

AMERICAN UNIVERSITY OF BEIRUT

OCCURRENCE AND RISK ASSESSMENT OF
PHARMACEUTICALS IN SURFACE WATERS OF THE
MIDDLE EAST AND NORTH AFRICA

by
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ABSTRACT OF THE THESIS OF

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Pharmaceuticals are classified as contaminants of emerging concern due to their occurrence and persistence in aquatic environment. However, scarce information is currently available about the long term-impacts and the associated environmental and human health risk of a large number of pharmaceuticals. In an attempt to address this issue, this study reviewed all openly published research conducted on the occurrence of pharmaceuticals in different water compartments from 2006 to 2022, with a primary focus on the MENA region. The review systematically identified, quantified, and categorized pharmaceutical compounds present in MENA water compartments, detailing their names, numbers, concentrations, and therapeutic groups.

In fact, 159 pharmaceutically active ingredients were detected in at least one of 14 MENA countries, with antibiotics being the most frequently detected therapeutic class (0.1–99,636 ng/L). To better understand the impact of this occurrence, an ecological, human health and antimicrobial risk assessment using minimum, median and maximum measured concentrations. 39 detected pharmaceuticals in MENA surface waters posed a possible ecological risk whereas a possible human health risk was registered for 8 out of 159 detected pharmaceuticals. 17 β estradiol, diclofenac, metoprolol, ethinylestradiol, and carbamazepine calculated an alarming environmental risk (>1000), the magnitude of which will definitely needs further investigations and regulatory actions. Of all therapeutic classes, hormones registered the highest health risk quotient via both pathways: drinking water and fish ingestion. Moreover, among the antibiotics detected, ciprofloxacin and norfloxacin showed the highest antimicrobial resistance risk in the order of 40. Based on this data compilation, the highest frequently detected pharmaceuticals were to be selected for fate modeling in one of the most polluted MENA rivers using available software. This modeling effort aimed to assess the impact of pharmaceutical contamination in regions lacking expertise and economic resources. However, due to the insufficient geo-processed information available, the research was unable to progress beyond the review stage with the intention to further developing the model and expanding the analysis once the necessary data becomes available.

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CHAPTER 1

INTRODUCTION

Pharmaceuticals occurrence and persistence in the aquatic environment have become an increasing global concern due to their potential toxicity on living organisms. In this context, most of the developed countries have established comprehensive monitoring systems for pharmaceutical contaminants in water. In comparison, developing nations, particularly those in Africa and Asia, face significant challenges due to limited resources for monitoring and management. These regions, often characterized by high populations and have economically poor standards, are subjected to pharmaceutical contamination resulting from improper usage, inadequate disposal practices, poor sanitation, and insufficient wastewater treatment infrastructure (Waleng and Nomngongo, 2022).

Pharmaceuticals are chemical compounds used for preventing or treating diseases. Recently, their global consumption has risen considerably due to the increasing world population and the expansion in use of medicines (Hawash et al., 2023). However, the limited knowledge about the sources, transport, accumulation and fate of pharmaceuticals in aquatic compartments leads to uncertainty regarding the environmental risks these substances pose to marine creatures. Classified as contaminants of emerging concern, pharmaceuticals have been detected in several water systems: rivers, lakes, wastewater effluents, groundwater and drinking water supplies worldwide (Liu et al., 2024, Wilkinson et al., 2022, Adedipe et al., 2024, Lahens et al., 2024, Khezami et al., 2024). These substances, which are primarily designed to develop

biological responses in specific organisms, are proven able to produce unintended biological effects when encountered by non-target species even at low environmental concentrations (ng L^{-1} to $\mu\text{g L}^{-1}$).

Globally, the pharmaceutical industry is vast, with over 4,000 drugs available and an annual consumption of approximately 100,000 tons (Hawash et al., 2023). The last decade saw an increase in the usage of antibiotics, and this trend is expected to reach a predicted 67% by the year 2030 (Klein et al., 2024). This scenario along with the increasing rates in self-medication, especially in developing countries, will definitely increase the occurrence and accumulation of pharmaceuticals in water systems. The shift in pharmaceutical consumption patterns, influenced by urbanization, the changes in lifestyles, and the COVID-19 pandemic, has introduced additional complexities in assessing their environmental distribution and reactivity. Since the beginning of the pandemic, studies have revealed that the concentrations of antiviral drugs and paracetamol in wastewater have significantly increased, further highlighting the growing threat to aquatic ecosystems (Begou and Kassomenos, 2023, Jiménez-Bambague et al., 2023).

In the context of this research, an apparent geographical bias is observed where occurrence studies were predominantly conducted in developed countries mainly European and North American (Aus der Beek et al., 2016, Lange et al., 2012), as opposed to the research performed in developing countries of the Globe. Hashim and co-workers identified that Southeast Asia countries (Malaysia, Philippines, Singapore, Thailand, Vietnam, Brunei, Cambodia and Lao PDR) lack the research knowledge in pharmaceutical occurrence issue as opposed to developed Asia countries such as China,

Korea and Hong Kong (Hashim et al., 2016). However, this topic is gaining more attention as more associated research is observed in countries such as Sri Lanka, Vietnam, Thailand and India (Goswami et al., 2022, Guruge et al., 2019, Sengar and Vijayanandan, 2022, Tran et al., 2019). This being said, few pharmaceutical monitoring studies were identified in South Africa with the alarming fact no similar studies were performed for most of the African countries (Madikizela et al., 2020). Similar trend was observed in the MENA region in which the number of studies discussing EC occurrence is much lower than that reported in developed countries (Segura et al., 2015). It is important to note that, with the growing concern over the persistence of pharmaceuticals in water systems and their significant threat to living organisms, this topic is gaining more attention in MENA area as the number of studies in these countries has clearly increased in recent years (Khezami et al., 2024, Nasri et al., 2024, Fakhri B et al., 2024, El Joumani et al., 2024).

Continuous monitoring of the rising concentrations of pharmaceutical in the environment presents significant financial and logistical challenges. As the number of pharmaceutical contaminants grows and our understanding of their release pathways remains limited, the sample collection process and the laboratory analysis become increasingly complex and expensive. In addition, the diverse physical and chemical properties of pharmaceuticals complicate the development of effective treatment systems capable of addressing the wide range of compounds detected in water environment (Osuoha et al., 2023). As a result, alternative solutions are necessary whereby mathematical models has emerged as valuable tool for simulating contaminant concentrations and thereby predicting risk assessments. Environmental fate models can be

used to predict the behavior (and eventually concentration) of pharmaceuticals in the water compartment of the environment. These models require hydrological data and environmental fate input in the form of emission rates, partitioning properties, and degradation/decay rates (Lindim et al., 2017). These models not only contribute in assessing the water quality but they can be also used to investigate the effectiveness of long-term action plans. The use of Geographic Information Systems (GIS) significantly improves the accuracy of these models by enabling geo-referenced simulations of contaminant concentrations with high spatial accuracy. This integration improves the precision of exposure assessments, allowing for localized and regional predictions on a broader scale. Several models are available for fate modeling of contaminants.

The aim of this thesis is to investigate the occurrence, distribution, and environmental hazards linked to pharmaceutical contamination in aquatic ecosystems, especially in regions lacking monitoring and management guidelines. By analyzing the environmental and public health impact of pharmaceuticals, this research contributes to a better understanding of the pharmaceutical pollution crisis and its potential long-term consequences. Key objectives are the following:

Literature Review: Conduct an extensive review of existing studies and literature related to the occurrence of pharmaceuticals in water bodies within the MENA region. This will include an assessment of the methodologies employed for detection and quantification.

Pathways of Contamination: Investigate and delineate the pathways through which pharmaceuticals enter MENA water bodies, focusing on wastewater treatment effluents and municipal wastewater discharge, as well as human and veterinary excretion.

Ecological Risk Assessment: Perform an ecological risk assessment to evaluate the potential impact of pharmaceuticals on aquatic ecosystems in the MENA region. This will involve assessing the concentration levels and potential effects on aquatic organisms and ecosystems.

Human Health Risk Assessment: Conduct a human health risk assessment to evaluate the potential health implications of pharmaceutical exposure through contaminated water sources in the MENA region. This will involve analyzing the concentration levels of pharmaceuticals and their potential effects on human health.

Antimicrobial Resistance (AMR) Assessment: Investigate the presence of antimicrobial resistance linked to pharmaceutical contamination in MENA water bodies. Assess the potential contribution of pharmaceuticals to the development and spread of antibiotic resistance.

Quantification and Status Evaluation: Evaluate the current status of pharmaceutical occurrence, detection, and risk quantification in different water compartments of the MENA region, including rivers, lakes, groundwater, and surface water.

Recommendations and Mitigation Strategies: Based on the findings, provide recommendations for future research directions and propose mitigation strategies to address pharmaceutical contamination in MENA water bodies, emphasizing sustainable water management practices.

Fate modeling: Based on the output of the data compilation and analysis, a set of criteria will be established to prioritize the pharmaceuticals most relevant for modeling. After pharmaceutical selection, the environmental fate in the receiving water body will be modeled using GREAT-ER software. This approach will enable an in-depth understanding

of the pharmaceutical distribution, persistence and evaluation of the water quality in the river. The primary aim of this research paper is to comprehensively investigate the occurrence of pharmaceuticals in water bodies across the Middle East and North Africa (MENA) region. The focus will be on understanding the pathways through which these emerging contaminants enter the environment, specifically via wastewater treatment effluents and municipal wastewater discharge, including contributions from human and veterinary excretion. Given the limited existing studies in the MENA region, the aim is to conduct a thorough review of all relevant research to establish a comprehensive understanding of the current status of pharmaceutical contamination in MENA water bodies.

CHAPTER 2

METHODOLOGY

In this section, the methodology used is outlined in Figure 1 where each section will address part of the work performed to conduct the research and will be further discussed in following sections.

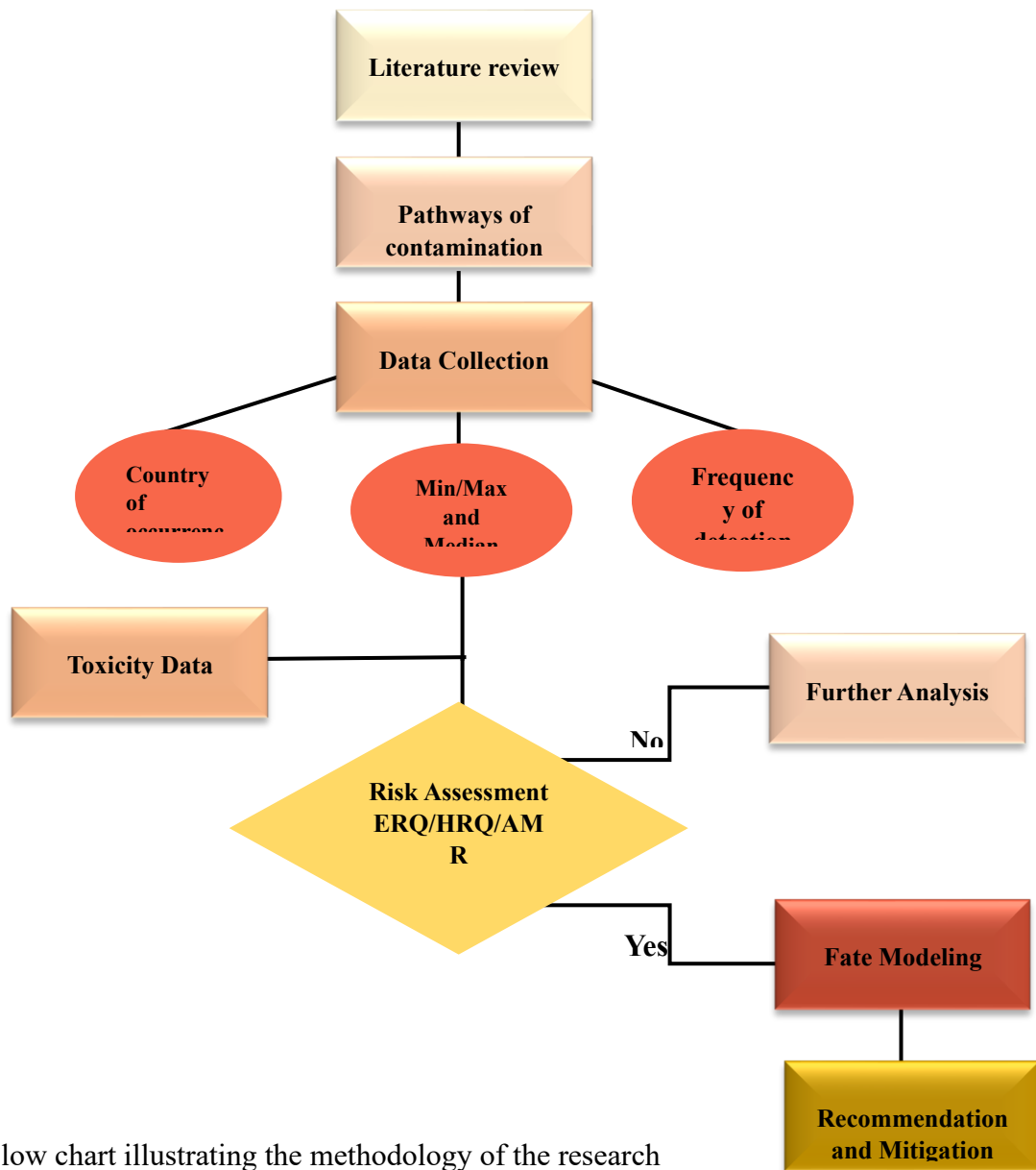


Figure 1: Flow chart illustrating the methodology of the research

2.1 Pathways of Contamination

Pharmaceuticals are a new type of contamination, the occurrence of which has been registered in freshwater and coastal environment. With a significantly increasing global population, and consequently increasing demand, thousands of what have come to be known as emerging contaminants (ECs) are consumed daily (Appendix A). These contaminants are able to reach the water environment through various pathways often as a result of human and veterinary use as seen in Figure 2. Human medicines are absorbed, metabolized and then excreted in urine or feces into the sewer system where they undergo a treatment process for removal. Despite this treatment, pharmaceuticals in different concentrations and form still make their way into the receiving waters but also lands through sewerage facilities particularly as fertilizers. (Avisar et al., 2009, Bavumiragira and Yin, 2022). In aquaculture, antibacterial used for the treatment of shrimp and fish for example, are directly released into the surrounding surface waters contributing directly to contamination. Furthermore, veterinary medicines used for the treatment of livestock, pets or wildlife are excreted directly into soils and surface waters. In intensive livestock treatments, these pharmaceuticals are likely to enter the environment through the application of fertilizers from infected slurry and manure. Additional routes for pharmaceutical entry include the emission to the air through manufacturing processes, the improper disposal of unused medicines and containers and wastewater from manufacturing or production facilities that are not adequately controlled. In fact, it has been identified that the primary pathway for pharmaceutical pollution is the urban sewage (Masanabo et al., 2022). The second largest contributor is the direct discharge of hospital wastewater, with the excretion of drugs and their metabolites by animals being the third major source

(Masanabo et al., 2022). All these pathways, without the appropriate removal techniques, play important role in the accumulation of pharmaceutically active ingredients in the aquatic environment day after day.

