for the control (Ctrl b = 0.064; Ctrl e = 42 days). However, the maximum BV of exposed worms is predicted to be lower ($5.72 \leq d \leq 7.17$ mm^3) than in Ctrl conditions (Ctrl d = 35.42 mm^3).

Thus, overall control worms seemed to have lower GR (b) compared to worms in the intermediate SER concentrations (0.33 - 33 μg/g dw) and reached their maximum BV (d) much later than exposed worms. Further, *C. teleta* exposed to low SER (0.33 - 33 μg/g dw) seemed to have increased, although not significant, GR and reached maximum BV faster compared to Ctrl worms. In contrast to our findings, Méndez and Barata, (2015) reported that chronic exposure to the SSRI, fluoxetine (0 - 3.3 μg/g dw sediment), induced a significant decrease in *C. teleta* growth compared to control worms. This indicates that *C. teleta* growth response varies despite exposure to a comparable range of concentrations of an antidepressant belonging to the same category as SER, which typically shares a similar Mode of Action (MoA). Consequently, relying solely on the MoA as a predictor of adverse effects on non-target organisms may not always be accurate. Moreover, the mussel *Mytilus californianus* chronically exposed (64d) to fluoxetine (0.3, 3, 30, 300 ng/L) showed a decreased growth (determined as biomass and shell length) after 47d of exposure, which was speculated to result from fluoxetine impairment of mussel clearance efficiency (Peters and Granek, 2016). An additional decrease in growth was observed in mussels exposed at the two highest concentrations after 107d of exposure (Peters and Granek, 2016). Chronic exposure to SER (3.3 - 100 μg/g dw) inhibited growth in the freshwater oligochaete *Tubifex tubifex* (Chan et al., 2024). Sandgaard et al., (2023) showed that juvenile *C. teleta* (5 days old) exposed to smoked (SCF) and non-smoked (NCF) cigarette filters, resulted in a significant decrease in juvenile BV at the highest SCF after 4 weeks of exposure. On the contrary, adult worms appeared to reach an even higher average BV (around 20 mm^3), even if not statistically significant, than Ctrl worms (around 10 mm^3) from week 9 up to the 15^{th} week of exposure (Sandgaard et al., 2023). These examples suggest that evaluating the effects of chemicals on non-target organisms throughout their life cycle, rather than solely depending on acute exposure testing, allows for a more comprehensive understanding of an organism's responses related to their life history traits.

Neither of the growth models fitted the BV for worms exposed to the highest SER (100 μg/g dw). This may be related to the higher variability of worm BV at this concentration. Alternatively, we hypothesize that SER may exert another MoA at very high concentrations compared to lower concentrations. However, it is advisable to enhance future research efforts to refine estimations and obtain more robust findings, potentially supporting the trends observed in the present study.

Antidepressants may undermine the hormone system when acting on monoamine levels, inducing endocrine disruption effects (Thompson and Vijayan, 2022). This is supported by Fong and Ford, (2014), who reported serotonin-induced spawning in the bivalves *Spisula spp*. and *Dreissena polymorpha,* and increased ovulation and oviposition in the freshwater snail *Biomphalaria glabrata*. Further, serotonin modulates developmental processes as exemplified in the marine snail, *Ilyanassa obsolete* where fluoxetine induced metamorphosis of the larvae through inhibition of serotonin reuptake (Couper and Leise, 1996). The action of SSRIs affecting serotoninergic neurons follows: the SSRIs may interfere with serotonin levels and neuromodulating action, therefore explaining the disruptive effects on their normal biological function and the interference with organisms' endocrine system (Fong and Ford, 2014). Indeed, as described by Thoré et al., (2020), fluoxetine (0.7 and 5.3 μg/L) enhanced mating behavior and fecundity in female turquoise killifish. Sánchez-Argüello et al., (2009), showed that low concentrations of fluoxetine (31.25 and 62.5 μg/L) induced reproduction in the freshwater snail *Physa acuta*, whilst the highest concentration (250 μg/L) showed an opposite trend. These findings are in accordance with our results: juveniles exposed to SER fastened maturation and copulation, especially at the lowest concentrations. Maturation was faster in *C. teleta* (census day 21) exposed at environmentally realistic SER concentrations (0.33 - 33 μg/g dw) compared to control worms (census day 35) and worms exposed at the highest concentration (100 μg/g dry wt), where only a few worms matured at census day 21, whereafter maturation boosted from census day 28 to 35. Accordingly, worms exposed to environmentally realistic concentrations of SER were also the fastest to reproduce, with the appearance of the first brooding tubes on census day 28 (worms aged 33 days old), whereas no brooding tube was produced from worms in uncontaminated sediment throughout the experimental duration. Brooding tubes for worms in 100 μg/g dry wt were not detected until day 35 (worms aged 40 days old). This is in contrast to results reported by Henry and Black, (2008) and Méndez and Barata, (2015), who examined the adverse effects triggered by exposure to fluoxetine. Henry and Black, (2008) found that chronic water exposure of juveniles of western mosquito fish to fluoxetine (7 - 71 ppb in 100L mesocosm tanks), increased juvenile developmental time of sexual adult traits compared to the control. Méndez and Barata, (2015) reported that maturation and copulating processes were delayed or inhibited in *C. teleta* chronically exposed to sediment-associated fluoxetine (0, 0.001 - 3.3 μg/g dw sediment), compared to worms in un-contaminated sediment as only non-exposed worms were able to produce brooding tubes with viable eggs (Méndez and Barata, 2015). Even though SSRIs, like fluoxetine and sertraline, share a similar MoA, the different responses of *C. teleta* to the two chemicals may be related to differences in pharmaco-kinetics and -dynamics, side effects, and efficacy (Edinoff et al., 2021). For example, fluoxetine's main metabolite, norfluoxetine (norFlu), has an extended half-life (7 - 15d) making it more persistent than its parent compound (fluoxetine half-life: 48-96h) and a longer environmental presence compared to other antidepressants like SER, which have shorter half-lives (26h; norSER: 56-120h) (Huddart et al., 2020). Further, norFlu has the same potency as fluoxetine in inhibiting serotonin reuptake (Catterson and Preskorn, 1996), whereas norSER has a lower potency than SER (Huddart et al., 2020; Tihanyi et al., 2006). Thus, we speculate that norFlu contributes to exerting long-term adverse effects in non-target species and that SER metabolites do not (Catterson and Preskorn, 1996). A second possible explanation for the difference between fluoxetine and sertraline is that fluoxetine is considered a more potent inhibitor of various cytochrome P450 forms (Alfaro et al., 2000), decreasing liver clearance. The stronger the CYPs are inhibited the lower the clearance efficiency leading to the impairment of the drug metabolism and thus its longer presence in the system (Preskorn, 1997). In addition, Méndez and Barata, (2015) found that fluoxetine induced the formation of abnormal spines in *C. teleta* males: an adverse effect that can impair copulation. We did not detect abnormal spines or ovaries in worms exposed to sediment-associated SER. The development of abnormal sexual traits in *C. teleta* exposed to fluoxetine may also explain the stronger decrease in reproductive success observed in Méndez and Barata, (2015) compared to our results with SER.

