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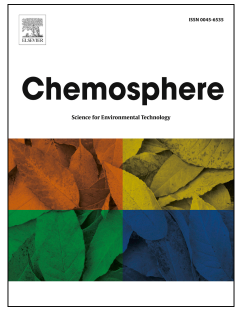

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Credit authorship contribution statement

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Caffeine as a Contaminant of Concern: a review on concentrations and impacts in marine coastal systems

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Abstract

Caffeine has been identified as emerging contaminant of concern due to its widespread occurrence in the aquatic environment and potential to be biologically active. Recently, these concerns have been translated in an increasing research on its occurrence and effects on biota. However, there is still a limited knowledge on the coastal and marine matrices and the implications of their presence in these ecosystems is not fully known. The present review aims to fill these knowledge gaps, analysing the existing literature regarding the occurrence, effects and potential risks of caffeine residues to coastal ecosystems, contributing to the risk assessment of this psychoactive drug in the aquatic environment. The analysed literature reported caffeine concentrations in the coastal ecosystems, raising high concerns about the potential adverse impacts on the ecological safety and human health. Caffeine has been found in tissues from coastal and marine biota including microalgae, coral reefs, bivalves and fish due to bioaccumulation after chronic, long-term exposures in a contaminated environment. Additionally, caffeine residues had been demonstrated to have adverse impacts on aquatic organisms, at environmentally realistic concentrations, inducing oxidative stress and lipid peroxidation, neurotoxicity, changing energy reserves and metabolic activity, affecting reproduction and development and, in some cases, causing mortality. Considering the increasing adverse impacts of caffeine pollution in the coastal environment, this review highlights the urgent need to minimize the increasing load of caffeine to the aquatic ecosystems; being imperative the implementation of scientific programs and projects to classify effectively the caffeine as a high-priority environmentally hazardous emerging pollutant**.**

Keywords: Caffeine; Risks; Effects; Coastal Ecosystems

1. INTRODUCTION

The industrial revolution had an important and unquestionable contribution to human comfort and welfare. However, this reality was accompanied by an increasing demand for anthropogenic activities, resulting in the production and use of new chemicals with consequent release and contamination of aquatic ecosystems (Rocha et al., 2018). In this context, in the last decades, pharmaceuticals were responsible for saving millions of lives. However, the increasing demand has emerged pharmaceuticals as a new class of environmental contaminants, being increasingly reported in almost all environmental matrices on every continent, including lakes, rivers, streams, estuaries and seas (Patel et al., 2019; Korekar et al., 2020). Recent evidences have highlighted the potential of these contaminants to be harmful for environmental health (Patel et al., 2019), with a rising concern on the preservation of aquatic ecosystems.

Among the most frequently detected pharmaceuticals in the aquatic compartments, it is possible to highlight analgesics, antibiotics, lipid regulators, anticancer drugs, antiepileptics/anticonvulsants, psychopharmacological agents, contraceptive hormones and ß-blockers (Ayscough et al., 2000; Fatta-Kassinos et al., 2011; Kümmerer, 2001; Nikolaou et al., 2007). In addition to these classes of pharmaceutical compounds, central nervous system stimulants are also frequently detected in environmental compartments at relevant concentrations. Among the compounds of this class is caffeine (1,3,7-trimethylxanthine), a natural alkaloid occurring in a wide variety of plants (Cappelletti et al., 2015; Mustard et al., 2012). Caffeine occurs naturally in approximately 60 plant species and it is a highly used stimulant contained in coffee, tea, caffeinated beverages as well as in several pharmaceutical products (Buerge et al., 2003; Fent et al., 2006; Gilbert, 1984; Moore et al., 2008; Palo and Choudhury, 2006), and it has been identified in different aquatic environments (Buerge et al., 2003; Sauvé et al., 2012). The caffeine concentrations in numerous consumed products ranges from 36-804 mgL^{-1} in coffee; 17-551 mgL^{-1} in chocolates; 13-68 mgL^{-1} in ice tea drinks; 267-340 mgL^{-1} in energetic drinks; 15-448 mgL^{-1} in coffee-based beverages and 1002-1353 mgL^{-1} in food supplements (Korekar et al., 2020; Rudolph et al., 2012). Recently, acetaminophen, an analgesic and antipyretic drug, has been combined with caffeine, which increases the pain-relieving effect. Due to its widespread use, its concentration in the water bodies has increased in the last two decades (Korekar et al., 2020).

The main recognized sources of this psychoactive drug in the aquatic environment include wastewater excretory residues, inappropriate deposition of expired or unwanted caffeine containing pharmaceutical products, manufacturing plant wastes, hospital wastes, within others (Cruz et al., 2016; Froehner et al., 2011). During wastewater treatment, caffeine generally shows excellent removal efficiency (Li et al., 2020), however, and because of its significant and increasing consumption, the input of this substance into the aquatic systems is much higher than that which is degraded (Zhou et al., 2018). Caffeine is relatively stable under different conditions, including seawater, having high-water solubility (approximately 13.0 g/L), low octanol-water coefficient (log kow = −0.07), low volatility (Beltrame et al., 2018; Edwards et al., 2015; Lin et al., 2009) and a reported half-life of 100 –240 days (Hillebrand et al., 2012), favouring its dispersion in the aquatic environment. Due to its high consumption coupled with its relative stability under environmental conditions, it is currently recognized as a marker of anthropogenic activity (Buerge et al., 2003; Quadra et al., 2020), being reported in several types of matrices, such as freshwater, estuarine and seawater, sediments and biota (Benotti and Brownawell, 2007; Buerge et al., 2003; Ferreira et al., 2005; Peeler et al., 2006; Sauvé et al., 2012). As a consequence, the research on its occurrence and effects on biota has increased in the last years. The presence of caffeine in freshwater has been significantly more widely studied (ex. Korekar et al., 2020; Hillebrand et al., 2012), with special focus on wastewater treatment plants (WWTPs) discharges (e.g. Afonso-Olivares et al., 2017; Ajo et al., 2018; reviewed by Dafouz et al., 2018 and Li et al., 2020). Compared to the research conducted in freshwater ecosystems, where concentrations of caffeine can be found up to 1500 ng/L (Buerge et al., 2003; Sauvé et al., 2012), there is still a limited knowledge regarding coastal and marine matrices and the implications of caffeine presence in these ecosystems is not fully known (among others del Rey et al., 2012; Sauvé et al., 2012). The present review aims to fill these knowledge gaps, analysing the existing literature regarding the occurrence, effects and potential risks of caffeine residues in marine and coastal ecosystems (including transitional waters), contributing to the risk assessment of this psychoactive drug in the aquatic environment.

For the manuscript preparation, ISI Web of Knowledge and SCOPUS were the platforms used, searching a combination of keywords including "caffeine AND marine"; "caffeine AND estuarine", "caffeine AND marine AND effects", "caffeine AND coastal AND effects". The compiled studies were reviewed and a total of 86 studies published after 2001 were considered (Figure 1).

2. OCCURRENCE OF CAFFEINE IN COASTAL AND MARINE ENVIRONMENTS

An increasing number of studies has confirmed the presence of caffeine in different aquatic environmental compartments, raising concerns about the potential adverse effects to wildlife. Caffeine contamination levels in coastal and marine environments has been estimated by analysing sediments and water (Nodler et al., 2014). These monitoring studies are necessary to assess spatial and temporal caffeine concentrations, identifying sources and, also, predicting bioaccumulation and toxicity to biota (Li et al., 2020; Roveri et al., 2020). The highest caffeine concentrations in aquatic ecosystems were reported in freshwater environments, as early as 1978 (Cain et al., 1980; Rogers et al., 1986), representing by far the majority of research works published (e.g. Alidina et al., 2014; Castiglioni, et al., 2018; French et al., 2015; Korekar et al., 2020; Li et al., 2020). In contrast, comparable analytical data from coastal and marine environments remains scarce.

