ECOTOXICOLOGICAL RISK ASSESSMENT OF ENDOCRINE-DISRUPTING COMPOUNDS IN FRESHWATER ECOSYSTEMS USING TROPICAL CLADOCERANS *Moina micrura* (KURZ, 1875)

By

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman : Professor Ahmad Zaharin Aris, PhD
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Despite the global recognition of the adverse effects of endocrine-disrupting compounds (EDCs) on human health and the environment, comprehensive regulations addressing these contaminants in water sources are lacking worldwide, including in Malaysia. Furthermore, the absence of a regulatory framework impedes systematic research and ecotoxicological risk assessment data on the effects of EDCs, complicating the development of effective mitigation strategies. This study employed tropical zooplankton (*Moina micrura*) as a model species to elucidate the toxicity pathway and establish adverse effects at different organizational levels (molecular, organ, individual, and population). The study focused on nine EDCs: bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), diclofenac (DCF), propranolol (PROP), 17α-ethinylestradiol (EE2), and 17β-estradiol (E2). Besides EDCs, the study also revealed that climate change significantly impacted the life-history traits of *M. micrura*. Lifespan, total number of offspring, heart rate, individual size, and total molting of *M. micrura* were significantly reduced ($p < 0.05$) under acidic (pH 5) and basic (pH 9) water conditions. Male offspring were observed only under conditions of no food supply and low food concentration (1×10^2 cells/mL). In the molecular evaluation, the study observed significant up-regulation of 15 genes that can serve as biomarkers under unfavorable environmental conditions. Hemoglobin (HBB), glutathione S-transferase (GST), doublesex (DSX), and juvenile hormone analog (JHA) gene expression levels were used to evaluate the molecular impact of EDCs on *M. micrura*. The results indicated significant upregulation ($p < 0.05$) of HBB and GST genes by at least 2-fold during all acute EDC exposures. DSX and JHA were only significantly upregulated ($p < 0.05$) by two-fold during exposure to EE2 and E2. At the organ and individual levels, significant reductions ($p < 0.05$) in the heart rate of *M. micrura* were observed. Subsequently, significant differences ($p < 0.05$) were noted in the individual sizes of *M. micrura* under the exposure to PFOS, PFOA, EE2, and E2. The adverse effects of EDCs at the population level were determined using the lethal concentration (LC_{50}) and predicted no-effect concentration (PNEC) to evaluate the risk associated with EDCs. Based on the LC_{50} values, the most hazardous EDCs to *M. micrura* were DCF (66.5 µg/L), followed by PROP (90.4 µg/L), EE2 (312.0 µg/L), E2 (374.8 µg/L), PFOA (474.7 µg/L), PFOS (549.6 µg/L), BPA (611.6 µg/L), BPF (632.0 µg/L), and BPS (819.1 µg/L). However, when utilizing the species sensitivity distribution to calculate PNEC ($PNEC_{SSD}$), the most toxic chemical was E2, followed by DCF, PROP, BPF, EE2, BPA, PFOS, and PFOA. Overall, the results of the toxicity pathway indicated that alterations in GST and HBB genes affected reactive oxygen species (ROS) production in *M. micrura*. ROS serve as a potential mechanism for EDCs, primarily through oxidative stress pathways, leading to outcomes such as mortality, growth reduction, and reproductive failure. Furthermore, the induction of HBB, JHA, and DSX contributes to the increase in male offspring. This comprehensive study is crucial for informed decision-making in environmental monitoring, effective water pollution mitigation, and the sustainability of riverine ecosystems.

Keywords: Ecotoxicology; risk assessment; endocrine disrupting compounds; *Moina micrura*; toxicity pathway

SDG: GOAL 6: Clean Water and Sanitation; 14: Life Below Water

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PEMBANGUNKAN METODOLOGI PENILAIAN RISIKO BAGI SEBATIAN PENGGANGGU ENDOKRIN MENGGUNAKAN CLADOCERAN TROPIKA *Moina micrura* (Kurz, 1875)

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Meskipun pengiktirafan global terhadap kesan buruk sebatian pengganggu endokrin (EDCs) terhadap kesihatan manusia dan alam sekitar, peraturan menyeluruh untuk menangani bahan pencemar ini dalam sumber air masih kurang di seluruh dunia, termasuk di Malaysia. Tambahan pula, ketiadaan rangka kerja telah menghalang penyelidikan yang sistematik dan mengurangkan kajian penilaian risiko ekotoksikologi terhadap kesan EDCs. Kajian ini menggunakan zooplankton tropika (*Moina micrura*) sebagai spesies model untuk mengkaji laluan ketoksikan dan kesan buruk EDCs pada pelbagai peringkat organisasi (molekul, organ, individu, dan populasi). Kajian ini memberi tumpuan kepada 9 EDCs: bisfenol A (BPA), bisfenol F (BPF), bisfenol S (BPS), asid perfluorooktanoik (PFOA), asid perfluorooktanesulfonik (PFOS), diklofenak (DCF), propranolol (PROP), 17α-etinilestradiol (EE2), dan 17β-estradiol (E2). Selain EDCs, kajian ini juga mendedahkan bahawa perubahan iklim memberi kesan signifikan kepada *M. micrura*. Jangka hayat,

