SIMULTANEOUS DETERMINATION OF ENDOCRINE DISRUPTING COMPOUNDS IN ESTUARINE WATER, SEDIMENT AND MARICULTURE FISHES THROUGH EXTRACTION COUPLED WITH LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY AND HUMAN HEALTH RISK MANAGEMENT

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the degree of Master of Science

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SIMULTANEOUS DETERMINATION OF ENDOCRINE DISRUPTING COMPOUNDS IN ESTUARINE WATER, SEDIMENT AND MARICULTURE FISHES THROUGH EXTRACTION COUPLED WITH LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY AND HUMAN HEALTH RISK MANAGEMENT

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February 2020

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Endocrine disrupting compounds (EDCs) are emerging pollutants causing global concern because they can disrupt the endocrine system in aquatic organisms, mammals, and humans. Because EDCs have been introduced into aquatic ecosystems, the exposure of humans and animals that depend on aquatic foods, especially fishes, should be seriously considered. These pollutants have been released into the environment through many sources, e.g., wastewater treatment plants, terrestrial run-off (industrial activities, pharmaceuticals, and household waste), and precipitation. The use of hormone, pharmaceuticals, pesticides, and fertilizers for maintaining and increasing fish health and growth also contributes to EDC pollution in the water body. Pulau Kukup, Johor, Malaysia is one of the biggest mariculture areas that is actively involved in marine fish export to other countries. As aquaculture production through mariculture activities in Malaysia support food production, the concentration and distribution of EDCs in aquatic ecosystem need to be monitored to secure the food safety. The aim of this study is to optimize a suitable and reliable method to be applied on environmental samples (estuarine water and sediment) and biota sample (mariculture fish) and for the determination of EDCs pollutant in Pulau Kukup, Johor. Besides, this study also presented the human health risk assessment associated with the consumption of fish from Pulau Kukup, Johor, Malaysia. The method displays a high extraction recovery for estuarine water sample, sediment, and mariculture fish in current study, ranging from 92.02% to 132.32 %, 50.39 to 129.10%, and 52.94- 125.95% respectively. The highest concentration EDCs detected in estuarine water sample is diclofenac (< 0.47-79.72 ng/L) followed by E2 (< 5.28-31.11 ng/L) and EE2 (< 0.30-7.69 ng/L). In sediment, bisphenol A (0.072-0.389 ng/g dry weight) was observed as the highest concentration, followed by diethylstilbestrol (< 0.208-0.331 ng/g dry weight) and propranolol (< 0.250-0.275 ng/g dry weight). Meanwhile in fish, the highest concentration of EDCs were detected in muscle, liver, and reproductive organ is dexamethasone (15.84 ng/g, dried muscle), dexamethasone (43.56 ng/g), and E2 (44.85 ng/g) respectively. Based on human health risk calculation in this study, five targeted EDCs (progesterone, bisphenol A, primidone, sulfamethoxazole, and diclofenac) shown no potential health risk (HQ < 1) with the consumption of fish from this mariculture site. This current study can be a baseline assessment for EDCs pollution profile and distribution in the coastal ecosystem from mariculture site throughout the world especially in Malaysia. The data obtained should be relevance to decision-making legislation and policy ratification for food safety to improve the quality of protein-based food and reduce environmental pollution. Owing to the significant concentration of targeted EDCs detected in estuarine water sample, sediment, and mariculture fish, the need to further monitoring in future are required. Although the concentration of targeted compounds obtained are low but their effects may appear in the long term period and this situation alarms not only the environment health but also cause the potential risk to human.

Keywords: Endocrine disrupting compounds, estuarine water sample, sediment, mariculture fish, liquid chromatography mass spectrometer.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENENTUAN SERENTAK SEBATIAN PENGENDALA ENDOKRIN (SPE) PELBAGAI KELAS DALAM AIR MUARA, SEDIMEN, IKAN MARIKULTUR DENGAN MENGGUNAKAN KAEDAH PENGEKSTRAKAN BERSAMA SPEKTROMETER JISIM KROMATOGRAFI CECAIR (SJKC) DAN PENGURUSAN RISIKO KESIHATAN MANUSIA