In the present review, a total of 49 studies reported caffeine concentrations in marine and coastal waters (including estuaries) and sediments (Table 1). The highest detected concentration found in seawater water was 11000 μg/L, reported by French et al. (2015) for the Darwin Harbour (Northern Australia). The majority of the studies on caffeine concentration in seawater matrices are from the USA, with concentrations ranging from 2 to 5860 ng/L (Benotti and Brownawell, 2007; Knee et al., 2010). In Europe, caffeine was detected in marine and coastal areas of 13 countries, with the highest concentrations being observed in the Aegean Sea (3068 ng/L) (Nodler et al., 2014) and in the Arade River estuary (Portugal) (600–804 ng/L) (Gonzalez-Rey et al., 2015). It was also identified in other countries (with the highest concentration), including Brazil (1300 ng/L), Canada (1400 ng/L), China (3060 ng/L), Costa Rica (1207 ng/L), Japan (8230 ng/L), Malaysia (0.33 ng/L), Singapore (1389 ng/L) and Taiwan (718 ng/L) (Table 1). Few studies (8%) have described the concentrations of caffeine in coastal sediments, with values ranging from 0.31 to 23.4 ng/g in Brazil (Beretta et al., 2014) and from 1.90 to 12.20 ng/g in Spain (Maranho et al., 2015a) (Table 1). A study by Romagnoli et al (2016) reported caffeine concentrations from the Southern and Eastern Mediterranean Sea, ranging from 0.01 to 0.17 ng/L (Table 1).

The average worldwide caffeine consumption is around 70 mg per person/day, with varying consumption depending on the country (Rigueto et al., 2020). Europe, Asia and North America lead the world coffee consumption during the last decade, according to the International Coffee Organization (ICO) (http://www.ico.org/). Thus, it is not surprising that the highest caffeine concentrations reported so far (Table 1) were observed in marine and coastal waters from those areas. Considering the relationship between the source of caffeine and its consumption, it is commonly observed that the highest caffeine concentrations found in WWTPs effluents are related to their proximity to populated regions (Dafouz et al., 2018; Li et al., 2020; Rodríguez-Gil et al., 2018). Approximately 5% of ingested caffeine is excreted in the urine and eventually reaches aquatic ecosystems (Montagner et al.,2014). The caffeine removal efficiency fluctuates depending on the system, which may be owing to the incomplete metabolism of caffeine by microorganisms found mostly in old and/or conventional WWTPs (Rigueto et al., 2020). In addition, several studies have reported higher caffeine concentrations in rivers and estuaries than in the WWTPs treated effluents, suggesting that in some areas untreated effluents are being discharged (some illegally), eventually reaching coastal areas (ex. Froehner et al., 2011; Munro et al., 2019; Williams et al., 2019). Untreated discharges and/or poorly managed effluents may have contributed to some of the highest reported caffeine concentrations in the marine and coastal areas.

The data available for marine and coastal areas is, still, very limited and inconsistent, resulting from different sampling and analytical approaches and methodologies, limiting a reliable characterization of caffeine concentrations. The seasonal variability in those areas, including hydrological processes, may affect caffeine transport into the coastal ecosystems (del Rey et al., 2011, 2012), being another factor contributing to caffeine concentration variability. The seasonal increase in population due to tourism into the coastal areas can, also, play an important role. The increase in tourism and recreational activities during the sea-bathing season has been correlated with a significant increase in caffeine concentrations in coastal waters (Paíga and Delerue-Matos, 2017). It is imperative further monitoring studies in marine and coastal areas, based on standardised sampling and analytical methods, including the biotic and abiotic matrices, contributing to future modelling programs in order to assess the main sources, distribution and impacts of this psychoactive drug.

3. OCCURRENCE OF CAFFEINE IN MARINE SPECIES

The assessment of caffeine concentration in marine organisms has been the subject of considerable interest in recent years because of serious concern that high levels may not only have harmful effects on biota, but also may limit their suitability for human consumption. Compared to water and sediment analyses, marine organisms exhibit greater spatial sensitivity and, consequently, can be considered reliable tools for identifying sources of biologically available pharmaceuticals, including caffeine (Korekar et al., 2020; Patel et al., 2019). Therefore, marine organisms have become increasingly used in the assessment of caffeine contamination (Korekar et al., 2020). Relevant caffeine concentrations have been documented in tissues of different coastal and marine species including corals, algae, mussels and fish due to bioaccumulation after long-term exposure to contaminated water (Table 2). Comparing with freshwater ecosystems, few studies aimed to detect caffeine on coastal and marine biota (5 in total, published between 2014 and 2020).

Caffeine concentrations ranging from 15.8 to 37.1 ng/g were recorded in Maldives coral reefs and ranging from 2.2 to 41.2 ng/g in Saudi Red Sea macroalgae (*Ulva lactuca*, *Turbinaria conoides* and *Hydroclathrus clathratus*) (Ali et al., 2018; Rizzi et al., 2020). In bivalves, concentrations varying from 19 to 68 ng/g were recorded in *Mytilus* spp. collected along the California coast (USA) (Maruya et al., 2014) and between 0.4 and 4.4 ng/g in *Perna viridis* collected in Singapore (Bayen et al., 2016). Regarding fish, concentrations between 2.5 and 73.6 ng/g were observed in Saudi Red Sea fish *(Gerres oyen*, *Chanos chanos* and *Lethrinus nebulosu*) (Ali et al., 2018) and in South Africa, with concentrations ranging from 1.76 to 64.78 ng/g (*Pterogymnus laniarius*, *Sarda orientalis* and *Pachymetopon blochii*) (Ojemaye and Petrik 2019). Considering that the reported fish and bivalve species are consumed by humans, the detected caffeine concentrations raise concern on the potential adverse effects to humans health. In addition, only few food web representatives were investigated. In fact, the caffeine concentrations on the marine ecosystems primary producers and consumers are still unknown. The comparison between the research monitoring studies focused in water and sediment analyses with these reported in the Table 2 highlights the need of include biota assessment on those studies, in order to obtain a more compressive temporal and spatial scenarios of caffeine contamination, also contributing to multidisciplinary predicting and management models. It is also important to highlight that, in published data, measured concentrations in aquatic organisms were not frequently accompanied by measures in water and sediments, making it difficult to estimate bioconcentration (BCF) levels and to model the caffeine effects on the different matrices for risk assessment.

4. EFFECTS OF CAFFEINE IN MARINE ORGANISMS

Pharmaceuticals, including caffeine, are considered a unique group of emerging environmental contaminants, especially due to their inherent ability to induce physiological effects in aquatic wildlife and in humans, even at relatively low concentrations (Ebele et al., 2017). Considering that in coastal and marine ecosystems caffeine has been detected at trace levels (ng/L to µg/L) (Tables 1 and 2), it is important to assess the potential effects at environmentally relevant concentrations. During the last years, environmentally realistic concentrations of caffeine, tested under laboratorial conditions, have demonstrated significant adverse impacts on several coastal species, including growth inhibition, lethality, affecting reproduction and development, altering energy reserves and metabolic activity, neurotoxic effects, oxidative stress and vellular damages. These impacts, observed in marine and costal species, are summarised in Table 3, reporting studies (11) published since 2011, including laboratorial effects on marine algae, bivalvia, polychaeta, echinoidea and malacostraca.