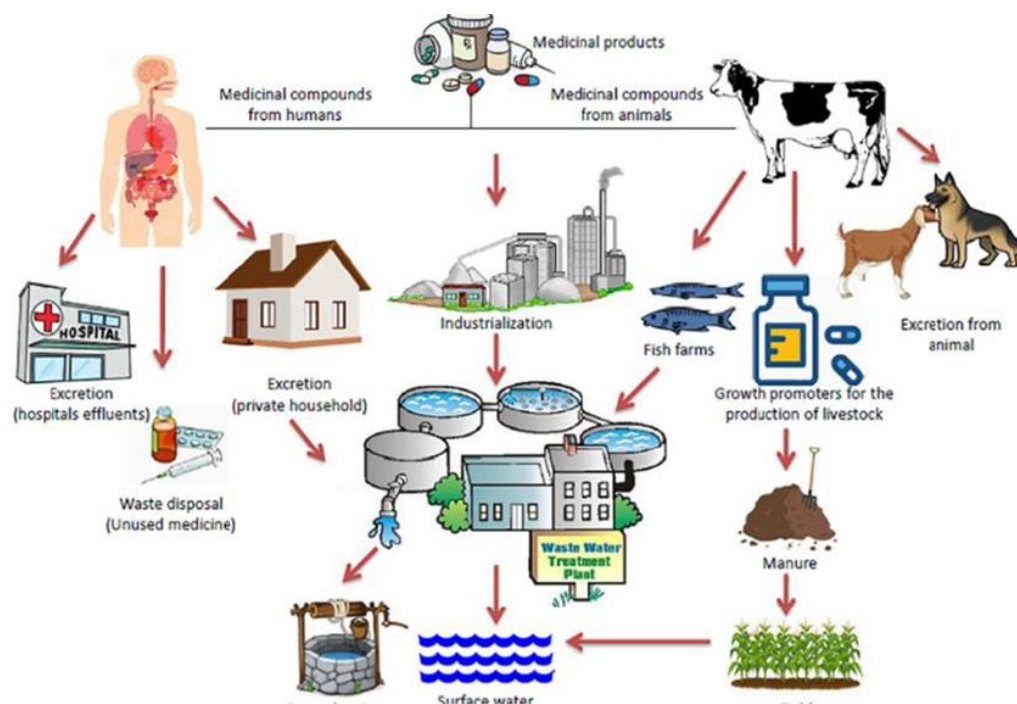


Figure 2: The different pathways undergone by pharmaceuticals to reach the aquatic environment (Masanabo et al., 2022).

Pharmaceuticals have been detected in the influents and effluents of wastewater treatment plants (WWTPs), as well as in rivers, lakes, seas, and groundwater, with concentrations varying from ng/L to $\mu\text{g/L}$ (Azzi et al., 2021, Lee and Choi, 2019, Wilkinson et al., 2022) The U.S. Environmental Protection Agency and the U.S. Geological Survey identified 118 pharmaceuticals in drinking water samples collected from 25 treatment plants nationwide (Glassmeyer et al., 2017). Additionally, Zhou et al.

(2019) reported the presence of 284 substances (243 pharmaceuticals and 41 metabolites and transformation products) out of 477 substances (411 pharmaceuticals and 66 metabolites) in surface waters across 33 European countries (Zhou et al., 2019).

2.2 Data Collection

Nineteen countries constitute the MENA region: Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates, and Yemen. The number of studies performed for the detection of pharmaceutical in the MENA countries is much lower than that reported in developed countries (Segura et al., 2015). Similarly, the number of pharmaceutically active ingredients experimentally detected and analyzed is very low (Appendix A). Mansour and colleagues reported that, from 2016, only 12 investigative studies are reported in the literature covering the six following countries of the MENA: Israel, Jordan, Lebanon, Palestine, Tunisia, and Saudi Arabia. These studies register the occurrence of 28 out of 42 compounds in both surface and groundwater (Mansour et al., 2016).

Recently, the number of studies reporting pharmaceutical contamination in aquatic environments across the MENA region has risen considerably (Harrabi et al., 2018, Picó et al., 2019, Picó et al., 2020, Tahrani et al., 2017). However, despite this trend, there remains a notable lack of data in certain countries. To the authors' knowledge, no occurrence studies have been reported in Bahrain, Syria, Oman, Yemen and Libya (Appendix A). This gap may be attributed to the absence of infrastructure for routine trace analysis of pharmaceutical pollution, the limited access to specialized equipment for water analysis, and the shortage of well-trained personnel to operate such equipment.

Additionally, most of these countries lack the environmental regulations to address data deficiency.

The web was thoroughly scanned to compile all occurrence studies that analyzed experimental samples of different water systems such as rivers, streams, lakes and coastal seawaters, wastewater treatment influents and effluents and groundwater over the period from 2006 to 2024. Based on these studies, measured concentrations of pharmaceutically active ingredients were extracted for each and every water sample type in the associated country of study. The data search was performed on the Web of Science, Scopus, and Google Scholar databases using the key words: “pharmaceuticals”, “drugs”, “occurrence” in combination with other words such as “river”, “surface water”, “groundwater” or “wastewater effluent”. The studies selected for this review were only ones performed in the MENA region. The pharmaceuticals detected, their concentration ranges in the respective sampling water bodies, and the country of occurrence are extracted from the studies to form the database (Table S1). The concentration data extracted were then classified into ranges from the minimum to the maximum concentration, and then classified into their respective therapeutic classes using the PubChem and World Health Organization (WHO) databases in addition to other publications (Tran et al., 2018, Zhou et al., 2019). To keep the focus on the pharmaceutical pollution in particular, personal care products, metabolites, natural hormones, and stimulants were excluded from this assessment and presented in Table S2.

As a result, for a better understanding and analyzing the current state of pharmaceutical contamination in MENA water bodies, the database is compiled to include the pharmaceutical analyzed and detected, its measured concentration and the

water body type of the sampling. This data is then used for the ecological and human health risk assessment as presented in the next section.

2.3 Environmental risk quotient (RQ)

The majority of MENA countries are developing nations where research analysis is not financially supported and suffer from the unavailability of some analytical equipment for the appropriate risk quantification method. As a result, it is required to employ an alternative risk quantification method for the evaluation of the possible threats the exposure to these compounds pose on the living organisms. As a result, The European Medicines Evaluation Agency (EMA) and the US Food and Drug Administration (FDA) proposed a combination of measured environmental concentrations (MECs) and predicted no-effect concentrations (PNECs) for environmental risk assessment (ERA) (Desbiolles et al., 2018, Lee and Choi, 2019, Thomaidi et al., 2017, Walter and Mitkidis, 2018) and human health risk assessment (HHRA) (Semerjian et al., 2018, Sharma and Kumar, 2024). In accordance with EU (European Union) legislations, the risk assessment is evaluated based on the quotient RQ that is the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) (Tran et al., 2019, Afsa et al., 2020, Dotan et al., 2017, Gredelj et al., 2018). In order to give a more realism to this study, measured environmental concentrations (MECs) detected in MENA water bodies were used instead of PECs for the risk quantification. As such, the RQ is then defined as the ratio of the MEC (ng/L) to the PNEC (ng/L) (Eq. (1)).

$$RQ = \frac{MEC}{PNEC} \quad (1)$$

PNEC values are usually extrapolated from chronic toxicity data based on four different toxicity concentrations:

1. chronic no-observed effect concentrations (NOECs)
2. chronic lowest-observed effect concentrations (LOECs)
3. short term median effective concentrations (EC₅₀)
4. short term median lethal concentrations (LC₅₀).

NOEC is the highest tested concentration for which there is no statistical significance when compared to a control group in a long-term toxicology study (Murado and Prieto, 2013). Meanwhile, LOEC is the lowest concentration for which an adverse effect is observed in a chronic toxicology study (Murado and Prieto, 2013). EC₅₀ refer to the concentration of a substance in an environmental medium expected to produce a certain effect in 50 % of test organisms and LC₅₀ is the concentration for which the result observed is death (Crowl and Louvar, 2001). To take into account the uncertainties of the evaluation, and to form a worst-case scenario, an assessment factor is incorporated as shown in Eq. 2. The assessment factor is usually measured in toxicity studies based on the number of assays and species used for the determination of toxicological data (Table S3). As such, toxicity concentrations are obtained from the literature on the three most sensitive species of the ecosystem, algae, daphnid and fish mainly from the USEPA's ECOTOX database (Agency, 2001), in addition to selected books, reports and papers for experimental toxicological data (Brausch et al., 2012, De Liguoro et al., 2012, Yamamoto et al., 2007, Yang et al., 2008). Google Scholar was also used with the search terms like “EC₅₀”,

“NOEC”, and “LOEC” combined with the compound of interest name (Appendix A). The minimum toxicity concentration is incorporated in the assessment of the PNECs. As such, the RQ is calculated in Eq. 2 as follows:

$$PNEC = \min \left(\frac{Ecotoxicity\ Green\ Algae}{AF}, \frac{Ecotoxicity\ Fish}{AF}, \frac{Ecotoxicity\ Daphnid}{AF} \right) \quad (2)$$

To reflect a worst-case scenario, the risk quotient was initially intended to be based on analytically measured toxicity data. However, such data are not always available for all pharmaceutical compounds. As a result, when measured ecotoxicity data are lacking, predicted toxicity values are used as a substitute (Riva et al., 2019). This approach ensures that the potential environmental risks of pharmaceuticals can still be assessed, even in the absence of direct experimental data. Acute toxicity values obtained from Pure predictive models using Quantitative Structure Activity Relationships ECOSARv1.11. The minimal toxicity concentration for each pharmaceutical is adopted when more than one toxicity data is available for the same organism as presented in Table S3. In turn, the smallest value between the PNECs calculated for the same pharmaceutical is employed in the risk quotient assessment to illustrate the idea that if the smallest concentration had an effect on any sensitive species, that any concentration above it would definitely cause an effect. As for the MEC, maximum, minimum, median, and mean concentrations were used for RQ calculations in Tables S3, S4, S5, and S6 respectively. This is done to account for differences in sampling methods and environmental conditions and to eliminate the bias in the data (Appendix A).

In accordance with the EMEA methodology, a binary ecological classification for risk assessment is employed, where for an $RQ < 1$, the risk is un-likely whereas an $RQ \geq 1$

implies appreciable risk (Tran et al., 2019).

Hence, the risk quotient (RQ) remains the primary indication of the direct ecotoxic effects expected to be caused at a given concentration. This type of analysis has been frequently and effectively reported in literature over time in an attempt for a fast and accurate threat mitigation action plan (Chen et al., 2016, Komori et al., 2013, Rivera-Jaimes et al., 2018, Verlicchi et al., 2012, Zhu et al., 2019).

2.4. Health risk characterization

Human Health risk refers to the likelihood of an adverse health effect on human health will occur as a result to a pharmaceutical exposure. This assessment evaluates both the potential hazard posed by the contaminant and the level of exposure that an individual might experience. Based on the data compilation as previously mentioned in section 3.2, pharmaceuticals that are positively detected in surface water only are subjected to this assessment. The particular focus on surface water comes in consequence to the diversity of its uses. Surface water often serves as a significant source of drinking water especially in rural and developing regions. Another primary use of surface water is recreational activities like swimming, fishing and boating. Contaminated water can directly expose individuals to gastrointestinal diseases, skin infection and ingestion of harmful chemicals. Moreover, surface water is widely used in MENA countries as a source for irrigation crops especially in Jordan, Tunisia and Egypt. The infection of surface water can lead to the infection of plants, potentially entering the human food chain through the consumption of contaminated crops. In this analysis, a conservative and regulatory HHRA approach is employed, where a health risk quotient (HRQ) is calculated for each identified

pharmaceutical. The worst-case potential health risk is determined by comparing the highest MEC of the pharmaceutical in surface water to its corresponding acceptable concentration (AC) (Eq. (3)). Additionally, other scenarios are explored using median, mean and minimum concentrations.

$$HRQ = \frac{MEC}{AC} \quad (3)$$

Acceptable concentration is typically based on toxicological data and health guidelines established by regulatory bodies. To determine the AC, acceptable daily intakes (ADIs) are combined with standard assumptions about potential exposure pathways (Appendix A). Values of ADIs are obtained from the literature (de Aquino et al., 2021, de Jesus Gaffney et al., 2015, Leung et al., 2013, Martínez-Morcillo et al., 2020, NRMCC-EPHC-AHMC, 2006, Prosser and Sibley, 2015, Schriks et al., 2010, Schwab et al., 2005, Sengar and Vijayanandan, 2022, Webb et al., 2003, Williams and Brooks, 2012, Zhu et al., 2020) and presented in Table S7. ADI values are not typically reported in literature for each and every pharmaceutical. If so, ADIs are then calculated by dividing the lowest therapeutic dose (LTD) to uncertainty factors to account for the variability within the human population (Eq. (4)), (Sengar and Vijayanandan, 2022). In the event where no clear LTD is found in the literature, the no-observed-effect-level (NOEL) is derived from the median lethal dose (LD₅₀) and used as a point of departure (Eqs. (5) and (6)) (Walsh et al., 2013, Mehdizadeh et al., 2022).

$$ADI = \frac{LTD}{BW \times SF} \quad (4)$$

$$NOEL = LD_{50} \times 0.5 \quad (5)$$

$$ADI = \frac{NOEL}{SF} \quad (6)$$

where ADI ($\mu\text{g}/\text{kg}\text{-day}$) is the acceptable daily intake, LTD ($\mu\text{g}/\text{day}$) is the lowest therapeutic intake, BW (kg) is the median body weight assumed to be 70 kg, SF (in the Eq. 4) is a safety factor of 1000, LD_{50} ($\mu\text{g}/\text{kg}$) is the median lethal dose, and NOEL ($\mu\text{g}/\text{kg}$) is the no-observed-effect-level. Upon comparison with the associated published work, as related to the previous calculation of ADI based on NOEL and BW, an error in the approach is identified upon division by BW. Hence, a revised equation is shown in Eq. 6 where SF depends on the therapeutic class of the pharmaceutical under test. Upon further review and comparison with recent literature, ADI values calculated based on NOEL are mainly calculated for personal care products and not pharmaceuticals (Sengar and Vijayanandan, 2022). Nevertheless, to avoid excluding pharmaceuticals that lacked any ADI or LTD values, this approach was adopted allowing the inclusion of pharmaceuticals in the assessment for which standard reference values were unavailable.

The calculation of acceptable concentration assumes that potentially exposed population varies by age and divided into healthy adults and children. To account for different exposure pathways, three categories of ACs are calculated: i) exposure through drinking water (Eq. (7)), ii) exposure through fish consumption (Eq. (8)), and iii) the combined exposure from both drinking water and fish consumption (Eq. (9)). In these calculations, the varying exposure levels between adults and children are considered, as children are often more vulnerable to environmental contaminants due to factors like

higher water consumption relative to body weight and greater metabolic rates. The combined exposure pathway reflects real-world conditions where individuals may be exposed to contaminants through multiple routes simultaneously. Furthermore, the assumptions for fish consumption also include factors such as the type and frequency of fish consumed, as well as the potential bioaccumulation of contaminants in aquatic organisms.

$$AC_{DW} \left(\frac{ng}{L} \right) = \frac{1000 \times ADI \times BW \times AT}{IR_{DW} \times EF \times ED} \quad (7)$$

$$AC_F \left(\frac{ng}{L} \right) = \frac{1000 \times ADI \times BW \times AT}{BCF \times IR_F \times EF \times ED} \quad (8)$$

$$AC_{combined} \left(\frac{ng}{L} \right) = \frac{1000 \times ADI \times BW \times AT}{(IR_{DW} + BCF \times IR_F) \times EF \times ED} \quad (9)$$

Where (Appendix A):

| | | |
|-----------|--|---|
| ADI | ($\mu\text{g}/\text{kg}\text{-day}$) | acceptable daily intake that should not result in an appreciable effect in the health of directly exposed population |
| 1000 | ($\text{ng}/\mu\text{g}$) | conversion factor |
| BW | (kg) | median body weight of age-specific group (14 kg for child and 70 kg for adult) |
| IR_{DW} | (L/day) | drinking water ingestion rate (1L/day for child and 2L/day for adult) |
| IR_F | (kg/day) | fish consumption rate (0.0065 kg/day for child and 0.0175 kg/day for adult) based on previous similar human health risk assessment studies (de Jesus Gaffney et al., 2015, Schwab et al., 2005) |
| BCF | (L/kg) | bioconcentration factor for fish obtained from EPI suite's BCFBAF |
| EF | (days/year) | exposure frequency assumed to be (350 days/year) (Schwab et al., 2005, de Jesus Gaffney et al., 2015) |
| ED | (years) | exposure duration (6 years for child and 30 years for adult) (de Jesus Gaffney et al., 2015) |

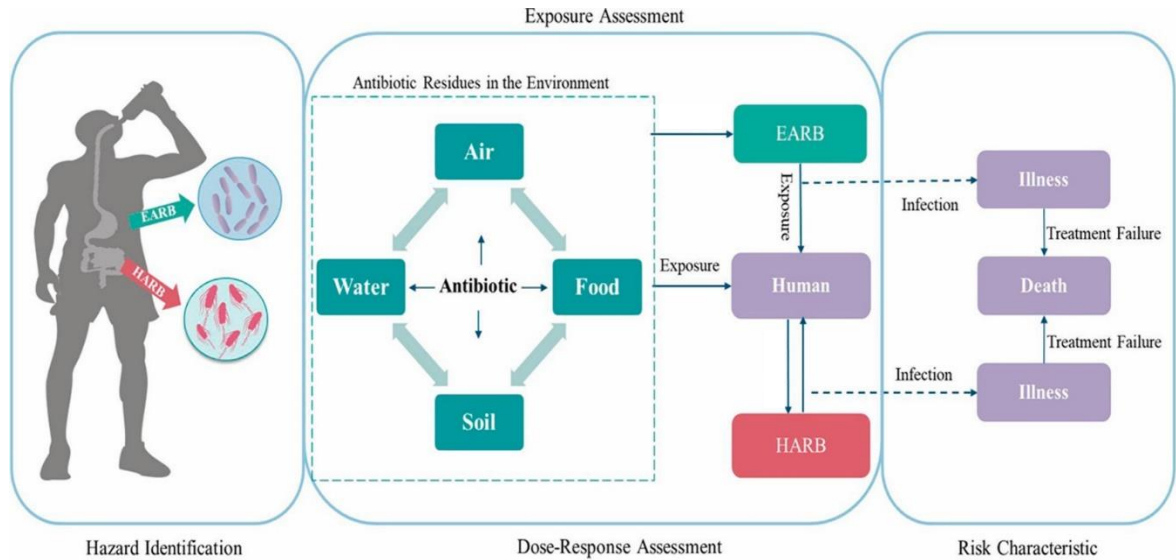
| | | |
|----|--------|--|
| AT | (days) | averaging time equivalent to ED (365 days) |
|----|--------|--|

In order to evaluate the results, an HRQ value ≤ 0.2 suggests that the pharmaceutical in question does not pose a significant risk on human health. An HRQ greater than 1 indicates a potential health risk while an HRQ value between 0.2 and 1 warrants a more in-depth assessment (Sharma et al., 2019). The HRQ values for maximum, minimum, median, and mean concentrations are provided in Tables S8, S9, S10, and S11 respectively of Appendix B.