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Sebatian Pengendala Endokrin (SPE) adalah bahan pencemar yang menyebabkan kebimbangan dunia kerana boleh mengganggu sistem endokrin dalam hidupan akuatik, mamalia, dan manusia.Oleh sebab sebatian SPE telah tersebar dalam ekosistem akuatik, pendedahan manusia dan haiwan lain terhadap makanan laut terutamanya ikan harus diberi pertimbangan yang serius. Bahan pencemar ini telah dibebaskan ke alam sekitar melalui pelbagai sumber, contohnya seperti loji rawatan air kumbahan, sisa daratan (aktiviti perindustrian, sisa ubat-ubatan, dan sisa isi rumah), dan hujan. Penggunaan hormone, ubat-ubatan, racun perosak, dan baja untuk menjaga dan meningkatkan tahap kesihatan dan tumbesaran ikan turut menyumbang kepada pencemaran SPE di dalam ekosistem akuatik. Pulau Kukup, Johor, Malaysia merupakan salah satu kawasan marikultur terbesar yang terlibat aktif dalam mengeksport ikan laut ke negara-negara lain. Sebagai pengeluar makanan akuakultur melalui aktiviti marikultur di Malaysia, kepekatan dan pengagihan SPE dalam ekosistem akuatik perlu dipantau untuk menjamin keselamatan makanan. Tujuan kajian ini adalah untuk mengoptimumkan kaedah yang sesuai dan boleh dipercayai untuk diguna pakai untuk mengekstrak sampel alam sekitar (air muara dan sedimen) dan sampel biota (ikan marikultur), dan dapat memberi input tentang pencemaran SPE di Pulau Kukup, Johor. Selain itu, kajian ini juga membentangkan penilaian risiko kesihatan manusia yang berkaitan dengan pemakanan ikan dari Pulau Kukup, Johor, Malaysia. Kaedah ini memaparkan pemulihan ekstraksi tinggi untuk sampel air muara, sedimen, dan ikan marikultur, dari linkungan 92.02% hingga 132.32%, 50.39 hingga 129.10%, dan 52.94-125.95% bagi sampel masing-masing. Kadar kepekatan SPE yang paling tinggi telah dikesan di dalam air muara adalah diclofenak (<0.47-79.72 ng / L) diikuti oleh E2 (< 5.28-31.11 ng/L) and EE2 (< 0.30-7.69 ng/L). Dalam sedimen, bisphenol A (0.072-0.389

ng / g berat kering) diperhatikan sebagai kepekatan tertinggi, diikuti oleh diethylstilbestrol (<0.208-0.331 ng / g berat kering) dan propranolol (<0.250-0.275 ng / g berat kering). Sementara itu, kepekatan tertinggi EDC yang dikesan dalam isi ikan, hati ikan, dan organ pembiakan ikan adalah dexamethasone (15.84 ng / g, otot kering), dexamethasone (43.56 ng / g) dan E2 (44.85 ng / g) masing- masing. Berdasarkan pengiraan risiko kesihatan manusia dalam kajian ini, lima jenis SPE (progesteron, bisfenol A, primidon, sulfametosazol, dan diklofenak) tidak menunjukkan risiko kesihatan yang berpotensi (HQ <1) jika dikaitkan dengan pengambilan ikan dari lokasi marikultur ini. Kajian semasa ini boleh menjadi penilaian asas untuk memahami profil pencemaran SPE dan penyebaran pencemaran ini dalam ekosistem pantai di tapak marikultur di seluruh dunia terutama di Malaysia. Data yang diperoleh harus relevan untuk merangka dan mengubal dasar bagi keselamatan makanan untuk meningkatkan kualiti makanan berasaskan protein dan mengurangkan pencemaran alam sekitar. Memandangkan kepekatan SPE yang nyata telah dikesan dalam sampel air muara, sedimen, dan ikan marikultur, pemantauan lanjut pada masa akan datang perlu dilakukan. Walaupun kepekatan sebatian pencemaran yang didapati rendah, tetapi kesannya mungkin muncul dalam tempoh jangka panjang dan keadaan ini tidak hanya menggangu kesihatan persekitaran tetapi juga menyebabkan potensi risiko kepada manusia.

Kata Kunci: Sebatian pemusnah endokrin, air muara, sedimen, ikan marikultur, spektrometer jisim kromatografi cecair.