4.1. Effects on development, reproduction and lethality

At least 5 studies indicated that long-term exposure caffeine affected severely the development, reproduction and, in some cases, cause lethality of different marine species (Table 3). Garcia et al. (2014) reported adverse effects in the shrimp *Palaemonetes pugio* development, from embryo to juvenile life stage, when exposed to 20 mg/L of caffeine for 5 days. These negative effects included delaying hatch time and embryos development, when exposed to caffeine. Pires et al. (2016a) investigated caffeine exposure effects on the polychaete *Diopatra neapolitana* regenerative capacity. According to this study, a long-term caffeine exposure, at environmentally relevant concentrations (0.5-18 µg/L), induced a significant regenerative capacity delay and originated less new segments for whole body repair. These negative impacts on the hatch mean time, embryo development and regenerative capacity will influence species health status with implications on species abundance, reproduction and population dynamics stability. The only available study on marine algae, by Aguirre-Martínez et al. (2015), reported significant effects on the growth inhibition when *Isochrysis galbana* was exposed to caffeine at 100 and 500 mg/L. Considering lethality, Pires et al. (2016 a, b) reported significant mortality percentages of 8.3%, 12.5% and 22.2%, in 3 polychaete species (*Hediste diversicolor*, *D. neapolitana* and *Arenicola marina*, respectively), when exposed for 28 days to caffeine concentrations between 0.5 and 18.0 µg/L.

4.2. Effects on metabolic activity, antioxidant defences and neurotoxicity

Published literature suggested that, under the presence of pharmaceuticals, including caffeine, marine organisms increase their metabolic activity and reduce their energy reserves (e.g. glycogen), which is used to fight against oxidative stress, with the induction of antioxidant defences in order to prevent cellular injuries (Cruz et al., 2016; Pires et al., 2016a,b). This response pattern was observed in the bivalve *Ruditapes philippinarum* (Cruz et al., 2016) and in the polychaetes *D. neapolitana* (Pires et al., 2016a) and *H. diversicolor* (Pires et al., 2016b), with a significant decrease of glycogen content, when exposed to environmental caffeine concentrations. In addition, the activity of electron transport system has been also used as a useful biomarker to measure metabolic activity in organisms exposed to caffeine (Cruz et al., 2016).

Recent evidences demonstrated that caffeine may enhance the production of reactive oxygen species (ROS), inducing antioxidant responses (Li et al., 2020; Pires et al., 2016a). In fact, the evaluation of the oxidative stress status has been recommended as early warning indicator of toxicity effects in aquatic organisms (Aguirre-Martinez et al., 2015, 2016). These responses are usually mediated by antioxidant enzymes, including superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase in order to prevent lipid peroxidation (LPO) as a consequence of oxidative stress (Aguirre-Martinez et al., 2013, 2016). The induction of these antioxidant defences and relevant levels of LPO have been demonstrated in some marine organisms exposed to caffeine trace levels, including bivalves (Aguirre-Martinez et al., 2015; Cruz et al., 2016), amphipods (Maranho et al., 2015a), polychaetes (Pires et al. 2016 a,b) and crabs (Aguirre-Martinez et al., 2013) (Table 3). For example, Pires et al. (2016a) observed the incapacity of antioxidant and biotransformation enzymes to prevent cells from LPO, after 28 days of exposure to caffeine. These studies also suggested that antioxidant defence may follow a time dependence pattern, with long-term caffeine exposure ultimately result in inefficient antioxidant defence and oxidative impairment, and, in some cases in cellular damage. Beyond LPO, the genotoxicity is, also, considered a consequence of oxidative stress (Maranho et al., 2015a). A study conducted by Aguirre-Martinez et al. (2013), using *Carcinus maenas* exposed to caffeine (50 µg/L) indicated evidences of DNA damage in different tissues (gills, muscle, hepatopancreas). Using lower concentrations, Maranho et al. (2015a) reported significant alterations on mitochondrial DNA in amphipods (*Ampelisca brevicornis*) at caffeine concentrations between 0.00015 and 1.5 µg/g.

Caffeine is considered a relevant central nervous system stimulant; thus, special attention has been paid to its potential neurotoxic effects (Aguirre-Martinez et al., 2016; Li et al., 2020). This psychoactive drug is a competitive antagonist of adenosine receptors, affecting the nervous system of animals (Stiles, 1992). The activity of acetylcholinesterase (AChE) has been used to assess potential neurotoxic effects of several classes of contaminants, including caffeine (Maranho et al., 2015a,b). In a study published by Aguirre-Martinez et al. (2016), the activity of AChE in the bivalves *R.*

philippinarum decreased by 79%, 54% or 56%, when exposed to 5, 10 or 50 µg/L caffeine, respectively. According to Ludke et al. (1975), the inhibition of AChE activity above 20%, indicates neurotoxic effects, thus, Aguirre-Martinez et al. (2016) concluded that caffeine concentrations above 5 µg/L may induce neurotoxicity on the selected bivalves.

Overall findings suggest that caffeine reaching to coastal and marine systems may influence species health status, affecting species abundance and biomass, reproduction and survival, with direct and indirect effects on ecosystems food web.

5. FUTURE CHALLENGES AND RECOMMENDATIONS

The literature reported so far showed caffeine in the coastal ecosystems, raising concerns about the potential adverse impacts on the wildlife safety and human health. According to the International Coffee Organization (ICO) (http://www.ico.org/), Europe, Asia & Oceania and North America lead the world coffee consumption with increases of 1.8%, 1.9% and 2.1% between the period 2016/17-2019/20. The countries with the highest average per capita of coffee consumption during 2020 were Netherlands, Finland and Sweden with 8.3, 7.8 and 7.6 kg/Year estimated average per capita (Alfawaz et al., 2020; ICO, 2020). Comparing these reports with the number of scientific studies on caffeine occurrence in the environment and effects on biota discussed in the present review, the majority of them are, in fact, from Europe, USA and Asia. However, the overall studies are still very scarce and did not cover other relevant global areas and ecosystems. In addition, the estimated vast distribution of caffeine along with its environmental impact on several ecosystems calls for an urgent research (Dafouz et al., 2018; Korekar et al., 2020). Caffeine has been found in tissues from several coastal and marine biota including macroalga, coral reefs, bivalves and fish due to bioaccumulation after long-term exposure to contaminated environment. The number of studies concerning caffeine levels in marine biota is still very limited, devoted essentially bivalves and fish species of human consumption, raising concerns on seafood safety. It is imperative to increase the temporal and spatial monitoring programs, covering all marine ecosystem matrices, including food web key species.

Several authors have highlighted the caffeine higher dilution in marine waters, thus, the concentrations are expected to be lower, comparing to freshwater and wastewater (Pomati et al., 2008), and the potential effects are assumed to be minor (Dafouz et al., 2018). However, caffeine had been demonstrated to have adverse impacts on marine and estuarine organisms, at environmentally realistic concentrations, inducing oxidative stress and lipid peroxidation, neurotoxicity, changing energy reserves and metabolic activity, affecting reproduction and development and, in some cases, causing mortality. Therefore, it is essential assess long-term environmental effects and risks posed to marine organisms, exposed to caffeine, including potential mixtures with other contaminants (Korekar et al., 2020).

Nevertheless, the overall available data indicate that caffeine, which has been traditionally accepted as posing low risk to aquatic environments, might deserve additional attention. Considering the alarming concentrations observed on abiotic and biotic samples and the reported effects, it is crucial to remove or significantly limit caffeine and its derivatives effectively from the water systems, investing efforts and research on the development effective treatment and removal technologies. It is, also, urgent to implement programs to minimize the environmental load of caffeine, including ecopharmacovigilance programs (EPV) targeting caffeine as a high-priority environmentally hazardous anthropogenic contaminant, inclusive in the context of the Marine Strategy Framework Directive (2008/56/EC).