2.5. Risk Assessment for antimicrobial resistance (AMR)

Antimicrobial resistance occurs when microorganisms such as bacteria, fungi, viruses and parasites, develop resistance to the antibiotic that are designed in the first place to kill them or at least inhibit their growth. In other words, the bacteria that once could be treated with antibiotics become resistant to the same antibiotic due to continuous contact resulting from the persistence of these pharmaceuticals in aqueous environment. In light of the extensive use of antibiotics that leads to the quick spread of antibiotic resistance, there is still insufficient quantitative models that typically assess the resistance risk (Al Maadheed, 2016, Craddock et al., 2020, Krzeminski et al., 2019). These concerns are primarily centered around i) the potential hazard of ingesting antibiotic residues in the environment which could have its major consequences in altering the human microbiome through the emergence of resistant bacteria inhabiting the human body, but also ii) the potential hazard of creating a selection pressure and fostering the formation of antibiotic

resistance reservoirs in the surrounding environment as shown in Figure 3 (Ben et al., 2019). As such, common medications become less potent or ineffective.



EARB: Environmental Antibiotic Resistant Bacteria; HARB: Human Antibiotic Resistant Bacteria.

Figure 3: Potential hazard identification of antimicrobial resistance, evaluation of the exposure pathways and characterization of the associated risk (Ben et al., 2019)

mean, and minimum) of antibiotics to the lowest PNEC-Minimum Inhibitory Concentration (PNEC-MIC) reported in the literature, as shown in Eq. (10).

$$RQ_{AMR} = \frac{MEC}{PNEC-MIC} \quad (10)$$

where RQ_{AMR} is the risk quotient for AMR, MEC is the measured environmental concentration (ng/L), and PNEC-MIC is the predicted no-effect concentration based on the minimum inhibitory concentration (PNEC-MIC)(ng/L). For $RQ_{AMR} \leq 1$, the AMR risk is unlikely; the risk is more likely when $RQ_{AMR} > 1$ (Tran et al., 2019) (Appendix A). The results are tabulated in Table S12 (Appendix B). 38 antibiotics out of 56 detected in

MENA water bodies, have published PNEC-MIC values reported in the literature (Bengtsson-Palme and Larsson, 2016, Kümmerer and Henninger, 2003, Zhang et al., 2020). The remaining unpublished PNEC-MIC are calculated for the 18 remaining antibiotics detected in the MENA region. Based on antimicrobial research studies, PNEC-MIC can be calculated by obtaining the lowest observed MIC value in databases such as the European Committee for Antimicrobial Susceptibility Testing (EUCAST)(Bengtsson-Palme and Larsson, 2016) and The Antimicrobial Index (TAMI) (Amirkia and Qiubao, 2011, Zhang et al., 2020). After this, the size-adjusted lowest MIC was calculated for antibiotics with <40 tested species using Eq. (11). For antibiotics tested on more than 40 species were tested, the lowest MIC was not adjusted (Zhang et al., 2020). This adjustment is done to ensure that 99 % of bacterial isolates would have a MIC higher than the size-adjusted MIC (Zhang et al., 2020)

$$MIC_{lowest,size-adjusted} = \frac{lowest\ observed\ MIC \times N}{41} \quad (11)$$

where the lowest observed MIC is the lowest observed minimum inhibitory concentration (ng/L) and N is the number of tested species. All the values were rounded to the closest value on the EUCAST scale for AMR selection (Bengtsson-Palme and Larsson, 2016, Zhang et al., 2020). At the end, an adjustment factor of 10 was applied to find the PNEC-MIC. This methodology was used to derive the PNEC-MIC for ten antibiotics not previously reported in the literature (Table S13). However, dapsons, metformin, and most of the compounds from the sulfonamide therapeutic class were not found in any of the aforementioned databases. This hindered the calculation of their PNEC- MIC, and hence their RQ_{AMR} (Appendix A).

2.6 Fate modeling

Several factors need to be taken into account in order to adequately design a transport and fate model: i) the possible sources of pharmaceutical emissions, ii) its chemical, biological and physical characteristics, iii) the different transport pathways and iv) the bio-geochemical processes resulting in the distribution of pharmaceutical concentration in the environment (Ashraf et al., 2022). As shown in Figure 4, the first step in fate modeling is the selection of the pharmaceutical compound of interest depending on previous prioritization studies, its frequency of occurrence or its high toxicity effects (phC means pharmaceutical).

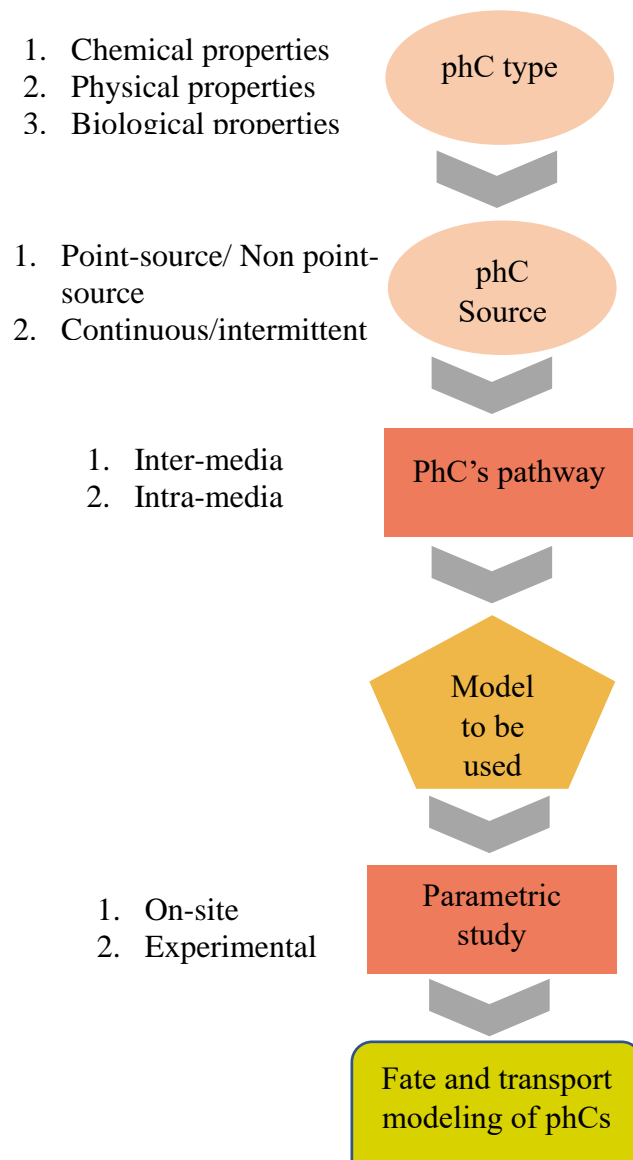


Figure 4: Steps in fate and transport study of pharmaceutical contamination

Next is the identification of point sources (such as WWTP effluents, manufacturing facilities and hospital discharge) and non-point sources of emissions (such as agricultural and urban runoff and leaching of drugs into soil and water systems through improper waste disposal). That being said, it must be identified if the source of emission is

either continuous or just instantaneously in order to elaborate on the different pathways and attenuation processes (namely biodegradation, adsorption and photochemical transformation) undergone by the contaminant from its source to reach its final destination. All these data are the inputs for the appropriate mathematical model developed to simulate the fate. The outcome of the study is further evaluated in a risk characterization strategy in an attempt to address policy making and framing of environmental laws. Modeling the fate of contaminants has been in practice since 1970s, at the time when data variability was less complex (well mixed and homogeneous medium) and models served as rough estimation of the real concentrations (Ashraf et al., 2022). Further realism was introduced with spatially explicit multimedia models with finer resolution with the variability of environmental characteristics. Subsequently, GIS based model gave more robustness to the computational framework through the definition of geo-referenced parameters varying at regular intervals, which in turn lead to more precise simulation of loads and fluxes in the surrounding medium.

Several models were developed in this regard, and some of them are summarized in Table 1. For further information about the details of the models, the reader is referred to Jagiello et al. (2015).

Table 1: Description of models used to model pharmaceutical fate in the water environment, adapted from (Jagiello et al. 2015).

| <i>Model</i> | <i>Description</i> |
|-------------------|--|
| <i>EUSES</i> | Local/ regional model that determines the PEC/PNEC ratio using physicochemical properties and emission data |
| <i>GREAT-ER</i> | Specific for the determination of aquatic exposure for chemicals thrown down the drain. A new version by Kahrein et al (2015) adds scenario creation and analyses. |
| <i>PhATE</i> | Local tool that estimates the concentrations of pollutants and risk characterization (PEC/PNEC) in surface water based on physicochemical properties and emission data |
| <i>STREAM-EU</i> | Simulates the movement and fate of organic contaminants in European river basins |
| <i>OCED Tool</i> | Global steady state model that determines overall persistence and characteristic travel distance |
| <i>CalTOX 4.0</i> | Regional steady state dynamic model that assesses human exposure |
| <i>GloboPOP</i> | Global dynamic model that determines Arctic contamination potential and overall persistence; it uses nine interconnected sub-models to represent a specific climate zone |
| <i>BETR</i> | Dynamic model that connects the fate models developed for individual regions in North America that determines overall persistence and the Great Lakes transfer potential |
| <i>EVN-BETR</i> | European version of the BETR model developed by Prevedourous et al (2004) |
| <i>G-CIEMS</i> | Regional to global dynamic model that incorporates spatial resolution using a geographic information system to determine the outflow ratio and exposure-weighted averaged |
| <i>FATE</i> | Global dynamic model that connects five environmental compartments in a non-steady biogeochemical cycle for non-polar pollutants; characterizes risk in the form of the PEC/PNEC ratio |

The GREAT-ER model has proven its efficiency in modeling contamination distribution for several European rivers (Kehrein et al., 2015, Lämmchen et al., 2021, De Girolamo et al., 2023). It assumes a steady-state model with both deterministic and stochastic approaches combining GIS with chemical fate processes at the river basin level. The output of GREAT-ER is a color-coded map highlighting the area with high expected concentration distribution. Such information is crucial in the selection of sampling sites and tests the priori effectiveness of selected reduction measured for

water managers. Corresponding parameters are natural environmental variability, uncertainty of substance parameters and temporal fluctuation of consumption patterns are defined as probability distribution of random variables (Lämmchen et al., 2021). An important built-in feature in GREAT-ER is the scenario builder option that enables user to witness the change in concentration distribution upon a defined change in boundary conditions.

The initial intention of this research was to perform a pharmaceutical fate modeling using the GREAT-ER model along Beirut river, one of the heavily polluted waterways in Lebanon. In order to prepare for GREAT-ER database, required geographical data were supposed to be stored in catchment-specific database at the pre-processing level. However, the lack of detailed topological river network and flow data, along with the insufficient information about the population under test and pharmaceutical consumption data, prompted a shift in the research direction. Despite this shift, efforts will be made to achieve the initial objective of the research by first addressing the scarcity of data through the integration of river flow simulation models, then trying to obtain the unpublished population and sales data by other means and at last, processing the data into the GREAT-ER database.

CHAPTER 3

RESULTS

This section includes the following results: i) the detection of pharmaceuticals in MENA water bodies with the identification of the mostly prevalent compounds, and ii) the results of the associated risk assessment in an attempt to highlight the pharmaceuticals posing potential risks to the environment and human health.

3.1 The identified Gap in occurrence studies among the MENA countries

Only fourteen out of nineteen countries spanning the MENA area, reported monitoring studies of pharmaceuticals in various aquatic ecosystems: Algeria, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Morocco, Palestine, Qatar, United Arab Emirates, Saudi Arabia and Tunisia. A total of 76 monitoring studies were published in the literature across the MENA region spanning the period from 2006 to 2024 (Appendix A). The highest frequency of occurrence studies was identified in Israel at nineteen studies. Tunisia ranked the second in terms of frequency of reported studies (fourteen) followed by Jordan (twelve). Only eight studies were reported in Iran, nine in Lebanon and Ten in Saudi Arabia. The frequency of occurrence studies majorly decreases in Qatar and Palestine with four studies for every country. Moreover, it is noticed that only two occurrence studies reported for each of Algeria and Egypt. Five countries in the MENA region lack any research on this topic namely Syria, Yemen, Oman, Bahrain and Libya. It is important to note that 50% of the studies spanned

the years from 2017 to 2022, indicating a rise in the interest of these countries with water contamination by pharmaceutical compounds. This trend is particularly evident in Tunisia, where seven studies out of fourteen on this subject were reported during this period (Appendix A). Fig. 5 shows the number of pharmaceuticals detected in each country.

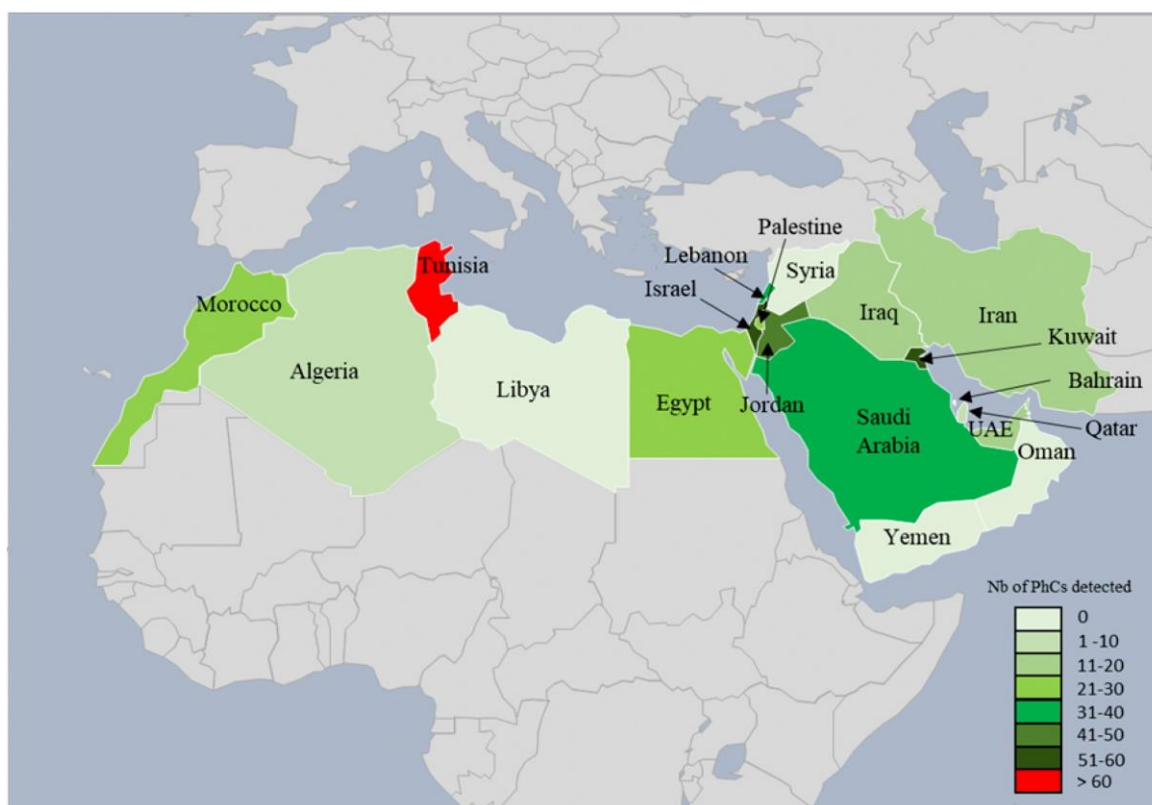


Figure 5: Number of pharmaceuticals (PhCs) positively detected in different water compartments across each country of the MENA region given as groups (Mheidli et al., 2022).