jumlah populasi, kadar denyutan jantung, saiz individu, dan jumlah penggantian kulit *M. micrura* telah menurun secara signifikan ($p < 0.05$) di bawah keadaan air berasid (pH 5) dan beralkali (pH 9). Populasi individu jantan hanya diperhatikan di bawah keadaan tiada bekalan makanan dan kepekatan makanan rendah (1×10^2 sel/mL). Semasa penilaian molekul, kajian ini telah mengenal pasti 15 gen dalam *M. micrura* yang boleh bertindak sebagai penanda biologi dalam *M. micrura* di bawah keadaan persekitaran yang buruk. Tahap ekspresi gen hemoglobin (HBB), glutathione S-transferase (GST), doublesex (DSX), dan analog hormon juvana (JHA) digunakan untuk menilai kesan molekul EDC pada *M. micrura*. Keputusan menunjukkan gen HBB dan GST meningkat secara signifikan ($p < 0.05$) sekurang-kurangnya 2 kali ganda semasa pendedahan akut pada semua sebatian EDC. DBX dan JHA hanya meningkat secara signifikan ($p < 0.05$) sebanyak dua kali ganda semasa pendedahan kepada EE2 dan E2. Pada tahap organ dan individu, kajian menunjukkan pengurangan yang signifikan ($p < 0.05$) dalam kadar denyutan jantung M. micrura. Seterusnya, terdapat perbezaan yang signifikan ($p < 0.05$) dalam saiz individu ketika eskperimen pendedahan pada sebatian PFOS, PFOA, EE2, dan E2. Risiko EDC dinilai dengan menentukan kesan buruk terhadap populasi menggunakan kepekatan maut median (LC_{50}) dan kepekatan tiada kesan yang diramalkan (PNEC). Berdasarkan nilai LC_{50}, DCF (66.5 µg/L) ialah EDC paling berbahaya kepada *M. micrura*, diikuti oleh PROP (90.4 µg/L), EE2 (312.0 µg/L), E2 (374.8 µg/L), PFOA (474.7 µg/L), PFOS (549.6 µg/L), BPA (611.6 µg/L), BPF (632.0 µg/L) dan BPS (819.1 µg/L). Walau bagaimanapun, apabila PNEC ($PNEC_{SSD}$) dikira menggunakan taburan sensitiviti spesies, bahan kimia paling toksik ialah E2, diikuti oleh DCF, PROP,

BPF, EE2, BPA, PFOS dan PFOA. Secara keseluruhan, dapatan daripada analisis laluan ketoksikan menunjukkan bahawa perubahan dalam gen GST dan HBB mempunyai kesan ke atas penjanaan spesies oksigen reaktif (ROS) dalam *M. micrura*. ROS berperanan sebagai mekanisme yang berpotensi untuk EDCs, terutama melalui laluan tekanan oksidatif, menyebabkan kesan buruk seperti kematian, penurunan pertumbuhan dan masalah pembiakan. Di samping itu, induksi HBB, JHA, dan DSX memainkan peranan dalam peningkatan populasi individu jantan. Kajian menyeluruh ini penting untuk membuat keputusan yang berinformasi dalam pemantauan alam sekitar, pengurangan pencemaran air yang berkesan, dan kelestarian ekosistem sungai.

Kata Kunci: Ekotoksikologi; penilaian risiko; sebatian pengganggu endokrin; *Moina microra*; laluan ketoksikan

SDG: *Matlamat 6: Air Bersih dan Sanitasi; 14: Kehidupan dalam Air*

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

20E	20-Hydroxyecdysone
3R	Replacement, reduction, and refinement
AChE	Acetylcholinesterase enzyme
AF	Assessment factor
ANOVA	Analysis of variance
AO	Adverse outcomes
AOP	Adverse outcome pathway
AOP-KB	AOP knowledge base
API	Active pharmaceutical ingredients
AQUAHEALTH	Aquatic Animal Health and Therapeutics Laboratory
BBM	Bold basal medium
bp	Base pair
BPA	Bisphenol A
BPAF	Bisphenol AF
BPAP	Bisphenol AP
BPB	Bisphenol B
BPF	Bisphenol F
BPS	Bisphenol S
BPZ	Bisphenol Z
BUSCO	Benchmarking Universal Single-Copy Orthologs
CAT	Catalase
cDNA	Complementary DNA
CECs	Contaminants of emerging concerns
Cl^-	Chloride ion
CO_2	Carbon dioxide