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6. REFERENCES

Afonso-Olivares, C., Sosa-Ferrera, Z., Santana-Rodríguez, J.J., 2017. Occurrence and environmental impact of pharmaceutical residues from conventional and natural wastewater treatment plants in Gran Canaria (Spain). Sci. Total Environ. 599-600, 934-943.

Aguirre-Martinez, G.V., Del Valls, T.A., Martin-Diaz, M.L., 2013. Identification of biomarkers responsive to chronic exposure to pharmaceuticals in target tissues of *Carcinus maenas*. Mar. Environ. Res. 87/88, 1-11.

Aguirre-Martínez, G.V., Owuor, M.A., Garrido-Pérez, C., Salamanca, M.J., Del Valls, T.A., Martín-Díaz, M.L., 2015. Are standard tests sensitive enough to evaluate effects of human pharmaceuticals in aquatic biota? Facing changes in research approaches when performing risk assessment of drugs. Chemosphere 120, 75-85.

Aguirre-Martinez, G.V., DelValls, T.A., Martin-Diaz, M.L., 2016. General stress, detoxification pathways, neurotoxicity and genotoxicity evaluated in *Ruditapes philippinarum* exposed to human pharmaceuticals. Ecotoxicol. Environ. Saf. 124, 18-31.

Ajo, P., Preis, S., Vornamo, T., Mänttäri, M., Kallioinen, M., Louhi-Kultanen, M., 2018. Hospital wastewater treatment with pilot-scale pulsed corona discharge for removal of pharmaceutical residues. J. Environ. Chem. Eng. 6, 1569-1577.

Alfawaz, H.A., Khan, N., Yakout, S.M., Khattak, M.N.K., Alsaikhan, A.A., Almousa, A.A., Alsuwailem, T.A., Almjlad, T.M., Alamri, N.A., Alshammari, S.G., Al-Daghri, N.M., 2020. Prevalence, predictors, and awareness of coffee consumption and its trend among Saudi female students. Int. J. Environ. Res. Public Health 17(19), 7020.

Ali, A.M., Rønning, H.T., Alarif, W., Kallenborn, R., Al-Lihaibi, S.S., 2017. Occurrence of pharmaceuticals and personal care products in effluent-dominated Saudi Arabian coastal waters of the Red Sea. Chemosphere 175, 505-513.

Ali, A.M., Rønning, H.T., Sydnes, L.K., Alarif, W.M., Kallenborn, R., Al-Lihaibi, S.S., 2018. Detection of PPCPs in marine organisms from contaminated coastal waters of the Saudi Red Sea. Sci. Total Environ. 621, 654-662.

Alidina, M., Hoppe-Jones, C., Yoon, M., Hamadeh, A.F., Li, D., Drewes, J.E., 2014. The occurrence of emerging trace organic chemicals in wastewater effluents in Saudi Arabia. Sci. Total Environ. 478, 152-162.

Alvarez, D.A., Maruya, K.A., Dodder, N.G., Lao, W., Furlong, E.T., Smalling, K.L., 2014. Occurrence of contaminants of emerging concern along the California coast (2009–10) using passive sampling devices. Mar. Pollut. Bull. 81, 347-354.

Alygizakis, N.A., Gago-Ferrero, P., Borova, V.L., Pavlidou, A., Hatzianestis, I., Thomaidis, N.S., 2016. Occurrence and spatial distribution of 158 pharmaceuticals, drugs of abuse and related metabolites in offshore seawater. Sci. Total Environ. 541, 1097-1105.

Ayscough, N.J., Fawell, J., Franklin, G., Young, W., 2000. Review of human pharmaceuticals in the environment. Environment Agency, Bristol (Technical report P390).

Bayen, S., Zhang, H., Desai, M.M., Ooi, S.K., Kelly, B.C., 2013. Occurrence and distribution of pharmaceutically active and endocrine disrupting compounds in Singapore's marine environment: influence of hydrodynamics and physical-chemical properties. Environ. Pollut. 182, 1-8.

Bayen, S., Estrada, E.S., Juhel, G., Kit, L.W., Kelly, B.C., 2016. Pharmaceutically active compounds and endocrine disrupting chemicals in water, sediments and mollusks in mangrove ecosystems from Singapore. Mar. Pollut. Bull. 109, 716-722.

Beltrame, K.K., Cazetta, A.L., de Souza, P.S.C., Spessato, L., Silva, T.L., Almeida, V.C., 2018. Adsorption of caffeine on mesoporous activated carbon fibers prepared from pineapple plant leaves. Ecotoxicol. Environ. Saf. 147, 64-71.

Benotti, M., Brownawell, B.J., 2007. Distribution of pharmaceuticals in an urban estuary during both dry and wet weather conditions. Environ. Sci. Technol. 41, 5795–5802.

Beretta, M., Britto, V., Tavares, T.M., da Silva, S.M.T., Pletsch, A.L., 2014. Occurrence of pharmaceutical and personal care products (PPCPs) in marine sediments in the Todos os Santos Bay and the north coast of Salvador, Bahia, Brazil. J. Soil Sediment. 14, 1278-1286.

Biel-Maeso, M., Baena-Nogueras, R.M., Corada-Fernández, C., Lara-Martín, P.A., 2018. Occurrence, distribution and environmental risk of pharmaceutically active compounds (PhACs) in coastal and ocean waters from the Gulf of Cadiz (SW Spain). Sci. Total Environ. 612, 649-659.

Brumovský, M., Bečanová, J., Kohoutek, J., Borghini, M., Nizzetto, L., 2017. Contaminants of emerging concern in the open sea waters of the Western Mediterranean. Environ. Pollut. 229, 976–983.

Buerge, I.J., Poiger, T., Muller, M.D., Buser, H.R., 2003. Caffeine, an anthropogenic marker for wastewater contamination of surface waters. Environ. Sci. Technol. 37, 691–700.

Cain, R., Clark, M, Zorkin, N., 1980. Trace Organic Constituents in Discharges. Background Report to the Fraser River Estuary Study of the Fraser River Estuary Study Steering Committee, Government of British Columbia, p. 56.

Cantwell, M.G., Katz, D.R., Sullivan, J.C., Ho, K., Burgess, R.M., 2017. Temporal and spatial behavior of pharmaceuticals in Narragansett Bay, Rhode Island, United States. Environ. Toxicol. Chem. 36, 1846–1855.

Capolupo, M., Valbonesi, P., Kiwan, A., Buratti, S., Franzellitti, S., Fabbri, E., 2016. Use of an integrated biomarker-based strategy to evaluate physiological stress responses induced by environmental concentrations of caffeine in the Mediterranean mussel *Mytilus galloprovincialis*. Sci. Total Environ. 563, 538-548.

Cappelletti, S., Piacentino, D., Sani, G., Aromatario, M., 2015. Caffeine: cognitive and physical performance enhancer or psychoactive drug? Curr. Neuropharmacol. 13(1), 71–88.

Castiglioni, S., Davoli, E., Riva, F., Palmiotto, M., Camporini, P., Manenti, A., Zuccato, E., 2018. Mass balance of emerging contaminants in the water cycle of a highly urbanized and industrialized area of Italy. Water Res. 131, 287-298.

Cole, B.J., Brander, S.M., Jeffries, K.M., Hasenbein, S., He, G.C., Denison, M.S., Fangue N.A, Connon, R.E., 2016. Changes in *Menidia beryllina* gene expression and *in vitro* hormone receptor activation after exposure to estuarine waters near treated wastewater outfalls. Arch. Environ. Contam. Toxicol. 71, 210-223.