3.2 Pharmaceutical Occurrence in the MENA region

Based on the monitoring studies, a total of 159 pharmaceuticals distributed over 30 therapeutic classes were detected in different types of MENA water bodies: WWTP

influent or effluent, surface water, or groundwater. Table 2 shows the distribution of retrieved studies across the MENA water compartments analyzed where the largest frequency of studies was registered for WWTP effluents followed by Surface water. Few studies were reported for groundwater despite its crucial role in supporting human life as many MENA countries rely on groundwater for drinking purposes. The entire database can be found in Table S1 (Appendix B).

Table 2: The frequency of studies reported in the MENA region following the water body type analyzed

| Type of water sample analyzed | Number of published studies |
|-------------------------------|-----------------------------|
| WWTP effluents | 46 |
| WWTP influents | 29 |
| Surface water | 40 |
| Groundwater | 14 |

The pharmaceuticals that were analyzed but not detected in MENA waters can be found in Table S14. Moreover, Table S15 lists the number of pharmaceuticals detected according to therapeutic class (Appendix A).

The largest number of the detected pharmaceuticals was reported for surface water. The corresponding therapeutic class distribution is presented in Fig. 6. The largest number of pharmaceuticals most commonly detected in MENA aquatic environment belongs to Antibiotic therapeutic class at 37%, followed by analgesics and anti-inflammatory drugs at 13%.

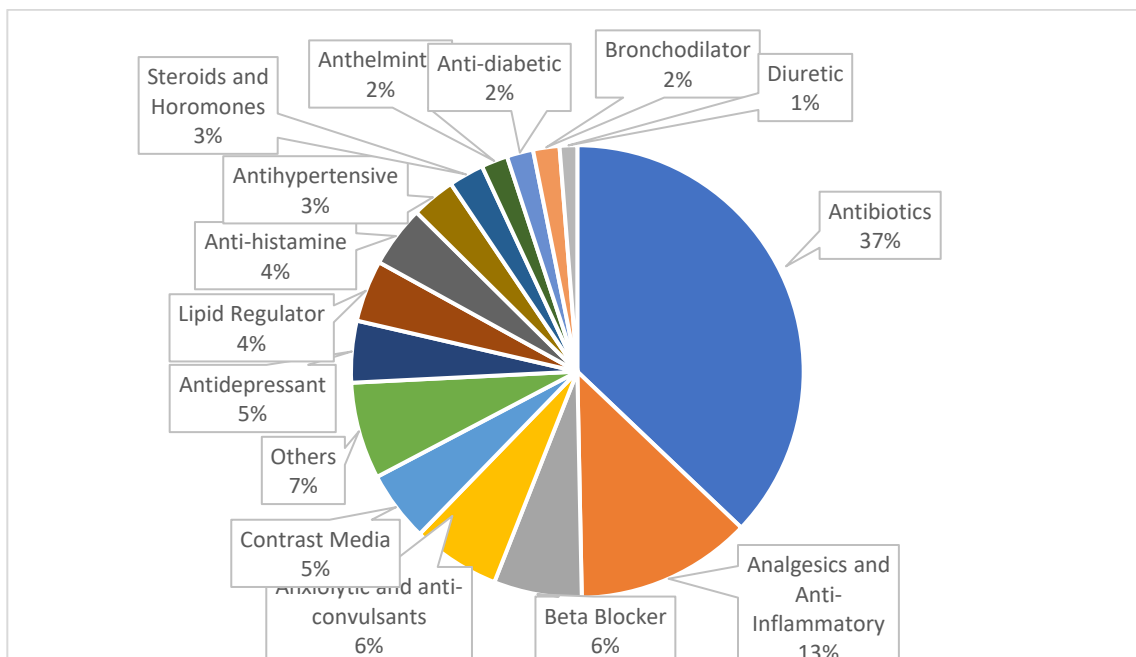


Figure 6: The number of pharmaceuticals (given as a number and a percentage relative to the total number) positively detected in MENA surface waters classified into therapeutic groups (Mheidli et al., 2022).

The least detected groups are antidiabetics, bronchodilators, and diuretics. This may be attributed to the pharmaceutical's frequency of analysis as most studies focused on antibiotics and analgesics and anti-inflammatory while very few target the others as is further detailed in Table S15. Carbamazepine, Diclofenac and sulfamethoxazole had a high number of positive reports, 45, 31 and 31 studies reported respectively as summarized in Table S16.

Fig. 7 is a logarithmic scale box and whisker plot illustrating the distribution in concentration levels of such pharmaceuticals in MENA surface waters and WWTP effluents. The plot shows the median values for the entire MENA region, the 25th and 75th quartiles in the data sets, the outlier points, and the number of data entries for each

compound. Interestingly, around 70 % of the overall detected antibiotics in the MENA waters were also detected in Tunisia.

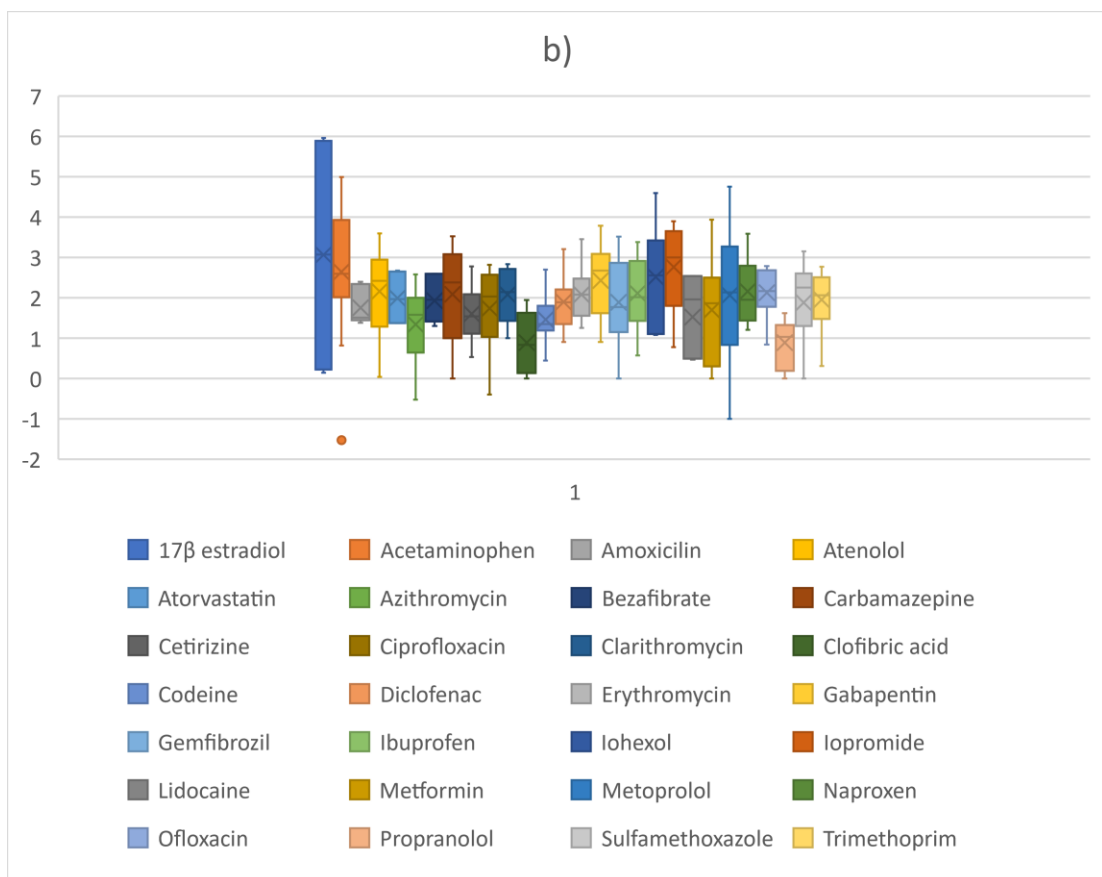
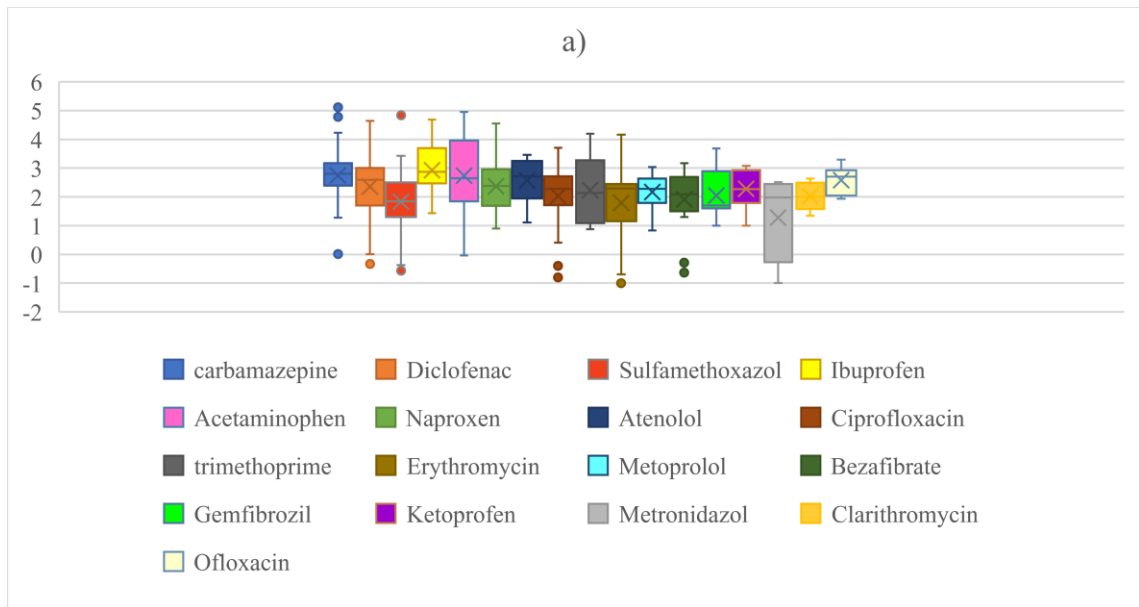


Figure 7: Median values and variation in the concentration levels of the most frequently detected pharmaceuticals in MENA (a) surface water and (b) WWTP effluents (n = number of data entries).

In terms of concentration, the highest level reported in the literature for MENA water bodies belongs to steroids and hormones across all the therapeutic classes detected, specifically 17 β estradiol in Egypt (Appendix A). The largest reported concentration of 17 β estradiol is 1,029,000 ng/L (1 mg/L) in wastewater and 900,000 ng/L in surface water (Elnwishi et al., 2012). Although certain compounds are not commonly analyzed or detected in the literature, they can still be found at very high concentrations. Iopamidol, although investigated in four studies only, has the highest occurrence concentration in a WWTP effluent (680,000 ng/L) and ground water (36,000 ng/L) across all other compounds (Zemann et al., 2015).

As mentioned previously, antibiotics group registered the highest frequency of detection on top of which sulfamethoxazole, reported in 31 studies. The highest concentration for sulfamethoxazole was detected at 68,700 ng/L in the effluent of a WWTP in Tunisia (Tahrani et al., 2017). Following is erythromycin, reported in 20 studies where its concentration ranges between 12.8 and 3900 ng/L in surface waters with the highest concentration registered at 14,700 ng/L in the effluent of WWTP (Tahrani et al., 2017) (Wilkinson et al., 2022). Examining the anxiolytic and anti-convulsant class, carbamazepine was detected with the largest values for WWTP influents (3020 ng/L in Jordan) (Shigei et al., 2021) and effluents (132,000 ng/L in Tunisia) (Khazri et al., 2019). It is important to note that this pharmaceutical was the most commonly studied pharmaceutical in MENA aquatic compartments. The highest concentration among this therapeutic class was reported for gabapentin in Israeli surface waters, and specifically river covering a range of 1060–6060 ng/L (Wilkinson et al., 2022).

Moreover, 31 studies covered the occurrence of diclofenac which was the most

frequently detected pharmaceutical Amongst the analgesic and anti-inflammatory class. Following is ibuprofen (23), acetaminophen (23), and naproxen (22). In terms of concentration, the highest one was reported for acetaminophen at 99,600 ng/L in WWTP influent and 90,500 ng/L in WWTP effluent in Saudi Arabia (Shraim et al., 2017). It reached a concentration of 98,300 ng/L in the riverine compartment in Tunisia (Khazri et al., 2019) and 214,29 ng/L in Kuwait seawater (Gevao et al., 2021). For the other classes, Table 3 presents a summary of the therapeutic groups detected with their associated measured concentration across the different water compartments of the MENA (Appendix A).

3.3. Pharmaceutical risk assessment

3.3.1 Risk assessment in surface waters

This section presents the results of risk assessment performed on pharmaceuticals detected in surface water specifically excluding those reported in other water bodies from evaluation. As such, 40 out of 159 pharmaceuticals were selected for risk evaluation as their measured concentration ranged between 10.1 and 900,000 ng/L in MENA surface waters and presented in Table 4. As appears in this Table, five pharmaceuticals calculated extremely high RQ: 17 β estradiol (562,500 in Egypt), diclofenac (10,221 in Saudi Arabia), metoprolol (5660 in Tunisia), ethinylestradiol (2500 in Morocco) and carbamazepine (1676 in Israel) (Appendix B). High RQ levels can be explained by either high MECs (as is the case for 17 β estradiol, diclofenac, metoprolol and carbamazepine) or very low PNECs as in the case of ethinylestradiol attributed to its high toxicity effects. That being said, it is important to note that RQs for these pharmaceuticals were calculated based on measured

toxicity data that had much lower values when compared with predicted ones (Appendix A).

When using median concentrations for risk evaluation, two compounds in the high-risk range showing an $RQ > 100$: 17β estradiol (150,058) and atorvastatin (147). Even using minimum concentrations, atorvastatin and ethinylestradiol even exhibited an RQ of 18 and 10 respectively. Hence, these compounds detected in MENA waters would definitely cause a risk on living organisms.

As shown in Figure 8, Israel, Iran and Iraq showed the highest percentage at 56.5%, 53.3% and 50% respectively in terms of pharmaceuticals detected at concentrations posing an RQ . The maximum RQ calculated in Iran was 25 for diclofenac. Lower percentages but not distant were registered for Jordan where fifteen risky pharmaceuticals correspond to 40.5 % and Lebanon with 38.7% of the detected compounds. The highest RQ level for Jordan was calculated for carbamazepine at 1676. Further reduced percentages were calculated for Kuwait and Palestine at 21,4% and 30% respectively.