The non-monotonic dose-response associated with antidepressant exposure has been frequently reported for endocrine disruptive chemicals (e.g. Lagarde et al., 2015). Thus, ecotoxicological testing based on the assumption of linear dose-response toxicity models using high unrealistic concentrations often cannot predict the safety of exposure of non-target organisms to lower doses (Hill et al., 2018). Consequently, the standard monotonic approach used by regulatory agencies to characterize the hazard of chemicals may not be accurate when addressing the ecological risk associated with neuroactive chemicals (Lagarde et al., 2015). In our study, we showed the non-monotonicity of juvenile *C. teleta* growth and reproduction, with a reduced, although not significant, BV and time to first reproduction at the highest SER concentration tested. These non-monotonic responses might be explained by the

saturation of the metabolic system induced by high doses of chemicals, therefore impairing the xenobiotic catabolisation into its metabolites as reviewed by Lagarde et al. (2015). Further, SER is mainly metabolized in the liver through cytochrome monooxygenases (CYPs or P450s), and has, as other SSRIs, a weak inhibitory effect on CYP activity (Alfaro et al., 2000). Thus, we speculate that the hormetic effect is the result of the combined saturation of sertraline metabolism as well as a higher cytochrome P450 inhibition at the highest SER concentration resulting in impaired metabolic efficiency causing a lower biotransformation capability and elimination (Preskorn, 1997). Alternatively, the hormetic effects may result from an increased food intake at intermediate concentrations, thus, increasing energy intake to activate detoxification processes and repair mechanisms in response to the SER stress (Jager et al., 2013). We also speculate that the effects at lower exposure concentrations may be "therapeutic" effects (i.e., unlike a typical stressor effect) while effects at the higher concentrations are toxic effects.

To our knowledge, this study is the first to investigate the effects of environmentally realistic and higher concentrations of sediment-associated SER on *C. teleta*. Our results show that SER acts as an endocrine disruptor, significantly enhancing maturation and reproduction, which were the most sensitive endpoints. We observed non-monotonic effects, with an increase in the feeding rate of adults and the growth of juveniles exposed to environmentally realistic concentrations, while elevated concentrations showed opposite trends. Since current literature regarding chemical effects on sediment-dwelling organisms is scarce, understanding the implications of the presence of ionizable chemicals, like SSRIs, in estuarine areas, where the higher pH can affect the outcomes of these compounds compared to freshwater environments, is crucial to preserve natural ecosystems. Further investigations assessing multiple endpoints over longer exposure periods are needed to better understand the hormetic effects, induced in the studied life history traits, caused by sertraline exposure to environmentally realistic concentrations. Moreover, future studies should explored the potential connection between SSRIs exposure and changes in serotonin levels, CYP enzymatic activity, and energy allocation in *C. teleta.* This will help determine the extent to which constant exposure to environmental concentrations of SSRIs can impact the physiology and energy reserves of non-target organisms. Additionally, investigating longer-term exposure and delving deeper into the mechanisms underlying SSRIs' effects on non-target organisms could reveal the consequences of the endocrine disruptive effects observed in *C. teleta* exposed to sertraline for population dynamics.

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Generative AI

During the preparation of this work the author(s) used Avidnote to: get inspiration for synonyms to improve clarity, and proofread some sentences. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Martina Santobuono: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Wing Sze Chan:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Elettra D'Amico:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Henriette Selck:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.aquatox.2024.107189.

Data availability

Data will be made available on request.

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