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LIST OF ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ADI	acceptable daily intake
AP	alkylphenolic
APEOs	alkylphenol ethoxylates
CE	collision energy
dSPE	dispersive solid phase extraction
DLLME	dispersive liquid-liquid microextraction
DO	dissolved oxygen
EDCs	endocrine disrupting compounds
EDI	estimated daily intake
EDTA	ethylenediamine-tetraacetate dehydrate
EP	entrance potential
FAO	Food and Agriculture Organization
FUSLE	focused ultrasound solid-liquid extraction
GH	growth hormone
GnRH	gonadotropin-releasing hormone
HI	health risk
HPA	hypothalamic–pituitary–adrenal
HPLC	high-performance liquid chromatograhy
HS-SPME	hollow-fiber liquid phase microextraction
LC-MS/MS	liquid chromatography mass spectrometry-mass spectrometry
LIT-MS	linear ion trap
MAE	microwave-assisted extraction

MDL	method detection limit
MQL	method quantification limit
MRM	multiple reaction monitoring
MS	mass-spectrometry
NABC	Needs, Approaches, Benefits, and Challenges
OPP	organophosphorus pesticides
PCA	principle component analysis
PCBs	polychlorinated biphenyls
PTFE	polytetrafluoroethylene
PhACs	Pharmaceutical Active Compounds
PLE	pressurized liquid extraction
POS	polycystic ovarian syndrome
QA	quality assurance
QC	quality control
QUeChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe
rsd	relative standard deviation
Rt	retention time
SPE	solid phase extraction
STP	sewage treatment plants
TDI	tolerable daily intake
TH	thyroid hormone
THQ	target hazard quotient
TOC	total organic carbon
TOF-MS	time-of-flight

TRH	thyrotropin-releasing hormone
TSH	thyroid stimulating hormone
UN	United Nations
UAE	ultrasound-assisted extraction
UHPLC	ultra-high-performance liquid chromatography
USEPA	United States Environmental Protection Agency
WWTPs	waste water treatment plants
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of study

The occurrence of endocrine disrupting chemicals (EDCs) in the environment has received broad interest over the past decades due to the hazardous characteristic. Over the past 10 years, the study of EDCs has been progress very fast but unfortunately the full range of early work is not presented. These pollutants are present in the environment and used in daily life as food and consumer product and are grouped to natural and artificial hormone, drugs and pharmaceuticals, industrial and household chemicals, pesticide, alkylphenol, and plasticizer (Olujimi et al., 2010; Kabir et al., 2015; Grześkowiak et al., 2016). EDCs generally are defined as chemicals that may interfere with the function of the endocrine system in living things (Barreiros et al., 2016). EDCs can disrupt various body functions with different pathways and mechanisms. EDCs have the ability to mimic and block the endocrine system in humans, have the potential to elicit negative impacts on the hormonal systems of organisms, and cause severe effect such as cancer, abnormal reproductive growth, and metabolic disorders (diabetes, obesity, and endometriosis), leading to a variety of health problems (Mills & Chichester, 2005; Campbell et al., 2006; Deblonde et al., 2011; Bayen et al., 2013; Aris et al., 2014; Esteban et al., 2014b; Kabir et al., 2015; Legler et al., 2015; Giulivo et al., 2016; Ismail et al., 2018).

EDCs can be grouped into natural or synthetic compounds and were produced and introduced to water bodies through waste water treatment plant (WWTP), industrial waste, household waste, agriculture, aquaculture, pharmaceutical waste, urban activities, and indirect sources such as storm-water runoff (Brion et al., 2004; Falconer et al., 2006; Wang et al., 2013; Esteban et al., 2014a; Camilleri and Vulliet, 2015; Salgueiro-González et al., 2015; Barreiros et al., 2016; Chen and Chou, 2016; Omar et al., 2016; Wee et al., 2016; Tan et al., 2018) (Figure 1.1). Then, these pollutants will be absorbed, accumulated, and biomagnified in air, water, sediment, and biota, respectively (Kabir et al., 2015). EDCs also can transport through the food chain via benthic algae and invertebrates (Omar et al., 2019), which may be consumed by fish or birds. Most of the EDCs waste were directly discharged into the aquatic ecosystem and the process of bioaccumulation and biomagnification were taken place here. EDCs which accumulate in water bodies can be transferred into biota matrixes (fish, clam and plankton). Therefore, this process creates potential routes or pathways for EDC exposure to inland and aquatic organisms. Humans can be exposed toward endocrine chemicals when fish and shellfish are consumed. Therefore, it is important to monitor the environmental concentration of EDCs, including in surface water, sediments, aquatic plants and animals, since human are potentially exposed to EDCs via several pathway (Ismail et al., 2017). In agriculture and aquaculture, these pollutants now are strictly banned in feed production and growth antibiotics usage (Wu et al., 2016). Aquaculture and mariculture practices play an important part in bioaccumulation and biomagnification of EDCs in the biota matrixes (fish and shrimp culture). The use of fertilizer and antibiotiocs for fish growth and reproduction also can contributed in EDCs pollution. The rate of bioaccumulation is higher in the fishes and highest consumers of the food web since most of the EDCs are lipophilic and concentrated in the fat of the ingesting organisms (Warring and Harris, 2005). The present of these pollutants in the aquatic ecosystem (aquaculture and mariculture ecosystem), can cause the production of fish decrease. EDCs can disturb and penetrated into endocrine system in human and also other organisms. Thus, some effects can be seen in fish, mammals, and also human when expose to the EDCs. In fish, for example can cause irregular vitellogenin induction, disturb sex determination, decrease growth rates, delayed reproduction, and altered fish behaviors (Melvin, 2017; Gilannejad et al., 2016; Aris et al., 2014; Segner et al., 2013). Meanwhile in human, EDCs can alter the reproductive system, obesity and diabetes, induce breast cancer cells, disrupt thyroid function, and affect the nervous system (Ismail et al., 2017; Wee and Aris, 2017).