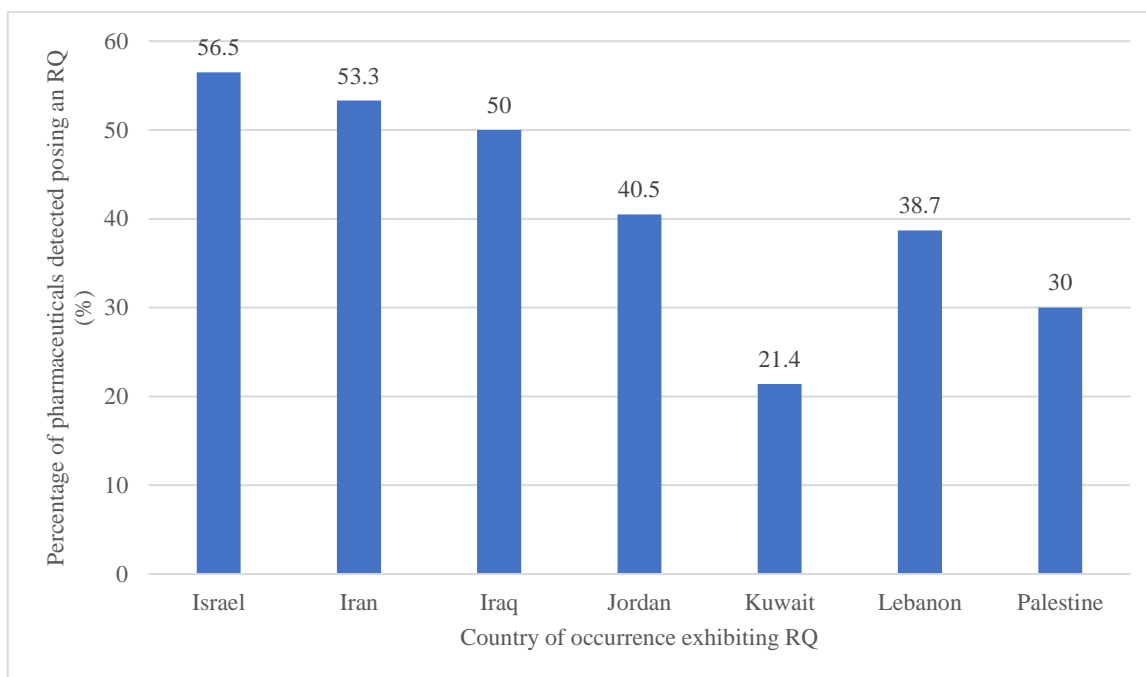


Figure 8: Percentage of pharmaceuticals detected in country of occurrence posing an RQ

Detailed calculations for each country are provided in Table S3 (Appendix B).

Table 3: Concentration ranges of therapeutic classes detected in MENA region water bodies. (NA: not available).

| Therapeutic group | Concentration (ng/L) | | | | |
|------------------------------|----------------------|--------------|------------|-------------|--------------|
| | Influent | Effluent | Sea water | Freshwater | Groundwater |
| Analgesics/anti-inflammatory | 3–99,600 | 0.47–90,500 | 0.2–21,429 | 0.03–98,300 | 0.52–6186.14 |
| Anthelmintic | NA | NA | 0.2–35.2 | NA | NA |
| Antibiotic | 0.1–99,636 | 0.1–68,700 | 0.1–66,400 | 0.03–8670 | 0.11–440 |
| Antidepressant | 0.3–11,720 | 2.8–11,340 | 0.2–18.9 | 1–1660 | 0.17–3.17 |
| Anti-diabetic | 7–450,000 | 15–618,000 | 2–14.3 | 31 | NA |
| Antihistamines | 230–9800 | 50–5200 | 0.2–1396 | 2.48–20,200 | NA |
| Antihypertensive | 4.66–2006.27 | 2.2–945.74 | 0.3–568.3 | 1–104 | 1.02–614.04 |
| Anxiolytic/anti-convulsant | 1.88–3020 | 2.21–132,000 | 0.3–109.6 | 1–6060 | 0.94–910 |
| Beta blockers | 1–4030 | 6.72–2900 | 0.2–1279.4 | 0.06–56,600 | 0.25–6.3 |
| Bronchodilator | 7.53–140 | 36–75 | <0.2 | 22–58 | NA |

| | | | | | |
|-------------------|-------------|--------------|------------|-------------|--------------|
| Contrast media | NA | 28–680,000 | 26 | 20–78,000 | 10–36,000 |
| Diuretics | 65–2800 | 37–2000 | 0.9–116 | 40–2100 | 0.68-1048.26 |
| Lipid regulator | 36–1000 | 0.23–7000 | 0.3–1620.6 | 1–3300 | 0.89–70 |
| Steroids/hormones | 1–1,029,000 | 0.07–684,000 | 36–184 | 0.2–900,000 | 0.16-10.43 |
| Others | 1.5–1200 | 1.4–18,537 | 0.2–55.4 | 1.97–348 | 2.01 |

Table 4: Maximum, median, and minimum measured environmental concentrations (ng/L) and RQs for pharmaceuticals showing at least one RQ > 1.

| Compound | Minimum PNEC | Maximum MEC | Maximum RQ | Median MEC | Median RQ | Minimum MEC | Minimum RQ |
|------------------|--------------|-------------|------------|------------|---------------------|-------------|---------------------|
| 17β estradiol | 1.6 | 900,000 | 562,500.00 | 240,092 | 150,057.50 | 36 | 22.5 |
| Diclofenac | 1 | 10,221 | 10,221.00 | 58.15 | 58.2 | 1.6 | 1.6 |
| Metoprolol | 10 | 56,600 | 5660 | 56.1 | 5.6 | 0.1 | 0.010 ^a |
| Ethinylestradiol | 0.02 | 50 | 2500 | 1.7 | 85 | 0.2 | 10 |
| Carbamazepine | 2 | 3353 | 1676.5 | 104.8 | 52.4 | 0.3 | 0.15 ^a |
| Gabapentin | 8.56 | 6060 | 707.8 | 476.5 | 55.7 | 8 | 0.93 ^a |
| Ranitidine | 4.92 | 2580 | 524.4 | 53 | 10.8 | 0.5 | 0.10 ^a |
| Atorvastatin | 1.3 | 474.7 | 365.2 | 23.55 | 18.1 | 12.1 | 9.3 |
| Sarafloxacin | 15 | 5300 | 353.3 | 74 | 4.9 | 49 | 3.3 |
| Estriol | 0.47 | 152 | 326.9 | 7.7 | 16.6 | 0.9 | 1.9 |
| Venlafaxine | 6.1 | 1660 | 272.1 | 25.4 | 4.2 | 0.3 | 0.049 ^a |
| Ibuprofen | 10 | 2407 | 240.7 | 91 | 9.1 | 3.73 | 0.37 ^a |
| Acetaminophen | 500 | 98,300 | 196.6 | 392 | 0.78 ^a | 0.03 | 0.0001 ^a |
| Norfloxacin | 160 | 20,700 | 129.4 | 50 | 0.31 ^a | 19.36 | 0.12 ^a |
| Erythromycin | 40 | 3900 | 97.5 | 121 | 3 | 7.8 | 0.20 ^a |
| Tetracycline | 50 | 3900 | 78 | 62.5 | 1.3 | 4 | 0.080 ^a |
| Bezafibrate | 23 | 1620.6 | 70.5 | 89 | 3.9 | 1.8 | 0.078 ^a |
| Ciprofloxacin | 50 | 2697.2 | 53.9 | 107 | 2.14 | 0.4 | 0.0080 ^a |
| Clarithromycin | 20 | 677 | 33.9 | 83.55 | 4.2 | 0.2 | 0.010 ^a |
| Gemfibrozil | 150 | 3300 | 22 | 23 | 0.15 ^a | 1 | 0.0067 ^a |
| Methotrexate | 34,926 | 618,000 | 17.7 | 31 | 0.0009 ^a | 95,000 | 2.7 |
| Amoxicillin | 15.6 | 2520 | 16,024.1 | 32 | 2.05 | 0.8 | 0.051 ^a |
| Fluoxetine | 3 | 41 | 13.7 | 20.5 | 6.8 | 1 | 0.33 ^a |
| Estrone | 20 | 265 | 13.3 | 111 | 5.6 | 1 | 0.050 ^a |
| Sulfamethoxazole | 120 | 1400 | 11.7 | 60 | 0.50 ^a | 0.8 | 0.0067 ^a |
| Amikacin | 170 | 1500 | 8.8 | 650 | 3.8 | 100 | 0.59 ^a |
| Atenolol | 760 | 3900 | 5.1 | 209 | 0.28 ^a | 0.5 | 0.0007 ^a |
| Theophylline | 14 | 58 | 4.2 | 40 | 2.9 | 22 | 1.6 |

| | | | | | | | |
|-------------------|--------|--------|-----|--------|-------------------|------|----------------------|
| Streptomycin | 1000 | 3400 | 3.4 | 2050 | 2.1 | 700 | 0.70 ^a |
| Clavulanic acid | 15,475 | 44,783 | 2.9 | 1721.9 | 0.11 ^a | 0.1 | 0.00001 ^a |
| Flumequine | 1590 | 4200 | 2.6 | 2200 | 1.4 | 200 | 0.13 ^a |
| Meclofenamic acid | 491 | 1000 | 2 | 755 | 1.5 | 510 | 1 |
| Diphenhydramine | 798 | 1300 | 1.6 | 675 | 0.85 ^a | 50 | 0.062 ^a |
| Dapsone | 1824 | 2800 | 1.5 | 2800 | 1.5 | 2800 | 1.5 |
| Sulfamethiazole | 2001 | 2800 | 1.4 | 205.5 | 0.10 ^a | 4 | 0.0020 ^a |
| Ofloxacin | 500 | 610.6 | 1.2 | 148 | 0.30 ^a | 0.8 | 0.0016 ^a |

^a The risk is unlikely.

Carbamazepine, diclofenac, sulfamethoxazole, and ibuprofen show the highest number of positive reports in MENA surface waters. Drastic RQ levels for carbamazepine and diclofenac can be explained by the high measured concentrations significantly above the PNEC levels in all the studied countries which explains the drastic RQ values obtained. The same applies to sulfamethoxazole and ibuprofen in all studied water compartments with the exception of a Jordanian river and Israeli seawater (Appendix A).

3.3.2. Human health risk assessment

The results of HHRA depicts the selection of 6 out of 159 detected pharmaceuticals posing a health risk to at least one age group via at least one mode of ingestion (Appendix A). Certain HHRQ reached levels >100. The highest HRQ value was calculated for 17 β estradiol at approximately 2880 for children following the combined effect of both fish ingestion and drinking. This large value is attributed to a very high MEC of 900 $\mu\text{g/L}$ in an Egyptian Lake (Elnwisy et al., 2012). It is important to note that, this order of magnitude in MEC i.e. $\mu\text{g/L}$ instead of ng/L in comparison to the remaining studies, was only reported in the work of Elnwisy and colleagues (Elnwisy et al., 2012). That being said, it is crucial to evaluate the results of this study carefully. The authors used

high-performance liquid chromatography (HPLC) coupled with fluorescence detector (FLD) for the hormone monitoring. They used an excitation wavelength of 420 nm as compares to 280 nm considered in other studies for the detection of 17β estradiol using a similar technique (Liz et al., 2017, Yoon et al., 2003). Moreover, when it comes to quality assurance, Elnwisy and co-workers only considered precision and accuracy without accounting for other factors such as selectivity, linearity, and detection limits of the HPLC-FLD technique (Elnwisy et al., 2012, Liz et al., 2017). To further scrutiny the results of the study, the HRQ evaluation expanded to include median and minimum concentrations instead of maximum measured concentration in an attempt to explore other scenarios and eliminate bias in the data. Nevertheless, the hormone 17β -estradiol still showed a possible health risk at median concentrations. Table 5 presents the compounds that pose a health risk to humans upon exposure, or in other words the compounds that have HRQ calculated to be >1 .

Interestingly, three out of four hormones (estrone, estradiol and 17β estradiol) calculated an $HRQ > 1$, the fourth hormone analyzed in this study is ethinylestradiol and its MEC does not pose a risk on humans. Other compounds presenting an $HRQ > 1$ belongs to anti-diabetics (1), antibiotics (1), anxiolytics and anticonvulsants (1). An important note is that all of these compounds have a minimal ADI value, the fact that results in a higher probability for inducing health risk. The results of this study compliment the expectation that Higher HRQs are calculated for the children group as they have lower body weight, thereby decreasing the acceptable concentration and increasing the HRQ value.

Abiding by the EU legislations, an HRQ level ranging between 0.2 and 1 calls for more assessment. This study revealed twenty-two pharmaceuticals that pose an uncertain risk to children with no risk to adults namely bisoprolol, clarithromycin, diclofenac,

diphenhydramine, florefenicol, gemfibrozil, glibenclamide, iomeprol, iopamidol, metoprolol, primidone, and venlafaxine (Appendix A). The common between all these pharmaceuticals is that the uncertain HRQ calculated is due to exposure via the drinking water and combined effect of both exposure pathways, but not through fish alone.

Furthermore, dimetridazole and lorazepam pose a definitive risk in children (HRQ > 1) but are of uncertain risk to adults. On the other hand, alprazolam, carbamazepine, cetirizine, fexofenadine, and sarafloxacin pose an uncertain risk to both children and adults via a combined exposure pathway (Appendix A).

Table 5: Pharmaceutical compounds that pose a human health risk after exposure from surface water through (a) drinking water, (b) fish, and (c) combined source (Mheidli et al., 2022).

| Compound | (a) Human risk quotient - drinking water | | | | | |
|---------------|--|-------------------|---------------------|--------------------|----------------------|---------------------|
| | Based on maximum MEC | | Based on median MEC | | Based on minimum MEC | |
| | Children | Adults | Children | Adults | Children | Adults |
| 17β estradiol | 1232.9 | 246.6 | 328.9 | 65.8 | 0.049 ^a | 0.0098 ^a |
| Dimetridazole | 2.1 | 0.42 ^b | 2.1 | 0.42 ^b | 2.1 | 0.42 ^b |
| Estrone | 21.1 | 4.2 | 8.8 | 1.8 | 0.079 ^a | 0.016 ^a |
| Estriol | 7.4 | 1.5 | 0.38 ^b | 0.075 ^a | 0.044 ^a | 0.0088 ^a |
| Glimepiride | 156.6 | 31.3 | 14.7 | 2.9 | 9.8 | 1.9 |
| Lorazepam | 2.5 | 0.50 ^b | 2.3 | 0.45 ^b | 2 | 0.41 ^b |

| Compound | (a) Human risk quotient - fish | | | | | |
|---------------|--------------------------------|--------|---------------------|--------|----------------------|--------------------|
| | Based on maximum MEC | | Based on median MEC | | Based on minimum MEC | |
| | Children | Adults | Children | Adults | Children | Adults |
| 17β estradiol | 1646.8 | 886.7 | 439.3 | 236.6 | 0.066 ^a | 0.035 ^a |
| Estrone | 7.4 | 3.9 | 3.1 | 1.7 | 0.028 ^a | 0.015 ^a |
| Glimepiride | 843.4 | 454.1 | 79.1 | 42.6 | 52.7 | 28.4 |

| Compound | (a) Human risk quotient - combined | | | | | |
|----------------------|------------------------------------|-------------------|---------------------|-------------------|----------------------|---------------------|
| | Based on maximum MEC | | Based on median MEC | | Based on minimum MEC | |
| | Children | Adults | Children | Adults | Children | Adults |
| 17 β estradiol | 2879.7 | 1379.9 | 768.2 | 368.1 | 0.12 ^a | 0.0055 ^a |
| Dimetridazole | 2.1 | 0.86 ^b | 2.1 | 0.86 ^b | 2.1 | 0.86 ^b |
| Estrone | 28.5 | 12.4 | 11.9 | 5.2 | 0.11 ^a | 0.047 ^a |
| Estriol | 8.2 | 3.4 | 0.41 ^b | 0.17 ^a | 0.048 ^a | 0.019 ^a |
| Glimepiride | 999.9 | 516.8 | 93.7 | 48.4 | 62.5 | 32.3 |
| Lorazepam | 2.8 | 1.1 | 2.5 | 1 | 2.3 | 0.93 ^b |

^a The risk is unlikely.

^b The risk is unknown

3.3.3. Risk assessment for AMR selection

This section reveals that around 46% of the antibiotics detected have their maximum MEC to pose a resistance risk upon their permanent occurrence in MENA surface waters. These antibiotics are summarized in Table 6 along with their corresponding RQ_{AMR} based on the three MEC levels minimum, median and maximum. The results show a remarkable antibacterial resistance risk for ciprofloxacin and norfloxacin at 42.1 and 41.4 respectively. In fact, the median concentration for ciprofloxacin still showed an RQ_{AMR} as compares to norfloxacin which no longer exhibited an appreciable risk once the median and the minimal concentration was used. It is worth mentioning that there was a lack of PNEC-MIC data for 5 out of 13 sulfonamides. However, only sulfathiazole showed AMR risk between the identified sulfonamide antibiotics with an RQ_{AMR} of 16. Moreover, even at minimal measured concentration, Enrofloxacin, Danofloxacin, Josamycin and Cefixime still show an antimicrobial resistance risk.

Table 6: Maximum, median, and minimum MEC (ng/L) and RQ_{AMR} for antibiotics showing AMR risk.

| Compound | PNEC-MIC (ng/L) | MEC (max) | RQ _{AMR} (max) | MEC (median) | RQ _{AMR} (median) | MEC (min) | RQ _{AMR} (min) |
|-----------------|-----------------|-----------|-------------------------|--------------|----------------------------|-----------|-------------------------|
| Ciprofloxacin | 64 | 2697.2 | 42.1 | 108 | 1.7 | 0.4 | 0.0063 ^a |
| Norfloxacin | 500 | 20,700 | 41.4 | 50 | 0.10 ^a | 19.36 | 0.039 ^a |
| Flumequine | 250 | 4200 | 16.8 | 2200 | 8.8 | 200 | 0.80 ^a |
| Sulfathiazole | 256 | 4100 | 16 | 2051.5 | 8 | 3 | 0.012 ^a |
| Sarafloxacin | 500 | 5300 | 10.6 | 74 | 0.15 ^a | 49 | 0.098 ^a |
| Florfenicol | 2000 | 18,400 | 9.2 | 1516 | 0.76 ^a | 9.1 | 0.0046 ^a |
| Trimethoprim | 500 | 3500 | 7 | 114 | 0.23 ^a | 0.2 | 0.0004 ^a |
| Enrofloxacin | 64 | 445 | 6.9 | 412 | 6.4 | 379 | 5.9 |
| Danofloxacin | 16 | 97 | 6.1 | 78 | 4.9 | 59 | 3.7 |
| Josamycin | 250 | 1500 | 6 | 1150 | 4.6 | 300 | 1.2 |
| Tetracycline | 1000 | 3900 | 3.9 | 62.5 | 0.063 ^a | 4 | 0.004 ^a |
| Erythromycin | 1000 | 3900 | 3.9 | 121 | 0.12 ^a | 7.8 | 0.0078 ^a |
| Clarithromycin | 250 | 677 | 2.7 | 83.55 | 0.33 ^a | 0.2 | 0.0008 ^a |
| Cefixime | 64 | 146 | 2.3 | 141.5 | 2.2 | 137 | 2.1 |
| Rifaximin | 250 | 542 | 2.2 | 348.5 | 1.4 | 155 | 0.62 ^a |
| Chloramphenicol | 8000 | 15,600 | 1.9 | 93 | 0.012 ^a | 0.1 | 1.25E-05 ^a |
| Metronidazole | 125 | 211 | 1.7 | 51 | 0.41 ^a | 0.1 | 0.0008 ^a |
| Azithromycin | 250 | 377.7 | 1.5 | 19.2 | 0.077 ^a | 0.2 | 0.0008 ^a |
| Gentamicin | 1000 | 1400 | 1.4 | 800 | 0.80 ^a | 200 | 0.2 ^a |
| Ofloxacin | 500 | 610.6 | 1.2 | 148 | 0.30 ^a | 0.8 | 0.0016 ^a |
| Naladixic acid | 16,000 | 16,700 | 1.04 | 8500 | 0.53 ^a | 300 | 0.019 ^a |

^a The risk is unlikely.

CHAPTER 4

DISCUSSION

4.1. Current status of occurrence studies in MENA region

4.1.1. Identified gap in the water monitoring research

The geographical distribution of the occurrence studies across the MENA region reveals an obvious bias to Israel, as the highest number of studies are published in this country. This might be attributed to the fact that Israel, the most scientifically advanced country in the region, has access to cutting-edge technology and scientific methods that facilitate this type of research. The second highest frequency of studies is observed for Tunisia that has been recently characterized as water-stressed country. Moreover, its arid and semi-arid climate which encourage policymakers to search for legislative solutions for water contamination issue. Nonetheless, a wider geographical scope is needed to assess the situation in other countries where a small number or no studies exist such as Syria, Iraq, Yemen, Oman, Morocco, Bahrain, Kuwait and Libya. The lack of research in this topic may be rendered to the fact that most of the aforementioned countries suffer from political instability and conflicts that have its direct consequences on infrastructure, governance and resources. Obviously, water contamination becomes a low priority issue as compares to immediate humanitarian concerns. Another factor is the long-term funding for such type of research as most of these countries face economic challenges. Moreover, there may be limited awareness or prioritization of pharmaceutical contamination as a significant environmental issue.

4.1.2. Limited research on groundwater and seawater quality

Only 19% of the published occurrence studies in the MENA region focus on groundwater resource. This reflects a very low research interest of environmental bodies in groundwater quality despite the fact that it is an essential source of potable water for many MENA countries (Yemen, Libya, Egypt, Algeria ...etc.) (Mirzaei et al., 2018, Mokh et al., 2017). Also, the MENA region is one of the most water-scarce areas in the world. Its contamination from agricultural runoff, industrial waste and untreated sewage is of serious concern. All in all, this highlights the limited attention that has been paid to groundwater and groundwater receptors among the countries of this region to date. Monitoring groundwater quality and identifying pollutants can prevent long-term environmental issues. Similarly, more occurrence studies are needed to examine seawater due to the increasing reliance of some MENA countries (mainly Saudi Arabia, Kuwait and UAE) on desalination to meet their water needs. That being said, it is worth noting that it is uncertain whether the desalination pretreatment steps effectively remove ECs (Nödler et al., 2014, Ouda et al., 2021) and thus, contaminants from seawater can affect the quality of the potable water produced inducing potential risk on public health.

4.1.3. Focused research on Surface waters and WWTP effluents

As mentioned in previous sections, most of the reviewed studies analyze surface water and WWTP effluent. For instance, it is noticed that the studies performed in Tunisia focus on WWTP effluents quality and coastal waters more than its focus on surface water bodies (Belhaj et al., 2015, Cary et al., 2013, Fries et al., 2016, Tahrani et al., 2016, Tahrani et al., 2017). In comparison, studies conducted in Jordan focus more on surface

water quality (Barel-Cohen et al., 2006, Tiehm et al., 2011, Zemmann et al., 2014). This result may be related to topological differences as there are more internally controlled surface water resources (rivers and lakes) in Tunisia. This means that most surface waters in Jordan are regionally shared surface water resources resulting in more research interest targeting regional surface water quality. As for the case of Lebanon, studies were concentrated on surface water only due to the abundance of surface water resources and the fact that very limited WWTP are operational (Doummar et al., 2014, Doummar and Aoun, 2018b, Doummar and Aoun, 2018a). In contrast, studies in Saudi Arabia target WWTP effluent contamination probably due to their high interest in wastewater reuse for agricultural purposes in light of limited natural freshwater resources (Alidina et al., 2014, Cellamare et al., 2016, Picó et al., 2019).

Furthermore, the number of studies that analyze surface water and groundwater at a time is also very limited. In fact, for the purposes of consistency, more transparent illustration of the results is obtained if a single study using the same equipment and under the same climatic and testing conditions analyzes samples from multiple water compartments at once. This will definitely have its direct consequences on preserving experimental control. Nevertheless, such collaboration within a single country is laden with difficulties, let alone across multiple countries (Appendix A).

4.1.4. Measured environmental concentration according to therapeutic class

As highlighted earlier, among all the detected therapeutic classes, antibiotics are the most frequently detected without clear specification about the reason for selecting this class for frequent analysis. Some reasons may be related to wide usage by large

populations, high toxicity effects from previous toxicology studies, their resistance to removal processes in wastewater treatment, the availability of associated experimental data, the emerging concerns and trends such as the spread of resistant bacteria, and the global monitoring initiatives such as the global water quality monitoring program that often focus on pharmaceutical classes known to have widespread use. The chemical stability of antibiotics in water systems coupled with the ineffectiveness of treatment processes lead to their accumulation while still being active for long periods. (Al Maadheed, 2016, Craddock et al., 2020, Krzeminski et al., 2019, Zhang et al., 2020). This in turn highlights the importance of upgrading conventional WWTPs to more effective technologies for antibiotic removal. Moreover, the development of comprehensive databases to report quantitative data on microbial selection for antibiotic resistance is critical to effectively monitor, understand, and manage the growing issue of antimicrobial resistance (AMR).

The limited detection of antihistamines, bronchodilators, and antihypertensives in water systems does not necessarily imply that their usage is entirely safe or that they are efficiently removed from the environment. Rather, it may be an indication of the lack of frequent or targeted analysis for these substances in water monitoring programs. Many studies on pharmaceutical contamination in water systems tend to focus on specific compounds that have already been extensively studied elsewhere. While this approach can provide valuable insights, it also presents certain limitations and challenges in fully understanding the broader impact of pharmaceuticals in the environment. In fact, prominent investigation of some pharmaceuticals is highly influenced by the attention devoted to them in the past (Gaston et al., 2019). For example, carbamazepine is found to

be one of the highly resilient pharmaceuticals to natural attenuation and treatment processes, which renders its water monitoring more recurrent (Andreozzi et al., 2002). The concentration of carbamazepine in MENA surface waters ranged between 0.3 and 3352 ng/L (Appendix B). Despite possible differences in sampling techniques, this is well-above concentrations reported in other regions such as Sri Lanka (n.d.–71.2 ng/L) (Guruge et al., 2019), Vietnam (n.d.–57.4 ng/L) (Van et al., 2021), and the United Kingdom (~826 ng/L) (Nakada et al., 2017). Unlike some other more commonly studied pollutants, sulfamethoxazole and similar pharmaceutical compounds were initially overlooked in environmental monitoring efforts. However, with growing concern over pharmaceutical pollution, sulfamethoxazole has garnered attention for its potential environmental and public health risks. (Avisar et al., 2009). The concentrations of this pharmaceutical in MENA surface waters ranged between 0.8 and 1400 ng/L. This is comparable to the results found by Van and co-workers where the concentration of sulfamethoxazole in the urban rivers of Metro Manila, Philippines was found to be between 16.66 and 1870 ng/L (Van et al., 2021). However, the focus on some pharmaceuticals, especially those most frequently analyzed like diclofenac, ibuprofen, naproxen, sulfamethoxazole and carbamazepine may result in other emerging pollutants escaping scrutiny. Researchers and regulatory agencies might prioritize these compounds because they are already well-characterized, making them convenient for long-term studies. However, this can distract attention from other pharmaceuticals that may be emerging as environmental pollutants, especially those with different usage patterns or less well-understood behaviors in ecosystems. There are thousands of pharmaceuticals in use worldwide, but only a small fraction of them are regularly monitored in water systems. As new drugs are developed and older compounds

are used in different combinations or in more widespread ways, the environmental behavior and ecotoxicological risks of these drugs may evolve. Research should therefore expand to include not only the commonly studied drugs but also other emerging compounds that could pose significant ecological or health risks.

4.2. Pharmaceutical risk and health assessment

4.2.1. *Factors that influence MECs*

The risk assessment of pharmaceuticals is primarily linked to their environmentally occurred concentrations. As expected, the concentration range registered for the detected pharmaceuticals differ from one country to another. There are several reasons as to why this is the case. Such variations may be attributed to: i) differences in consumption patterns (Countries with more advanced healthcare systems and widespread access to pharmaceuticals tend to have higher consumption rates of certain drugs.), ii) presence or absence of WWTPs (Comparable to more developed regions, certain MENA countries have very few number of operational wastewater treatment plants) iii) removal efficiency in existing WWTP (the effectiveness of wastewater treatment plays a major role in determining the concentrations of pharmaceuticals found in water bodies).

Countries with advanced wastewater treatment systems, such as those in Europe or North America, may be better equipped to remove pharmaceuticals from effluents, leading to lower concentrations in surface water or groundwater.), pharmaceutical disposal practices (The way unused or expired medications are disposed of by the public can impact the levels of pharmaceuticals in the environment. In some countries, there may be high levels of improper disposal, with people flushing unused drugs down the toilet or

discarding them in landfills. This can result in significant contamination of local water systems) and iv) pharmaceutical characteristics (The stability of the active ingredients in different pharmaceuticals can affect their persistence in the environment).

For instance, starting from the year 2019, Iran has 190 WWTPs comparable to the case of Lebanon where only seven are completed with two being operational (Karam et al., 2013, Yazdandoost, 2020). This will eventually lead to the increased likelihood of detecting pharmaceuticals typically not removed by WWTP in Lebanese water (Kodom et al., 2021). Discrepancies in measured concentrations between different MENA countries may also be due to differences in dilution effects once discharged into the receiving water compartments. This is more likely to occur in places with frequent rainfall events (which can lead to surface runoff carrying pharmaceuticals from various sources introducing large quantities of pharmaceutical residues into rivers and lakes over a short period) or water bodies with tributaries (Pharmaceuticals entering a main river may be diluted or spread through the tributaries, creating a wider distribution of contaminants across a larger area). Another contributor to MEC variation is the difference in removal efficiencies between compounds. Poor removals are documented for compounds featuring aromatic rings like naproxen and ketoprofen and for small molecules containing halogen groups like clofibric acid and diclofenac (Petrovic et al., 2013). Moreover, small differences in the chemical structure or physical properties result in different behavior in the environment. For example, the hormones estradiol and ethinylestradiol only differ by one ethinyl group, but this difference significantly changes the biodegradability of one compound compared to the other, and ultimately impacts the MEC value (Appendix A).

Furthermore, another important factor that contributes to variation in MEC

values is different testing conditions between countries, and inside the same country itself. Across the studies considered, LC-MS/MS is a highly effective method, particularly for detecting and quantifying trace levels of pharmaceuticals in complex environmental samples (Álvarez-Ruiz et al., 2020, Mordechay et al., 2021, Eslami et al., 2015, Semreen et al., 2019). This method is consistently used for its broad applicability and reliability in environmental monitoring. While comparisons between studies are often made within the same water compartments (e.g., surface water, groundwater, etc.), the environmental conditions under which these measurements are made can differ significantly. Conditions such as temperature, season, and dilution can all impact the concentrations of the chemicals being measured, leading to variations in the final Maximum Expected Concentration (MEC) values. As such, it is essential to acknowledge the complexities and limitations inherent in these studies. Different water compartments may have very different characteristics, influencing how chemicals behave, degrade, or accumulate. Thus, given the experimental nature of these studies, reproducibility is nearly impossible across the studies and there will remain a substantial margin of difference.

4.2.2. Limitations of risk assessment calculations

As pertains to the risk assessment calculations, the use of MECs is considered a reliable representation of environmental exposure given that it is directly reflective of real-world exposure levels rather than empirical estimates. Nevertheless, it is important to point out that the elimination of MEC values below the limit of detection may result in an underestimation of the potential risk. When a chemical concentration falls below the LOD, it means that the measurement cannot confidently determine its presence or

concentration, often leading to it being recorded as "not detected" or considered to be zero in some cases. If MEC values fall below the LOD, the true extent of contamination may not be fully accounted for, especially in cases where low levels of toxic substances might still have serious environmental or health implications. Moreover, PNEC values should have been derived from actual experimental data. Using measured EC50s from toxicity tests reflects real-world biological responses to specific concentrations of a chemical. However, one limitation is that for some contaminants, experimental toxicity data were not available, and thus substituted by predictive models which carry their own uncertainties. Thus, the results were based on mixed monitored and predicted values by ECOSAR, which might affect the accuracy of realistic risk quantification. This is further confirmed upon the comparison between the RQs calculated based on measured data (Table S3) and predicted data (Table S17) (Appendix B). Most of the RQs exhibited discrepancies >90 % (Appendix A). Moreover, even when trying to address the unavailability of measured toxicity data through estimated one, there remained a lack of ecotoxicological data for some compounds that resulted in their exclusion from the analysis (Table S18 of Appendix B). This exclusion is typically done to avoid inaccurate or unreliable conclusions in the analysis. However, excluding certain chemicals also means that their potential risk is not evaluated. As such, more research is needed to fill data gaps for less studied pharmaceuticals. Another worthy point of discussion is that PNECs were typically calculated for surface water only (Appendix A). This matter will inherently bias the risk assessment towards this single compartment and will in turn disregard the likelihood of appreciable risk in other important compartments like groundwater resources. Moreover, using a surface water specific PNEC for all

compartments creates a lack of compartment-specific analysis, meaning that the risk assessments do not reflect the unique characteristics and specific risks associated with each environmental medium. This can result in inaccurate risk estimates, especially for groundwater where risks might be higher or persist longer.

Interpretation of RQ results

The results of calculated RQ show exponential values indicating that the pharmaceutical concentrations in the environment are far exceeding safe thresholds and it is necessary to conduct additional rigorous assessment and establish regulatory actions. The high values (>1000) were comparable to other studies conducted in India (Sengar and Vijayanandan, 2022), Vietnam (Tran et al., 2019), and Europe (Zhou et al., 2019). In accordance with other studies, diclofenac was calculated to have an RQ value of 10,221 and thus ranked among the pharmaceuticals with high potential risk. This trend is observed in the case of European surface waters where it was reported an RQ value of 18,740 for the same pharmaceutical (Zhou et al., 2019). The high RQ value is verified by its observed toxicity effects through high ability for bioaccumulation in fatty tissues, especially in fish bodies. Subsequently this will cause secondary poisoning within the aquatic food chain and to fish-eating birds (Mommert et al., 2013). Another alarming RQ value is noticed for carbamazepine at 1676, which was found to physiologically and morphologically induce toxic effects (changes in behavior, swimming patterns, feeding habits, or even cause lethal or sub-lethal effects) on aquatic organisms when present in high concentrations (Ali et al., 2019, Vernouillet et al., 2010). Other studies worldwide reported the occurrence of pharmaceuticals with high risk in Sri Lanka (Guruge et al., 2019) and Vietnam (Van et al., 2021), yet RQ values ranged

between 1 and 100. It is worth noting that these values are based on maximum MECs which carry some uncertainty in a sense that they may exacerbate the imposed risk by assuming a worst-case scenario. However, due to the discrepancies caused by the aforementioned factors in section 5.2.2, it was necessary to look at average MECs in an attempt to better assess the environmental risk.

4.2.3. Interpretation of HRQ results

The use of maximum detected concentrations as the basis for calculating HRQs represents a worst-case scenario approach. This method assumes that the highest observed concentration of a pharmaceutical in surface waters will be a consistent or typical exposure level. In reality, pharmaceutical concentrations may fluctuate depending on various factors, such as seasonal changes, water flow, or local pollution events. The maximum concentration represents the peak of these fluctuations, potentially overestimating the risk. The results of this study reveal that eight pharmaceuticals had an $HRQ > 1$ as presented in Table 3. On top of the risky pharmaceuticals, 17β estradiol exhibited the largest HRQ value following the three evaluated exposure pathways with higher risk observed for children in the studies MENA water bodies.

Comparing to worldwide studies, pharmaceuticals detected in Dutch drinking water (Houtman et al., 2014), Serbian surface water (Škrbić et al., 2018), and Chinese reservoirs (Chen et al., 2020) did not pose any human health risk in surface water. To elaborate, all HRQs found by (Škrbić et al., 2018) ranged between 10^{-6} and 10^{-2} based on dermal and ingestion exposure pathways. In contrast to the studies conducted in Europe and China, research conducted in India identified pharmaceuticals with potential

human health risks in surface waters. Specifically, 11 out of 49 detected compounds posed a significant risk to human health. This suggests a higher level of pharmaceutical contamination in Indian surface waters, and these compounds likely exceeded safe thresholds, possibly due to inadequate wastewater treatment, overuse of pharmaceuticals, or poor waste management strategies (Dai et al., 2021, Sengar and Vijayanandan, 2022). Moreover, estrone, 17β estradiol, and estrogen detected in two Chinese river basins had an HRQ > 1 for children (Dai et al., 2021), which is corresponding with the outcome of this study. It is clear that drinking water represents the primary route of exposure for most of the pharmaceuticals studied. While Human Risk Quotients (HRQs) based on drinking water are commonly used to assess the potential health risks associated with pharmaceutical contamination, these values might not always accurately reflect the actual risk to human health. This is particularly true when the measured concentrations of pharmaceuticals in surface waters are used to calculate HRQs for drinking water exposure. Surface waters are not generally used as a direct source for drinking water, instead, drinking water is typically derived from groundwater, treated water or specially purified reservoirs. These sources usually undergo a set of water purification stages (e.g., carbon adsorption, ozonation, or reverse osmosis) that significantly reduce the concentrations of these compounds. Moreover, the study assumes exposure occurs individually to one pharmaceutical compound at a time. Nevertheless, exposure through drinking water or fish may result in exposure to several pharmaceutical compounds simultaneously. The key issue here is that while the effects of individual pharmaceutical compounds are relatively well understood, the combined effects of multiple drugs (mixture toxicity) are less clear. These combined effects could potentially lead to

synergistic or additive health risks, where the presence of two or more compounds in the body may result in an effect greater than the sum of their individual impacts. It is still unclear whether a synergic adverse health effect would arise due to this exposure (Sharma et al., 2019). As previously mentioned, this evaluation assumes people are drinking water and consuming fish with the highest MEC level. As such, this review provides a conservative estimate of risk, it also exaggerates the true exposure levels by assuming that the highest observed concentration is the most common scenario. Given the overestimation of the potential health risk resulted from such method, more realistic scenarios using median and minimum MECs are adopted. As expected, applying this correction significantly reduced the estimated health risk, as the lower concentrations considered in the median and minimum scenarios result in lower HRQs. However, despite the reduction in risk estimates when using median and minimum MECs, 17 β estradiol, and glimepiride still pose a considerable risk. Thus, the persistent toxicity of these compounds, especially in environments where they accumulate over time, suggests that they should continue to be monitored and managed effectively to prevent long term health impacts.

4.2.4. Interpretation of AMR results

When considering the risk of Antimicrobial Resistance, previous studies have reported significantly higher RQ_{AMR} values than those found in this study. For example, (Tran et al., 2019) reported RQ_{AMR} values greater than 1000 for erythromycin and over 100 for amoxicillin and ciprofloxacin. In contrast, a study in Kenya identified ciprofloxacin ($RQ_{AMR} = 40.8$) and norfloxacin ($RQ_{AMR} = 5.8$) as having a significant risk of promoting resistance (Kairigo et al., 2020), which aligns more closely with our findings, particularly

for ciprofloxacin. This suggests that while our study found relatively lower AMR risks, ciprofloxacin still presents a considerable concern for resistance development in both our study and in other regions. Moreover, fluoroquinolones, the class of antibiotics to which ciprofloxacin and norfloxacin belong, are widely recognized as high-risk antibiotics for resistance selection. Several studies (Sengar and Vijayanandan, 2022, Zhang et al., 2020) have emphasized the critical need to monitor and regulate the use of these antibiotics, as they are commonly associated with antimicrobial resistance issues in both human health and environmental contexts. Thus, while the findings of this study may show lower overall RQ_{AMR} values, the persistence of high-risk antibiotics highlights the ongoing need for management to prevent the spread of resistance.

4.3. Challenges and Adaptations in Fate modeling

During my research, I initially focused on fate modeling using the GREAT-ER software to assess pharmaceutical residues in the Beirut River watershed. To begin, I reached out to the GREAT-ER developers, who provided an outdated version of the software. They assured that additional files and tutorials for geoprocessing the map of the Beirut River would follow. However, significant challenges emerged from both external and technical aspects, which ultimately led to slowing the progress on this topic and keeping it at the review stage.

Obtaining the necessary data for fate modeling was difficult due to limited published resources and incomplete datasets specific to the Beirut River watershed. Key gaps included:

- Geospatial Data: The digital elevation model (DEM) available was of high resolution, and data on land cover and land use were insufficient for accurate geoprocessing.
- Demographic Data: Precise population data within the watershed region were unreachable.
- Hydrological Data: No comprehensive flow rate measurements existed for the smaller reaches of the river.
- Pollution Sources: Information on hospital loads, such as the number of beds and patients, was inaccessible.
- Pharmaceutical Sales Data: Reliable sales statistics, crucial for estimating chemical excretion into the environment, were not obtainable.

Initially, GREAT-ER's capabilities were limited to European catchments. The version provided lacked tools for geoprocessing new, non-European watersheds, such as the Beirut River. Furthermore, during the COVID-19 pandemic, communication with the GREAT-ER developers ceased. This interruption delayed the promised software updates that would have included geoprocessing capabilities for non-European catchments.

Recently, communication with the GREAT-ER developers was reestablished, resulting in renewed efforts on this research. Several solutions were implemented to overcome the initial challenges and will be further explained in future publications.

CHAPTER 5

CONCLUSION

In this work, all pharmaceuticals detected across the MENA countries through previously published work over the years 2006-2022 were compiled into a database with a concentration range in the ng/L–low mg/L. Measured concentration values were used to evaluate the ecological risk associated with the occurrence of the pharmaceutical. The main outcomes of the study are as follows:

- 26.5 %of the detected pharmaceuticals pose a potential ecological risk in MENA water bodies.
- RQs calculation ranged between 1.2 and 562,500 with the most problematic pharmaceuticals being 17 β -estradiol, diclofenac, metoprolol, ethinylestradiol, and carbamazepine.
- Eight pharmaceuticals, belonging to the hormones class, were found to pose a risk to human health. 17 β estradiol had the highest HRQ value of approximately 2880 for children (based on combined fish and drinking water exposure routes).
- A geographical bias with most studies being conducted in Tunisia, Israel, and Jordan was revealed.
- While the findings provide valuable insights, several shortcomings were noted:
- The overestimation of the risks through focus on maximum measured concentrations.
- The lack of detailed toxicological data for many pharmaceutical compounds,

especially in mixtures.

- The reliance of ecotoxicity studies on surface water resources specifically and overlooking toxicity testing in other water compartments.
- The limited monitoring research performed on groundwater and seawater.

In terms of future research directions, this work sets the stage for future prioritization studies across MENA countries. A recommended focus is on extending research to additional MENA nations, particularly those with limited data, to better understand the hotspots of pharmaceutical contamination in regional waters. Further assessments should consider the use of median and minimum concentration for more realistic risk evaluation. It is also important to highlight the need for further research into the chronic effects of individual pharmaceuticals and their potential synergistic interactions. The results underscore the importance of addressing both human health and ecological risks, as well as implementing treatment standards at Wastewater Treatment Plants (WWTPs) to ensure the removal of pharmaceutical contaminants. Furthermore, the increasing population, rising pharmaceutical consumption, and unregulated access to drugs in the region are contributing to the escalation of pharmaceutical contamination, which necessitates strong legislative and regulatory action to mitigate these risks. Another area that could be explored further is the implementation of one of the initial purposes of this thesis by modeling the fate of pharmaceuticals along Beirut river using appropriate software such as GREAT-ER software.

APPENDIX A

OCCURRENCE AND RISK ASSESSMENT OF PHARMACEUTICALS IN SURFACE WATERS OF THE MIDDLE EAST AND NORTH AFRICA: A REVIEW

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APPENDIX B

SUPPLEMENTARY DATA

Spreadsheet available on the American University of Beirut [ScholarWorks](#) under the name:
“MhaidliNourhane_AppendixB-SupplementaryData_2025”

REFERENCES

- ADEDIPE, D. T., CHEN, C., LAI, R. W. S., XU, S., LUO, Q., ZHOU, G.-J., BOXALL, A., BROOKS, B. W., DOBLIN, M. A. & WANG, X. 2024. Occurrence and potential risks of pharmaceutical contamination in global Estuaries: A critical review and analysis. *Environment International*, 109031.
- AFSA, S., HAMDEN, K., LARA MARTIN, P. A. & MANSOUR, H. B. 2020. Occurrence of 40 pharmaceutically active compounds in hospital and urban wastewaters and their contribution to Mahdia coastal seawater contamination. *Environmental Science and Pollution Research*, 27, 1941-1955.
- AGENCY 2001. USEP ECOTOX Database.
- AL MAADHEED, S. T. A. A. 2016. *Determination of antibiotics and caffeine in hospital wastewater and wastewater treatment plants (WWTPs) in Doha, Qatar*. Qatar University (Qatar).
- ALI, A. M., SYDNES, L. K., ALARIF, W. M., AL-LIHAIBI, S. S., ALY, M. M., AANRUD, S. G. & KALLENBORN, R. 2019. Diclofenac and two of its photooxidation products in the marine environment: their toxicology and occurrence in Red Sea coastal waters. *Environmental Chemistry and Ecotoxicology*, 1, 19-25.
- ALIDINA, M., HOPPE-JONES, C., YOON, M., HAMADEH, A. F., LI, D. & DREWES, J. E. 2014. The occurrence of emerging trace organic chemicals in wastewater effluents in Saudi Arabia. *Science of the Total Environment*, 478, 152-162.
- ÁLVAREZ-RUIZ, R., PICÓ, Y., ALFARHAN, A. H., EL-SHEIKH, M. A., ALSHAHRANI, H. O. & BARCELÓ, D. 2020. Dataset of pesticides, pharmaceuticals and personal care products occurrence in wetlands of Saudi Arabia. *Data in brief*, 31, 105776.
- AMIRKIA, V. D. & QIUBAO, P. 2011. The Antimicrobial Index: a comprehensive literature-based antimicrobial database and reference work. *Bioinformatics*, 5, 365.
- ANDREOZZI, R., MAROTTA, R., PINTO, G. & POLLIO, A. 2002. Carbamazepine in water: persistence in the environment, ozonation treatment and preliminary assessment on algal toxicity. *Water research*, 36, 2869-2877.
- ASHRAF, M., AHAMMAD, S. Z. & CHAKMA, S. 2022. Recent Advances in the Occurrence, Transport, Fate, and Distribution Modeling of Emerging Contaminants—A Review. In: DUBEY, S. K., JHA, P. K., GUPTA, P. K., NANDA, A. & GUPTA, V. (eds.) *Soil-Water, Agriculture, and Climate Change: Exploring Linkages*. Cham: Springer International Publishing.

- AUS DER BEEK, T., WEBER, F. A., BERGMANN, A., HICKMANN, S., EBERT, I., HEIN, A. & KÜSTER, A. 2016. Pharmaceuticals in the environment—Global occurrences and perspectives. *Environmental toxicology and chemistry*, 35, 823-835.
- AVISAR, D., LESTER, Y. & RONEN, D. 2009. Sulfamethoxazole contamination of a deep phreatic aquifer. *Science of the Total Environment*, 407, 4278-4282.
- AZZI, M., RAVIER, S., ELKAK, A., COULOMB, B. & BOUDENNE, J.-L. 2021. Fast UHPLC-MS/MS for the simultaneous determination of azithromycin, erythromycin, fluoxetine and sotalol in surface water samples. *Applied Sciences*, 11, 8316.
- BAREL-COHEN, K., SHORE, L. S., SHEMESH, M., WENZEL, A., MUELLER, J. & KRONFELD-SCHOR, N. 2006. Monitoring of natural and synthetic hormones in a polluted river. *Journal of environmental management*, 78, 16-23.
- BAVUMIRAGIRA, J. P. & YIN, H. 2022. Fate and transport of pharmaceuticals in water systems: A processes review. *Science of The Total Environment*, 823, 153635.
- BEGOU, P. & KASSOMENOS, P. 2023. The ecosyndemic framework of the global environmental change and the COVID-19 pandemic. *Science of The Total Environment*, 857, 159327.
- BELHAJ, D., BACCAR, R., JAABIRI, I., BOUZID, J., KALLEL, M., AYADI, H. & ZHOU, J. L. 2015. Fate of selected estrogenic hormones in an urban sewage treatment plant in Tunisia (North Africa). *Science of the total Environment*, 505, 154-160.
- BEN, Y., FU, C., HU, M., LIU, L., WONG, M. H. & ZHENG, C. 2019. Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A review. *Environmental research*, 169, 483-493.
- BENGTSSON-PALME, J. & LARSSON, D. J. 2016. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment international*, 86, 140-149.
- BRAUSCH, J. M., CONNORS, K. A., BROOKS, B. W. & RAND, G. M. 2012. Human pharmaceuticals in the aquatic environment: a review of recent toxicological studies and considerations for toxicity testing. *Reviews of Environmental Contamination and Toxicology Volume 218*, 1-99.
- CARY, L., CASANOVA, J., GAALOUL, N. & GUERROT, C. 2013. Combining boron isotopes and carbamazepine to trace sewage in salinized groundwater: a case study in Cap Bon, Tunisia. *Applied Geochemistry*, 34, 126-139.

