



UNIVERSITI PUTRA MALAYSIA

***EFFECTS OF DIURON AND 3,4-DICHLOROANILINE (3,4-DCA) ON
REPRODUCTION AND EARLY DEVELOPMENT OF JAVANESE
MEDAKA (*Oryzias javanicus*, BLEEKER 1854)***

IBRAHIM MUSA ADAMU

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By

IBRAHIM MUSA ADAMU

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in
Fulfilment of the Requirements for the Degree of Doctor of Philosophy**

February 2021

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DEDICATION

Dedicated to my late parents, and my family



Abstract to Thesis Presented to the Senate of Universiti Putra Malaysia in fulfilments
of the requirement for the degree of Doctor of Philosophy

**EFFECTS OF DIURON AND 3, 4-DICHLOROANILINE (3, 4-DCA) ON
REPRODUCTION AND EARLY DEVELOPMENT OF JAVANESE MEDAKA
(*Oryzias javanicus*, BLEEKER 1854)**

By

IBRAHIM MUSA ADAMU

February 2021

Chairman : Syaizwan Zahmir bin Zulkifli, PhD
Faculty : Science

The indiscriminate application of pesticides in the environment affects human and wildlife health worldwide. Diuron, a chlorinated phenylurea herbicide and its primary metabolite, 3,4-dichloroaniline (3,4-DCA) exert toxic effects on non-target organisms. Growth, survival, and reproduction are the primary factors determining an organism's population structure in its habitat. Javanese medaka (*Oryzias javanicus*) is an emerging euryhaline model fish distributed around the coastal and estuarine regions of Peninsular Malaysia and other parts of Southeast Asia. The fish is a sentinel species that bioindicates ecosystem health. The objectives of this study were to evaluate the acute toxicity of diuron and 3,4-DCA on different life stages of Javanese medaka, to determine the effect of diuron and 3,4-DCA on the fecundity and reproductive biomarkers of Javanese medaka, and to evaluate the embryotoxicity of diuron and 3,4-DCA on Javanese medaka. Larvae, juveniles, and adults of Javanese medaka were exposed to diuron and 3,4-DCA for 96 hours to determine mortality (96 hour-LC₅₀; 50% lethal concentration to exposed organisms) and behavioural toxicity symptoms. Fish embryo toxicity (FET) test; mortality (LC₅₀) at 10-days and 96-hour for diuron and 3,4-DCA, and subchronic embryonic toxicity (20 days) for both diuron and 3,4-DCA were also evaluated. Reproductively active adults were used for a 21-day diuron and 3,4-DCA fish short-term reproductive assay (FSTRA). All the bioassays were conducted in a semi-static method. The LC₅₀ of diuron and 3,4-DCA for embryo were; 632.5 mg/L (95% CI = 622.6 – 645, R² = 0.98, 10 days) and 32.87 mg/L (95% CI = 27.90 - 38.74, R² = 0.95, 96-hours), respectively. No behavioural toxicity symptoms were observed in both diuron and 3,4-DCA exposed individuals. The curve fit models (concentration-mortality) indicate a low concentration-dependent increase in the mortality rate for diuron and 3,4-DCA exposed adults. The LC₅₀ trend was; larvae > juveniles > adults for both diuron and 3,4-DCA. Adult Javanese medaka was less susceptible to a slight increase in the concentration of diuron and 3,4-DCA. The fecundity of Javanese medaka exposed to diuron and 3,4-DCA were significantly affected ($p < 0.05$). Vitellogenin (VTG) concentration of diuron-exposed females was significantly higher ($p < 0.05$) with 58.62 ± 0.29 ng/L and 55.64 ± 7.60 ng/L at 0.5 mg/L and 1.0 mg/L, respectively, but there was no significant difference