Fish are a primary source of protein for humans, and aquaculture is one of the fastest-growing activities globally. The decline in global fish populations has been exacerbated by increase in the pollution released into the environment. Currently, a global concern is the occurrence of EDCs in the aquatic ecosystem. Asia accounts for 88% of global aquaculture production and is by far the most intense growth in aquaculture (Fiedler et al. 2016). In the 11^{th} Malaysia Plan (2016–2020), aquaculture had become a very crucial activity where it was appointed as the next (third) engine of nation growth (Zainol et al., 2016). Pulau Kukup, Johor, Malaysia is among the largest mariculture sites and involved in active mariculture activity, industrial and commercial activities (Ismail et al., 2018). Fish and other marine products here are actively export to the neighbor countries like Indonesia and Singapore. Near the mariculture cage, there is a national park (Pulau Kukup National Park) protected by the state of Johor. Thus, this current study was performed to examine the level of pollution of multi-class EDCs in this active mariculture cages. About, 20 multi-residues of EDCs consist of pesticides (quinalphos, diazinon, and chlorpyrifos), pharmaceuticals and medical drugs (caffeine, chloramphenicol, amoxicillin, propranolol, atorvastatin, diethylstilbestrol, nitrofurazone, dexamethasone, primidone, sulfamethoxazole, and diclofenac), steroid hormone (testosterone, progesterone, 17β-estradiol, estrone, and 17α-ethynylestradiol), and phenolic compound (bisphenol A) were examined in the seawater, sediment, and mariculture fish using analytical procedure. Due to the importance of coastal ecosystem to the human and mainly to aquatic life, some monitoring activities need to be done regularly to provide a monitoring data on the occurrence and distribution profile of these emerging pollutants mainly EDCs in the mariculture area. The data obtained should be of relevance to decision-making legislation and policy ratification for food safety to improve the quality of protein-based food and reduce environmental pollution.

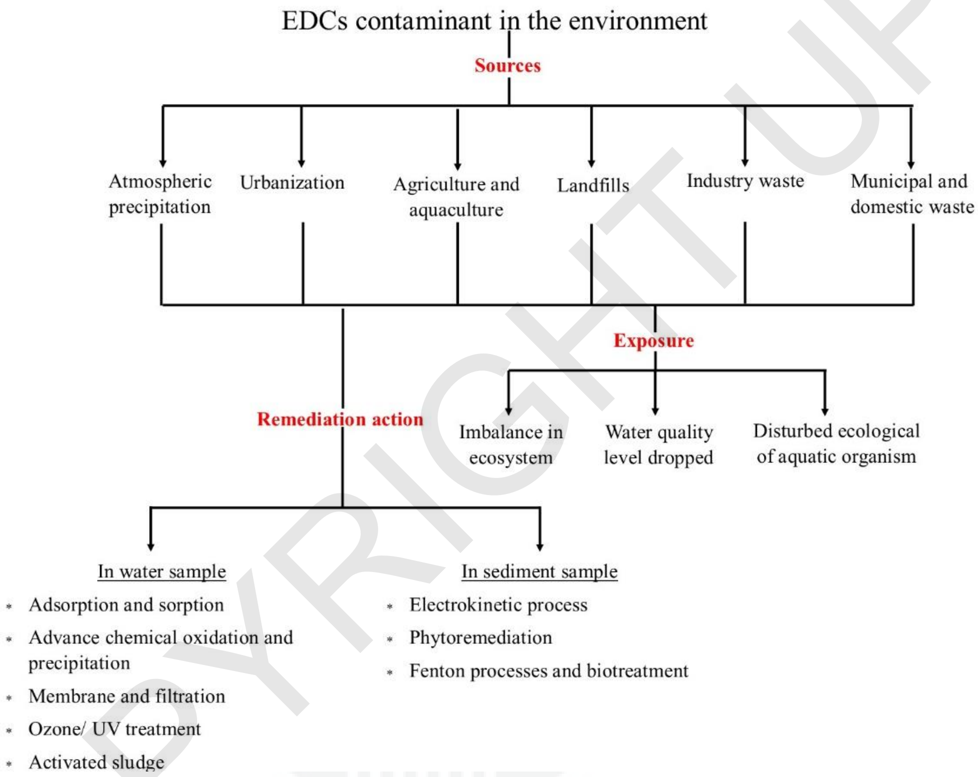

Figure 1.1: Conceptual diagram of occurrence and remediation action of EDCs in the environment.

1.2 Problem statement

EDCs have been identified as an emerging pollutant that arise the awareness around the researchers because of their hazardous and toxicant properties. EDCs have the ability to disrupt and cause the malfunction of endocrine disrupting system in human, terrestrial animals, aquatic organisms, and plants. A very low concentration (pg/L to ng/L) still can give a serious impact to the environment. Although there are lots of studies on EDCs pollutants in environmental matrices, but the suitable method for quantifying multi-residues of EDCs is still inadequate (Kim and Carlson, 2005). In environment, both natural and artificial EDCs are commonly present in the range of pg/L to ng/L (Beck et al., 2005; Hibberd et al., 2009). However, due to the lack of research done on estuarine ecosystem mainly mariculture area, these pollutants remain very much unknown due to the variety and complex of matrixes (Bayen et al., 2013).

Owing to the low concentration of EDCs found in the environment, highly sensitive analytical procedures are needed to identify and quantify these low environmental levels (Álvarez-Muñoz et al., 2015; Yu and Wu, 2015; Ros et al., 2016). In the current study, analytical method for the analysis of a wide range of multi-class EDCs in water sample was optimized using solid phase extraction (SPE). SPE is the simplest and less complex extraction and cleanup steps. Meanwhile, for sediment, the extraction was performed using Soxhlet extraction coupled with SPE and biota sample (mariculture fish) were extracted by sonicator extraction altogether with SPE clean-up method. Furthermore, without considering the selectivity of residues, it is challenging to optimize chromatographic condition and recovery for each of residue when determining multi-residues in a single analytical run (Wee at al., 2016). Due to the others limitation like different solubility for each multi-residue, it is very difficult to determine the high recovery percentage (%) for each of the compounds.

Although the existence of these organic pollutants in water body is still poorly regulated, it still can be a good marker of the human impact on the environment plus be an excellent indicator for water quality (Esteban et al., 2014b). Furthermore, due to the higher dilution in estuarine water, the concentrations of EDCs are expected to be low and these have led to aquatic ecosystems receiving only a little attention in recent years (Beck et al., 2005). Several studies have been conducted to examine heavy metal contaminants in the water, sediment and in other aquatic matrices of marine and estuarine ecosystems in Malaysia (Looi et al., 2013; Achary et al., 2017; Zhang et al., 2017; Wang et al., 2018). However, there is limited information on the organic chemical pollutants in the Malaysia coastal ecosystem particularly for EDCs. In a previous report, organophosphorus pesticides were detected in the Langat River, Selangor, Malaysia (Wee et al., 2016) and multi-residues of pharmaceutically active compounds were detected in the Klang River estuary, Malaysia (Omar et al., 2018). Other studies by Osman et al. (2012), Santhi and Mustafa (2013), Veerasingam and Mustafa, (2013), and Fang et al. (2019) have reported organic pollutants in surface river water in Malaysia. To date, there is scarce literature review has shown on the presence of EDCs in the mariculture site. Due to the importance of coastal ecosystem to the human and mainly to aquatic life, some monitoring activities on organic pollutants, in Pulau Kukup, Johor will be provided a baseline data on the occurrence and profile of these emerging pollutants in the mariculture area.

In addition, due to the sedimentation, resuspension of the bed sediment, high salinity, high matrix effect, and contain lots of various organic matter, analysis of sediment matrices from coastal ecosystem are difficult to be achieved compared to the other matrices. Numerous analytical procedures have been developed and optimized to measure EDCs presence in environment, but the previous studies only focused on the water samples and leaving sediment analyses largely less concerned. According to Zhou and Broodbank (2014), to understand the long-term occurrence of EDCs pollutant, sediment analysis is highly required rather than only water analyses.

Sediment is one of the crucial environmental matrices in the surrounding ecosystem and numerous types of chemicals and pollutants precipitate sank in the sediment (Zhou and Broodbank, 2014; Pintado-Herrera et al., 2016; Omar et al., 2017). Various types of pollutants that are deposited and accumulated in the sediment, may disrupt the ecosystem directly or indirectly and impact the surrounding as sediment plays an extremely important role to maintain the food web and acts as a pool of pollutants for bioaccumulation and trophic transfer (Burton, 2002). The information about the level concentration of EDCs might be a key tool to evaluate the impact of human activities towards aquatic ecosystem although there is no data that has been published in Directive 2008/105/EC (Pintado-Herrera et al., 2016).

Furthermore, the information on level of EDCs pollutants in fish culture is important because the fish production from Pulau Kukup's mariculture site are exported to the other neighbor countries as mentioned in previous section. However, like other farming systems, aquaculture is plagued with disease problems resulting from its intensification and commercialization (Bonded-Reantaso et al., 2005). Natural and synthetic substances such as antibiotocs, disinfectants, water and soil treatment compounds, pesticides, fertilizers, probiotic, and other feed additives have become crucial inputs to treat and prevent bacterial and parasitic disease, to improve water quality, to increase pond natural productivity and/ or as growth promoters (Bonded-Reantaso et al., 2005; Ali et al., 2016). The usage of these EDCs can contribute to the improvement of the productivity and increased growth of the aquaculture sector. However, it also can cause negative impacts to human and environmental health (Ali et al., 2016).

Among the seafood product, fish is the most consumable protein for human nutrition because it has high source of nutrient such as variable type of vitamin, minerals, and fatty acids that are needed by the human body. For example, high levels of polyunsaturated omega-3 fatty acids cannot be generated by human body and only can be obtained from fish lipids through diet. Increasing of global consuming seafood since 1950s regardless of nature's limitation, the seafood intake still keeps growing till now (Cunha et al., 2017). Owing to the high demands of fish worldwide (Chatterjee et al., 2016) especially for Asian people, who consume large quantity of fish in their daily diet and the occurrence and distribution of organic emerging pollutants has become a hot issue in edible fish species, some precaution action need to be done for ecology and human health (Cheung et al., 2008). Therefore, the study on the quality of seafood by examine the level of targeted multi-class of EDCs in the most consumed fish species in Malaysia is important.

Due to the lack of information on the human health risk assessment for mariculture fish, a good human health risk assessment cannot be reported. Results on monitoring, human health assessment, and managing mariculture activity in relation to environmental protection and food safety cannot be provided due to the inadequate data obtained. Thus, the NABC (Needs, Approaches, Benefits, and Challenges) analysis was conducted in the present study to identify the knowledge gaps of the previous research that needed to be addressed regarding the monitoring studies of EDCs in mariculture ecosystem at Pulau Kukup, Johor (Table 1.1). In addition, the NABC analysis could also assist the present study to overcome the possible limit of the previous studies.

Table 1.1: Needs, Approaches, Benefits, and Challenges (NABC) analysis for recent monitoring studies of EDCs in estuarine water, sediment, and mariculture fish.

	Outputs
Needs	• Baseline records on EDCs contaminants in estuarine water, sediment, and culture fish in one of largest and active mariculture site in Malaysia. • Information on the EDCs concentration in mariculture fish is needed to evaluate the degree of EDCs contaminants and associated with human health risks assessment. • Continuous monitoring studies are needed in mariculture area in Pulau Kukup, Johor because aquaculture activity is one of the biggest economic contribution in Malaysia.
Approaches	• Determine the concentration of selected targeted EDCs in the estuarine water, sediment, and mariculture fish collected using solid-phase extraction, soxhlet extraction and ultrasonic extraction respectively. • Monitor the level of EDCs contaminants in the estuarine water, sediment, and mariculture fish by using analytical analyses of LC-MS/MS. • Assess the potential human health risk by calculating the human health risk assessment associated with the edible mariculture fish muscle.
Benefits	• Provide a better insights on the background concentration of EDCs pollution in aquatic ecosystem mainly in estuarine area. • Provide baseline data on EDCs contaminants status in mariculture site. • Create awareness about the toxicity of EDCs contaminant in the environmental mainly in aquatic ecosystem. • To provide the researchers and government the baseline of guideline on food safety using the result of human health risk assessment.
Challenges	• A simple, cheap, and green-based analytical method is needed to extract multi-residue of EDCs in three difference complex matrices (water, sediment, and fish). • A sensitive and accurate chromatogram analysis is needed to analyse and examine the multi-residue of EDCs in a single run time.

1.3 Objectives of the study

The research framework developed for the monitoring study of multi-class EDCs on the estuarine water, sediment, and mariculture fish and the human health risk assessment (Figure 1.2). Generally, the main objective of this study was to monitor the level of multi-class EDCs in estuarine water, sediment, and six different species of mariculture fish (*Trichinous blochii*, *Lutjanus campechanus*, *Lutjanus erythropterus*, *Lutjanus argentimaculatus*, *Carangoides armatu*, and *Lates calcarifer*) at Pulau Kukup, Johor. The specific research objectives are stated as follows:

i. To modify and optimize the analytical method for simultaneous determination of multi-class EDCs (hormone, pharmaceutical, pesticides, and phenolic compounds) in estuarine water, sediment, and mariculture fish's samples using respectively extraction methods coupled with LC-MS/MS.
ii. To identify and quantify the occurrence and distribution of multi-class EDCs in environmental matrices (estuarine water and sediment) and elucidate the relationship between multi-class EDCs in environmental matrices with environmental variables.
iii. To identify and quantify the occurrence and distribution of multi-class EDCs in different part of mariculture fishes (muscle, liver, and reproductive organ) samples and elucidate the relationship between EDCs level with fish size (weight and length).
iv. To assess the potential human health risk assessment associated with targeted multi-class EDCs contamination in muscle of six different fish species (*T. blochii*, *L. campechanus*, *L. erythropterus*, *L. argentimaculatus*, *C. armatu*, and *L. calcarifer)* from mariculture site.

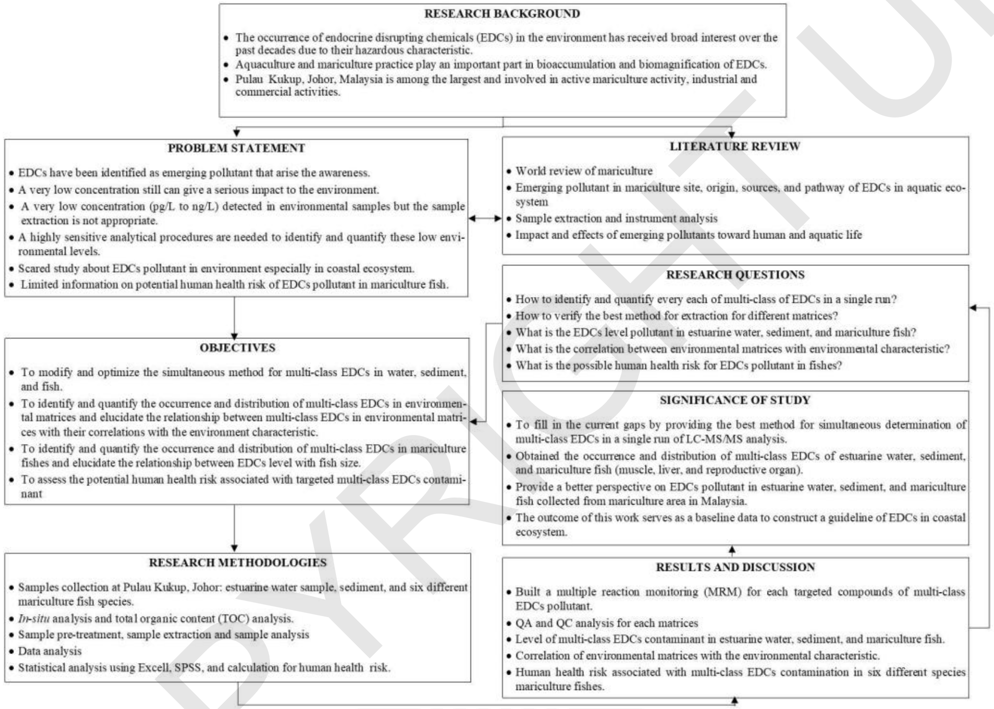

Figure 1.2: Research framework for the analytical study on estuarine water, sediment, and mariculture fish and risk assessment of Pulau Kukup, Johor, Malaysia.

1.4 Scopes of the study

This study generally covers the area as follows:

i) Involved in the modification and optimization of the method for simultaneous determination of multi-class EDCs (pharmaceutical, phenolic compounds, hormone and pesticides) in estuarine water, sediment, and mariculture fishes samples using SPE extraction, soxhlet extraction, and sonicator extraction respectively.

ii) Multiple reaction monitoring (MRM) for each targeted compound of multi-residues EDCs, quinalphos, diazinon, chlorpyrifos, caffeine, chloramphenicol, amoxicillin, propranolol, atorvastatin, diethylstilbestrol, nitrofurazone, dexamethasone, primidone, sulfamethoxazole, and diclofenac, testosterone, progesterone, 17β-estradiol, estrone, 17α-ethynylestradiol, and bisphenol A was conducted by optimizing the compound-dependent parameters such as declustering potential, entrance potential (EP), exit potential (EP), and collision energy (CE).

iii) This study focused on the occurrence and distribution of multi-class EDCs in environmental matrices (estuarine water and sediment) and six different species of mariculture fish (*T. blochii, L. campechanus, L. erythropterus, L. argentimaculatus, C. armatu*, and *L. calcarifer*) from mariculture site.

iv) This study also narrowed down to evaluate the relationship between level of multi-class EDCs in samples with environmental variable (environmental matrices) and fish size (mariculture fish).

v) To assess the potential human health risk assessment associated with multi-class EDCs contamination in muscle of six different species from mariculture site.

1.5 Significance of the study

To date, the previous studies from the literatures have some gaps of knowledge on the multi-class of EDCs monitoring in the tropical estuarine and coastal ecosystem, especially in the mariculture area. The present study is conducted to fill in such information gaps by providing the best method for simultaneous determination of multi-class EDCs in a single run of LC-MS/MS analysis, and using that method, the occurrence and distribution of multi-class EDCs can be obtained for estuarine water, sediment, and mariculture fish (muscle, liver, and reproductive organ). This work uses environmental forensic approach by combining analytical and statistical analyses to trace and interpret the collected data. This study aims to provide the data on EDCs pollutant in estuarine ecosystem focusing on mariculture area at Pulau Kukup, Johor. Quantitative outputs from this study include i) the QA and QC analysis for each matrices collected from Pulau Kukup, Johor, ii) the concentration of EDCs in the estuarine water, sediment, and mariculture fish, and iii) the potential human health risk associated with multi-class EDCs contamination in six different species of mariculture fishes. The outcome of this work serves as a baseline data to construct a guideline of EDCs in water, sediment, and fish in estuarine ecosystem.

Meanwhile, for qualitative outputs include i) the distribution pattern of multi-class EDCs in estuarine ecosystem, ii) the EDCs pollution status of mariculture cages in Pulau Kukup, Johor, Malaysia, iii) the correlation of multi-class EDCs level between environmental matrices (estuarine water and sediment) with the environment characteristic, and iv) the correlation of multi-class EDCs level between mariculture fish with fish size (weight and length). This study can serve as a baseline study to provide a better perspective on EDCs pollutant in estuarine water, sediment, and mariculture fish collected from mariculture area in Malaysia. Finding from this study could also benefit the relevant agencies in setting priorities and allocating resources based on the organic pollution status. The estimated risk could also help to increase the public awareness of the organic pollutant in primary protein sources (mariculture fish).

1.5 Thesis outline

This thesis mainly consists of five chapters which are the Introduction, Literature Review, Methodologies, Results and Discussion, and Summary, Conclusion and Recommendations to provide monitoring data for level concentration of EDCs pollutants in the estuarine water, sediment and mariculture fish. These monitoring data will be the baseline data for constructing a new guideline for EDCs in the marine ecosystem. The chapters of this thesis are arranged as the following flow:

i. Chapter 1 is an introduction with a brief description of study background, objectives, problem statements, scope and significance of the study.

ii. Chapter 2 provided a comprehensive literature review related to the world review of aquaculture/mariculture activiti, emerging pollutants in aquaculture/mariculture (origin, sources, and pathway of pollutant), types of analytical procedures to detect the pollutant in environment samples, impacts and effect the pollutant toward other organisms, and potential environmental risk.

iii. Chapter 3 consists of the materials and method applied in this study. This chapter include sampling activities such sample collection and lab analysis like sample preservation, sample pre-treatment, sample extraction, and sample analysis.

v. Chapter 4 elaborates on the results and discussion of multiple reaction monitoring (MRM) for each targeted compounds of multi-class EDCs pollutant, the occurrence and distribution of multi-class EDCs in samples (estuarine water, sediment, and mariculture fish), correlation of samples with the environment characteristic, and potential human health risk in mariculture fish.

vi. Chapter 5 summarizes and concludes on the findings and recommendation made on appropriates measures for managing EDCs pollutants in estuarine ecosystem.

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