Comeau, F., Surette, C., Brun, G.L., Losier, R., 2008. The occurrence of acidic drugs and caffeine in sewage effluents and receiving waters from three coastal watersheds in Atlantic Canada. Sci Total Environ. 396, 132-46.

Cruz, D., Almeida, A., Calisto, V., Esteves, V.I., Schneider, R.J., Wrona, F.J., Soares, A.M., Figueira, E., Freitas, R., 2016. Caffeine impacts in the clam *Ruditapes philippinarum*: alterations on energy reserves, metabolic activity and oxidative stress biomarkers. Chemosphere 160, 95-103.

Dafouz, R., Caceres, N., Rodriguez-Gil, J.L., Mastroianni, N., Lopez de Alda, M., Barcelo, D., de Miguel, A.G., Valcarcel, Y., 2018. Does the presence of caffeine in the marine environment represent an environmental risk? A regional and global study. Sci. Total Environ. 615, 632-642.

del Rey, Z.R., Granek, E.F., Buckley, B.A., 2011. Expression of HSP70 in *Mytilus californianus* following exposure to caffeine. Ecotoxicology 20, 855.

del Rey, R., Z., Granek, E.F., Sylvester, S., 2012. Occurrence and concentration of caffeine in Oregon coastal waters. Mar. Pollut. Bull. 64, 1417–1424.

Ebele, A.J., Abou-Elwafa Abdallah, M., Harrad, S., 2017. Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. Emerg. Contam. 3, 1-16.

Edwards, Q.A., Kulikov, S.M., Garner-O'Neale, L.D., 2015. Caffeine in surface and wastewaters in Barbados, West Indies. Springer Plus 4, 57.

Fang, T.-H., Lin, C.-W., Kao, C.-H., 2019. Occurrence and distribution of pharmaceutical compounds in the Danshuei River Estuary and the Northern Taiwan Strait. Mar. Pollut. Bull. 146, 509-520.

Fatta-Kassinos, D., Meric, S., Nikolaou, A., 2011. Pharmaceutical residues in environmental waters and wastewater: current state of knowledge and future research. Anal Bioanal. Chem. 399, 251–275.

Fent, K., Weston, A.A., Caminada, D., 2006. Ecotoxicology of human pharmaceuticals. Aquat. Toxicol. 76, 122-159.

Ferreira, A.P., de Lourdes, C., da Cunha, N., 2005. Anthropic pollution in aquatic environment: development of a caffeine indicator. Int. J. Environ. Health Res. 15, 303–311.

French, V.A., King, S.C., Kumar, A., Northcott, G., McGuinness, K., Parry, D., 2015. Characterisation of microcontaminants in Darwin Harbour, a tropical estuary of northern Australia undergoing rapid development. Sci. Total Environ. 536, 639–647.

Froehner, S., Piccioni, W., Machado, K.S., Aisse, M.M., 2011. Removal Capacity of Caffeine, Hormones, and Bisphenol by Aerobic and Anaerobic Sewage Treatment. Water Air Soil Pollut. 216, 463-471.

Garcia, R.N., Chung, K.W., DeLorenzo, M.E., Curran, M.C., 2014. Individual and mixture effects of caffeine and sulfamethoxazole on the dagger blade grass shrimp *Palaemonetes pugio* following maternal exposure. nviron. Toxicol. Chem. 33, 2120-2125.

Gardinali, P.R., Zhao, X., 2002. Trace determination of caffeine in surface water samples by liquid chromatography - atmospheric pressure chemical ionization - mass spectrometry (LC-APCI-MS). Environ. Int. 28, 521–528.

Ghoshdastidar, A.J., Fox, S., Tong, A.Z., 2015. The presence of the top prescribed pharmaceuticals in treated sewage effluents and receiving waters in southwest Nova Scotia, Canada. Environ. Sci. Pollut. Res. 22, 689–700.

Giandomenico, S., Cardellicchio, N., Annicchiarico, C., Lopez, L., Maggi, M., Spada, L., Di Leo, A., 2011. Simultaneous determination of pharmaceutical compounds in environmental samples by solid-phase extraction and gas chromatography–mass spectrometry. Chem Ecol. 27, 127-136.

Gilbert, R.M., 1984. Caffeine consumption. Prog Clin Biol Res. 158,185-213.

Goh, S.G., Bayen, S., Burger, D., Kelly, B.C., Han, P., Babovic, V., Gin, K.Y.-H., 2017. Occurrence and distribution of bacteria indicators, chemical tracers and pathogenic vibrios in Singapore coastal waters. Mar. Pollut. Bull. 114, 627-634.

Gonzalez-Rey, M., Tapie, N., Le Menach, K., Devier, M.H., Budzinski, H., Bebianno, M.J., 2015. Occurrence of pharmaceutical compounds and pesticides in aquatic systems. Mar. Pollut. Bull. 96, 384–400.

Hillebrand, O., Nodler, K., Licha, T., Sauter, M., Geyer, T., 2012. Caffeine as an indicator for the quantification of untreated wastewater in karst systems. Water Res. 46, 395-402.

International Coffee Organization (ICO). 2020. Coffee Market Report, London, UK, 2019. Available online: http://www.ico.org/Market-Report-19-20-e.asp.

Ismail, N.A.H., Wee, S.Y., Kamarulzaman, N.H., Aris, A.Z., 2019. Quantification of multi-classes of endocrine-disrupting compounds in estuarine water. Environ. Pollut. 249, 1019-1028.

Jiang, J.J., Lee, C.L., Fang, M.D., 2014. Emerging organic contaminants in coastal waters: anthropogenic impact, environmental release and ecological risk. Mar. Pollut. Bull. 85, 391–399.

Keil, R., Salemme, K., Forrest, B., Neibauer, J., Logsdon, M., 2011. Differential presence of anthropogenic compounds dissolved in the marine waters of Puget Sound, WA and Barkley Sound, BC. Mar. Pollut. Bull. 62, 2404-2411.

Knee, K.L., Gossett, R., Boehm, A.B., Paytan, A., 2010. Caffeine and agricultural pesticide concentrations in surface water and groundwater on the north shore of Kauai (Hawaii, USA). Mar. Pollut. Bull. 60, 1376–1382.

Korekar, G., Kumar, A., Ugale, C., 2020. Occurrence, fate, persistence and remediation of caffeine: a review. Environ. Sci. Pollut. Res. 27, 34715-34733.

Kümmerer, K., 2001. Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources-a review. Chemosphere 45, 957-969.

Li, S., He, B., Wang, J., Liu, J., Hu, X., 2020. Risks of caffeine residues in the environment: Necessity for a targeted ecopharmacovigilance program. Chemosphere 243, 125343.

Lin, A.Y.C., Yu, T.H., Lateef, S.K., 2009. Removal of pharmaceuticals in secondary wastewater treatment processes in Taiwan. J. Hazard. Mater. 167(1–3), 1163–1169.

Loos, R., Tavazzi, S., Paracchini, B., Canuti, E., Weissteiner, C., 2013. Analysis of polar organic contaminants in surface water of the northern Adriatic Sea by solid-phase extraction followed by ultrahigh-pressure liquid chromatography-QTRAP® MS using a hybrid triple-quadrupole linear ion trap instrument. Anal. Bioanal. Chem 405, 5875–5885.

Ludke, J.L., Hill, E.F., Dieter, M.P., 1975. Cholinesterase (ChE) response and related mortality among birds fed ChE inhibitors. Arch. Environ. Contam. Toxicol. 3 (1), 1–21.