CORSET	Coordination of Regulatory Sequence Elements and Transcription
CYP	Cytochrome
DSX	Doublesex
DEG	Differential expressed genes
DESeq2	Differential expression analysis of RNA-seq data 2
DNA	Deoxyribonucleic acid
DO	Dissolved oxygen
dTTP	Deoxythymidine triphosphate
dUTP	Deoxyuridine triphosphate
E2	17β-estradiol
Eawag	Swiss Federal Institute of Aquatic Science and Technology
ECOTOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECOTOX	ECOTOXicology Knowledgebase
ECR	Nonsteroidal ecdysone receptor
EDCs	Endocrine disrupting compounds
EDSP	Endocrine Disruptor Screening Program
EE2	17α-ethinylestradiol
ERA	Environmental risk assessment
ERK	Extracellular signal-regulated kinase
ESD	Environmental sex determination
ESI	Electrospray ionization
FBN	Fibrillin
FDR	False discovery rate
FPKM	Fragments per kilobase of mapped reads
GFAP	Glial fibrillary acidic protein

GO	Gene Ontology Consortium Database
GPX	Glutathione peroxidase
GST	Glutathione S-transferase
H^+	Hydrogen ion
HBB	Hemoglobin
HC_5	Hazardous concentration for 5% of species
HSP	Heat shock protein
IPCS	International Programme on Chemical Safety
ISO	International Organization for Standardization
JHA	Juvenile hormone analogues
JHAMT	Juvenile hormone acid O-methyltransferase
JNK	Jun N-terminal kinase
KE	Key event
KEGG	Kyoto Encyclopedia of Genes and Genomes database
KERs	Key event relationships
KOG	EuKaryotic Orthologous Groups
LC	Lethal concentration
LC-MS	Liquid chromatography-mass spectrometry
MAPK	Mitogen-activated protein kinases
MEC	Measured concentration of pollutant
MET	Methoprene-tolerant
METT	Methyltransferase
MIE	Molecular initiating event
MRM	Multiple reaction monitoring
mRNA	Messenger RNA
MYO	Myosin

N/A	Not avaiable
Na^+	Sodium ion
NB	Negative binomial
NCBI	National Center for Biotechnology Information
ND	Not detected
NGS	Next-generation sequencing
NIH	National Institutes of Health
NMR	Nuclear magnetic resonance
NO_x	Nitrogen oxides
Nr	Nonredundant protein database
NSAID	Nonsteroidal anti-inflammatory drug
Nt	Nonredundant nucleotide database
nt	Nucleotides
OECD	Organisation for Economic Co-operation and Development
OH^-	Hydroxyl ion
Org/L	Organisms per liter
PCA	Principal component analysis
Pfam	Protein Family Database
PFAS	Perfluoroalkyl and polyfluoroalkyl substances
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonate
PNEC	Predicted no-effect concentration
PPCP	Pharmaceuticals and personal care products
PVC	Polyvinyl chloride
Q	Phred score

qRT-PCR	Quantitative reverse transcription polymerase chain reaction
REACH	European Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals
RIN	RNA integrity number
RNA	Ribonucleic acid
RNase	Ribonuclease
RNAseq	RNA sequence
ROS	Reactive oxidative stress
RQ	Risk quotient
rRNA	Ribosomal RNA
RSEM	RNA-seq by expectation maximisation
SO_2	Sulfur dioxide
SOD	Superoxide dismutase
SSD	Species sensitivity distributions
STP	Sewage treatment plant
SVHC	Substances of very high concern
SWOT	Strengths, weaknesses, opportunities and threats
TDRR	Time and dose-response relationship
TEB	Insecticide tebufenozide
TGD	Technical guidance document
TGFB	Transforming growth factor beta
Uniprot	Swiss-Prot for Functional Annotation
UPM	Universiti Putra Malaysia
US EPA	United States Environmental Protection Agency
VTG	Vitellogenin
WFD	Water Framework Directive

WHO	World Health Organization
WHO-ICPS	International Programme on Chemical Safety of The World Health Organization
WWTP	Wastewater treatment plant

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The legacy of industrial expansion and urbanisation has led to the emergence of contaminants that have negative effects on both the environment and human health. Progress in industrial applications has resulted in revolutionary and accelerated production of novel chemicals. To grant or restrict the use of these manufactured chemicals, it is imperative that newly synthesised substances undergo a series of toxicity tests to establish a solid scientific foundation. In 1970, the global chemical output was valued at US$171 billion, and over the years, the chemical industry has witnessed rapid growth, surging to a staggering $3.58 trillion by 2013 (Steger-Hartmann & Pognan, 2018). This expansion in chemical production has led to an alarming scarcity of ecotoxicological data, especially with the global production of chemicals reaching 400 billion tons owing to the discovery of new industrial applications (Casals-Casas & Desvergne, 2011; Golberg et al., 2016; Raso et al., 2016).

