UNIVERSITI PUTRA MALAYSIA

HEALTH RISK ASSESSMENT OF MERCURY IN MARINE FISH AND FORMULATION OF ITS CONSUMPTION ADVISORY FOR REPRODUCTIVE AGED WOMEN IN SELECTED AREAS IN SELANGOR

PRAVINA DELIGANNU

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By

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

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November 2016

Chair : Prof. Zailina Hashim, PhD
Faculty : Medicine and Health Sciences

Mercury is a potential toxicant that can permanently damage brain, kidney and developing fetus. Fish consumption has been identified as the major exposure route. Being one of the highest marine fish consuming communities in the region, Malaysians are probably at mercury exposure risk. This study was undertaken to assess the health risk of mercury via marine fish intake and to formulate its' consumption advisory among reproductive-aged women, one of the most sensitive group. This was a comparative cross-sectional study, conducted in urban and coastal rural part of Selangor. Women ages between 18 to 49 years old (n=311) participated in the community survey which included screening, interview, anthropometric measurements and hair sample collection. Nineteen commonly consumed marine fish species were identified from interview responses and purchased from five selected fish markets (n=175). Multiwave 3000 (Anton Paar) was used to digest the hair and fish samples while VP90 cold vapor AAS was used for THg quantitation in the samples. Statistical analyses were performed using IBM SPSS version 21. The predictors of THg accumulation in fish muscles, the non-carcinogenic health risk for women, and dietary pattern for THg exposure and the contributors for THg accumulation in hair samples were determined which led to the formulation of marine fish consumption advisory. Analysis showed that the geometric mean THg in fish muscles was 0.31µg/g, with 9% exceeded the WHO guideline (0.5µg/g). Fish with greater weight, live in the demersal ecosystem and of higher trophic levels (≥ 4.0) significantly accumulated more THg ($p<0.05$). Marine fish intake rate differed significantly between coastal rural and urban women (median = 691.1 vs 516.4 g/week; $p<0.003$). Consistently, hazard quotient showed that coastal rural women had higher non-carcinogenic health risks than their urban counterpart. Likewise, hair THg was significantly higher among coastal rural women compared to urban (median = 0.98 vs 0.82 µg/g; $p<0.030$). However, there was no significant difference between the two groups in percentage exceeding the reference dose (49.0 vs 40.9%;

p=0.150). Five principal components (PC) were retained as dietary patterns for Hg exposure but only three were selected based on the elbow of scree plot (54.5% variation). The patterns were Pelagic Fish Diet (PC1&PC3) and Demersal-Predatory Fish Diet (PC2). The significant contributors to hair THg were marital status, the percentage of total body fat, eating fish angled from marine water environment and Hg exposure from pelagic as well as demersal-predatory fish diet (28.3% variation). The formulated consumption advisory showed that marine fish can be consumed for a maximum of 14 servings / week (1 serving ~ 85g). Nevertheless, predatory fish should be limited to 3 - 4 servings / week. As a conclusion, there were Hg contaminations in marine fish species analyzed and possibilities for Hg exposure risk. The formulated consumption advisory identified the types of marine fish that has to be limited which allows the sensitive populations to be continually protected from dietary mercury exposure.

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

PENILAIAN RISIKO KESIHATAN MERKURI DALAM IKAN LAUT DAN FORMULASI PENASIHAT PEMAKANAN DI KALANGAN WANITA BERUMUR REPRODUKTIF DI KAWASAN TERPILIH DI SELANGOR