Lv, M., Sun, Q., Hu, A.Y., Hou, L.Y., Li, J.W., Cai, X., Yu, C.P., 2014. Pharmaceuticals and personal care products in a mesoscale subtropical watershed and their application as sewage markers. J. Hazard. Mater. 280, 696–705.

Magner, J., Filipovic, M., Alsberg, T., 2010. Application of a novel solid-phase-extraction sampler and ultra-performance liquid chromatography quadrupole-time-of-flight mass spectrometry for determination of pharmaceutical residues in surface sea water. Chemosphere 80, 1255–1260.

Maranho, L.A., Moreira, L.B., Baena-Nogueras, R.M., Lara-Martín, P.A., DelValls, T.A., Martín-Díaz, M.L., 2015a. A candidate short-term toxicity test using *Ampelisca brevicornis* to assess sublethal responses to pharmaceuticals bound to marine sediments. Arch. Environ. Contam. Toxicol. 68, 237-258.

Maranho, L.A., Andre, C., DelValls, T.A., Gagne, F., Martín-Díaz, M.L., 2015b. Adverse effects of wastewater discharges in reproduction, energy budget, neuroendocrine and inflammation processes observed in marine clams *Ruditapes philippinarum*. Coast. Shelf Sci. 164, 324e334.

Maruya, K.A., Dodder, N.G., Weisberg, S.B., Gregorio, D., Bishop, J.S., Klosterhaus, S., Alvarez, D.A., Furlong, E.T., Bricker, S., Kimbrough, K.L., Lauenstein, G.G., 2014. The Mussel Watch California pilot study on contaminants of emerging concern (CECs): Synthesis and next steps. Mar. Pollut. Bull. 81, 355-363.

Montagner, C.C., Umbuzeiro, G.A., Pasquini, C., Jardim, W.F., 2014. Caffeine as an indicator of estrogenic activity in source water. Environ Sci: Processes & Impacts 16, 1866-1869.

Moore, M.T., Greenway, S.L., Farris, J.L., Guerra, B., 2008. Assessing Caffeine as an Emerging Environmental Concern Using Conventional Approaches. Arch Environ Contam. Toxicol. 54, 31–35.

Munari, M., Matozzo, V., Benetello, G., Riedl, V., Pastore, P., Badocco, D., Marin, M.G., 2020. Exposure to Decreased pH and Caffeine Affects Hemocyte Parameters in the Mussel *Mytilus galloprovincialis*. J. Mar. Sci. Eng. 8, 238.

Munaron, D., Tapie, N., Budzinski, H., Andral, B., Gonzalez, J.L., 2012. Pharmaceuticals, alkylphenols and pesticides in Mediterranean coastal waters: results from a pilot survey using passive samplers. Estuar. Coast. Shelf Sci. 114, 82–92.

Munro, K., Martins, C.P.B., Loewenthal, M., Comber, S., Cowan, D.A., Pereira, L., Barron, L.P., 2019. Evaluation of combined sewer overflow impacts on short-term pharmaceutical and illicit drug occurrence in a heavily urbanised tidal river catchment (London, UK). Sci. Total Environ. 657, 1099-1111.

Murakami, M., Morita, C., Morimoto, T., Takada, H., 2011. Source analysis of perfluorocarboxylates in Tokyo Bay during dry weather and wet weather using sewage markers. Environ. Chem. 8, 355-362.

Mustard, J.A., Dews, L., Brugato, A., Dey, K., Wright, G.A., 2012. Consumption of an acute dose of caffeine reduces acquisition but not memory in the honey bee. Behav. Brain Res. 232, 217-224.

Nikolaou, A., Meric, S., Fatta, D., 2007. Occurrence patterns of pharmaceuticals in water and wastewater environments. Anal Bioanal Chem 387, 1225–1234 (2007).

Nodler, K., Voutsa, D., Licha, T., 2014. Polar organic micropollutants in the coastal environment of different marine systems. Mar. Pollut. Bull. 85, 50–59.

Nodler, K., Tsakiri, M., Aloupi, M., Gatidou, G., Stasinakis, A.S., Licha, T., 2016. Evaluation of polar organic micropollutants as indicators for wastewater-related coastal water quality impairment. Environ. Poll. 211, 282-290.

Ojemaye, C.Y., Petrik, L., 2019. Occurrences, levels and risk assessment studies of emerging pollutants (pharmaceuticals, perfluoroalkyl and endocrine disrupting compounds) in fish samples from Kalk Bay harbour, South Africa. Environ. Poll. 252, 562-572.

Paíga, P., Delerue-Matos, C., 2017. Anthropogenic contamination of Portuguese coastal waters during the bathing season: Assessment using caffeine as a chemical marker. Mar. Pollut. Bull. 120, 355-363.

Palo, A.K., Choudhury, R.C., 2006. Modulation of methotrexate-induced cytogenotoxicity in mouse spermatogonia and its transmission in the male germline by caffeine. Environ Toxicol. Pharmacol. 21, 254-259.

Patel, M., Kumar, R., Kishor, K., Mlsna, T., Pittman, C.U., Mohan, D., 2019. Pharmaceuticals of Emerging Concern in Aquatic Systems: Chemistry, Occurrence, Effects, and Removal Methods. Chem. Rev. 119, 3510-3673.

Peeler, K.A., Opsahl, S.P., Chanton, J.P., 2006. Tracking anthropogenic inputs using caffeine, indicator bacteria, and nutrients in rural freshwater and urban marine systems. Environ. Sci. Technol. 40, 7616–7622.

Pereira, C.D.S., Maranho, L.A., Cortez, F.S., Pusceddu, F.H., Santos, A.R., Ribeiro, D.A., Cesar, A., Luciana, L.L.L., 2016. Occurrence of pharmaceuticals and cocaine in a Brazilian coastal zone. Sci. Total Environ. 548-549, 148–154.

Pires, A., Almeida, A., Calisto, V., Schneider, R.J., Esteves, V.I., Wrona, F.J., Soares, A.M.V.M., Figueira, E., Freitas, R., 2016a. Long-term exposure of polychaetes to caffeine: biochemical alterations induced in *Diopatra neapolitana* and *Arenicola marina*. Environ. Poll. 214, 456-463.

Pires, A., Almeida, A., Calisto, V., Schneider, R.J., Esteves, V.I., Wrona, F.J., Soares, A.M., Figueira, E., Freitas, R., 2016b. *Hediste diversicolor* as bioindicator of pharmaceutical pollution: results from single and combined exposure to carbamazepine and caffeine. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 188, 30-38.

Pomati, F., Orlandi, C., Clerici, M., Luciani, F., Zuccato, E., 2008. Effects and Interactions in an Environmentally Relevant Mixture of Pharmaceuticals. Toxicol. Sci. 102, 129-137.

Quadra, G.R., Paranaíba, J.R., Vilas-Boas, J., Roland, F., Amado, A.M., Barros, N., Dias, R.J.P., Cardoso, S.J., 2020. A global trend of caffeine consumption over time and related-environmental impacts. Environ. Poll. 256, 113343.

Rigueto, C.V.T., Nazari, M.T., De Souza, C.F., Cadore, J.S., Brião, V.B., Piccin, J.S., 2020. Alternative techniques for caffeine removal from wastewater: An overview of opportunities and challenges. J. Water Process Eng. 35, 101231.

Rizzi, C., Seveso, D., Galli, P., Villa, S., 2020. First record of emerging contaminants in sponges of an inhabited island in the Maldives. Mar. Pollut. Bull. 156, 111273.