Currently, a staggering array of 100,000 different chemicals is employed worldwide. However, only fractions of these chemicals available in the market have undergone comprehensive evaluation of their impact on human health and environmental safety (Mahdi & Aziz, 2018). The mounting concern over this insufficiency of ecotoxicological data is amplified by the high expenses, time-consuming protocols, and heavy dependence on animal experimentation inherent in chemical assessment methodologies (Berggren et al., 2015; Doke

& Dhawale, 2015). Notably, ecotoxicology tests relying on animal experimentation involve the annual utilisation of more than 115 million animals, incurring expenses exceeding US $ 1 billion (Berggren et al., 2015). Ironically, more than 90% of these chemicals fail to accurately predict human responses (Bailey & Balls, 2019). This further exacerbates the ongoing accumulation of toxic substances in aquatic environments, which is a critical contemporary issue of global concern.

To address these challenges, international bodies such as the Organization for Economic Co-operation and Development (OECD), World Health Organization (WHO), National Institute of Health (NIH), International Programme on Chemical Safety (IPCS), and the United States Environmental Protection Agency (US EPA) have devised a multitude of regulations and guidelines aimed at establishing comprehensive ecotoxicological risk assessments (British Columbia Ministry of Environment, 2017; ECETOC, 2016; Huang et al., 2015; May et al., 2016; Ministry of Health, 2008; OECD, 2017; US EPA, 2020c). **Figure 1.1** depicts the comprehensive pathway outlined in the Technical Guidance Document (TGD) for developing an environmental risk assessment.