($p > 0.05$) in male fish at the concentrations tested. Non-monotonic dose-response (NMDR) in the gonadal tissues was observed. Abnormal gametogenesis was less prominent in exposed-male Javanese medaka but more obvious in the female Javanese medaka exposed to both diuron and 3,4-DCA. The 20-days exposed embryos to both diuron and 3,4-DCA showed significant difference ($p < 0.05$) NMDR physiological and morphological features. The acute toxicity on the different life stages indicated that diuron was less potent than 3,4-DCA. Conversely, the chronic exposure showed that diuron exerted more toxicity effects to Javanese medaka compared to 3,4-DCA. The disruption of fecundity and alteration in gonads histology implied reproductive toxicity of diuron and 3,4-DCA on Javanese medaka. The NMDR indicates a disruption in normal hormonal activity during embryonic development. The increase in VTG implied an oestrogenic effect on female Javanese medaka but no effect on male Javanese medaka at a concentration up to 1.0 mg/L. The non-linear/NMDR in embryonic development signified disruption of endocrine activity by diuron and 3,4-DCA. Generally, the age of Javanese medaka plays a vital role in its susceptibility to diuron and 3,4-DCA. Both diuron and 3,4-DCA disrupt the hormonal activities during reproduction and embryonic development of Javanese medaka. Therefore, they are potential endocrine-disrupting chemicals (EDCs). This finding strengthens the potential endocrine-disrupting effect of diuron and 3,4-DCA on non-target aquatic organisms. The response of Javanese medaka to diuron and 3,4-DCA can predict the potential developmental and reproductive effects on other exposed aquatic vertebrates. Further research on multi-generation and ecotoxicogenomics to support these results would add information to existing data on the effect of diuron and 3,4-DCA on the survival, growth, and reproduction of Javanese medaka.

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

**KESAN DIURON DAN 3, 4- DIKLOROANILIN (3,4-DCA) TERHADAP
REPRODUKSI DAN PEMBANGUNAN AWAL IKAN BERAS (*Oryzias
javanicus*, BLEEKER 1854)**

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Penggunaan racun perosak secara berleluasa di persekitaran amat mempengaruhi kesihatan manusia dan hidupan liar di seluruh dunia. Diuron, sejenis racun rumput rumput berklorin dan metabolit utamanya, 3,4-dikloroanilin (3,4-DCA) didapati memberikan kesan toksik kepada organisma bukan sasaran. Pertumbuhan, kelangsungan hidup, dan pembiakan semula adalah merupakan faktor utama yang menentukan struktur populasi sesuatu organisma di dalam habitatnya. Ikan beras (*Oryzias javanicus*) adalah merupakan ikan model eurihalin yang baru muncul dan terdapat di sekitar kawasan pesisir dan muara Semenanjung Malaysia dan beberapa bahagian lain di Asia Tenggara. Ikan medaka adalah spesies sentinel yang berupaya menunjukkan kesihatan ekosistem. Antara objektif kajian ini adalah untuk menilai ketoksikan akut diuron dan 3,4-DCA pada tahap kehidupan ikan medaka yang berbeza, untuk menentukan kesan diuron dan 3,4-DCA pada kesuburan dan biomarker pembiakan ikan medaka, dan untuk menilai embriotoksikiti diuron dan 3,4-DCA pada ikan medaka. Larva, juvenil dan ikan medaka dewasa telah didedahkan dengan diuron dan 3,4-DCA selama 96 jam untuk menentukan kematian (96 jam-LC₅₀; kepekatan mematikan 50% kepada organisma terdedah) dan tanda-tanda gejala ketoksikan. Ujian ketoksikan embrio ikan (FET); kematian (LC₅₀) selama 10 hari dan 96 jam untuk diuron dan 3,4-DCA, serta subkronik ketoksikan embrio (20 hari) bagi kedua-dua diuron dan 3,4-DCA juga telah dinilai. Ikan dewasa yang aktif membiak telah digunakan untuk ujian 21 hari diuron dan 3,4-DCA pembiakan jangka pendek ikan (FSTRA). Kesemua ujian-bio dilakukan dengan kaedah separa statik. LC₅₀ diuron dan 3,4-DCA untuk embrio masing-masing adalah; 632.5 mg/L (95% CI = 622.6 - 645, R₂ = 0.98, 10 hari) dan 32.87 mg/L (95% CI = 27.90 - 38.74, R₂ = 0.95, 96-jam). Tiada tanda-tanda gejala ketoksikan yang diperhatikan pada individu yang didedahkan dengan diuron dan 3,4-DCA. Model keluk sesuai (kepekatan-kematian) menunjukkan peningkatan kepekatan-bergantung rendah dalam kadar kematian bagi ikan dewasa yang terdedah dengan diuron dan 3,4-DCA. Trend LC₅₀ adalah; larva > juvenil > dewasa bagi kedua-dua diuron dan 3,4-DCA. Ikan medaka dewasa adalah kurang rentan terhadap sedikit peningkatan kepekatan diuron dan 3,4-DCA. Kesuburan ikan medaka yang terdedah dengan diuron dan 3,4-DCA adalah terjejas secara signifikan (p < 0.05).

Kepekatan Vitellogenin (VTG) pada ikan betina yang terdedah dengan diuron jauh lebih tinggi ($p < 0.05$) dengan bacaan 58.62 ± 0.29 ng/L dan 55.64 ± 7.60 ng/L pada 0.5 mg/L dan 1.0 mg/L, tetapi tidak ada perbezaan yang signifikan ($p > 0.05$) terhadap ikan jantan yang diuji dengan kepekatan tersebut. Tindak balas dos bukan monotonik (NMDR) dalam tisu gonad juga diperhatikan. Gametogenesis yang tidak normal kurang menonjol pada medaka jantan tetapi lebih jelas pada medaka betina yang didedahkan dengan diuron dan 3,4-DCA. Embrio 20 hari untuk kedua diuron dan 3,4-DCA menunjukkan ciri fisiologi dan morfologi NMDR ($p < 0.05$) yang ketara. Ketoksikan akut pada tahap kehidupan yang berbeza menunjukkan bahawa diuron kurang berkesan berbanding 3,4-DCA. Sebaliknya, pendedahan kronik menunjukkan bahawa diuron memberikan kesan toksik yang tinggi kepada ikan medaka berbanding dengan 3,4-DCA. Gangguan kesuburan dan perubahan histologi gonad menunjukkan kesan ketoksikan diuron dan 3,4-DCA kepada pembiakan ikan medaka. NMDR menunjukkan terdapat gangguan aktiviti normal hormon semasa perkembangan embrio. Peningkatan VTG menunjukkan kesan estrogenik kepada medaka betina tetapi tidak ada kesan ditemui pada medaka jantan pada kepekatan sehingga 1.0 mg/L. Tidak linear/NMDR dalam perkembangan embrio menandakan terdapat gangguan aktiviti endokrin oleh diuron dan 3,4-DCA. Umumnya, usia ikan medaka memainkan peranan penting dalam kerentanannya terhadap diuron dan 3,4-DCA. Kedua-dua diuron dan 3,4-DCA mengganggu aktiviti hormon semasa pembiakan dan perkembangan embrio ikan medaka. Oleh itu, mereka adalah bahan kimia yang berpotensi mengganggu endokrin (EDCs). Penemuan ini memperkuat lagi potensi diuron dan 3,4-DCA mengganggu sistem endokrin pada organisma akuatik bukan sasaran. Tindak balas ikan medaka terhadap diuron dan 3,4-DCA dapat meramalkan kesan perkembangan dan pembiakan pada vertebrata akuatik lain yang terdedah. Penyelidikan lebih lanjut mengenai multi-generasi dan ekotoksikogenik untuk menyokong hasil kajian ini akan menambahkan lagi maklumat pada data yang ada mengenai kesan diuron dan 3,4-DCA terhadap kelangsungan hidup, pertumbuhan, dan pembiakan ikan medaka.

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LIST OF SYMBOLS AND ABBREVIATIONS

%	Parts per thousand
AhR	Aryl Hydrocarbon Receptor
ANOVA	Analysis of Variance
CAS	Chemical Abstracts Service
CI	Confidence Interval
DART	Developmental and Reproductive Toxicity
DCA	Dichloroaniline
DMSO	Dimethyl Sulfoxide
DO	Dissolved Oxygen
dpe	Days post exposure
dpf	Days post fertilisation
dph	Days post hatched
EC ₅₀	Median effective concentration
ED	Endocrine disruptor
EDC	Endocrine Disrupting Chemical
ELISA	Enzyme-Linked Immunosorbent Assay
ERA	Ecological Risk Assessment
EU	European Union
etOH	Ethanol
FET	Fish Embryo Toxicity
F _i	<i>i</i> th generation
FSTRA	Fish Short-Term Reproductive Assay
GSI	Gonadosomatic index
H&E	Haematoxylin and eosin
HSI	Hepatosomatic index