Rocha, A.C., Camacho, C., Eljarrat, E., Peris, A., Aminot, Y., Readman, J.W., Boti, V., Nannou, C., Marques, A., Nunes, M.L., Almeida, C.M., 2018. Bioaccumulation of persistent and emerging pollutants in wild sea urchin *Paracentrotus lividus*. Environ. Res. 161, 354-363.

Rodríguez-Gil, J.L., Cáceres, N., Dafouz, R., Valcárcel, Y., 2018. Caffeine and paraxanthine in aquatic systems: Global exposure distributions and probabilistic risk assessment. Sci. Total Environ. 612, 1058-1071.

Rogers, I.H., Birtwell, I.K., Kruzynski, G.M., 1986. Canadian Department of fisheries and Oceans - Fisheries Research Branch (Ed.), Organic Extractables in Primary-treated Municipal Wastewater and Uptake in Exposed Juvenile Chinook Salmon a Preliminary Study at Iona Island Sewage

Treatment Plant, Vancouver, B.C. - Canadian Technical Report of Fisheries and Aquatic Sciences No. 1433 (97-6/1433e), Minister of Supply and Services Canada, Vancouver, BC (1986), p. 35.

Romagnoli, P., Balducci, C., Perilli, M., Perreca, E., Cecinato, A., 2016. Particulate PAHs and n-alkanes in the air over Southern and Eastern Mediterranean Sea. Chemosphere. 159, 516-525.

Roveri, V., Guimarães, L.L., Toma, W., Correia, A.T., 2020. Occurrence and ecological risk assessment of pharmaceuticals and cocaine in a beach area of Guarujá, São Paulo State, Brazil, under the influence of urban surface runoff. Environ. Sci. Pollut. Res. 27, 45063-45075.

Rudolph, E., Färbinger, A., König J., 2012. Determination of the caffeine contents of various food items within the Austrian market and validation of a caffeine assessment tool (CAT). Food Addit Contam. Part A Chem Anal Control Expo. Risk Assess. 29, 1849–1860.

Sauvé, S., Aboulfadl, K., Dorner, S., Payment, P., Deschamps, G., 2012. Fecal coliforms, caffeine and carbamazepine in storm water collection systems in a large urban area. Chemosphere 770, 86, 118-123.

Siegener, R., Chen, R.F., 2002. Caffeine in Boston harbor seawater. Mar. Pollut. Bull. 44, 383–387.

Singh, S.P., Azua, A., Chaudhary, A. Khan, S., Willett, K.L., Gardinali, P.R., 2010. Occurrence and distribution of steroids, hormones and selected pharmaceuticals in South Florida coastal environments. Ecotoxicology 19, 338–350.

Spongberg, A.L., Witter, J.D., Acuña, J., Vargas, J., Murillo, M., Umaña, G., Gómez, E., Perez, G., 2011. Reconnaissance of selected PPCP compounds in Costa Rican surface waters. Water Res. 45, 6709-6717.

Stiles, G.L., 1992. Adenosine receptors. J. Biol. Chem. 267, 6451-6454.

Sun, Q., Li, Y., Li, M., Ashfaq, M., Lv, M., Wang, H., Hu, A., Yu, C.-P., 2016. PPCPs in Jiulong River estuary (China): Spatiotemporal distributions, fate, and their use as chemical markers of wastewater. Chemosphere 150, 596-604.

Tian, Z., Peter, K.T., Gipe, A.D., Zhao, H., Hou, F., Wark, D.A., Khangaonkar, T., Kolodziej, E.P., James, C.A., 2020. Suspect and non-target screening for contaminants of emerging concern in an urban estuary. Environ Sci. Technol. 54, 889-901.

Verenitch, S.S., Mazumder, A., 2008. Development of a methodology utilizing gas chromatography ion-trap tandem mass spectrometry for the determination of low levels of caffeine in surface marine and freshwater samples. Anal. Bioanal. Chem. 391, 2635–2646.

Weigel, S., Bester, K., Huhnerfuss, H., 2001. New method for rapid solid-phase extraction of large-volume water samples and its application to non-target screening of North Sea water for organic contaminants by gas chromatography-mass spectrometry. J. Chromatogr. A 912 (1), 151–161.

Weigel, S., Kuhlmann, J., Hühnerfuss, H., 2002. Drugs and personal care products as ubiquitous pollutants: occurrence and distribution of clofibric acid, caffeine and DEET in the North Sea. Sci. Total Environ. 295, 131-141.

Weigel, S., Berger, U., Jensen, E., Kallenborn, R., Thoresen H., Hühnerfuss, H., 2004. Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. Chemosphere. 56(6), 583-92.

Williams, M., Kookana, R.S., Mehta, A., Yadav, S.K., Tailor, B.L., Maheshwari, B., 2019. Emerging contaminants in a river receiving untreated wastewater from an Indian urban centre. Sci. Total Environ. 647, 1256-1265.

Yang, L., Zhou, Y., Shi, B., Meng, J., He, B., Yang, H., Yoon, S.J., Kim, T., Kwon, B.O., Khim, J.S., Wang, T., 2020. Anthropogenic impacts on the contamination of pharmaceuticals and personal care products (PPCPs) in the coastal environments of the Yellow and Bohai seas. Environ. Int. 135, 105306.

Zhou, B., Ma, C., Wang, H., Xia, T., 2018. Biodegradation of caffeine by whole cells of tea-derived fungi *Aspergillus sydowii*, *Aspergillus niger* and optimization for caffeine degradation. BMC Microbiol. 18, 1–10.

Figure1. Papers published per year, considering the occurrence and effects of caffeine on marine and coastal environments.

TABLES

Table 1. Occurrence of caffeine residues on marine and coastal waters (ng/L) and sediments (ng/g dry weight).

Country/Area	Ecosystem	Range (ng/L or ng/g)		Reference
		min	max	
Adriatic Sea	Seawater	82	366.9	Loos et al., 2013
Australia	Seawater	140	11000	French et al., 2015
Australia	Seawater	20	210	French et al., 2015
Brasil	Seawater	-	147	Ferreira et al., 2005
Brasil	Sediment	0.31	23.4	Beretta et al. 2014
Brasil	Seawater	84.4	648.9	Pereira et al., 2016
Brasil	Seawater	350	1300	Roveri et al., 2020
Brasil	Sediment	0.28	23.4	Beretta et al. 2014
Canada	Seawater	130	1400	Comeau et al. 2008
Canada	Seawater	98	382	Ghoshdastidar et al., 2015
Canada	Seawater	-	5	Keil et al., 2011
Canada	Seawater	4.5	149	Verenitch and Mazumder, 2008
China	Seawater	14.8	1930	Lv et al., 2014
China	Seawater	-	421	Yang et al., 2020
China	Seawater	8.07	3060	Sun et al., 2016
Costa Rica	Seawater	38	1207	Spongberg et al., 2011
Costa Rica	Seawater	-	40	Spongberg et al., 2011
Denmark	Seawater	6.3	9.7	Weigel et al., 2002
France	Seawater	8	32	Munaron et al., 2012
Germany	Seawater	-	677	Nodler et al., 2014
Germany	Seawater	-	2	Weigel et al., 2001
Germany	Seawater	4.9	16.1	Weigel et al., 2002
Greece	Seawater	5.2	78.2	Alygizakis et al., 2016
Greece	Seawater	4.5	522	Nodler et al., 2016
Greece-Turkey	Seawater	-	3068	Nodler et al., 2014
Italy	Seawater	82	366.9	Loos et al., 2013
Italy	Seawater	-	2	Giandomenico et al., 2011
Italy	Seawater	-	1110	Nodler et al., 2014
Italy	Seawater	-	58	Nodler et al., 2014
Japan	Seawater	100	8230	Murakami et al., 2011
Malaysia	Seawater	0.12	0.33	Ismail et al., 2019
Mediterranean Sea	Seawater	0.01	0.17	Romagnoli et al., 2016
Netherlands	Seawater	-	9	Weigel et al., 2002
North Sea	Seawater	2	6.6	Weigel et al., 2002
Norway	Seawater	5.8	6.1	Weigel et al., 2002
Norway	Seawater	7	87	Weigel et al., 2004