Oleh

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Merkuri adalah racun yang berpotensi untuk merosakkan otak, buah pinggang dan perkembangan janin selama-lamanya. Pemakanan ikan telah dikenal pasti sebagai laluan pendedahan utama. Sebagai masyarakat dengan kadar pemakanan ikan yang tertinggi di rantau ini, rakyat Malaysia mungkin menghadapi risiko pendedahan merkuri. Kajian ini telah dijalankan untuk menilai risiko kesihatan oleh merkuri melalui pengambilan ikan laut dan merumuskan panduan pemakanannya di kalangan wanita pada umur reprodukif, iaitu salah satu kumpulan yang diaggap paling sensitif. Kajian ini adalah satu kajian keratan rentas perbandingan, yang dijalankan di kawasan bandar dan luar bandar di persisiran pantai, Selangor. Seramai 311 orang wanita yang berumur antara 18 hingga 49 tahun (n=311) telah mengambil bahagian di dalam kaji selidik ini yang merangkumi ujian penyaringan, soal selidik, ukuran antropometri dan pengambilan sampel rambut. Hasil daripada soal selidik yang dijalankan, 19 spesies ikan marin yang biasa dimakan telah dikenal pasti dan dibeli daripada lima pasar terpilih (n = 175). Multiwave 3000 (Anton Paar) telah digunakan untuk mencerna rambut dan sampel ikan manakala VP90 AAS wap sejuk telah digunakan untuk menilai kuantiti THg dalam kedua-dua sampel tersebut. Analisis statistik telah dilakukan dengan IBM SPSS versi 21. Peramal pengumpulan THg dalam otot ikan, risiko kesihatan bukan karsinogenik bagi wanita, corak pemakanan untuk pendedahan kepada THg dan faktor yang menyumbang kepada pengumpulan THg dalam sampel rambut telah dikenalpasti membolehkan penggubalan panduan pemakanan ikan marin. Analisis menunjukkan bahawa purata geometri THg dalam otot ikan adalah sebanyak 0.31μg/g, dengan 9% sampel melebihi garis panduan FAO/WHO (0.5μg/g). Ikan yang lebih berat, hidup dalam ekosistem demersal dan tahap trofik yang lebih tinggi (≥ 4.0) mengumpul lebih banyak THg ($p<0.05$). Kadar pengambilan ikan laut adalah jauh lebih tinggi di kalangan wanita yang tinggal di persisiran pantai berbanding di bandar (median = 691.1 vs 516.4 g/minggu; $p <0.003$). Selari dengan ini, penilaian risiko kesihatan menunjukkan bahawa wanita di

persisiran pantai mempunyai risiko kesihatan bukan karsinogen yang lebih tinggi daripada mereka di bandar. Kumpulan itu juga mempunyai nilai THg dalam rambut yang lebih tinggi daripada mereka di bandar (median = 0.98 vs 0.82 μg/g; $p < 0.030$). Walau bagaimanapun, tidak terdapat perbezaan yang signifikan antara kedua-dua kumpulan tersebut bagi peratusan melebihi dos rujukan untuk THg rambut (1 μg /g) (49.0 vs 40.9%; $p = 0.150$). Tiga komponen (PC) telah dikenal pasti sebagai corak pemakanan bagi pendedahan Hg berdasarkan siku gambarajah scree (54.5% variasi). Corak yang dikenal pasti adalah Diet Ikan Pelagik (PC1 & PC3) dan Diet Ikan Demersal-Pemangsa (PC2). Faktor-faktor yang menyumbang kepada pengumpulan THg di dalam rambut adalah status perkahwinan, peratusan jumlah lemak badan, pemakanan ikan dipancing dari persekitaran air marin dan pendedahan Hg dari diet pelagik serta ikan demersal-pemangsa (variasi 28.3%). Panduan pemakanan menunjukkan bahawa ikan laut boleh dimakan sebanyak 14 hidangan/minggu (1 hidangan ~ 85g) maksimum. Namun begitu, ikan pemangsa harus dihadkan kepada 3 - 4 hidangan/minggu. Kesimpulannya, terdapat pencemaran Hg dalam spesies ikan laut yang telah dianalisis dan potensi risiko pendedahan kepada Hg. Penggubalan panduan pemakanan telah mengenal pasti jenis ikan marin yang perlu dihadkan supaya kumpulan sensitif terus dilindungi daripada pendedahan kepada merkuri melalui pemakanan.

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nirvighnam kuru me deva sarvakaaryeshu sarvada

saraswati namastubhyam varade kaama roopini
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gurur brahmaa gurur vishnu gurur devo maheshwarah
guru saakshaat parabrahma tasmai shri guruve namah

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I certify that a Thesis Examination Committee has met on 25 November 2016 to conduct the final examination of Pravina Deligannu on her thesis entitled "Health Risk Assessment of Mercury in Marine Fish and Formulation of its Consumption Advisory for Reproductive Aged Women in Selected Areas in Selangor" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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Declaration by graduate student