K_{oc}	Octanol–water partitioning coefficient
LC_{10}	10% Lethal Concentration
LC_{50}	Median (50%) Lethal Concentration
LOEC	Lowest Observed Effect Concentration
mph	Month post-hatch
NMDR	Non-Monotonic Dose-Response
NOEC	No Observed Effect Concentration
OECD	Organization for Economic Co-operation Development
PE	Pericardial oedema
SEM	Standard Error of Mean
USEPA	United States Environmental Protection Agency
VTG	Vitellogenin
YSE	Yolk-sac oedema
v/v	Volume per volume

CHAPTER 1

INTRODUCTION

1.1 General introduction

As far back as 1950, about 140,000 new chemicals and pesticides have been produced and distributed around the globe (Landrigan et al., 2019). Aquatic organisms accumulate pollutants from contaminated water or through ingestion of contaminated food; therefore the pollutants may lead the contamination not only of the aquatic life but also of the entire ecosystem, including man, through the food chain (Mai et al., 2013). Aquatic ecosystems are frequently contaminated with pesticides from diverse sources, mostly from agriculture run-off, causing potential hazardous effects to non-target living things. The extensive use of biocides as antifoulant and pesticides including their metabolites on the aquatic and terrestrial environment has drawn more concern for the monitoring of these chemicals (Maragou et al., 2011). The persistent and continuous rise in use pesticides cause a major threat to aquatic environments depending on exposure in time (Vieira et al., 2020).

Pesticides are used all over the world as a means of controlling hostile organisms in agricultural activities or as antifouling biocides in paint formulations. They may enter the environment by a variety of routes including through urban (parking lots and residential areas) and run-off from farmlands, leaching or spray drift, contaminated soils and aquatic sediments. Pesticide contamination has now been widely recorded in waters and sediments from a number of European estuaries, coastal areas, and lakes. Once pesticide residues have been released into aquatic environments, they can persist from a few months to a number of years (Mai et al., 2013). Herbicides are one of the major classes of pollutants contaminating coastal ecosystem across the globe (Behrens et al., 2016). Pesticides are not highly selective but are generally toxic to many non-target organisms in aquatic ecosystem, which affect the physiology of organisms (Mukadam & Kulkarni, 2014). In 2014, it was reported that herbicides account for 83% of the total pesticide usage in Malaysia (Dilipkumar, 2017).

Numerous pesticides are described as endocrine disrupting chemicals (EDCs) (Mnif et al., 2011). However, more than 800 different chemical structures present in air, land, drinking water, and foodstuffs of plant and animal origin, consumer goods and personal care products, fuels, pharmaceuticals, and synthetic hormones are EDCs (Scognamiglio et al., 2016). A joined and organized international effort is required to define the effect of EDCs due to current decrease in both the health and populations of human and wildlife (Soares et al., 2014). Exposure to pesticides was linked to carcinogenicity, allergy, neurological and reproductive interference (Mnif et al., 2011).

Diuron, 3-(3,4-Dichlorophenyl)-1,1-dimethylurea; DCMU also known as Dynex; and many other trade names is suspected to be an endocrine disrupting chemical (EDC) and it may likely result into toxic developmental and reproductive effects (Huovinen et al., 2015; Pereira et al., 2015; Pereira et al., 2016; Kamarudin et al., 2020).

Reduction in reproduction might interfere with the population dynamic and survival of Javanese medaka in the future, thereby affecting the general ecosystem structure, and loss local or regional aquatic biodiversity in the distant future. Developmental toxicity studies provide an exclusive standpoint on ecological and organismal health. Organisms at the early developmental stage are the most vulnerable to toxicity of chemical due to a lack of protective mechanisms. Besides, tissue and vital organ systems are differentiating and developing, therefore any disruption or effect can result into lifelong consequences such as deformities. The cumulative effect of these factors makes developing organisms ideal for toxicological research studies (Wagner et al., 2017).