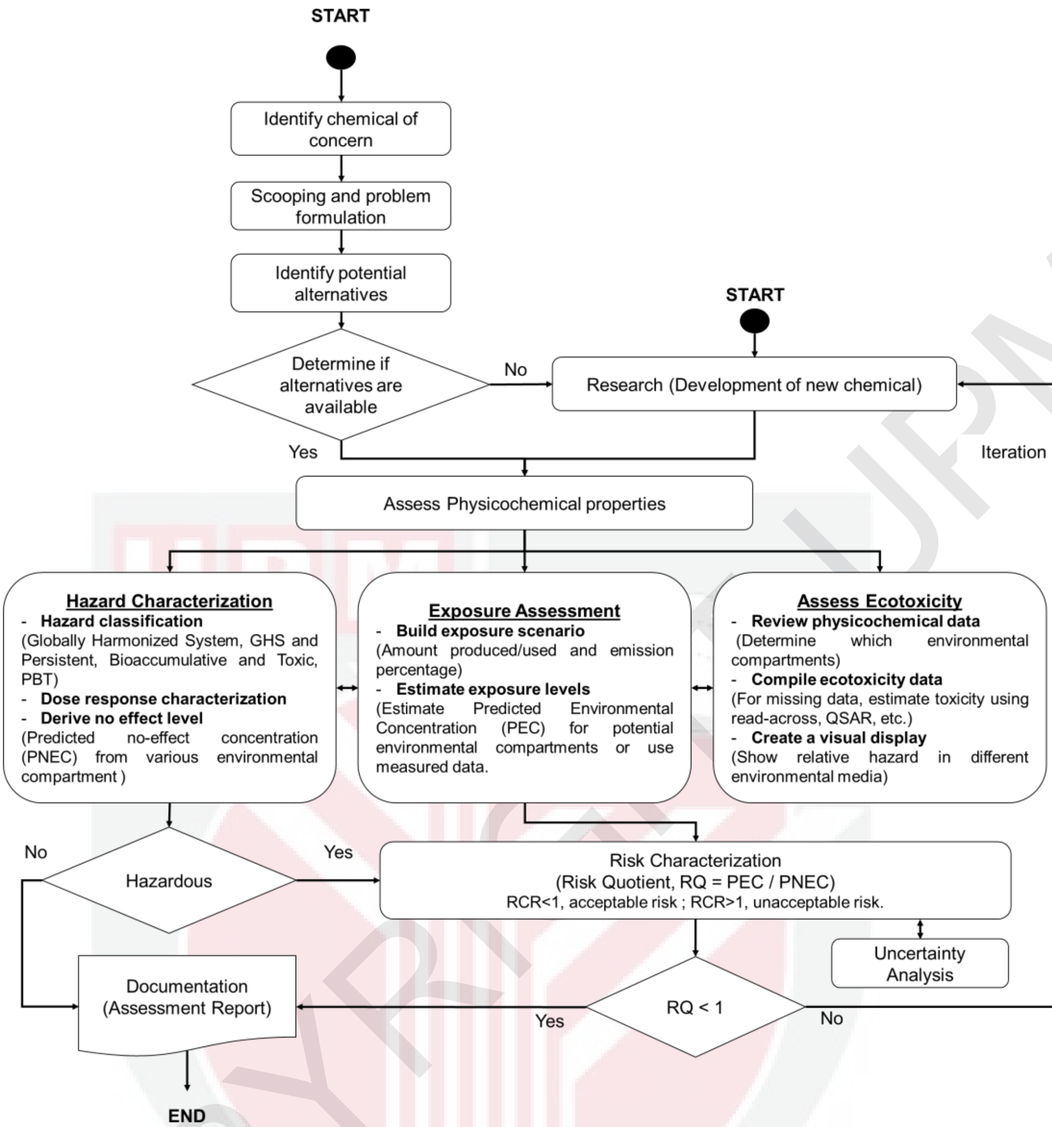

Figure 1.1 : The procedure for assessing the risk of newly synthesised chemicals

Significant strides in analytical chemistry have emerged in recent decades, enabling the detection of substances even at miniscule levels (ng/L and pg/L) (Wee et al., 2022a). Notably, advanced instruments such as liquid chromatography-mass spectrometry (LC-MS) have facilitated the identification of numerous newly synthesised substances that now pervade aquatic environments (Carvalho et al., 2019). These "new" environmentally relevant substances that are known or suspected to have adverse effects on the environment or human health are referred to as " emerging contaminants" or "contaminants of emerging concern" (CECs) (Wee & Aris, 2019; Zhang et al., 2021). Since the mid-1990s, CECs have garnered global attention because of their toxicity, persistence, bioaccumulation, and oestrogenic effects. Consequently, a significant proportion of structurally diverse CECs found in aquatic environments has been identified or projected as endocrine-disrupting compounds (EDCs).

The selection of appropriate model organisms is necessitated by the advancement of this critical research. *Moina micrura*, commonly known as the water flea, is perceived as a highly suitable candidate for ecotoxicological studies due to its rapid reproduction, sensitivity to environmental changes, and its middle position within aquatic food webs. The utilisation of *M. micrura* enables insights into the potential impacts of EDC contaminants on tropical aquatic ecosystems, with it serving as early warning system for environmental perturbations. Consequently, in this study, *M. micrura* is chosen as the model organism for the assessment of the ecotoxicological effects of EDCs.

Furthermore, the world's largest chemical testing program, the European Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), classifies EDCs as substances of very high concern (SVHC). Accordingly, EDCs are focal areas in ecotoxicology and are a priority for identification and regulation. Subsequently, precise reports on the exposure, dose response, and hazard towards each specific chemical are required for the complete evaluation of the risk assessment and impacts of these EDCs on the well-being of ecosystems and human societies (Berggren et al., 2015).

1.2 Problem statement

Presently, Malaysia does not have specific legislation or regulations addressing the presence of EDCs in its national drinking water or water quality standards (Hasni et al., 2023). In contrast, other regions, such as the European Union, have established regulations to manage or prohibit the use of EDCs in their products. Notable examples include the Plant Protection Products Regulation in 2009, the Biocidal Products Regulation in 2012, and REACH program in 2006. This disparity in regulatory approaches and monitoring practices highlights a significant gap in Malaysia's water quality management framework. The absence of comprehensive legislation on EDCs poses potential risks to public health and the environment, as these chemicals can disrupt endocrine functions even at ng/L. Moreover, the quantity and types of EDCs being monitored in Malaysia are currently limited, primarily focusing on pesticides and a few other categories of EDCs (Wee & Aris, 2019). This is in contrast to other Asian countries, such as Thailand, Vietnam, and Taiwan, as well as other nations globally, where a broader range of EDCs are being monitored. This limited monitoring scope underscores the problem of less comprehensive ecotoxicology studies in Malaysia, which hampers a full assessment and understanding of the presence and impact of EDCs in the environment.

EDCs have been consistently detected in aquatic ecosystems across several countries, including the United States (Jones et al., 2020), Canada (Atkinson et al., 2012), Spain (Gorga et al., 2015), England (Lusher et al., 2017), Italy (Pignotti & Dinelli, 2018), Brazil (Weber et al., 2017), Malaysia (Wee & Aris, 2017), China (Li et al., 2018; Niu & Zhang, 2018), Japan (Yamazaki et al., 2015), and Singapore (You et al., 2015). The pathways through which EDCs enter the environment primarily include agricultural activities, residential waste, and discharge from sewage treatment plants (STPs) and wastewater treatment plants (WWTPs) (Aris et al., 2020). However, due to inadequate and inefficient water treatment facilities, EDCs are being released into the environment, leading to the contamination of aquatic ecosystems. The extensive prevalence of EDCs has triggered various harmful effects on aquatic organisms across diverse trophic levels, including algae (Czarny et al., 2019; Mao et al., 2017), phytoplankton (M'rabet et al., 2019), zooplankton (In et al., 2019; Navis et al., 2018), and fishes (Rämö et al., 2018; Tinguely et al., 2021; Zhang et al., 2017). Recent research indicates that EDCs can disrupt an organism's endocrine system, resulting in adverse reproductive, immune, neurological, and developmental outcomes (Ismail et al., 2020; Santoro et al., 2019).

Currently, the standard method for assessing the levels of EDC contaminants in freshwater is to monitor rivers, lakes, and water reservoirs (Čelić et al., 2020; He & Aga, 2019; Li et al., 2018; Wee et al., 2020a). However, these monitoring approaches often prove to be too late for effective decision making to mitigate EDC contamination. Consequently, risk-based approach such as environmental risk assessment (ERA) has been established to identify, analyse, and estimate the likelihood of potential consequences that could negatively impact aquatic organisms, public health, and the environment (Agathokleous et al., 2019; Van den Berg et al., 2019). Nonetheless, the lack of sufficient ecotoxicology data, such as lethal concentration 50 (LC_{50}), hazardous concentration for 5% of species (HC_5) and predicted no-effect concentration (PNEC) for the majority of EDCs hinders chemical characterisation and risk assessment processes.

Additionally, the European Union has imposed restrictions on the use of vertebrate animals in ecotoxicological assessments, encouraging the use of alternative species bioindicators such as zooplankton (Cozigou et al., 2015; Doke & Dhawale, 2015; European Commission, 2000). Nonetheless, obstacles arise in assessing EDCs in zooplankton because of the limited understanding of their hormone systems and biomarker genes compared with vertebrates (Matthiessen et al., 2018). Furthermore, most regulators employ temperate *Daphnia magna* as an ecotoxicological model, whereas tropical zooplankton species remain understudied (Ghose et al., 2014; Pham & Bui, 2018). The use of temperate *D. magna* for ecotoxicity and risk assessment in tropical freshwater ecosystems lacks accuracy, owing to ecological differences (Oliveira et al., 2018). Thus, the inclusion of tropical native freshwater species such as *Moina micrura* is crucial for accurately depicting the state of tropical freshwater ecosystems.

Comprehensive reports on hazards, dose-response relationships, and exposure are essential for achieving a precise assessment of the effects of chemicals on humans and ecosystems (Hamm et al., 2017). Conventional ecotoxicological assessments are expensive, time-consuming and rely heavily on animal testing as a proxy for human exposure (Bopp et al., 2019). Despite their ability to predict adverse outcomes, these assessments are often challenging to reproduce, interpret, and riddle with uncertain factors (Skinner et al., 2016). Moreover, current ecotoxicity assessments mainly focus on apical adverse effect endpoints, neglecting to delve into the mechanisms of toxicity (Jeong & Choi, 2018). This approach also fails to acknowledge the intricate mechanistic responses of organisms, including interactions between biological organisations (Archer et al., 2017).

Tropical rivers boast diverse freshwater ecosystems and remain highly vulnerable to anthropogenic activities and climate change (Bello et al., 2017). The acceleration of global warming and climate change in recent years has amplified the adverse effects on aquatic environments. The responses and sensitivities of aquatic organisms to various environmental stressors vary, resulting in imbalanced reactions across the trophic levels in rivers. Similarly, environmental stressors such as climate change, water quality, and food availability alter the abundance and diversity of zooplankton species (Yuslan et al., 2021). These stressors can potentially affect zooplankton physiology, behaviour, and reproduction (Gökçe & Turhan, 2014). Hence, assessing the effects of environmental stressors is essential because the significant impact of climate change on zooplankton populations could disrupt the entire aquatic food chain, raising more severe concerns at higher trophic levels (Arafat et al., 2021). Moreover, findings from environmental stressors can provide foundational data for comparing the impacts of EDCs. Therefore, this study aimed to address the following research question:

1. What are the adverse effects of the environmental stressors on *M. micrura*?
2. What are the biomarker genes and the adverse effects of EDCs on *M. micrura* at the molecular level?
3. What are the adverse effects of EDCs on *M. micrura* at the organ and individual level?
4. What are the predicted non-effect concentration (PNEC) values and toxicity pathways of the EDCs in *M. micrura*?

1.3 Objectives of the study

This project aims to achieve a more comprehensive ecotoxicological and risk assessment, focusing on early-stage diagnosis, synergistic interactions, and biological impacts of EDCs to promote the sustainability of freshwater ecosystems. The present study used a native tropical cladoceran species, *M. micrura*, as a bioindicator. The specific objectives of this study were as follows:

1. To elucidate the environmental stressors that trigger adverse effects in *M. micrura*
2. To examine the molecular assessment of *M. micrura* using de novo transcriptomic and differentially expressed gene (DEG) analysis.
3. To evaluate the adverse effects of EDCs at the organ and individual organisation levels in *M. micrura*.

4. To establish the predicted non-effect concentration (PNEC) and pathway assessment of selected EDCs in *M. micrura*.

1.4 Scope of the study

This research covers the following areas:

i) The utilisation of the native tropical cladoceran species *M. micrura*, as a biological bioindicator for conducting acute toxicity tests.

ii) Development of a reliable and simple RNA extraction method for the molecular assessment of *M. micrura*, with potential downstream applications such as DEG and de novo transcriptomic analysis.

iii) Analysis of de novo transcriptomics in three distinct developmental stages (juvenile, adult, and male) of *M. micrura* to determine the biomarker genes.

iv) The impact of environmental stressors and EDCs on *M. micrura* across multiple organisation levels (molecular, organ, individual and population)

v) Generation of PNEC values using assessment factor (AF) and species sensitivity distribution (SSD) approaches.

vi) Establishment of the potential underlying mechanisms of action exerted by EDCs on *M. micrura*.

1.5 Significance of the study

This study aims to construct a comprehensive toxicity database for EDCs, which can subsequently serve as a baseline data for environmental risk assessments. In particular, the absence of a toxicity database detailing risk assessments for specific EDCs, including bisphenol analogues, perfluoroalkyl and polyfluoroalkyl substances (PFAS), active pharmaceutical ingredients (API), and hormones, within tropical freshwater ecosystems highlights critical gaps in current knowledge. The assessment and quantification of toxicity and risks, such as PNEC values for EDCs, have pivotal significance as decision-making tools. These tools contribute to the establishment of environmental quality criteria, serve as baseline data for initial screening assessments, and facilitate the accurate estimation of the environmental risks in freshwater ecosystems. This study provides comprehensive insights into pollution risks, thereby offering valuable guidance to legislators in the evaluation of risk-mitigation strategies, informed decision making, and policy endorsement. Moreover, the data generated from this study substantially enriches the knowledge pool for ecotoxicological and risk assessments of EDCs.

The determination of responses across various organizational levels adopted in this study holistically elucidated the toxic effects of EDCs. This approach not only provides an all-encompassing perspective on the impact of EDCs but also provides deeper insights into the underlying mechanisms of toxicity within exposed organisms. Furthermore, a profound understanding of the biology, genomics, and transcriptomic study of *M. micrura* provide researchers with valuable resources for future gene expression investigations and comparative reproductive genome analyses. This holds particular significance for researchers seeking to decode *M. micrura* sequences, thereby enriching the exploration of gene expression patterns and facilitating comparative genome analyses within both the broader Moina genus and cladoceran families. The identification of novel molecular markers represents a promising avenue for further exploration, elevating *M. micrura* as a model species for intricate investigations that are yet to be conducted.

1.6 Research framework of the study

The research framework for the ecotoxicological risk assessment of endocrine disrupting compounds in tropical freshwater ecosystems using cladocerans *M. micrura* is illustrated in **Figure 1.2**.

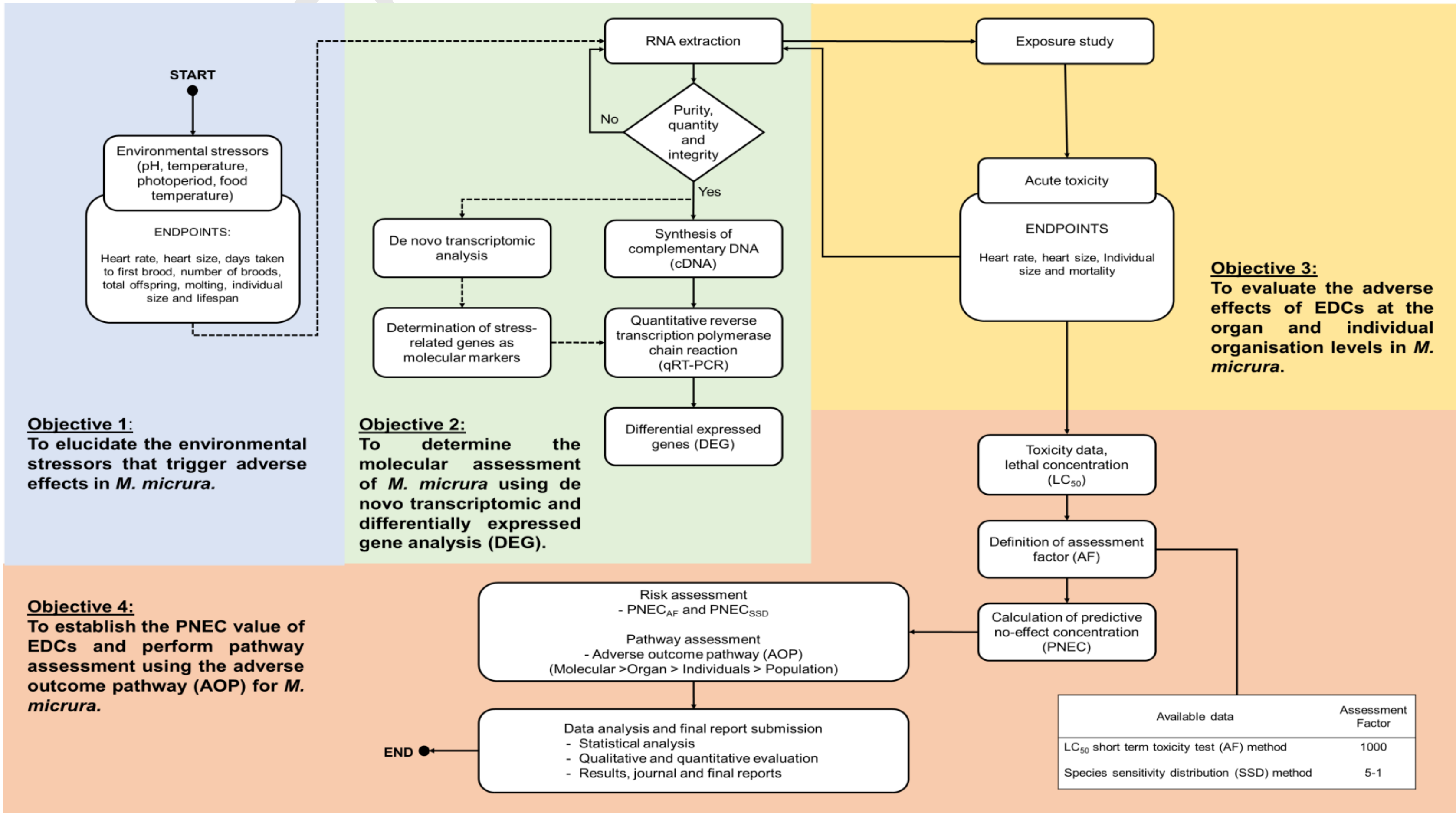

Figure 1.2 : The research framework for the ecotoxicological risk assessment of endocrine disrupting compounds in tropical freshwater ecosystems using cladocerans [*Moina micrura* (Kurz, 1875)]

1.7 Thesis outline

This thesis is structured into eight chapters, each contributing to the comprehensive exploration of the objectives of the study.

i) Chapter 1 provides a concise introduction, background of the study, problem statement, objectives of the study, elucidating their significance, and outlining the research framework.

ii) Chapter 2 extensively reviews prior literature, encompassing a range of themes. These include the use of zooplankton as a bioindicator, an exploration of morphological, phenological, and life-history traits of *M. micrura*, an investigation into the impacts and risks posed by environmental stressors and EDCs in zooplankton, the integration of aquatic toxicity data within the context of ERA, introduction to the concept of AOP, and utilisation of zooplankton in AOP development.

iii) Chapter 3 provides the general methodology of the current study.

iv) Chapter 4 discusses the intricate effects of environmental stressors on *M. micrura*, providing a comprehensive understanding of the organism's responses to environmental stressors, such as pH, temperature, photoperiod, and food concentration.

v) Chapter 5 discusses the molecular assessment of *M. micrura*, focusing on de novo transcriptomic analysis to assess the functional gene annotation and biomarker genes under unfavourable environmental conditions. Four (4) biomarker genes (GST, HBB, DSX and JHA) identified from the de novo transcriptomic study were used to assess acute toxicity effects through DEG analysis of *M. micrura*.

vi) Chapter 6 describes the effects of EDCs on *M. micrura* at both organ and (heart rate and heart size) individual levels (individual size and mortality), employing acute toxicity exposure.

vii) Chapter 7 examines the influence of EDCs on *M. micrura* at the population level with a focus on generating PNEC values. Additionally, this chapter delves into the potential underlying mechanisms of EDC based on insights from the AOP database.

viii) Chapter 8 provides a comprehensive synthesis of the findings and draws conclusions based on the study outcomes. Moreover, it offers recommendations for future research, outlining areas that warrant further investigation.

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