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AAS	Atomic Absorption Spectroscopy
ADD	Average Daily Dose
ADHD	Attention-Deficit Hyperactivity Disorder
AE	Absorption Efficiencies
ANVISA	Brazilian Health Surveillance Agency
AOAC	Association Of Analytical Communities
As	Arsenic
ASD	Autism Spectrum Disorder
ATL	Advisory Tissue Level
BMI	Body Mass Index
BP	Blood Pressure
Bw	Body Weight
Cd	Cadmium
CH_3Hg^+	Methylmercury Cation
CNS	Central Nervous System
CNSA	Chinese National Standard Agency
Cr	Chromium
DHHS	North Carolina Department Of Health And Human
DOC	Dissolved Organic Compound
DOS	Department Of Statistics
EU	European Union
EWI	Estimated Weekly Intake
FFQ	Food Frequency Questionnaire
GIT	Gastrointestinal Tract
FAO	Food and Agriculture Organization of the United Nations
HCl	Hydrochloric Acid
H_2O_2	Hydrogen Peroxide
H_2SO_4	Sulphuric Acid
Hg	Mercury
[(HgeSe)n]m	Mercury Selenoprotein Complex
HgS	Mercuric Sulphide / Cinnabar
HgO	Mercuric Oxide
$HgCl_2$	Mercuric Chloride
HgSe	Mercury Selenide Complex
HNO_3	Nitric Acid
HRA	Health Risk Assessment
HQ	Hazard Quotient
IAEA	International Atomic Energy Agency
ICC	Intra-Class Correlation Coefficient
IHg	Inorganic Mercury
JECFA	Joint FAO/WHO Expert Committee On Food Additives
JKEUPM	Ethic Committee For Research Involving Human Subject
KDHE	Kansas Department Of Health And Environment
KMO	Keiser-Meyer-Olkin Measure Of Sampling Adequacy
LKIM	Fisheries Development Authority Of Malaysia
LOD	Limit Of Detection

LOQ	Limit Of Quantification
MANS	Malaysian Adult Nutrition Survey
MeHg	Methylmercury
Me-Hg-Cl_2	Methylmercuric Chloride
MHLW	Ministry Of Health, Labour And Welfare, Japan
MIR	Maximum Intake Rate
MOH	Ministry Of Health, Malaysia
MWQCS	Malaysian Marine Water Quality Criteria And Standards
NEI	United States National Emissions Inventory
NHSF	National Household Sampling Frame
NOAEL	No Observable Adverse Effect Level
Pb	Lead
PC	Principal Component
PCA	Principal Component Analysis
PNN	National Fishermen's Association
PPS	Probability Proportionate To Size
PTWI	Provisional Tolerable Weekly Intakes
RfD	Reference Dose
R-Hg	Alkyl-Mercury
RSD	Relative Standard Deviation
Se	Selenium
SFA	Fisherman's Associations of Selangor
TDI	Tolerable Daily Intake
THg	Total Mercury
USDOA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
VIF	Variance Inflation Factor
WHR	Waist To Hip Ratio
WWF	World Wide Fund For Nature

CHAPTER 1

INTRODUCTION

1.1 Background

Mercury (Hg) is a heavy metal that occurs in the environment naturally and through human activities (Salehi et al., 2010), the latter being the major pathway introducing Hg into aquatic system (Church et al., 1998). Mercury emission from industrial activities was expected to rise 5% a year (Zhang et al., 2002), largely caused by coal smoke (Zahir et al., 2005). According to the United States Environmental Protection Agency (USEPA), National Emissions Inventory (NEI), about 52.7% of Hg emissions were from coal-fired electrical utilities. Other sources include power generation, chlor-alkali production and waste incineration (UNEP, 2002).

Scientists are worried about the rising concentrations of Hg in the air, sediment and water for it is persistent in the environment and accumulates in aquatic organisms. In addition, Hg has been recognized as the most toxic metal found in the freshwater and marine environment (Churchill, Meathrel and Suter, 2004). Mercury released to atmosphere settles onto sediment and aquatic environment where it is microbiologically transformed into organic form namely methylmercury (MeHg) through a process called methylation (Zahir et al., 2005). Methylmercury is the most toxic form of Hg and the most commonly occurring Hg species in biological materials.

Since Minamata disease in 1950, multiple pathways of Hg exposure have been recognized. Among the pathways are air, water, food, pharmaceuticals and cosmetic products. Nevertheless, fish consumption is the foremost Hg exposure route for human, exclusively MeHg (Ni et al., 2011; WHO 2008 and Dietz et al., 2000). This is due to the fact that MeHg has a strong tendency to bioaccumulate in seafood (Houserova et al., 2007). Fish of higher trophic in the food web accumulated Hg at a greater level, a large proportion as MeHg (NRC, 2000). Being at the top of food chain, humans are the group most affected by Hg toxicity owe to biomagnificent (Zahir et al., 2005). Daily Hg dose depends on an individual's' dietary habits such as fish intake rate and Hg contamination in the consumed fish (Chapman and Chan, 2000).

The extent of Hg exposure in population can be assessed by detecting Hg concentration in several biological samples such as blood, hair, urine as well as toe and finger nail (Molina-Villalba et al., 2015; Sakamoto et al., 2015; Schoeman et al., 2010; WHO, 2008). However, hair THg was frequently used as the biomarker to assess Hg exposure via fish consumption (Hajeb et al., 2008; WHO, 2008; Ohno et

al., 2007; Dakeishi et al., 2005). This is because 80% - 90% of hair THg present in MeHg form which is also the main Hg species found in fish and seafood.

1.2 Problem Statement

From a dietetic standpoint, fish is an important source of various nutrients. Oily fish and other seafood products contain high levels of protein, minerals, vitamins, and omega-3 fatty-acids. These nutrients are attributed to lowering the risks of coronary heart diseases and stroke (Din, Newby, and Flapan, 2004).

Fish has been the main supply of cheap and healthy protein to a large percentage of the world's population and is the main source of protein in Asian's diet particularly Southeast Asian. Fish consumption have seen an increasing pattern among Malaysians from 1980 to 2002 (Tan & Lee, 2005) and continued to increase for up to 50000 metric tons in 2014 (Figure 1.1). Food and Agriculture Organisation (FAO) reported that Malaysia is one of the top fish-consuming countries in Asia (above 40kg/capita/year), almost double the average in Thailand and China, although still below the levels in Japan and South Korea (Teh, 2012).

According to World Wide Fund for Nature (WWF), Malaysian's count on seafood, especially fish as their primary source of animal protein and are the highest seafood consumer in the Southeast Asia in terms of per capita intake. Apparently, this is in agreement with the total protein intake between 1960 and 1990 whereby average Malaysian's protein intake from marine products grew from 49% to 62% of the total protein count (Ahmad et al., 2003). In another study, Ahmed et al. (2011) found that annual per capita fish consumption increased from 49 kg in 2000 to 53 kg in 2005 while Ministry of Health Malaysia (2006) reported that average Malaysian consumed 59–62.5 kg/year of marine fish annually. Malaysian Adult Nutrition Survey (MANS) found that 51.3% rural and 33.6% urban population consumes fish at least once a day (Norimah et al., 2008). Among female university students (n=347), Gan et al. (2011) found that 81.8% (n=284) consumed fish at least once a week with 33.8% (n=117) daily.

While epidemiological studies have suggested links between fish consumption and reduction in risk of succumbing many chronic diseases, it is also one of the main source of exposure to several environmental pollutants, including Hg. Mercury, mainly MeHg, is found predominantly in muscle tissues of fish (~90%) rather than the fatty deposits. For this reason, trimming and skinning does not reduce the MeHg content in fish muscle (WHO, 2008). Methylmercury is remarkably toxic, stable in the environment and bioaccumulative with long biological half-life, 44 to 80 days (UNEP, 2002). To make it worse, MeHg are attached to thiol group of cysteine residues in fish protein (Clarkson & Magos, 2006) which are not destroyed by any cooking or cleaning process (Li et al., 2010; WHO, 2008).

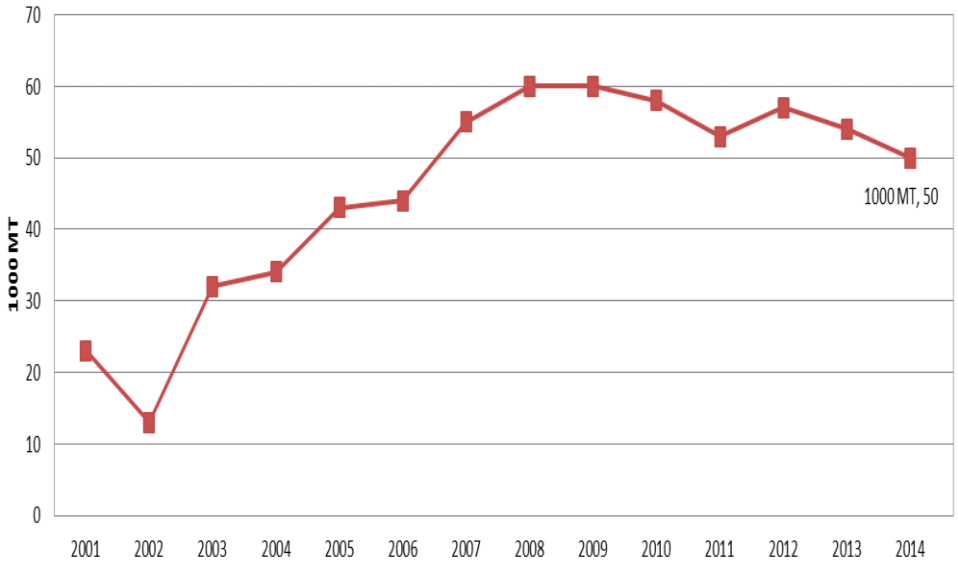

Figure 1.1: Malaysia: Fish Meal Domestic Consumption by Year
(Source: US DOA)

Mercury is a potential toxicant to human (Tchounwou et al., 2012; WHO, 2008; Duffus et al., 2002) and developing brain is the prime target organs particularly by MeHg (Salehi et al., 2010). Methylmercury is able to cross the placental–blood and blood-brain barrier, accumulating at a greater concentration in fetus, ultimately causing impairments related to fetal brain development (Ni et al., 2011; WHO, 2008). Animal data showed MeHg concentration in the brain of new-born to be five times the corresponding levels in the mother (Clarkson & Magos, 2006). Hence, maternal MeHg exposure is a matter of great concern. Inorganic Hg (IHg) exposure from fish intake is also a threat for it is absorbed in the gastrointestinal tract (GIT) to express urological defects (Cheng et al., 2009; WHO, 2008; Ohno et al., 2007).

Despite the excessive fish intake rate among Malaysians, some studies have reported that certain fish species collected from Malaysian local markets or coastal waters had high Hg concentration (Hajeb et al., 2009; Agusa et al., 2005; Yap, Ismail & Tan, 2003; Ahmad et al., 2014). This can be explained by the fact that an important fishing ground of Malaysia, the Straits of Malacca, is seriously contaminated by international shipping activities, heavy industrialization and urbanization, and oil spills (Agusa et al., 2007) that may ultimately release Hg into the aquatic environment.

Based on the Hg toxicity reported, the population at utmost risk are fetus, children and adults' especially pregnant, breastfeeding and future mothers (reproductive aged women) (Hesse, 2005). Not only that, having fishing as their main trade, population of fishing villages are at higher risk too owe to frequent fish consumption. It is therefore crucial to examine the fish consuming pregnant, lactating and potential mothers and children in Malaysia for exposure risk. Regrettably, to date there is

neither a systematic study focused on these groups of population nor any guidelines developed to reduce their exposure. Hence, an assessment is desired for these groups along with the development of consumption advisory to protect their health.

1.3 Significance of the Study

This study produced information on mercury exposure status among one of the most sensitive population for Hg exposure, women at reproductive age, in Selangor, the densest and developed state of Malaysia. Mercury contamination status examined in the marine fish commonly consumed delivered a better understanding on the safe level of Malaysian marine fish and the health risk upon consumption.

According to Mercury and Fish Consumption Fact Sheet (2006), until Hg contamination is reduced, health of the sensitive population shall be protected by avoiding certain kinds of fish and eating other kinds of fish instead. In this study, an enhanced picture on the dietary pattern for Hg exposure via fish consumption was envisaged. This is especially important for population that eat various kinds of fish such as Malaysian. The dietary pattern of greater risk was ruled out via available statistical tools which aided in the formulation of consumption advisory on the types of fish to be avoided, limited and increased consumption.

1.4 Objectives of the Study

1.4.1 General Objective

This study aims to fulfil the following general objective:

To assess the health risk of dietary mercury exposure via marine fish intake among women at reproductive age and formulate marine fish consumption advisory.

1.4.2 Specific Objectives

This study aims to fulfil the following specific objectives:

1. To determine the types of marine fish commonly consumed by the respondents, the fish characteristics (length, weight, trophic level, habitat and feeding habit), total mercury concentration (mg/kg) in fish muscles and factors predicting the total mercury accumulation in fish muscles (species, length, weight, trophic level, habitat and feeding habit).
2. To determine and compare the dietary intake of fish, shellfish and processed seafood as well as the dietary patterns for mercury exposure via marine fish consumption between the two groups of respondent.

3. To estimate the average daily dose (µg/kg bw-day) of mercury via marine fish consumption and the non-carcinogenic health risk through marine fish ingestion exposure pathway.
4. To determine the concentration of total mercury (µg/g) in hair samples and compare between the two groups of respondent as well as between the dietary patterns for mercury intake.
5. To determine the selected factors (respondent's characteristics; dietary intake of processed seafood, shellfish and freshwater fish; dietary pattern for mercury intake via fish consumption) that significantly contribute to hair total mercury concentrations.
6. To formulate marine fish consumption advisory for women at reproductive age.

1.5 Research Hypothesis

1. There is a significant association between total mercury accumulation in fish muscles and the fish characteristics (length, weight and trophic level).
2. There is a significant difference in mean total mercury concentration between the pelagic and demersal as well as between the carnivorous and non-carnivorous fish.
3. At least one of the fish characteristics (habitat, feeding habit, trophic level and body size) significantly predicts the total mercury concentration in fish muscles.
4. There is a significant difference in dietary intake of fish, processed seafood and shellfish as well as the dietary patterns for mercury exposure via marine fish consumption between the two groups of respondent.
5. There is a significant difference in the hair total mercury between the two groups of respondent and between the dietary patterns for mercury exposure.
6. At least one of the factors (respondent's characteristics; dietary intake of processed seafood, shellfish and freshwater fish; patterns of dietary mercury intake via marine fish) significantly related to hair total mercury concentrations.

1.6 Definition of Terms

a) Mercury

Mercury (Hg) is a heavy metal and the one and only metallic element that exist in liquid form at room temperature. This naturally occurring element is at least 5 times denser than water. Mercury can be found in the 'd' block of periodic table at Group XII and period VI with an atomic number of 80, mass number of 200.592 g/mol, electron configuration of [Xe] $4f^{14}5d^{10}6s^2$ and ^{202}Hg as the key isotope. In this study, the Hg concentration measured in hair and fish muscles was THg.

b) Women at Reproductive Age

Reproductive age is the child bearing age range of women, assumed to be 15-44 or 15-49 years of age (WHO, 2008). In this study, the age limit was 18-49 to exclude female who fall under child category according to Malaysian Child Act 2001.

c) Biomarker

Gil and Hernández (2009) described biomarker as a tool for exposure assessment to harmful substances and evaluation of temporal changes in populations exposed to a defined environmental contaminant. Biomarkers of this study are total mercury (THg) in human hair and fish muscles.

d) Habitat

Habitat, in this study was referred to marine fish habitat. As far as marine fish are concerned, habitat can be classified as demersal and pelagic. Demersal fish generally live on or near the ocean floor usually at depths of more than 20 metres whereas their pelagic counterpart normally inhabits the surface or the middle depths of the ocean (Marine WATERs, 2016).

e) Feeding Habit

FishBase Information (2015) classified feeding habits of fish as carnivorous, omnivorous and herbivorous. Carnivorous are fish preying on other animals and are also known as predators; herbivorous feeds on plants and plankton only and commonly referred as planktivorous; omnivorous feeds on both plant and animal materials.

f) Trophic Level

Trophic level or troph describes the feeding positions of fish in a food chain or web and take a numeric value. The lowest trophic level would be 1.0 for producers or autotrophs which comprises mainly of plants followed by 2.0 for primary consumers, 3.0 for secondary consumers, 4.0 for tertiary consumers and 5.0 for quaternary consumers (Osborne, 2000; Mathews 1993).

A single species may form part of many different food chains and not always occupying the same trophic level in each chain (Tolle and Toole, 1999). Therefore,

trophs are estimated considering both the diet composition and mean trophic level of the food items (FishBase Information, 2015), and may take any value from 1.0 to 5.0.

$$\text{Troph} = 1 + \text{mean troph of the food items}$$

g) Health Risk Assessment

In this study, health risk assessment (HRA) estimated the nature and probability of Hg exposure via marine fish consumption. The risk acceptability is given in Table 1.1. In cases where the non-cancer HQ does not exceed unity (HQ < 1), it is assumed that no chronic risks are likely to occur.

Table 1.1: Risk Acceptability for Non-Carcinogenic Health Effect

Hazard Quotient (HQ)	
>1	Unacceptable
<1	Acceptable

(Source: USEPA, 2007)

h) Dietary Pattern

Dietary patterns reflect the combinations of food intake and its relationship with disease risk (Hu 2002). In this study, dietary patterns are defined as combination intake of different marine fish species that track together to cause Hg exposure.

i) Fish Consumption Advisory

Fish consumption advisory is a recommendation issued to limit or avoid eating certain species of fish caught from specific water bodies or types of water bodies due to chemical contamination (Fish and Shellfish Advisories and Safe Eating Guidelines, 2016). In this research, fish consumption advisory is defined as the guideline developed for women at reproductive age on weekly tolerable marine fish servings to reduce Hg exposure.

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