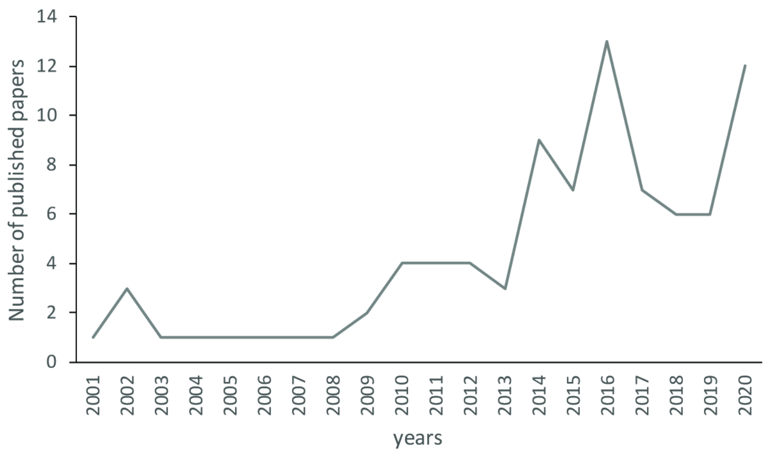
Portugal	Seawater	600	804	Gonzalez-Rey et al., 2015
Portugal	Seawater	18	264	Paíga and Delerue-Matos, 2017
Red Sea	Seawater	420.9	7708	Ali et al., 2017
Singapore	Seawater	-	847	Goh et al., 2017
Singapore	Seawater	59	655	Bayen et al., 2013
Singapore	Seawater	5	1389	Bayen et al., 2016
Spain	Seawater	4.3	96.6	Biel-Maeso et al., 2018
Spain	Seawater	6.1	327.3	Biel-Maeso et al., 2018
Spain	Sediment	1.90	12.20	Maranho et al., 2015a
Spain	Seawater	4	5	Buerge et al., 2003
Spain	Sediment	3.5	12.2	Maranho et al., 2015a
Spain	Seawater	-	37	Nodler et al., 2014
Sweeden	Seawater	30	74.8	Magner et al., 2010
Taiwan	Seawater	1.24	16.92	Jiang et al., 2014
Taiwan	Seawater	130	718	Fang et al., 2019
UK	Seawater	3	15	Weigel et al., 2002
USA	Seawater	-	32	Alvarez et al., 2014
USA	Seawater	9	45	del Rey et al., 2012
USA	Seawater	-	22	Tian et al., 2020
USA	Seawater	11.9	5860	Benotti and Brownawell, 2007
USA	Seawater	25	185	Cantwell et al., 2017
USA	Seawater	15	61	Cantwell et al., 2017
USA	Seawater	52	81	Cole et al., 2016
USA	Seawater	21.8	41.2	Gardinali and Zhao, 2002
USA	Seawater	7.47	11.9	Gardinali and Zhao, 2002
USA	Seawater	2	28	Knee et al., 2010
USA	Seawater	-	96	Nodler et al., 2014
USA	Seawater	-	85	Nodler et al., 2014
USA	Seawater	5	165.8	Peeler et al., 2006
USA	Seawater	7.7	44.9	Peeler et al., 2006
USA	Seawater	4.4	1600	Siegener and Chen, 2002
USA	Seawater	180	1600	Siegener and Chen, 2002
USA	Seawater	5.7	52	Singh et al., 2010
Western Mediterranean	Seawater	0.3	0.11	Brumovský et al., 2017

Table 2. Occurrence of caffeine residues in marine and coastal species (ng/g dry weight).

Country/Area	Group	Species	Range (ng/g) min	Range (ng/g) max	Reference
Maldives	Corals	*Coral reefs*	15.8	37.1	Rizzi et al., 2020
Saudi Red Sea	Algae	*Ulva lactuca*	3.8	8.3	Ali et al., 2018
	Algae	*Turbinaria conoides*	36.1	41.2	
	Algae	*Hydroclathrus clathratus*	2.2	6.3	
	Fish	*Gerres oyen*	-	73.6	
	Fish	*Chanos chanos*	2.5	6.2	
	Fish	*Lethrinus nebulosus*	-	7.9	
South Africa	Fish	*Pterogymnus laniarius*	-	2.03	Ojemaye and Petrik, 2019
	Fish	*Sarda orientalis*	50.49	64.78	
	Fish	*Pachymetopon blochii*	1.76	1.77	
Singapore	Bivalves	*Perna viridis*	0.4	4.4	Bayen et al., 2016
USA	Bivalves	*Mytilus spp.*	19	68	Maruya et al., 2014

Table 3. Effects of caffeine on coastal and marine *taxa*, under laboratorial conditions. The experimental conditions, including the exposure period, minimum and maximum tested concentrations, tested media and observed significant impacts are indicated.

Group	Species	Exposure period	Concentrations (min-max)		Medium	Endpoints	Reference
Algae	*Isochrysis galbana*	72–96 h	0.05	500000 µg/L	Seawater	Growth inhibition	Aguirre-Martínez et al., 2015
Bivalvia	*Ruditapes philippinarum*	14 days	0.1	50 µg/L	Seawater	Oxidative stress, neurotoxicity	Aguirre-Martínez et al., 2016
	Ruditapes philippinarum	28 days	0.5	18 µg/L	Seawater	Oxidative stress	Cruz et al., 2016
	Mytilus galloprovincialis	21 days	0.05	0.5 µg/L	Seawater	Haemocyte parameters	Munari et al., 2020
	Mytilus californianus	30 days	0.05	0.5 µg/L	Seawater	Expression of Hsp70	del Rey et al., 2011
	Mytilus galloprovincialis	7 days	0.005	0.5 µg/L	Seawater	Oxidative stress	Capolupo et al., 2016
Polychaeta	*Diopatra neapolitana*	28 days	0.5	18 µg/L	Seawater	Mortality, Regeneration Capacity, oxidative stress	Pires et al., 2016a
	Arenicola marina	28 days	0.5	18 µg/L	Seawater	Mortality, oxidative stress	Pires et al., 2016a
	Hediste diversicolor	29 days	0.5	18 µg/L	Seawater	Mortality, Lipid Peroxidation , Oxidative stress	Pires et al., 2016b
Echinoidea	*Paracentrotus lividus*	48h	0.01	15 µg/L	Seawater	Reproduction	Aguirre-Martínez et al., 2015
Malacostraca	*Ampelisca brevicornis*	10 days	0.00015	1.5 µg/g	Sediment	DNA alterations, Oxidative stress	Maranho et al., 2015a
	Palaemonetes pugio	5 days	-	20000 µg/L	Seawater	Reproduction/development	Garcia et al., 2014
	Carcinus maenas	28 days	0.1	50 µg/L	Seawater	Lysosomal membrane stability, Lipid peroxidation, oxidative stress	Aguirre-Martínez et al., 2013


Number of published papers
14
12
10
8
6
4
2
0
2001
2002
2003
2004
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years

- Most of the studies on caffeine concentration in seawater are from the USA;
- Caffeine was detected in marine and coastal areas of 13 European countries;
- In Europe the highest caffeine concentration was found in the Aegean Sea (3068 ng/L);
- Caffeine was found in tissues of coastal *taxa* from contaminated environments

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: