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# Pharmaceuticals and endocrine disruptors in raw and cooked seafood from European market: Concentrations and human exposure levels

Diana Álvarez-Muñoz[a,b], Sara Rodríguez-Mozaz[a,*], Silke Jacobs[c], Albert Serra-Compte[a], Nuria Cáceres[a], Isabelle Sioen[d], Wim Verbeke[c], Vera Barbosa[e], Federico Ferrari[f], Margarita Fernández-Tejedor[g], Sara Cunha[h], Kit Granby[i], Johan Robbens[j], Michiel Kotterman[k], Antonio Marques[e], Damià Barceló[a,b]

[a] *Water Quality Area, Catalan Institute for Water Research (ICRA), Girona, Spain*
[b] *Water and Soil Quality Research Group, Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Spain*
[c] *Department of Agricultural Economics, Ghent University, Ghent, Belgium*
[d] *Department of Food Technology, Safety and Health, Ghent University, Ghent, Belgium*
[e] *Division of Aquaculture and Upgrading, Portuguese Institute for the Sea and Atmosphere (IPMA), Lisbon, Portugal*
[f] *Aeiforia Srl, Gariga di Podenzano (PC), Italy*
[g] *Institute of Agriculture and Food Research and Technology (IRTA), Tarragona, Spain*
[h] *LAQV-REQUIMTE, Faculty of Pharmacy, University of Porto, Porto, Portugal*
[i] *National Food Institute, Technical University of Denmark (DTU Food), Lyngby, Denmark*
[j] *Institute for Agricultural and Fisheries Research (ILVO), Animal Sciences Unit – Fisheries, Oostende, Belgium*
[k] *Institute for Marine Resources and Ecosystem Studies (IMARES), Wageningen University and Research Centre, Ijmuiden, Netherlands*

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## ABSTRACT

Pharmaceuticals (PhACs) and endocrine disrupting compounds (EDCs) are chemicals of emerging concern that can accumulate in seafood sold in markets. These compounds may represent a risk to consumers through effects on the human reproductive system, metabolic disorders, pathogenesis of breast cancer or development of microbial resistance. Measuring their levels in highly consumed seafood is important to assess the potential risks to human health. Besides, the effect of cooking on contaminant levels is relevant to investigate. Therefore, the objectives of this research were to study the presence and levels of PhACs and EDCs in commercially available seafood in the European Union market, to investigate the effect of cooking on contaminant levels, and to evaluate the dietary exposure of humans to these compounds through seafood consumption. A sampling survey of seafood from 11 European countries was undertaken. Twelve highly consumed seafood types were analysed raw and cooked with 3 analytical methods (65 samples, 195 analysis). PhACs were mostly not detectable or below quantification limits in seafood whereas EDCs were a recurrent group of contaminants quantified in the majority of the samples. Besides, cooking by steaming significantly increased their levels in seafood from 2 to 46-fold increase. Based on occurrence and levels, bisphenol A, methylparaben and triclosan were selected for performing a human exposure assessment and health risk characterisation through seafood consumption. The results indicate that the Spanish population has the highest exposure to the selected EDCs through seafood consumption, although the exposure via seafood remained below the current toxicological reference values.

## 1. Introduction

Pharmaceuticals (PhACs) and endocrine disrupting compounds (EDCs) have large volumes of production and can find their way to the environment through different paths, being considered as Contaminants of Emerging Concern (CEC) (Workgroup, 2008). Pharmaceuticals are drugs used for medicinal purposes and they are classified according to their therapeutic family, such as antibiotics, psychiatric drugs, analgesics, anti-inflammatories, tranquilizers, hormones, β-blockers, or diuretics, for example (Álvarez-Muñoz et al., 2016). EDCs are compounds with the ability to interfere with the endocrine system of organisms causing potential alterations in their normal development

* Corresponding author at: Catalan Institute for Water Research (ICRA), Parc Científic i Tecnològic de la Universitat de Girona, C/Emili Grahit, 101 Edifici H2O, E-17003 Girona, Spain.
*E-mail address:* srodriguez@icra.cat (S. Rodríguez-Mozaz).

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(Programme, 2013). A wide range of chemicals can cause endocrine disruption, and this group encompasses a heterogeneous class of substances, such as plasticizers, pesticides, fungicides, surfactants, flame retardants, and hormones. For instance, triclosan is a broad spectrum anti-bacterial agent usually known as personal care product but there is strong evidence for its disrupting effects on the endocrine system, especially on reproductive hormones (Wang and Tian, 2015). The population is directly exposed to both PhACs and EDCs through the use of essential products in the daily life, and indirectly due to their incomplete removal from waste water treatment plants, where these compounds can reach the aquatic environment (Hofman-Caris et al., 2017; Koumaki et al., 2018). Coastal areas are considered the ultimate sink for sewage and monitoring studies have been actively undertaken in the last years showing the wide occurrence of PhACs and EDCs in the marine environment (Álvarez-Muñoz et al., 2016; Rodríguez-Mozaz et al., 2017). These compounds may potentially accumulate in resident organisms that later on end up on the food chain, such as seafood (Vandermeersch et al., 2015). Seafood is consumed all over the world and in many countries it is a prime source of high-quality protein. Research has shown that eating regularly fish and shellfish is beneficial to human health in many ways (Lund, 2013). However, seafood can also be a source of harmful environmental contaminants, like PhACs and EDCs, with the potential to negatively impact human health (Vandermeersch et al., 2015). PhACs in seafood may potentially represent a risk for consumers either through direct effects of allergy and toxicity, or through the development of potential anti-microbial resistance (Cabello, 2006). EDCs are of great concern since they may have effects on the human reproductive system like menstrual cycle irregularities, impaired fertility, endometriosis, polycystic ovarian syndrome, spontaneous abortion, and alteration of female hormone concentrations (Giulivo et al., 2016). They have also been related to metabolic disorders like obesity, insulin resistance, type-2 diabetes, hepatic injuries, dyslipidaemia and cardiovascular diseases (Desai et al., 2015). There are also studies that point out the potential role of EDCs in the pathogenesis of breast cancer due to their estrogenic properties (Barr et al., 2012; Chen and Chien, 2014; Wetherill et al., 2007).

Measuring the levels of these substances in seafood, especially in highly consumed species, is the first step to assess their potential risk for human health through fish and shellfish consumption. A recent publication has reviewed the levels of CEC in seafood and their toxicological values established by the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (Vandermeersch et al., 2015). The majority of studies on PhACs occurrence and levels in seafood have focused on marine mussels as it is widely use as sentinel organism for monitoring of contamination in environmental waters (Alvarez-Muñoz et al., 2015a; Dodder et al., 2014; Klosterhaus et al., 2013; Li et al., 2012; Martinez Bueno et al., 2013, 2014; McEneff et al., 2014; Wille et al., 2011). PhACs presence was also investigated in marine macroalgae and fish (in addition to molluscs) from coastal areas in Europe, and a list of priority candidates' compounds for future studies was proposed (Álvarez-Muñoz et al., 2015b). The concentrations of PhACs reported in those studies in environmental fish and shellfish samples were usually in the low ng/g (dry weight (dw)) levels (Alvarez-Muñoz et al., 2015a; Dodder et al., 2014; Martinez Bueno et al., 2014; Wille et al., 2011), although sometimes reaching a few hundreds of ng/g (dw) (Li et al., 2012; Wille et al., 2011). The study of PhACs presence in commercially available seafood has been mainly focused on antibiotics because of their widespread use in aquaculture (Azzouz et al., 2011; Berrada et al., 2008; Chafer-Pericas et al., 2011, 2010b; Chafer-Pericas et al., 2010c, 2010a; Fernandez-Torres et al., 2011; Serra-Compte et al., 2017). Only a couple of recent publications have investigated the presence of other types of PhACs in seafood for human consumption (Mottaleb et al., 2016) (Kim et al., 2017), and the concentrations found were lower than the ones reported in environmental fish. To the best of our knowledge, there is not any work performed yet that aimed to study the presence and levels of relevant PhACs in commercially available seafood, on a large geographical scale, for assessing their potential risk to human health through the diet. The papers published so far have been mainly focused on human health risk assessment of PhACs in drinking water (Leung et al., 2013; Lin et al., 2016; Simazaki et al., 2015), and only one recent work has undertaken a risk assessment of PhACs in field grown vegetables irrigated with treated municipal waste water (Riemenschneider et al., 2016).

The number of papers published regarding the presence and levels of EDCs in species of commercial interest is considerably higher (Vandermeersch et al., 2015). The concentrations reported in marine organisms from local markets depend on the type of contaminant and the origin of the samples. Usually they range from < 100 ng/g (dw) for contaminants such as parabens (Liao et al., 2013a; 2013b; Liao and Kannan, 2013), bisphenol A (Cunha et al., 2012; Podlipna and Cichna-Markl, 2007), *per*- and poly- fluorinated alkyl substances (Gulkowska et al., 2006; Llorca et al., 2009), or hormones (Azzouz et al., 2011; Pojana et al., 2007), up to 1000 ng/g (dw) for alkylphenols (Ferrara et al., 2008). Dietary exposure to some relevant EDCs has been previously investigated. Bisphenol A (BPA) is the contaminant that has attracted most attention due to its wide use in food contact materials (Liao and Kannan, 2013) (He et al., 2015; Sakhi et al., 2014; Chen et al., 2016). Its estimated dietary exposure was lower than its maximum acceptable dose established by the U.S. Environmental Protection Agency (USEPA) (50 μg/kg-bw/day) (Agency, 1993) and the EFSA (4 μg/kg-bw/day) (EFSA, 2015). The occurrence and dietary exposure to parabens were also assessed (Liao et al., 2013b; Liao et al., 2013a) and the estimated daily intake was below the acceptable daily intake recommended by JECFA (1974). In order to find out if the consumption of seafood is an important source of EDCs that significantly contributes to their total intake, studies on their presence and human health risk assessment in species of high commercial interest are required. Yet, so far only a limited number of papers have been focused on this (Ramaswamy et al., 2011; Wei et al., 2011; Lee et al., 2015). They performed the respective assessment of human dietary exposure and no exceedance of the toxicological reference value was found. A recent publication by Cano-Sancho et al. (2015) built an integrated risk index for seafood contaminants (IRISC), where EDCs held the fourth position, contributing to this risk index, after heavy metals, polychlorinated biphenyls and polychlorinated dibenzo-*p*-dioxins and dibenzofurans.

Although in most cases fish and shellfish are consumed after cooking, the majority of studies reporting the presence and daily intake of EDCs through seafood consumption use contaminant concentration data obtained from uncooked/raw products. Few works considered processed seafood, mainly canned tuna due to the migration of BPA from can coating (Cao and Popovic, 2015; Cunha et al., 2012; Fattore et al., 2015), but in general the effect of cooking on levels of EDCs and human PhACs has been rarely investigated (Alves et al., 2017; Fierens et al., 2012; McEneff et al., 2013). Studying the effects of cooking on contaminant levels in seafood becomes a relevant issue since their concentrations may change, thus affecting humans' dietary exposure. Indeed, the levels of the chemical can decrease (e.g. phthalates and perfluorinated compounds (PFOA) (Del Gobbo et al., 2008; Fierens et al., 2012)), increase (e.g. pharmaceuticals, metals, hexachlorobenzene (HCB) and polycyclic aromatic hydrocarbon (PAHs) (Kalogeropoulos et al., 2012; McEneff et al., 2013; Perello et al., 2009)), or remain unchanged (e.g. hexabromocyclododecane (α-HBCD), perfluorooctanoic acid (PFOs), perfluorooctanesulfonic acid (PFUnA), venlafaxine and methylparaben (Alves et al., 2017)).

In the present work 65 seafood samples, representing 12 highly consumed fish and shellfish species, from 11 European countries were analysed for eight PhACs (diclofenac, diazepam, sotalol, carbamazepine, citalopram, venlafaxine, azithromycin and sulfamethoxazole) and four EDCs (triclosan, BPA, methylparaben and tris(2-butoxyethyl) phosphate (TBEP)) (195 analysis performed in total). These 12 target compounds were selected as priority contaminants based on the