Javanese medaka (*Oryzias javanicus*) inhabit estuarine ecosystems of Peninsular Malaysia, Singapore, Indonesia and Thailand (Yusof, Ismail, & Alias, 2014; Aziz, Zulkifli, Mohamat-yusuff, Azmai, & Ismail, 2017; Ibrahim et al., 2020;). Javanese medaka possessed significant features that make it applicable as the other the widely used model fish and it is considered as sentinel species (Amal et al., 2019; Aziz et al., 2017; Rusni, Sassa, Takehana, Kinoshita, & Inoue, 2020; Salleh et al., 2017).

1.2 Problem statement

There is a substantial increase in the application of herbicides in Malaysia over the recent years (Ng, 2017). Agrochemicals disrupt the normal growth and reproduction of fish as bioindicators for evaluation of the ecosystem health (Celino-Brady et al., 2019). Diuron and its metabolites can be present in soil, surface and ground water, and sediment (Huovinen et al., 2015). Up to 3.9 mg/L of diuron was detected in water bodies around plantations and paddy fields in Malaysia (Mohamat-Yusuff et al., 2020). Degradation of diuron release metabolites that are more toxic in the environment (Coelho-Moreira et al., 2013).

Growth, survival and reproduction are the primary factors that regulate the population structure of any organism in its environment. To our knowledge, research on the early development and reproductive impairments of diuron and 3,4-DCA using sentinel organism in Malaysia is limited. Thus, the need for more toxicological research on native indicator species to evaluate the potential effects of diuron and 3,4-DCA on the reproduction and early development of Javanese medaka.

1.3 Objectives of the study

Toxicological and other biological research using Javanese medaka (*Oryzias javanicus*) has increased in recent times. However, there is still a need for more toxicological studies especially on the growth, survival and reproduction which are the key factors affecting its population structure and dynamics. This species has some special features that make it a suitable aquatic vertebrate model. Reproductive and developmental toxicity studies would give insight on the population dynamics due to biotic and abiotic stressors in the environment. The major aim of this study was to evaluate the effect of diuron and its primary metabolite, 3,4-dichloroaniline (3,4-DCA) on Javanese medaka (*Oryzias javanicus*), and to strengthen its suitability as a sentinel species for monitoring the health of aquatic ecosystems of Malaysia.

The specific objectives of this study were:

1. To determine the acute toxicity of diuron and 3,4-DCA on different life stages of Javanese medaka (*Oryzias javanicus*)
2. To evaluate the effect of diuron on reproduction of Javanese medaka (*Oryzias javanicus*).
3. To determine the effect of diuron on embryonic development of Javanese medaka (*Oryzias javanicus*).
4. To evaluate the effect of 3,4-DCA on reproduction of Javanese medaka (*Oryzias javanicus*).
5. To determine the effect of 3,4-DCA on embryonic development of Javanese medaka (*Oryzias javanicus*).

1.4 Hypotheses

Hypothesis 1:

H_0 : Acute toxicity of diuron and 3,4-DCA is not different between different life stages of Javanese medaka (*Oryzias javanicus*).

H_a : Acute toxicity of diuron and 3,4-DCA is different between different life stages of Javanese medaka (*Oryzias javanicus*)

Hypothesis 2:

H_0 : diuron does not affect reproduction in Javanese medaka (*Oryzias javanicus*).

H_a : diuron affects the reproduction in Javanese medaka (*Oryzias javanicus*).

Hypothesis 3:

H_0 : 3,4-DCA does not affect reproduction in Javanese medaka (*Oryzias javanicus*).

H_a : 3,4-DCA affect reproduction in Javanese medaka (*Oryzias javanicus*).

Hypothesis 4:

H_0 : diuron affects the early development of Javanese medaka (*Oryzias javanicus*) embryo.

H_a : diuron affects the early development of Javanese medaka (*Oryzias javanicus*) embryo.

Hypothesis 5:

H_0 : 3,4-DCA affects the early development of Javanese medaka (*Oryzias javanicus*) embryo.

H_a : 3,4-DCA affects the early development of Javanese medaka (*Oryzias javanicus*) embryo.



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