



**UNIVERSITI PUTRA MALAYSIA**

***AWARENESS LEVEL OF DRINKING WATER QUALITY,  
PHARMACEUTICAL HANDLING AND OCCURRENCE OF  
PHARMACEUTICAL RESIDUES IN DRINKING WATER WITH ITS  
POTENTIAL HUMAN HEALTH RISK AMONG PUTRAJAYA  
RESIDENTS***

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AMONG PUTRAJAYA RESIDENTS**

**BY**

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**Thesis submitted in fulfilment of the requirement for the degree of Bachelor  
Science (Environmental and Occupational Health) from the Faculty of Medicine  
and Health Sciences, Universiti Putra Malaysia**

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## **ABSTRACT**

### **AWARENESS LEVEL OF DRINKING WATER QUALITY, PHARMACEUTICAL HANDLING AND OCCURRENCE OF PHARMACEUTICAL RESIDUES IN DRINKING WATER WITH ITS POTENTIAL HUMAN HEALTH RISK AMONG PUTRAJAYA RESIDENTS**

**MAIZATUL ZAHIRAH BINTI MOHD RASHID**

**Introduction:** The occurrence of pharmaceuticals throughout aquatic environment such as lakes, river and drinking water sources has been widely discussed and raised questions on potential impact to human health. **Objectives:** This study assessed levels of knowledge, attitude and practice of drinking water quality and human pharmaceuticals handling involving Putrajaya residents and investigated pharmaceuticals residues occurrence to evaluate the potential human health risks in Putrajaya, Malaysia. **Methodology:** The study was conducted by distributing questionnaires and collecting drinking water samples from 80 households in Putrajaya. The drinking water samples undergo in-vitro digestion process and were extracted by using solid phase extraction then analysed by Enzyme-linked Immunosorbent Assay (ELISA) for the detection of nine selected pharmaceuticals residues (amoxicillin, caffeine, chloramphenicol, ciprofloxacin, dexamethasone, diclofenac, nitrofurazone, sulfamethoxazole, and triclosan). The risk quotient (RQ) was calculated to assess the potential health risks. **Results:** This study determined the knowledge of Putrajaya residents for drinking water quality and human pharmaceuticals handling was poor, the attitude and practice were considered good. Revealed the pharmaceuticals detection in all drinking water sample with the highest concentration of caffeine (0.410 ng/L) followed by triclosan (0.363 ng/L), dexamethasone (0.323 ng/L), ciprofloxacin (0.322 ng/L), amoxicillin (0.311 ng/L), nitrofurazone (0.186 ng/L), chloramphenicol (0.172 ng/L), sulfamethazole (0.165 ng/L) and diclofenac (0.138 ng/L). Results from RQ ratio which are less than 1 ( $RQ < 1$ ) for all pharmaceuticals indicated no appreciable potential health risk from all drinking water samples. **Conclusion:** This quantitative occurrences of pharmaceutical residues in drinking water can be considered as proactive human health risk assessment and help in water risk management and regulation in Malaysia.

**Keywords:** Pharmaceuticals, drinking water, awareness, potential health risk

## ABSTRAK

### TAHAP KESEDARAN KUALITI AIR MINUMAN, PENGENDALIAN FARMASEUTIKAL DAN TABURAN SISA FARMASEUTIKAL DALAM AIR MINUMAN DENGAN POTENSI RISIKO KESIHATAN DI KALANGAN PENDUDUK DI PUTRAJAYA, MALAYSIA

MAIZATUL ZAHIRAH BINTI MOHD RASHID

**Pengenalan:** Taburan farmaseutikal di seluruh persekitaran akuatik seperti tasik, sungai dan sumber air minum telah dibincangkan secara meluas dan menimbulkan persoalan mengenai potensi kesan kepada kesihatan manusia. **Objektif:** Kajian ini menentukan pengetahuan, sikap dan amalan kualiti air minuman dan pengendalian farmaseutikal melibatkan warga Putrajaya dan menyiasat taburan sisa-sisa farmaseutikal dalam air minuman dan menilai potensi risiko kesihatan manusia di Putrajaya, Malaysia. **Kaedah:** Kajian ini dilakukan dengan mendedarkan borang soal selidik dan mengumpul sampel air minuman dari 80 isi rumah di Putrajaya. Sampel air minuman menjalani proses pencernaan '*in vitro*' dan telah diekstrak dengan menggunakan pengekstrakan fasa pepejal yang kemudian dianalisis melalui '*Enzyme-linked Immunosorbent Assay*' (ELISA) untuk pengesanan sembilan sisa farmaseutikal terpilih (amoxicillin, kafein, chloramphenicol, ciprofloxacin, dexamethasone, diclofenac, nitrofurazone, sulfamethoxazole, dan triclosan). diperolehi untuk nilai paras setara air minum (DWEL) bagi setiap farmaseutikal. Nisbah risiko (RQ) dinilai dengan membandingkan DWEL dengan kepekatan farmaseutikal yang diukur. Hasilnya dianggap tidak ada risiko kesihatan yang berpotensi apabila nisbahnya kurang dari 1. **Hasil:** Kajian ini menentukan pengetahuan penduduk Putrajaya untuk kualiti air minum dan pengendalian farmasi manusia adalah rendah, sikap dan praktik dianggap tinggi. Sisa farmaseutikal dapat dikesan dalam semua sampel air minum dengan kepekatan kafein (0.410 ng / L) diikuti oleh triclosan (0.363 ng/L), dexamethasone (0.323 ng/L), ciprofloxacin (0.322 ng/L), amoxicillin (0.311 ng/L), nitrofurazone (0.186 ng/L), chloramphenicol (0.172 ng/L), sulfamethazole (0.165 ng/L) and diclofenac (0.138 ng/L). Hasil daripada nisbah RQ yang kurang daripada 1 ( $RQ < 1$ ) untuk semua farmaseutikal menunjukkan tiada risiko kesihatan manusia yang ketara daripada semua sampel air minuman. **Kesimpulan:** Taburan kuantitatif terhadap sisa farmaseutikal dalam air minuman boleh dianggap sebagai penilaian risiko kesihatan manusia yang proaktif dan membantu dalam pengurusan dan peraturan risiko air di Malaysia.

Kata kunci: *Farmaseutikal, air minuman, kesedaran, potensi risiko kesihatan*



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## **LIST OF ABBREVIATIONS**

|              |                                             |
|--------------|---------------------------------------------|
| <b>WHO</b>   | <b>World Health Organization</b>            |
| <b>EDCs</b>  | <b>Endocrine Disrupting Compounds</b>       |
| <b>EPs</b>   | <b>Emerging Pollutants</b>                  |
| <b>ELISA</b> | <b>Enzyme-linked Immunosorbent Assay</b>    |
| <b>DOE</b>   | <b>Department of Environment</b>            |
| <b>SPE</b>   | <b>Solid Phase Extraction</b>               |
| <b>ADI</b>   | <b>Acceptable Daily Intake</b>              |
| <b>DWEL</b>  | <b>Drinking Water Equivalent Level</b>      |
| <b>STP</b>   | <b>Sewage Treatment Plant</b>               |
| <b>CNS</b>   | <b>Central Nervous System</b>               |
| <b>NSAID</b> | <b>Nonsteroidal Anti-Inflammatory Drugs</b> |
| <b>USEPA</b> | <b>US Environmental Protection Agency</b>   |
| <b>RQ</b>    | <b>Risk Quotient</b>                        |
| <b>EC</b>    | <b>Electrical conductivity</b>              |
| <b>ND</b>    | <b>Not detected</b>                         |
| <b>MOH</b>   | <b>Ministry of Health</b>                   |



## **CHAPTER 1**

### **INTRODUCTION**

#### **1.1 Background**

Emerging pollutants (EPs) refer to any synthetic or naturally occurring compound that not being concerned and commonly monitored over the past decades but now are more widely detected and have the potential to enter the environment and cause known or suspected adverse ecological and human (UNESCO, 2017). Similarly like plasticizers, surfactants, pesticides and others, pharmaceuticals are one of the EPs (Geissen et al., 2015). Pharmaceuticals are synthetic or natural chemicals that can be found in prescription, over-the-counter drugs use for treatment and prevention of disease (WHO, 2012). According to Deo (2014), pharmaceutical products have an important role in the treatment and prevention of disease in both humans and animals. Pharmaceuticals evoke pharmacological effects and give significant benefits to society such as for treatment of diseases, injuries, or illnesses, in addition to their use as personal care products (Bulaj et al., 2016). However, a global view on understanding what is happening when these pharmaceuticals are discharged into the environment is not widely acknowledged.

Nowadays, the demand for pharmaceuticals by consumer is keep increasing and the pharmaceutical industry is growing rapidly (Suchomel et al., 2015). In Malaysia, there was an increment in the utilisation of drug by 31.4% in 2014 compare to 2011 and according to Malaysian Statistics on Medicine (2014), the total utilisation

of medicines in the country are 569.55 (DDD/1,000 inhabitants/day) in 2014. In addition, the expenditure for pharmaceuticals in the Ministry of Health (2015) has grown almost 3-fold within 10 years which is the MOH annual drug spending increased from RM 808 million in the year 2004 to RM 2.38 billion in the year 2014. Increment in the utilization and expenditure of pharmaceuticals indicate a high usage of pharmaceuticals in the country. Consequently, the high pharmaceuticals usage has led to the continual release of a wide array of pharmaceutical chemicals into our environment especially from human and veterinary applications.

According to Gaffney et al., (2015) and Leung et al., (2013), human and veterinary applications are the main sources of pharmaceuticals residues to be release into the environment. The presence of pharmaceuticals residues although in very low concentration in aquatic environment can gives critical effects to the ecosystem and human health. This is due to pharmaceutical are known as endocrine disrupting compound which is a group of exogenous organic substances that disturb the endocrine system and the physiological function of hormones. Those EDCs can interfere the hormone at any stage of human development and alter its action. Referring to World Health Organization report (Bergman et al., 2012) the exposure to these compounds during foetal development and puberty plays role in increasing the incidence of reproductive disease (endometriosis, infertility and early puberty), cancer (breast or prostate), nervous system diseases (Alzheimer's, Parkinson's, behavioural and learning disorders), infections, asthma, hypertension, obesity and diabetes in humans.



## **1.2 Problem Statement**

Occurrence of pharmaceuticals residues has been documented in drinking water worldwide by Finnegan, Simonson, & Meyer (2010), Padhye et al. (2014) and Benotti et al. (2009) in US, Gaffney et al. (2015) in Portugal, Leung et al. (2013) in China and Al-Badaii & Shuhaimi-Othman, (2014) in Malaysia. Consequently, pharmaceuticals residues can enter drinking water as none of the wide range of drinking water treatment plant process designed specifically to remove pharmaceuticals (WHO 2011). In Malaysia, the level of pharmaceuticals in drinking water is less known. Up to the present time, only a few of published studies reported the pharmaceutical concentrations found in drinking waters of Malaysia (Al-Badaii & Shuhaimi-Othman, 2014). Besides, there are knowledge gaps in terms of study on wider range pharmaceutical (WHO, 2012).

The continuously releases and chronic exposure to these chemicals can result not only in subtle effects on aquatic species but could also pose health risk associated with consuming contaminated drinking water over a lifetime. Some of these pharmaceuticals have been linked to adverse health and ecological effects including endocrine disruption, antibiotic resistance, inhibition of primary productivity, alteration of chemical communication, and others (Daughton and Ternes, 1999). According to (Crawford et., 2017), pharmaceutical is one of the endocrine disrupting chemicals present in aquatic environment. EDCs will mimic, block or interfere with hormones in the body's endocrine system and lead to possible effects which are reduction in male fertility, early puberty in females and cancer. In addition, human health impact may occur when people might have allergies to some of the

pharmaceuticals that contaminate the water. Previous investigations only provide limited data on the occurrence of pharmaceuticals in drinking water. Following that, the potential risk to human health of current drinking water that reaches the residential areas remain unknown. Moreover, there are limited studies have been conducted on the bioavailability of pharmaceuticals in drinking water of Malaysia.

### **1.3 Research Justification**

In Malaysia, the level of pharmaceuticals in drinking water is less known. Even there are several monitoring and studies on this issue, but the information and awareness on emerging pollutions still lacking. As occurrence of pharmaceuticals in drinking water in other countries was identified from several studies, it become major concern to increase the knowledge and findings for conditions of water system in Malaysia as efforts to improve the quality of environment and human health. This study is useful for authorities to improve the management of drinking water quality for the community and in expanding the limited data and information available on the distribution and occurrence of pharmaceuticals in Malaysia. Therefore, a further investigation must be done to fill the knowledge gap for the consumer to get safe drinking water.

Furthermore, this study analysed the bioavailability of pharmaceuticals concentration and not the total active pharmaceuticals. Total active pharmaceuticals will determine all the chemicals that are present in the investigated compound whereas in bioavailability, it only determines the proportion of the ingested compound that reaches systemic circulation and can exert its toxic effects (Yuswir et al, 2013).



Understanding bioavailability of pharmaceuticals concentration would be a better appropriate method for determination of potential human health risk from drinking water of residential area. The studies of occurrence and potential health risk of pharmaceuticals residues in drinking water will be beneficial in future studies even the specific studies on EDCs impact due to pharmaceutical pollutions is still inadequate. Therefore, this research was done to fill in the gap of knowledge of potential health risk in the intake of pharmaceutical residues via drinking water and can be consider as proactive human health risk assessment of pharmaceuticals in Malaysia drinking waters.

#### **1.4 Conceptual Framework**

Figure 1.1 shows the conceptual framework of the study. This study is focus on two parts which are on the awareness level of drinking water quality, pharmaceutical handling and occurrence of pharmaceuticals residues in drinking waters with its potential human health risks. Pharmaceuticals can enter the surface water through pharmaceuticals human use and veterinary use. Inefficiency of drinking water treatment plant technologies that unable to filter the pharmaceuticals that contain in the surface water might cause the residents to indirectly consume pharmaceuticals residues via drinking water and gives potential health risk

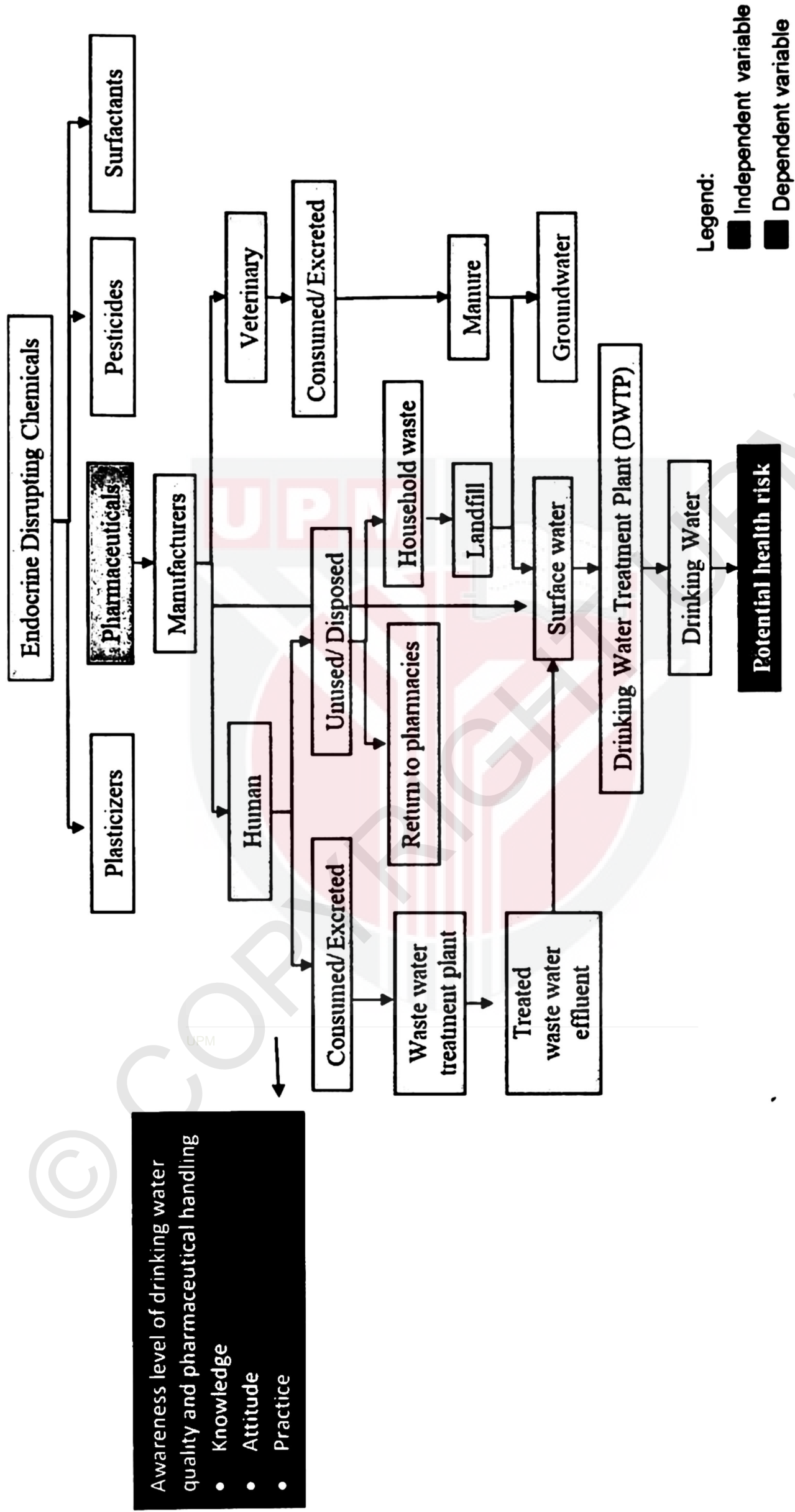


Figure 1.1: Conceptual Framework involving drinking water

## **1.5 Research Objectives**

### **1.5.1 General Objective**

- i) To determine the awareness level of drinking water quality, pharmaceutical handling and occurrence of pharmaceutical residues in drinking water with its potential human health risk in Putrajaya residential area.

### **1.5.2 Specific Objectives:**

- i) To determine the knowledge, attitude and practice of drinking water quality and human pharmaceuticals handling involving Putrajaya residents
- ii) To determine the bioavailability of pharmaceutical concentration in drinking water from Putrajaya residential area
- iii) To assess potential human health risk associated with pharmaceutical residues in drinking water from Putrajaya residential area

## **1.6 Hypothesis**

- i) There is no potential human health risk associated with pharmaceutical residues in drinking water from Putrajaya residential area

## **1..7 Definition of Terms**

### **1.7.1 Pharmaceuticals**

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs that contain active ingredients that evoke pharmacological effects and confer significant benefits to society (WHO, 2011)

### **1.7.2 Drinking Water Treatment Plant (DWTP)**

Process to treat surface water before the water is supplied to consumers. In Malaysia treatment technologies such as filtration, aeration, sedimentation, coagulation and flocculation are design to remove heavy metal, taste, odour, coliform, etc in drinking water (Forum Air Malaysia, 2014).

### **1.7.3 In-vitro Digestion**

In vitro digestion model by Minekus et al., (2014), was used to study the structural changes, digestibility, and release of food components. It seeks to mimic the processes that occur in three areas of human digestive system: mouth, stomach, and small intestine.



#### **1.7.4 Solid Phase Extraction (SPE)**

Solid phase extraction (SPE) is defined as useful sample preparation technique that most often to prepare liquid samples, including semi-volatile or non-volatile analytes. Besides, it is rapid, easy to be performed and can be automated. The information is according to Guide to Solid Phase Extraction by Sigma-Aldrich (1998), which problems that related with liquid or liquid extraction also can be avoided.

#### **1.7.5 Enzyme-linked Immunosorbent Assay (ELISA)**

ELISA will be used to quantitatively analyse the sample extraction to detect occurrence of pharmaceuticals and the absorbance will be read by microplate reader at their different value of wavelength. It is a cost efficient tool for the specific and highly sensitive detection of many toxic analytes in food and environmental samples as well as clinical diagnosis. (Hlaváček et al., 2016).

#### **1.7.6 Human Health Risk Assessment**

The assessment through Risk Quotient (RQ) involving determination acceptable daily intake (ADI) and Drinking Water Equivalent Level (DWEL) values. The method for health risk assessment in this study was adapted from Leung et al., (2013) which the ratio of measured concentration to DWEL value with ratios less than 1 are presumed to present no appreciable risk to human health.

## **CHAPTER 2**

### **LITERATURE REVIEW**

#### **2.1 Pharmaceuticals**

According to WHO (2011), pharmaceuticals can be defined as natural or synthetic chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. There are different therapeutic classes for all pharmaceuticals. Therapeutic classes are the term that is used the pharmaceutical industries to describe the drugs which are classified into the different groups according to their chemical structure, characteristics and how they benefit and treat diseases (Natural Wellness, n.d.). There are several different therapeutic classes focused in this study such as antibiotic, central nervous system (CNS) stimulant, nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoids and veterinary drugs.

Antibiotics which also known as antibacterial are medication for any infection that used to destroy or slow down the growth of the bacteria. However, the overuse of antibiotic is contributing to the growing bacterial infection and becoming resistant to antibacterial medication (CDC, 2017). Antibiotic resistant bacteria cannot be fully inhibited or killed by an antibiotic even the antibiotic have worked effectively before. Example of antibiotics that commonly used are amoxicillin, doxycycline, cephalexin, ciprofloxacin, clindamycin, metronidazole, azithromycin, sulfamethoxazole and levofloxacin (Anderson, 2016).

While for central nervous system (CNS) stimulants, it functions to stimulate the brain, speeding up both mental and physical processes by increase energy, elevate blood pressure, heart rate and respiratory rate and improve attention and alertness. Besides CNS stimulants also decrease the need for sleep, improve confidence and concentration, lessen inhibitions and reduce appetite (Drugs.com, n.d.). Moreover, Nehlig (1992) stated that caffeine is the most widely consumed and increases energy metabolisms throughout the brain but decreases at the same time cerebral blood flow by inducing a relative brain hypo-perfusion.

According to Ministry of Health Malaysia (2017), Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used for treating the acute chronic conditions where pain and inflammation are present. The medicine also available as creams and gels for topical use for apply to direct skin, which have similar benefits with pill form of NSAIDs for osteoarthritis and low back pain. In addition, the most NSAIDs used in Malaysia are diclofenac, mefenamic acid and celecoxib.

Other than that, glucocorticoids also one of the therapeutic classes of pharmaceuticals. Van Der Velden, (1998) stated that glucocorticoids are potent inhibitors of inflammatory process and widely used in asthma treatment. One of the medicine that classed in glucocorticoids in dexamethasone, which are used in Malaysia as mainstay steroid choice and partly due to increase number of surgical procedure in both private and public sector (Ministry of Health, 2014).



## **2.2 Sources of Pharmaceuticals in Drinking Water**

The main sources for human pharmaceuticals are including pharmaceuticals manufacturer sites (Gaw, Thomas, & Hutchinson, 2014), hospitals or health care facilities (Daouk et al., 2016) and households that discharge into their wastewater treatment facilities, or municipal sewage treatment plant facilities (Al-Odaini et al., 2013). Unfortunately, the actual data on the discharge of pharmaceuticals from manufacturing sites are not available and private to public. However, there is a possibility that the inputs of pharmaceuticals and their active ingredients are from these sources if the wastewater treatment plants in manufacturing sites unable to completely remove the compounds. Municipal landfills are also sources of pharmaceuticals entering the water course for drinking water intake points. Some of the pharmaceuticals almost unchanged and may persist in the environment, and even leach or run-off into groundwater or surface water. Besides, pharmaceuticals can enter the environment from animal husbandry and horticulture operations have been estimated to represent a significant source, where they are derived primarily from spills from anaerobic manure storage lagoons, manure fertilization of farm fields, run-off from farm fields. (National Association of Clean Water Agencies, 2015).



## 2.3 Pathways of Pharmaceuticals in Drinking Water

Figure 2.1 shows the pathways of pharmaceuticals in drinking water. Pharmaceuticals are commonly used in human and veterinary medical practices which are widely released into environment and water system. It is primarily starts from the distribution of the pharmaceuticals produced by manufactures. After the pharmaceuticals reach the consumers, the expired or unfinished medicine can enter water supplies through improper disposal which are by flushing into the toilet or sink or by discard into municipal waste bins. Municipal waste will end up in landfill and through leaching, it will enter the surface water. Besides, pharmaceuticals can enter the environment through the excretion via urine and faeces, extensively metabolized drugs are released into the receiving waters, the topically applied pharmaceuticals, when washed off (WHO,2011).

Other than that, pharmaceuticals for animals such as antibiotic which widely used for growth promoters in livestock animal production, feed additives in fish farming and drugs in the poultry industry can be related with the discharge of animal manure into surface water (Kim & Aga, 2007). These pharmaceuticals can enter the surface water through leaching or runoff. Veterinary pharmaceuticals are introduced to the environment when manure is spread on fields. If not degraded, these pharmaceuticals may end up in soil or in groundwater and by runoff they may be swept into surface water (Kümmerer,2008).

The release of pharmaceuticals into our environment such as surface water and groundwater increase the possibilities of pharmaceuticals in drinking water. Municipal water consisting of untreated surface water needs to be treated at DWTP before the water is made potable to consumers. According to WHO (2011), none of the wide range of drinking water treatment process designed specifically to remove pharmaceuticals. Besides, conventional drinking water treatment plant was largely ineffective in removing pharmaceuticals by coagulation process while advanced water treatment process such as ozonation, advanced oxidation and membrane process such as nanofiltration and reverse osmosis were demonstrated to achieve higher removal rates. In this context, removal of pharmaceuticals was actually depending on drinking water treatment plant technology being used. In Malaysia treatment technologies such as filtration, aeration, sedimentation, coagulation and flocculation are design to remove heavy metal, taste, odour, coliform, etc. in drinking water (Forum Air Malaysia, 2014). However, this conventional treatment is not specifically effective to remove pharmaceutical residues in drinking water (Tijani et al., 2013). Thus, drinking water may have contaminated with pharmaceutical residues.





**Figure 2.1: Pathways of pharmaceuticals in drinking water**  
(Modified from WHO (2011))

## 2.4 Past Studies of Pharmaceuticals Residues in Drinking Waters

Table 2.1 shows the range of detected pharmaceuticals from previous studies worldwide. These pharmaceuticals are one of the top drug use in Malaysia with different therapeutic classes. Several studies involved detection of several pharmaceuticals including amoxicillin, caffeine, ciprofloxacin, diclofenac, sulfamethoxazole and triclosan. Amoxicillin which is a veterinary pharmaceutical was detected at concentration 0.010 ng/L in US. Caffeine which is CNS class were detected with range 0.09-46 ng/L in Portugal and 24.4-564 ng/L in China. Ciprofloxacin which is antibiotic drugs was detected with range 7.6-18 ng/L in US, sulfamethoxazole at 12.7 ng/L in USA and 8.0–21.3 ng/L in China. Diclofenac does not been detected in drinking water in Malaysia however were detected 2.5-35 ng/L in US. Triclosan which is an antibacterial was detected at 1.4 -59.6 ng/L in US.



**Table 2.1: Past studies of pharmaceuticals residues in drinking waters**

| <b>Pharmaceuticals</b> | <b>Therapeutic class</b> | <b>Findings (ng/L)</b>                 | <b>References</b>                                           |
|------------------------|--------------------------|----------------------------------------|-------------------------------------------------------------|
| Amoxicillin            | Veterinary class         | US (0.010)                             | Finnegan et al., (2010)                                     |
| Caffeine               | CNS stimulants           | Portugal (0.09-46)<br>China (24.4-564) | Gaffney et al. (2015)<br>Leung et al. (2013)                |
| Ciprofloxacin          | Antibiotic               | US (0.005)                             | (Finnegan et al., 2010)                                     |
| Diclofenac             | NSAID                    | Malaysia (ND)<br>US (2.5–35)           | Al-Badaii & Shuhaimi-Othman (2014)<br>Benotti et al. (2009) |
| Sulfamethoxazole       | Antibiotic               | USA (12.7)<br>China (8.0–21.3)         | Padhye et al., (2014)<br>Leung et al. (2013)                |
| Triclosan              | Antibacterial            | US (1.4 -59.6)                         | Padhye et al., (2014)                                       |

### **2.5 Potential Health Risk from Exposure of Pharmaceuticals Pollutant**

According to US Environmental Protection Agency (USEPA), a human health risk assessment approach is to evaluate the nature and probability of human adverse health effect due to exposures to contaminated chemicals in environment. There are several studies which commonly assess the potential health risk due to occurrence of pharmaceuticals in drinking waters which is sources of human consumption. Among all the studies conducted there is no study of health risk assessment based on the

bioavailability of pharmaceuticals residues in drinking water as previous investigations only considered the total active pharmaceuticals concentration.

For pharmaceuticals determination in water, total active pharmaceuticals concentration is commonly measured (Caldas et al., 2013). However, total pharmaceuticals concentration will overestimate pollution level and impacts of pharmaceuticals in drinking water (Wang et al., 2013). Therefore, a better appropriate method in drinking water analysis is crucial to determine its bioavailability. Understanding bioavailability of pharmaceutical concentration in drinking water is capable to estimate amount of pharmaceutical concentration which can be absorbed by human body. Bioavailability is a term used to describe the proportion of the ingested contaminant that can reach the systemic circulation and exert toxic effects. Using in vitro digestion model, bioavailability of pharmaceutical from drinking water to human in gastrointestinal tract can be investigated as aspect of internal exposure. Determining the bioavailability of pharmaceutical concentration can facilitate more realistic exposure and health risk assessment (Guney & Zagury, 2012)

As for health risk assessment, Leung et al., (2013) have studied on potential health risk from detected pharmaceutical concentration by comparing of measured concentration and drinking water equivalent level (DWEL) value. The derivation of DWEL value was involved the determination of acceptable daily intake (ADI) value. ADI value is represent of daily intake that not result in an adverse health effect from the direct exposure. Derivation of DWEL values also including body weight of population, ingestion rate, and relative source contribution of acceptable dose from drinking water. By comparing measured concentration and DWEL value, the ratios

that indicated less than 1 is presumed no present of appreciable risk to human health. Nevertheless, Leung et al. (2013) stated that the presence of low detection of pharmaceuticals in drinking waters in China was pose no appreciable risk to human health.

However, according to WHO (2011), there were human health risk assessment for pharmaceuticals in drinking water which involve determination of margin of safety associated with human consumption. The risk assessment also involves several values which are acceptable daily intake (ADI) or tolerable daily intake (TDI), point of departure (POD) derivation and minimum therapeutic dose (MTD). The risk was assessed from United Kingdom, USA and Australia in conjunction of uncertainty factors, and the analysis of the results were indicated that exposure to the trace concentrations of pharmaceuticals that could potentially be found in treated drinking water posed very unlikely adverse human health impacts. However, the study was suggested improvement to methodology of risk assessment by address concerns including the effect of chronic, low level exposure to pharmaceutical and susceptible population



## **CHAPTER 3**

### **METHODOLOGY**

#### **3.1 Study Design**

The study design for this study was a cross sectional study that study pharmaceuticals residues and its potential risk to human health among Putrajaya population. The cross sectional study was chosen because the research was conducted at one point of time to estimate the prevalence of the expected outcome from the pharmaceuticals residues among Putrajaya population. In addition, the study was relatively inexpensive and takes up a little time to conduct and there is no loss to follow up (Levin, 2006). Figure 3.1 shows the methodology flow of this study.



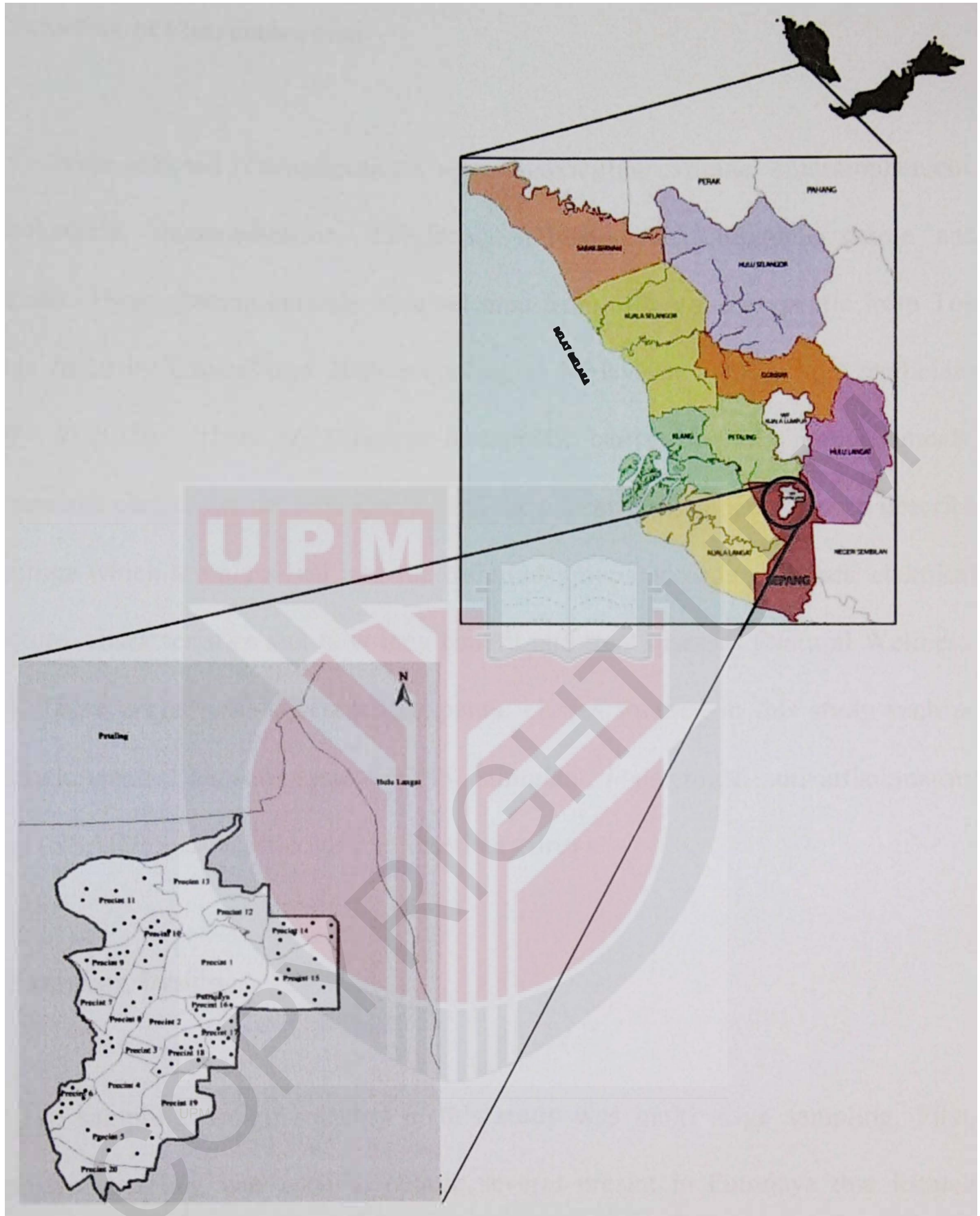
**Figure 3.1: Methodology flow of the study**

### **3.2 Study Location**

Putrajaya is a planned city and the federal administrative centre of Malaysia located in west-central Peninsular Malaysia. It is situated 15 miles (25 km) south of the capital, Kuala Lumpur. According to Department of Statistics Malaysia Official Portal (2011), the total population in Putrajaya is 72, 413 and the total residential units are 19, 511.

Drinking water supplied to Putrajaya originates from the Semenyih River, and is treated using a conventional water treatment system at Putrajaya Water Treatment Plant. Reported that Semenyih River is one of the rivers in Malaysia in which human activities associated with urbanization, industrialization, agricultural, and mining activities are extremely main sources of pollution (Fawaz Al-Badaii, Mohammad Shuhaimi-Othman, 2013). Despite being an important water source, Semenyih River increasingly being contaminated with direct discharge of untreated sewage, raw industrial effluents as well as wastewater from industrial, commercial, and domestic establishments (Al-Badaii, Gasim, Mokhtar, Toriman, & Rahim, 2012; Al-Badaii & Shuhaimi-Othman, 2014).





**Figure 3.2: Location map of Putrajaya for drinking water sampling sites**

### **3.3 Selection of Pharmaceutical**

Nine selected pharmaceuticals were amoxicillin, caffeine, chloramphenicol, ciprofloxacin, dexamethasone, diclofenac, nitrofurazone, sulfamethoxazole and triclosan. These pharmaceuticals were selected from different therapeutic from Top Drugs listed by Expenditure 2009 according to Malaysian Statistics on Medicines (2009 & 2010). There are different therapeutic classes for all pharmaceuticals. Therapeutic classes are the term that is used the pharmaceutical industries to describe the drugs which are classified into the different groups according to their chemical structure, characteristics and how they benefit and treat diseases (Natural Wellness, n.d.). There are several different therapeutic classes focused in this study such as antibiotic, central nervous system (CNS) stimulant, nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoids and veterinary drugs.

### **3.4 Sampling Design**

The sampling design selected in this study was multi stage sampling. First, purposive sampling was used to choose several presint in Putrajaya that located residential area which total of twelve presint. Next, was stratified random sampling by focusing around five to six households in each presint. Simple random sampling was done for each households by randomizer apps.

### **3.5 Study Population**

80 Putrajaya Residents

### **3.5.1 Inclusion Criteria**

- i) Respondents lives in Putrajaya more than one year
- ii) Respondents using drinking water source come from tap water or filtered water.

### **3.5.2 Exclusion Criteria**

Respondents consume other sources of drinking water, such as bottled water. Source of bottled water may come from ground water or tap water which are not from the study area.

### **3.6 Sample Size**

Sample size calculation for Putrajaya was done based on Daniel (1999) and the description is as follows:

$$n = \frac{z^2_{1-\frac{\alpha}{2}} P(1 - P)}{d^2}$$

n = sample size

z = level of confidence (for a level of confidence of 95%, z= 1.96)

P = estimated proportion

d = desired precision

Since prevalence value for pharmaceutical exposure to health is still in search (Lichtenberg, 2005), the nearest prevalence value was 0.083 to represent total death attributed to environmental exposure (Pruss-ustin, Vickers, Haeffliger, & Bertollini,



2011). The total respondents selected in this study are 64, with 20% response rate, total respondents involve in this study are 80.

### **3.7 Sampling Method**

#### **3.7.1 Questionnaire Survey**

A self-administered questionnaire in Malay version was used in this study to collect data which comprised of 4 parts which were socio-demographic, knowledge, attitude and practice towards pharmaceuticals contamination in drinking water. The questionnaire consisted of 37 closed-ended question based on studies by (Ab Razak, Praveena, Aris, & Hashim, 2016). The reliability of the questionnaires designed was determined by a pilot study on 30 households in Kajang area and by using Cronbach's Alpha test, the reliability coefficient test for the questionnaire was 0.744. A minimum standard of 0.7 indicate acceptable internal consistency for each questionnaire (Reynaldo & Santos, 1999).

Socio-demographic questions established respondents' age, gender, marital status, height, weight, length of residence, type of daily drinking water and frequency of drinking water intake. Knowledge on the pharmaceuticals contamination of drinking water was measured through questions such as the source of drinking water supply by SYABAS, drinking water may contain contamination such as pharmaceuticals, know what is pharmaceuticals, does pharmaceuticals in tap water can affect human health and others. The respondents' attitudes towards drinking water were assessed through statements on the quality of drinking water, problems with

drinking water, whether or not they boiled their drinking water before consumption, and their belief on the correct way of pharmaceuticals disposal. Respondents' practices were determined through questions on their main source of drinking water, type of drinking water treatment at home, and the disposal of unfinished medicines.

### **3.7.2 Collection of Drinking Water Samples**

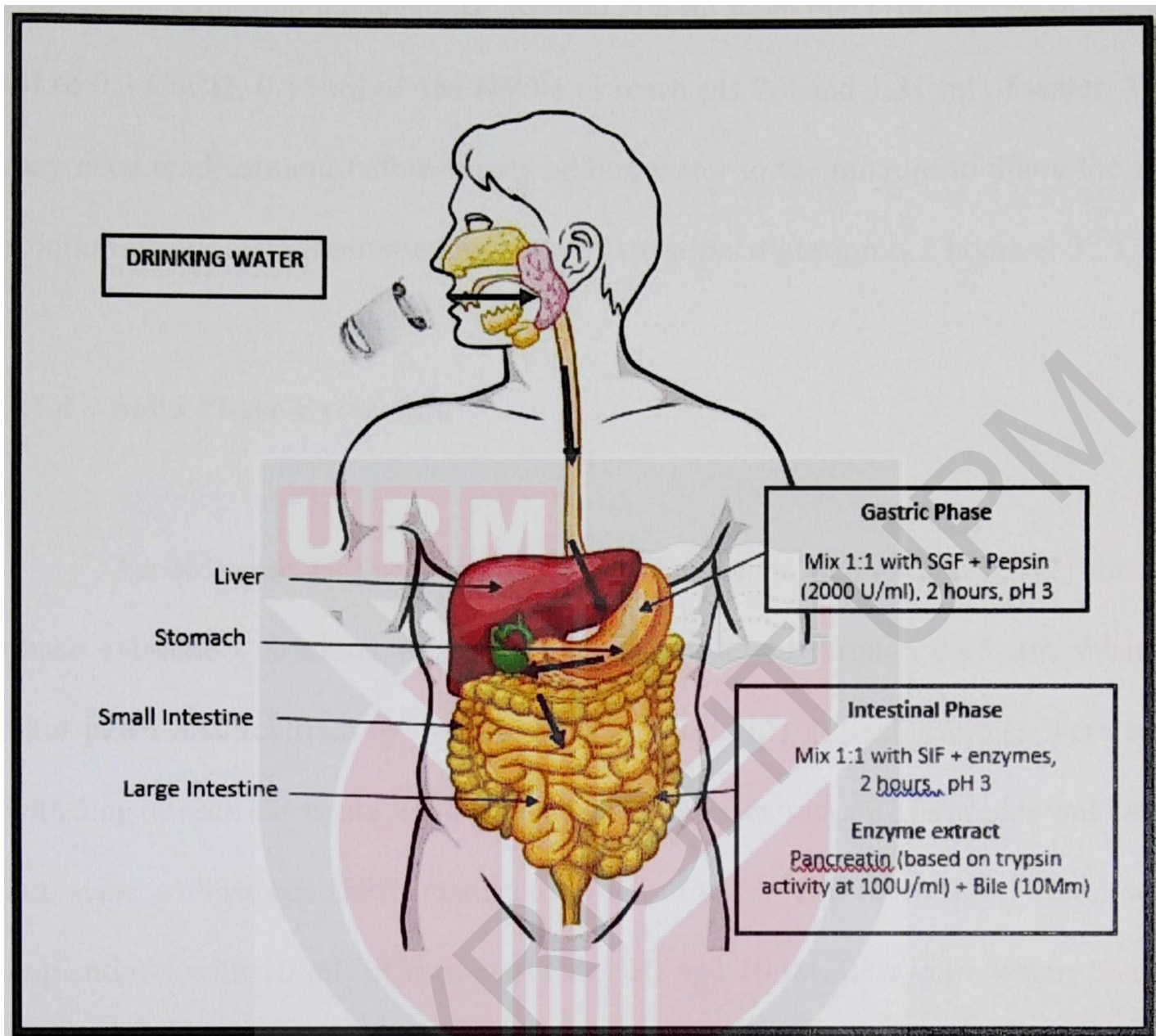
In total, 80 houses were visited to collect drinking water samples between September and December 2018. Respondents using other sources of drinking water, such as bottled water were excluded from this study. One litre Schott bottles were acid washed and pre-rinsed with ultrapure water for sample collection. Drinking water samples were collected from the kitchen tap after 2 min of flushing (Azlan, Khoo, Idris, Ismail, & Razman, 2012). All drinking water samples were transported in dark, cool containers and refrigerated at 4°C until analysis (Kavcar, Odabasi, Kitis, Inal, & Sofuoglu, 2006).

### **3.7.3 In-vitro Digestion**

In vitro digestion model by Minekus et al. (2014) was used to study the structural changes, digestibility, and release of food components. It seeks to mimic the processes that occur in three areas of human digestive system: mouth, stomach, and small intestine. The key factors that control this digestion of food are characteristics of foods, enzyme type, and enzyme concentrations.

Figure 3.2 shows an overview and flow diagram of a simulated in vitro digestion method by Mineskus et al. 2014 which will be adopted in this analysis. There are two important stages in this study which were gastric phase and intestinal phase. In vitro digestion simulation begins with the water intake. The water usually directly goes to the gastric phase because no mastication and enzymatic reaction involved. Upon entering the stomach, at the lower part of the stomach, the water is mixed and digested with secreted enzymes and hydrochloric acid. Following that, ground by antral movements and gradually emptied into the duodenum. In gastric phase, the only proteolytic enzyme involved is pepsin. Once the food has been through the simulated gastric phase, it is transferred to a simulate intestinal phase. The most important components of the simulated small intestinal digestion are the pancreatic enzymes and the bile.





**Figure 3.3: Overview and flow diagram of a simulated in vitro digestion method**

Simulated gastric fluid (SGF) for this model was prepared by mixing 10 ml of liquid sample is with 7.5 ml of SGF electrolyte stock solution, 1.6 ml porcine pepsin stock solution of 25 000 U/ml made up in SGF electrolyte stock solution (pepsin from porcine gastric mucus 3200-4500, 5 ml of 0.3M CaCL<sub>2</sub>, 0.2 ml of 1 M HCL) to reach pH 3.0 and 0.695 ml of water.

Simulated intestinal fluid (SIF) for this model was prepared by mixing 20 ml of gastric chime with 11 ml of SIF electrolyte stock solution, 5.0 ml of pancreatin

solution 800 U/ml made up in SIF electrolyte stock solution based on trypsin activity (pancreatin from porcine pancreas, Sigma), 2.5 ml fresh bile (160 min fresh bile), 40 ml of 0.3 CaCl<sub>2</sub>, 0.15 ml of 1M NaOH to reach pH 7.0 and 1.31 ml of water. There may need readjustment before finally adding water to the mixture to dilute the stock solution of SIF. The recommended time of intestinal digestion is 2 hours at 37°C.

#### **3.7.4 Solid Phase Extraction**

According to Grabic, Fick, Lindberg, Fedorova, & Tysklind (2012) for solid phase extraction, drinking water samples were filtered through 0.45 µm Whatman filter paper and acidified by using sulphuric acid to pH 3. Each samples were added with 5 ng of each surrogate standard. The solid phase extraction of samples was carried out with a Visiprep SPE manifold. Then, Oasis HLB cartridges were added sequentially with 10 mL of methanol (MeOH) and 10 mL ultra-pure water. Samples were applied to the SPE cartridges at a flow rate 5 mL/min. The SPE column was washed by addition of 200 mL filtered surface water samples with 10 mL methanol, then eluted with 5 mL methanol and 3 mL ethyl acetate. After that, eluate was evaporated by using shaking incubator SI-300 until a final volume became 2.0 mL.

#### **3.7.5 Enzyme-linked Immunosorbent Assay (ELISA)**

In this study, pharmaceutical determination in extracted drinking water samples were performed using commercial competitive ELISA kit which the steps are shown in figure 3.3. The standards provided by the manufacturer and the drinking samples were pipetted at a predetermined volume into different wells to enable it to be



precoated with specific antibody for selected pharmaceutical. Then enzyme conjugate was added and the wells were incubated for certain period of time. Next, washing step using wash solution were performed and each well was added with buffer solution before the plate was reincubated at room temperature for a certain period of time. Finally, stop buffer containing sulphuric acid were added to stop the enzyme reaction and the plates were read immediately a microplate spectrophotometer (Dynex MRX Revelation and Revelation TC 96 Well Microplate Reader) at 450 nm wavelength. The data was analysed using the Revelation Software (Version 4.25)

The drinking water sample were analyzed by using competitive ELISA as the tendency of ELISA to analyse digestive sample is higher accuracy compare to other instrumental. ELISA is suitable for high-throughput analysis as it also simplicity of operation and easily corrected by dilution or compensating medium for construction of the standard curve (Shelver, Shappell, Franek, & Rubio, 2008). Besides, ELISA also simple, inexpensive and accurate method with simple sample preparation like filtration, acidification and readjustment to neutral pH value (Deng et al., 2003). Other instrumental method except ELISA is expensive, need high cost for operation and not suitable for analysis that involve routine monitoring. Besides the adaptation as to improve or recover some problems stated that quite difficult and leading to inaccurate quantitation (Shelver, Shappell, Franek, & Rubio, 2008). Nine different ELISA test kits were used for the analysis shown in Table 3.1. For analysis method, drinking water samples from solid phase extraction and in-vitro digestion were used for analysis by using Enzyme-Linked Immunosorbent Assay (ELISA) to detect nine selected pharmaceuticals in drinking water samples.



**Table 3.1: ELISA kits and manufacturers**

| Pharmaceuticals  | ELISA test kits            | Manufacturers  |
|------------------|----------------------------|----------------|
| Amoxicillin      | Amoxicillin ELISA kit      | MaxSignal      |
| Caffeine         | Caffeine ELISA kit         | Abraxis        |
| Chloramphenicol  | Chloramphenicol ELISA kit  | MaxSignal      |
| Ciprofloxacin    | Ciprofloxacin ELISA kit    | MaxSignal      |
| Dexamethasone    | Dexamethasone ELISA kit    | MaxSignal      |
| Diclofenac       | Diclofenac ELISA kit       | Bio Scientific |
| Nitrofurazone    | Nitrofurazone ELISA kit    | MaxSignal      |
| Sulfamethoxazole | Sulfamethoxazole ELISA kit | MaxSignal      |
| Triclosan        | Triclosan ELISA kit        | Abraxis        |

**3.7.6 Human Health Risk Assessment**

The human health risk assessment was performed to determine the potential risks of pharmaceuticals in drinking water. The acceptable daily intake (ADI) were adopted from provisional values established in the literature and ADI was combined with standard assumptions about potential exposure via drinking water. These general exposure equations (Equation 1) are consistent with those used by US Environmental Protection Agency and also adapted from Leung et al. (2013).

Acceptable daily intake was derived to determine health risk due to occurrence of pharmaceuticals in drinking waters. It was derived based on variety on uncertainty factors with calculation of point of departure from database of toxicological and

epidemiological. According to WHO Pharmaceuticals in Drinking Waters, point of departure is commonly accepted as the concentration of no observed adverse effect level optimally, lowest observed adverse effect level, in combination with additional uncertainty factors. If the concentration is below the screening value or ADI, adverse health impact strongly suggested should not be expected. Table 3.3 shows ADI values in  $\mu\text{g/kg.day}$  with references.

**Table 3.3: Value of acceptable daily intake (ADI)**

| Pharmaceuticals  | Therapeutic class | ADI<br>( $\mu\text{g/kg.day}$ ) | References            |
|------------------|-------------------|---------------------------------|-----------------------|
| Amoxicillin      | Veterinary drug   | 12.5                            | JECFA WHO, 2018       |
| Caffeine         | CNS stimulants    | 150                             | Gaffney et al., 2014  |
| Chloramphenicol  | Antibiotic        | 71.1                            | K. Choi et al., 2008  |
| Ciprofloxacin    | Antibiotic        | 1.6                             | Schwab et al., 2005   |
| Dexamethasone    | Glucocorticoids   | 0.02                            | JECFA WHO, 2018       |
| Diclofenac       | NSAID             | 1.6                             | Gaffney et al., 2014  |
| Nitrofurazone    | Antibacterial     | 10                              | HSDB Database, 2018   |
| Sulfamethoxazole | Antibiotic        | 130                             | Schwab et al., 2005   |
| Triclosan        | Antibacterial     | 49.3                            | Olaniyan et al., 2016 |

Equation 1:

$$DWEL = \frac{ADI \times RSC \times BW \times 1000}{IngR}$$

In this study, the acceptable daily intake (ADI) values of targeted pharmaceuticals were adapted from provisional values established in the literature. Where RSCDW represents the relative source contribution of acceptable dose from drinking water, assumed to be 100% for screening purposes because unintended ingestion of pharmaceuticals occurs mainly via drinking water (Cunningham et al. 2009) except for caffeine, for which 10% was used as a default factor for general contaminants (WHO 2008); BW represent body weight is 68.74 kg taken from the body weight mean of 80 respondent; 1,000 represents the unit conversion from micrograms to nanograms and IngRDW represents the daily ingestion rate of water which is 1.8 litre taken from mean of daily water intake from all respondents.

Potential human health risk by using risk quotient (RQ) was calculated based on:

$$RQ = \frac{\text{Measured pharmaceutical concentration}}{DWEL}$$

RQ presumed to indicated no appreciable risk to human health when the value is less than 1 ( $RQ < 1$ ). The human health risk potentially occurred when RQ is more than 1 ( $HQ > 1$ ).



### **3.6 Quality Control**

Bottles and glassware used during the sampling and analysis procedures were soaked in 5% nitric acid solution overnight and rinsed twice using deionized water (Azlan et al., 2012). After washing, the apparatus was dried at room temperature and kept sealed to prevent any accumulation of dust or other contaminants (Azlan et al., 2012; Kavcar et al., 2006). All drinking water samples were transported in dark, cool containers at 4°C until analysis (Kavcar, Odabasi, Kitis, Inal, & Sofuoglu, 2006).

For ELISA analysis, all reagents are brought up to room temperature (1-2 hours at room temperature) before use. Calibration curve were obtained for all analytes to determine the concentration of pharmaceuticals in drinking water samples. A standard curve was constructed by plotting the mean relative absorbance percentage ( $B/B_0$ ) obtained from each reference standard against its concentration in ng/mL on a logarithmic curve. All calibration curve of the target compounds showed the regression line perfectly fits the data.

### **3.9 Statistical Analysis**

In determining the level of KAP of the respondents, a scoring system was used. The scoring system has been used widely in extracting KAP from questionnaires (Ab Razak et al., 2016; Desai, Panchal, Dikshit, Iyer, & Shah, 2011). Respondents who answer Yes were given 1 score, while respondents who answer No or Not sure were

scored as 0. Different with attitude which was measured using a score of 1 for respondents who agreed with positive attitudes and 0 for respondent who disagreed with negative attitudes. The total score for each respondent was determined and a frequency distribution table was used to determine the cut-off point for poor or good KAP. The percentages of respondents with poor and good results for each KAP variable are presented in the Results section.

The Statistical Package for the Social Sciences (SPSS) version 23.0 was used to perform the analysis. Descriptive analysis was used to determine mean concentration of pharmaceuticals in drinking waters and was presented in tabular form. Shapiro Wilkinon test was used in determine the normality of the data.

## **CHAPTER 4**

### **RESULTS AND DISCUSION**

#### **4.1 Knowledge, attitude and practice of drinking water quality and human pharmaceuticals handling involving Putrajaya residents**

In total, 80 respondents participated in the questionnaire survey. The respondents were aged 18-63 years old, and 47.5% were female and 52.5% were male. The majority of the population has married (76%), while others are single (24%). The average length of residence was 11 years.

Tables 4.1, 4.2 and 4.3 show the results of knowledge, attitude and practice (KAP) towards pharmaceuticals residues contamination of drinking water in Putrajaya. The analysis of KAP through the scoring system revealed that 63% of the respondents have poor knowledge, however, 75% have a highly positive attitude, and 71% have poor practices towards pharmaceuticals contamination of drinking water. Information on KAP is crucial in order to understand the perceptions of the study population regarding the quality of drinking water and their practices to minimize pharmaceuticals exposure.

Fifty nine percent of the respondents knew that their drinking water was supplied by Syarikat Bekalan Air Selangor (SYABAS), knew the source was from river water (53%) and 75% respondents knew that their drinking water had been treated. Thirty five percent of the respondents knew about pharmaceuticals



contamination of drinking water, and 44% knew what pharmaceuticals are. 48% of the respondents knew pharmaceuticals in tap water can affect human health through the consumption of drinking water and pharmaceuticals can affect aquatic life (46%). 43% of the respondents from Putrajaya had received information regarding the quality of drinking water and majority of them used water filter machine to filtered their water (73%), while only 14% respondent do not sure the role of water filter machine.

Seventy five percent of the respondents had a positive attitude, as they reported that the quality of the drinking water supplied by SYABAS is good. Ninety six percent of the respondents disagreed with the statement that the supplied drinking water was safe to drink directly from the tap. Results from this study are higher compared with those reported by Ab Razak (2016) in Pasir Mas, Kelantan. This is likely to be due to the level of education of the population of Putrajaya. Reported problems with drinking water included colour, odour and taste (70%), precipitation (80%), heavy metals (42%) pharmaceuticals (15%). Besides, 60% respondents think that routine monitoring and inspection of tap water (at home) should be implemented for safe drinking water.

Regarding practice, majority respondents reported good practices (71%), such as every respondent boil drinking water before consume. The results of this study are higher than those reported by Ozdemir et al. from a study in Vietnam, which reported that 79% of respondents boiled their drinking water. Although boiling does not eliminate contamination of drinking water, it is considered to be a good practice as it helps to eliminate bacteria contamination. Fifty-five percent of respondents reported the use of filter units, and the majority reported that they maintained their filter units monthly. However, 40% practice a proper way of disposal of pharmaceutical by

returning it back to hospital or clinic whereas, 60% kept in rug cabinet, 60% discard into municipal waste bins and 16% flush into toilet or sink.

**Table 4.1: Knowledge scores of drinking water quality and human pharmaceuticals handling involving Putrajaya residents**

| Variables                                                                                       | n  | %  |
|-------------------------------------------------------------------------------------------------|----|----|
| Know the source of drinking water supplied by SYABAS?                                           |    |    |
| Yes                                                                                             | 59 | 74 |
| No/not sure                                                                                     | 21 | 26 |
| Source of drinking water supplied by SYABAS.                                                    |    |    |
| River                                                                                           | 53 | 66 |
| Ground/not sure                                                                                 | 27 | 34 |
| Drinking water supplied by SYABAS is treated.                                                   |    |    |
| Yes                                                                                             | 75 | 94 |
| No/not sure                                                                                     | 5  | 6  |
| Drinking water may contain contamination such as pharmaceuticals.                               |    |    |
| Yes                                                                                             | 35 | 44 |
| No/not sure                                                                                     | 45 | 56 |
| Know what is pharmaceuticals?                                                                   |    |    |
| Yes                                                                                             | 44 | 55 |
| No/not sure                                                                                     | 36 | 45 |
| Pharmaceuticals in tap water can affect human health through the consumption of drinking water. |    |    |
| Yes                                                                                             | 48 | 60 |
| No/not sure                                                                                     | 32 | 40 |
| Pharmaceuticals exposure through drinking water can cause harm to your body.                    |    |    |
| Yes                                                                                             | 39 | 49 |
| No/not sure                                                                                     | 41 | 51 |
| Pharmaceuticals in the water can affect aquatic life                                            |    |    |
| Yes                                                                                             | 46 | 58 |
| No/not sure                                                                                     | 34 | 42 |
| Boiling tap water can reduce the concentration of pharmaceuticals in drinking water.            |    |    |
| Yes                                                                                             | 36 | 45 |
| No/not sure                                                                                     | 44 | 55 |
| Have you received education/ information about the quality of drinking water?                   |    |    |
| Yes                                                                                             | 43 | 54 |
| No/not sure                                                                                     | 37 | 46 |
| Use of water filter machine to filter drinking water.                                           |    |    |
| Yes                                                                                             | 73 | 91 |
| No/not sure                                                                                     | 7  | 9  |
| Role of water filter machine.                                                                   |    |    |
| Remove the contaminants.                                                                        | 53 | 66 |
| Neutralize the drinking water                                                                   | 49 | 61 |
| Reduce odour and colour                                                                         | 61 | 76 |



|                                       |      |         |
|---------------------------------------|------|---------|
| Not sure.                             | 14   | 18      |
| Total given score                     |      | 12      |
| Total mean score (Standard Deviation) | 64.1 | (18.97) |
| % Good Knowledge score (score >9)     |      | 37      |
| % Poor Knowledge score (score <8)     |      | 63      |

**Table 4.2: Attitude scores of drinking water quality and human pharmaceuticals handling involving Putrajaya residents**

| Variables                                                                                                          | Agree<br>% | Disagree<br>% |
|--------------------------------------------------------------------------------------------------------------------|------------|---------------|
| Believe that drinking water supplied by SYABAS is good.                                                            | 46         | 54            |
| Believe that supplied drinking water is safe to drink directly from tap.                                           | 4          | 96            |
| Drinking water supply problem in your house.                                                                       |            |               |
| Colour, odour and taste                                                                                            | 70         | 30            |
| Precipitation.                                                                                                     | 80         | 20            |
| Heavy metals.                                                                                                      | 42         | 38            |
| Pharmaceuticals.                                                                                                   | 15         | 65            |
| None of the above.                                                                                                 | 9          | 71            |
| Not sure.                                                                                                          | 38         | 42            |
| Believe drinking water filtration is required for safe drinking water.                                             | 96         | 4             |
| Believe that boiling drinking water can remove pharmaceuticals.                                                    | 69         | 31            |
| Think that routine monitoring and inspection of tap water (at home) should be implemented for safe drinking water. | 91         | 9             |
| Prefer conventional medicines instead alternatives medicines.                                                      | 60         | 40            |
| Finish the whole medical prescription.                                                                             | 36         | 64            |
| Realize the date of expiry of the medicines being used.                                                            | 91         | 9             |
| Appropriate to discard unused/ unfinished/ expired medicines into municipal waste bins?                            | 51         | 49            |
| Believe that flushing unused/ unfinished/ expired medicines into the toilet and sink is the best disposal method   | 16         | 84            |
| Total given score                                                                                                  |            | 11            |
| Total mean score (Standard Deviation)                                                                              |            | 22.72(28.57)  |
| % of highly positive (score > 1)                                                                                   |            | 75            |
| % of less positive (score < 0)                                                                                     |            | 25            |



**Table 4.3: Practice scores of drinking water quality and human pharmaceuticals handling involving Putrajaya residents**

| Variables                                                     | n            | %     |
|---------------------------------------------------------------|--------------|-------|
| Process tap water before preparing drinks                     |              |       |
| Boiled tap water                                              | 59           | 73.75 |
| Boiled filtered water                                         | 21           | 26.25 |
| None                                                          |              |       |
| Drink tap water directly.                                     |              |       |
| Yes                                                           | 79           | 99    |
| No                                                            | 1            | 1     |
| Used water filter at home.                                    |              |       |
| Yes.                                                          | 75           | 94    |
| No.                                                           | 5            | 6     |
| Clean of drinking water container.                            |              |       |
| Once every day                                                | 20           | 25    |
| 2-3 times a week                                              | 25           | 31    |
| Once a week                                                   | 20           | 25    |
| Others                                                        | 15           | 19    |
| Cleaning drinking water filtration system.                    |              |       |
| Once every six months                                         | 15           | 19    |
| Others                                                        | 51           | 64    |
| Once in a year                                                | 30           | 38    |
| None                                                          | 6            | 8     |
| Once in a year                                                | 30           | 38    |
| Others                                                        | 35           | 44    |
| What do you do with the unused/ unfinished/ expired medicine? |              |       |
| Keep in drug cabinet                                          | 48           | 60    |
| Return to the hospital/ clinic for disposal                   | 32           | 40    |
| Discard into municipal waste bins                             | 48           | 60    |
| Flush into the toilet or sink                                 | 13           | 16    |
| Total given score                                             | 6            |       |
| Total mean score (Standard Deviation)                         | 80.42(14.47) |       |
| % Good Practice score (score >5)                              | 71           |       |
| % Good Practice score (score <4)                              | 29           |       |

## 4.2 Pharmaceuticals Concentrations in Drinking Water Samples

Table 4.4 show the pharmaceuticals concentration in drinking water sample for 80 households in Putrajaya. The highest mean concentration of nine selected pharmaceuticals is caffeine with mean concentration of 0.382 ng/L. Then, followed by triclosan, dexamethasone, ciprofloxacin and amoxicillin which are among the highest mean concentration detected. The mean concentration detected for triclosan is 0.363 ng/L, dexamethasone is 0.323 ng/L, ciprofloxacin is 0.322 ng/L and amoxicillin is 0.311 ng/L. Next are mean concentration of nitrofurazone (0.186 ng/L), chloramphenicol (0.172 ng/L), sulfamethazole (0.165 ng/L) and diclofenac (0.138 ng/L).

Overall, levels of pharmaceuticals detected in water sources and drinking water did not exceed 50 ng/L, which is in accordance with the values reported in other studies (Stackelberg et al., 2007; Huerta-Fontela et al., 2008; Leung et al., 2013; Gaffney et al., 2014).

**Table 4.4: Concentration of pharmaceutical in drinking water samples**

| Pharmaceuticals  | Concentrations (ng/L) |         |       |                |
|------------------|-----------------------|---------|-------|----------------|
|                  | Minimum               | Maximum | Mean  | Std. Deviation |
| Chloramphenicol  | 0.163                 | 0.178   | 0.172 | 0.004          |
| Nitrofurazone    | 0.172                 | 0.200   | 0.186 | 0.007          |
| Ciprofloxacin    | 0.305                 | 0.329   | 0.322 | 0.009          |
| Sulfamethoxazole | 0.156                 | 0.173   | 0.165 | 0.004          |
| Amoxicillin      | 0.309                 | 0.319   | 0.311 | 0.003          |
| Diclofenac       | 0.124                 | 0.180   | 0.138 | 0.016          |
| Dexamethasone    | 0.305                 | 0.373   | 0.323 | 0.019          |
| Triclosan        | 0.354                 | 0.375   | 0.362 | 0.006          |
| Caffeine         | 0.366                 | 0.410   | 0.382 | 0.012          |

**4.2.1 Chloramphenicol**

Chloramphenicol is detected low in concentrations of drinking water samples at mean of 0.172 ng/L. This can be supported by prohibition of chloramphenicol in Malaysia Food Regulations 1985 under Fifteenth Schedule (Regulation 40) (Malaysia, 1985). Chloramphenicol are prohibited drugs in food as it related to misuse in food producing animals such as poultry and livestock. Besides, chloramphenicol that mostly been used as antibiotic agent in the treatment and surgery of eye has been banned in Malaysia due to their physicochemical properties and potential health risk (Ministry of Health Malaysia, 2017). The detection of chloramphenicol in drinking water was believed to be originated from illegal antibiotic usage in the aquaculture sector (Ng et al., 2014; Zainudin, 2010).



#### **4.2.1 Nitrofurazone**

Nitrofurazone were detected in all drinking water samples at mean of 0.186 ng/L. The concentration is consider low as this pharmaceuticals have been ban because it can potentially gives human risk related with its toxicity and carcinogenicity (Department of Chemistry, 2016) therefore, the detection of nitrofurazone in drinking water is still a major concern despite its low concentration. It is believed that the presence of this compound was to be originated from illegal antibiotic usage in the aquaculture sector (Ng et al., 2014; Zainudin, 2010). Besides, nitrofurazone that is classed as antibiotic contains in creams or lotion medicine is possible to washed off into wastewater and contribute to pollution problem in water cycles due to unabsorbed portion of the pharmaceutical (Havard Health, 2011).

#### **4.2.3 Ciprofloxacin**

Ciprofloxacin which has been listed as one of the five common antibacterial agents used in 2009 and 2010 that is utilised to treat upper respiratory tract infection (URTI) and urinary tract infection (UTI) (Ministry of Health Malaysia, 2014; Teng et al., 2011) were detected in the drinking water samples at mean of 0.322 ng/L. Similarly, URTI has been reported as the most common infection cases (51%) in Malaysian hospitals, thus requiring the prescription of antibiotics and ciprofloxacin due to their excellent efficacy across a wide spectrum of infection with minimal side effects (Teng et al., 2004).

#### **4.2.4 Sulfamethoxazole**

Sulfamethoxazole which is antibiotics therapeutical classes were found at the mean of 0.165 ng/L. The detected concentration is consider as one of the lowest mean concentration as it has been reported that the number of this combination drug in Malaysia healthcare system has been decreasing due to the side effects of sulphur component found in sulfamethoxazole (Ministry of Health Malaysia, 2014).

#### **4.2.5 Amoxicillin**

Amoxicillin which is classed as veterinary drugs and broad spectrum penicillin were detected with the mean concentration of 0.311 ng/L in all drinking water samples as it is widely used antibacterial agent for both the public and private sectors in the Malaysian primary healthcare system in 2009 and 2010. Moreover, amoxicillin also classed as veterinary drugs used for the treatment of susceptible infections of the alimentary, urogenital and respiratory tracts (Ramos, Boison, & G Friedlander, 2012).

#### **4.2.6 Diclofenac**

The only nonsteroidal anti-inflammatory drugs (NSAIDs) from all nine selected pharmaceuticals in this study was diclofenac. Diclofenac which is non-steroidal anti-inflammatory drugs was detected the lowest in drinking water samples at the mean concentration of 0.138 ng/. This might be cause of diclofenac particles can degrade easily compares to others as study by (Al-Odaini, Zakaria, Yaziz, & Surif,

2015) detected 105 ng/L of diclofnac in river water however diclofenac were not detected at all at tap water.

#### **4.2.7 Dexamethasone**

Dexamethasone is the third highest detected with mean of 0.323. Dexamethasone is classed as glucocorticoids which remained the second most commonly used from year 2011 to 2014 with 11.1% in 2011, increased to 19.5% in 2014. In addition, dexamethasone used in Malaysia as mainstay steroid choice and partly due to increase number of surgical procedure done in both private and public sector (MOH, 2017).

#### **4.2.8 Triclosan**

Triclosan is the second highest detected with mean of 0.362. According to Olaniyan et al. (2016), triclosan is used as a broad spectrum antimicrobial agent in most of personal care products such as soap, sanitizer and skin cream. Widespread used in homes which explained it as water micropollutant.

#### **4.2.9 Caffeine**

Caffeine is human pharmaceutical that occurs both naturally and as food additive, was detected with the highest mean concentration as 0.382 ng/L. This is not suprising considering caffeine contains in beverages such as coffee and tea. Caffeine consumption and usage is common in this country supported by Caffeine Informer that



Malaysia was in Top 50 of Coffee Consuming Countries ranked at 45 with 1.3 kg per capita. Caffeine is most consumed classed as central nervous system (CNS) stimulant to boost brain activity with increase energy, attention and alertness, elevate blood pressure, heart rate and respiratory rate. Al Qaim et al. (2017) stated that caffeine content in medicine tablet such as anacin and excedrin is within range of 30-200 mg concentration per tablet. This can be related with the location of Semenyih River which is near to most contribution of caffeine residue such as residential area and health services (hospitals and clinics). The occurrence may from consumption of caffeine followed excretion process and improper disposal such as flushing unwanted or excess drugs down toilets and sinks.

#### **4.3 Potential human health impact of pharmaceuticals exposure**

From the RQ results by considering measured concentration and DWEL value, all selected pharmaceuticals indicated RQs less than 1 ( $RQ < 1$ ) pose no appreciable human health risk, shown in Table 4.5. Human health risk may possibly occur when the HQ value is more than 1 ( $HQ > 1$ ). However, according to (Schwab et al., 2005) some human-use pharmaceuticals characteristics could trigger a more thorough evaluation of their risk to human health.

**Table: Hazard Quotients of pharmaceuticals residues in drinking waters**

| Pharmaceuticals  | Hazard Quotients        |
|------------------|-------------------------|
| Chloramphenicol  | $6.556 \times 10^{-10}$ |
| Nitrofurazone    | $5.237 \times 10^{-9}$  |
| Ciprofloxacin    | $5.384 \times 10^{-8}$  |
| Sulfamethoxazole | $3.485 \times 10^{-10}$ |
| Amoxicillin      | $6.683 \times 10^{-9}$  |
| Diclofenac       | $2.946 \times 10^{-8}$  |
| Dexamethasone    | $4.884 \times 10^{-6}$  |
| Triclosan        | $1.992 \times 10^{-9}$  |
| Caffeine         | $7.158 \times 10^{-10}$ |

Even though the concentration detected were extremely low and all pharmaceuticals pose no appreciable human health risk, this study can be considered a proactive human health risk assessment of pharmaceuticals in Malaysia drinking waters and as references for future risk management in Malaysia. This emerging pollution was becoming concern due to pharmaceuticals is other endocrine disrupting compounds (EDCs) that introduced into natural water system that threaten aquatic populations and impact human health. According to Crawford et al. (2017). EDCs can work in combination with their by-product or other EDCs, but it is difficult to identify potential EDCs as there is absence of endocrine disrupting testing data. The possible effects on humans could include reductions in male fertility, abnormalities in male reproductive organs, decline in number of males born, increase in female reproductive diseases including early puberty, fertility problems increase in memory loss and reproductive cancer.

## **CHAPTER 5**

### **CONCLUSION AND RECOMMENDATION**

In conclusion, the knowledge of Putrajaya residents for drinking water quality and human pharmaceuticals handling was poor, the attitude and practice were considered good. The selected pharmaceuticals residues were detected in all drinking water samples and caffeine was the highest detected pharmaceutical residues with mean concentration of 0.382 ng/L. The RQ values were less than one which indicates no potential human health risk for all pharmaceutical residues. Even though it was no potential human health risk, future research in these areas may be beneficial to better characterize potential health risks from long-term, low-level exposure to pharmaceuticals residues, particularly for sensitive sub populations. This study can be considered as proactive human health risk assessment of pharmaceuticals in Malaysia drinking waters.

The awareness among consumer should be increased by promoting and organize education program related to the adverse health effect in consuming pharmaceuticals via drinking water and the proper ways of disposing expired or unused pharmaceuticals by returning it back to the hospitals or clinics. Besides, to reduce the occurrence of pharmaceuticals in drinking waters, enforcement should be made for pharmaceuticals manufacturer in controlling their pharmaceuticals effluent. Besides, to upgrading water treatment plant into full advanced process is required high cost, other ways to reduce this emerging pollutant can be started from consumer itself.



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**APPENDIX I**  
**ETHICAL APPROVAL LETTER**





**APPENDIX II**  
**BPH PUTRAJAYA APPROVAL LETTER**



**BAHAGIAN PENGURUSAN HARTANAH**  
**JABATAN PERDAMA MENTERI**  
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**f Jun 2018**

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YBhg. Dr.,

**PERMOHONAN UNTUK MENJALANKAN KAJIAN PENELITIAN KUALITI AIR  
PAIP DI KAWASAN PERUMAHAN PUTRAJAYA**

Dengan hormatnya saya merujuk kepada perkara di atas dan surai YBhg. Dr. dengan nombor rujukan UPM/FPSK/JOPP/A03905 bertarikh 17 Mei 2018 adalah berkaitan:

2. Bahagian Pengurusan Hartanah (BPH) Jabatan Perdana Menteri telah menerima dan menerima permohonan YBhg. Dr. berkaitan kajian yang akan dijalankan di kawasan kuarters seliaan BPH di sekitar Putrajaya. Sukasta dimaklumkan bahawa Bahagian ini **TIDAK HALANGAN** bagi pihak YBhg. Dr. menjalankan kajian tersebut sebagaimana butiran berikut:

- I. Tempoh kajian : 1 Julai 2018 hingga 31 Oktober 2018
- II. Lokasi terlibat : Kuarters Kerajaan Seliaan BPH, Putrajaya
- III. Penyelidik :
  - I. Profesor Madya Dr. Sarva Mangala Praveena  
(Nombor Matrik Staf : A03905)
  - II. Puan Siti Norasholihah binti Mohamad Shaifuddin  
(Nombor Matrik Staf : 187320)
  - III. Puan Mazharul Zaharah binti Mohd Rashid  
(Nombor Matrik Staf : 182179)
  - iv. Puan Wee Sze Yee  
(Nombor Matrik Staf : 188549)

3. Walau bagaimanapun, kebenaran ini hanya bagi tujuan memasuki kawasan kuarters Kerajaan seliaan BPH dan menjalankan kajian sahaja. Kebenaran daripada penghuni hendaklah diperoleh terlebih dahulu sebelum pihak YBhg. Dr. memasuki rumah kediaman mereka dan mendapatkan sampel kajian yang diperlukan. Pihak YBhg. Dr. juga dinasihat supaya sentiasa membawa pengenal diri dan surai kebenaran daripada BPH semasa menjalankan kajian bagi memastikan tiada kesukuan berlaku.