- CELLAMARE, C., CASELLA, P., PETTA, L., FARINA, R. & DE GISI, S. Reuse of treated municipal wastewater in agriculture in Mena countries: The Lebanese case study. Simposio Italo-Brasiliano Di Ingegneria Sanitaria Ambientale, 2016.
- CHEN, Y., VYMAZAL, J., BŘEZINOVÁ, T., KOŽELUH, M., KULE, L., HUANG, J. & CHEN, Z. 2016. Occurrence, removal and environmental risk assessment of pharmaceuticals and personal care products in rural wastewater treatment wetlands. *Science of the Total Environment*, 566, 1660-1669.
- CHEN, Y., XIE, Q., WAN, J., YANG, S., WANG, Y. & FAN, H. 2020. Occurrence and risk assessment of antibiotics in multifunctional reservoirs in Dongguan, China. *Environmental Science and Pollution Research*, 27, 13565-13574.
- CRADDOCK, H. A., PANTHI, S., RJOUB, Y., LIPCHIN, C., SAPKOTA, A. & SAPKOTA, A. R. 2020. Antibiotic and herbicide concentrations in household greywater reuse systems and pond water used for food crop irrigation: West Bank, Palestinian Territories. *Science of the Total Environment*, 699, 134205.
- CROWL, D. A. & LOUVAR, J. F. 2001. *Chemical process safety: fundamentals with applications*, Pearson Education.
- DAI, C., LI, S., DUAN, Y., LEONG, K. H., TU, Y. & ZHOU, L. 2021. Human health risk assessment of selected pharmaceuticals in the five major river basins, China. *Science of The Total Environment*, 801, 149730.
- DE AQUINO, S. F., BRANDT, E. M. F., BOTTREL, S. E. C., GOMES, F. B. R. & SILVA, S. D. Q. 2021. Occurrence of pharmaceuticals and endocrine disrupting compounds in Brazilian water and the risks they may represent to human health. *International journal of environmental research and public health*, 18, 11765.
- DE GIROLAMO, A. M., PARETE, G., RICCI, G. F., GÓMEZ-NAVARRO, O., PÉREZ, S. & GENTILE, F. Risk assessment of antibiotics in surface waters: applying SWAT and GREAT-ER in a modelling cascade. INTERNATIONAL SOIL AND WATER ASSESSMENT TOOL CONFERENCE Book of Abstracts, 2023.
- DE JESUS GAFFNEY, V., ALMEIDA, C. M., RODRIGUES, A., FERREIRA, E., BENOLIEL, M. J. & CARDOSO, V. V. 2015. Occurrence of pharmaceuticals in a water supply system and related human health risk assessment. *Water research*, 72, 199-208.
- DE LIGUORO, M., DI LEVA, V., DALLA BONA, M., MERLANTI, R., CAPORALE, G. & RADAELLI, G. 2012. Sublethal effects of trimethoprim on four freshwater organisms. *Ecotoxicology and environmental safety*, 82, 114-121.

- DESBIOLLES, F., MALLERET, L., TILIACOS, C., WONG-WAH-CHUNG, P. & LAFFONT-SCHWOB, I. 2018. Occurrence and ecotoxicological assessment of pharmaceuticals: is there a risk for the Mediterranean aquatic environment? *Science of the Total Environment*, 639, 1334-1348.
- DOTAN, P., YESHAYAHU, M., GORDON-KIRSCH, N., GROISMAN, L., AL-KHATEEB, N., RABBO, A. A., TAL, A. & ARNON, S. 2017. Endocrine disrupting compounds in streams in Israel and the Palestinian West Bank: Implications for transboundary basin management. *Journal of environmental management*, 204, 355-364.
- DOUMMAR, J. & AOUN, M. 2018a. Assessment of the origin and transport of four selected emerging micropollutants sucralose, Acesulfame-K, gemfibrozil, and iohexol in a karst spring during a multi-event spring response. *Journal of contaminant hydrology*, 215, 11-20.
- DOUMMAR, J. & AOUN, M. 2018b. Occurrence of selected domestic and hospital emerging micropollutants on a rural surface water basin linked to a groundwater karst catchment. *Environmental Earth Sciences*, 77, 1-16.
- DOUMMAR, J., GEYER, T., BAIERL, M., NÖDLER, K., LICHA, T. & SAUTER, M. 2014. Carbamazepine breakthrough as indicator for specific vulnerability of karst springs: Application on the Jeita spring, Lebanon. *Applied geochemistry*, 47, 150-156.
- EL JOUMANI, H., BERREBAAN, I., EL ALAMI, M. & NACIRI, M. 2024. ACUTE AND CHRONIC ECOTOXICITY OF A PHARMACEUTICAL EFFLUENT ON DAPHNIA MAGNA IN MOROCCO. *Applied Ecology & Environmental Research*, 22.
- ELNWISHY, N., HANORA, A., HEDSTRÖM, M. & OMRAN, H. 2012. Monitoring of 17 β -estradiol residues in the Suez Canal region. *Egyptian Journal of Aquatic Biology and Fisheries*, 16, 73-81.
- ESLAMI, A., AMINI, M. M., YAZDANBAKHSH, A. R., RASTKARI, N., MOHSENI-BANDPEI, A., NASSERI, S., PIROTI, E. & ASADI, A. 2015. Occurrence of non-steroidal anti-inflammatory drugs in Tehran source water, municipal and hospital wastewaters, and their ecotoxicological risk assessment. *Environmental monitoring and assessment*, 187, 1-15.
- FAKHRI B, M. S., GHASSEMI BARGHI, N., MORADNIA MEHDIKHANMAHALEH, M., RAEIS ZADEH, S. M. M., MOUSAVI, T., REZAEI, R., DAGHIGHI, M. & ABDOLLAHI, M. 2024. Pharmaceutical wastewater toxicity: An ignored threat to the public health. *Sustainable Environment*, 10, 2322821.

- FRIES, E., MAHJOUB, O., MAHJOUB, B., BERREHOUC, A., LIONS, J. & BAHADIR, M. 2016. Occurrence of contaminants of emerging concern (CEC) in conventional and non-conventional water resources in Tunisia. *Fresenius Environ. Bull*, 25, 3317-3339.
- GASTON, L., LAPWORTH, D. J., STUART, M. & ARNSCHEIDT, J. 2019. Prioritization approaches for substances of emerging concern in groundwater: a critical review. *Environmental science & technology*, 53, 6107-6122.
- GEVAO, B., UDDIN, S. & DUPONT, S. 2021. Baseline concentrations of pharmaceuticals in Kuwait's coastal marine environment. *Marine Pollution Bulletin*, 173, 113040.
- GLASSMEYER, S. T., FURLONG, E. T., KOLPIN, D. W., BATT, A. L., BENSON, R., BOONE, J. S., CONERLY, O., DONOHUE, M. J., KING, D. N. & KOSTICH, M. S. 2017. Nationwide reconnaissance of contaminants of emerging concern in source and treated drinking waters of the United States. *Science of the Total Environment*, 581, 909-922.
- GOSWAMI, P., GURUGE, K. S., TANOUE, R., TAMAMURA, Y. A., JINADASA, K., NOMIYAMA, K., KUNISUE, T. & TANABE, S. 2022. Occurrence of pharmaceutically active compounds and potential ecological risks in wastewater from hospitals and receiving waters in Sri Lanka. *Environmental Toxicology and Chemistry*, 41, 298-311.
- GREDELJ, A., BARAUSSE, A., GRECHI, L. & PALMERI, L. 2018. Deriving predicted no-effect concentrations (PNECs) for emerging contaminants in the river Po, Italy, using three approaches: assessment factor, species sensitivity distribution and AQUATOX ecosystem modelling. *Environment International*, 119, 66-78.
- GURUGE, K. S., GOSWAMI, P., TANOUE, R., NOMIYAMA, K., WIJESEKARA, R. & DHARMARATNE, T. S. 2019. First nationwide investigation and environmental risk assessment of 72 pharmaceuticals and personal care products from Sri Lankan surface waterways. *Science of the Total Environment*, 690, 683-695.
- HARRABI, M., DELLA GIUSTINA, S. V., ALOULOU, F., RODRIGUEZ-MOZAZ, S., BARCELÓ, D. & ELLEUCH, B. 2018. Analysis of multiclass antibiotic residues in urban wastewater in Tunisia. *Environmental nanotechnology, monitoring & management*, 10, 163-170.
- HASHIM, N. H., NASIR, M. H. & RAMLEE, M. S. Emerging pollutant of concern: occurrence of pharmaceutical compounds in Asia with particular preference to southeast Asia countries. MATEC Web of Conferences, 2016. EDP Sciences, 05026.

- HAWASH, H. B., MONEER, A. A., GALHOUM, A. A., ELGARAHY, A. M., MOHAMED, W. A., SAMY, M., EL-SEEDI, H. R., GABALLAH, M. S., MUBARAK, M. F. & ATTIA, N. F. 2023. Occurrence and spatial distribution of pharmaceuticals and personal care products (PPCPs) in the aquatic environment, their characteristics, and adopted legislations. *Journal of Water Process Engineering*, 52, 103490.
- HOUTMAN, C. J., KROESBERGEN, J., LEKKERKERKER-TEUNISSEN, K. & VAN DER HOEK, J. P. 2014. Human health risk assessment of the mixture of pharmaceuticals in Dutch drinking water and its sources based on frequent monitoring data. *Science of the Total Environment*, 496, 54-62.
- JAGIELLO, K., MOSTRAG-SZLICHTYNG, A., GAJEWICZ, A., KAWAI, T., IMAIZUMI, Y., SAKURAI, T., YAMAMOTO, H., TATARAZAKO, N., MIZUKAWA, K., AOKI, Y., SUZUKI, N., WATANABE, H. & PUZYN, T. 2015. Towards modelling of the environmental fate of pharmaceuticals using the QSPR-MM scheme. *Environmental Modelling & Software*, 72, 147-154.
- JIMÉNEZ-BAMBAGUE, E. M., MADERA-PARRA, C. A. & MACHUCA-MARTINEZ, F. 2023. The occurrence of emerging compounds in real urban wastewater before and after the COVID-19 pandemic in Cali, Colombia. *Current Opinion in Environmental Science & Health*, 33, 100457.
- KAIRIGO, P., NGUMBA, E., SUNDBERG, L.-R., GACHANJA, A. & TUHKANEN, T. 2020. Occurrence of antibiotics and risk of antibiotic resistance evolution in selected Kenyan wastewaters, surface waters and sediments. *Science of the Total Environment*, 720, 137580.
- KARAM, F., MOUNEIMNE, A. H., EL-ALI, F., MORDOVANAKI, G. & ROUPHAEL, Y. 2013. Wastewater management and reuse in Lebanon.
- KEHREIN, N., BERLEKAMP, J. & KLASMEIER, J. 2015. Modeling the fate of down-the-drain chemicals in whole watersheds: New version of the GREAT-ER software. *Environmental Modelling & Software*, 64, 1-8.
- KHAZRI, H., BEN HASSINE, S., GHORBEL-ABID, I., KALFAT, R. & TRABELSI-AYADI, M. 2019. Presence of carbamazepine, naproxen, and ibuprofen in wastewater from northern Tunisia. *Environmental Forensics*, 20, 121-128.
- KHEZAMI, F., GÓMEZ-NAVARRO, O., BARBIERI, M. V., KHIARI, N., CHKIRBENE, A., CHIRON, S., KHADHAR, S. & PÉREZ, S. 2024. Occurrence of contaminants of emerging concern and pesticides and relative risk assessment in Tunisian groundwater. *Science of the Total Environment*, 906, 167319.

- KLEIN, E. Y., IMPALLI, I., POLEON, S., DENOEL, P., CIPRIANO, M., VAN BOECKEL, T. P., PECETTA, S., BLOOM, D. E. & NANDI, A. 2024. Global trends in antibiotic consumption during 2016–2023 and future projections through 2030. *Proceedings of the National Academy of Sciences*, 121, e2411919121.
- KODOM, K., ATTIOGBE, F. & KURANCHIE, F. A. 2021. Assessment of removal efficiency of pharmaceutical products from wastewater in sewage treatment plants: A case of the sewerage systems Ghana limited, Accra. *Heliyon*, 7.
- KOMORI, K., SUZUKI, Y., MINAMIYAMA, M. & HARADA, A. 2013. Occurrence of selected pharmaceuticals in river water in Japan and assessment of their environmental risk. *Environmental monitoring and assessment*, 185, 4529-4536.
- KRZEMINSKI, P., TOMEI, M. C., KARAOLIA, P., LANGENHOFF, A., ALMEIDA, C. M. R., FELIS, E., GRITTEN, F., ANDERSEN, H. R., FERNANDES, T. & MANAIA, C. M. 2019. Performance of secondary wastewater treatment methods for the removal of contaminants of emerging concern implicated in crop uptake and antibiotic resistance spread: A review. *Science of the Total Environment*, 648, 1052-1081.
- KÜMMERER, K. & HENNINGER, A. 2003. Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clinical microbiology and infection*, 9, 1203-1214.
- LAHENS, L., CABANA, H., HUOT, Y. & SEGURA, P. A. 2024. Trace organic contaminants in lake waters: Occurrence and environmental risk assessment at the national scale in Canada. *Environmental Pollution*, 347, 123764.
- LÄMMCHEN, V., NIEBAUM, G., BERLEKAMP, J. & KLASMEIER, J. 2021. Geo-referenced simulation of pharmaceuticals in whole watersheds: application of GREAT-ER 4.1 in Germany. *Environmental Science and Pollution Research*, 28, 21926-21935.
- LANGE, F. T., SCHEURER, M. & BRAUCH, H.-J. 2012. Artificial sweeteners—a recently recognized class of emerging environmental contaminants: a review. *Analytical and bioanalytical chemistry*, 403, 2503-2518.
- LEE, D. & CHOI, K. 2019. Comparison of regulatory frameworks of environmental risk assessments for human pharmaceuticals in EU, USA, and Canada. *Science of the Total Environment*, 671, 1026-1035.
- LEUNG, H. W., JIN, L., WEI, S., TSUI, M. M. P., ZHOU, B., JIAO, L., CHEUNG, P. C., CHUN, Y. K., MURPHY, M. B. & LAM, P. K. S. 2013. Pharmaceuticals in tap water: human health risk assessment and proposed monitoring framework in China. *Environmental health perspectives*, 121, 839-846.

- LINDIM, C., VAN GILS, J., COUSINS, I., KÜHNE, R., GEORGIEVA, D., KUTSAROVA, S. & MEKENYAN, O. 2017. Model-predicted occurrence of multiple pharmaceuticals in Swedish surface waters and their flushing to the Baltic Sea. *Environmental Pollution*, 223, 595-604.
- LIU, S., YANG, H., WANG, Z., WU, J., LIU, Z., MAO, H., ZHOU, Z., MA, B., WEI, X. & SHANG, Q. 2024. Occurrence, source apportionment and risk assessment of selected pharmaceuticals and their transformation products in the effluent-impacted rivers. *Regional Studies in Marine Science*, 73, 103461.
- LIZ, M. V. D., AMARAL, B. D., STETS, S., NAGATA, N. & PERALTA-ZAMORA, P. 2017. Sensitive estrogens determination in wastewater samples by HPLC and fluorescence detection. *Journal of the Brazilian Chemical Society*, 28, 1453-1460.
- MADIKIZELA, L. M., NCUBE, S. & CHIMUKA, L. 2020. Analysis, occurrence and removal of pharmaceuticals in African water resources: A current status. *Journal of environmental management*, 253, 109741.
- MANSOUR, F., AL-HINDI, M., SAAD, W. & SALAM, D. 2016. Environmental risk analysis and prioritization of pharmaceuticals in a developing world context. *Science of The Total Environment*, 557, 31-43.
- MARTÍNEZ-MORCILLO, S., RODRÍGUEZ-GIL, J. L., FERNÁNDEZ-RUBIO, J., RODRÍGUEZ-MOZAZ, S., MÍGUEZ-SANTIYÁN, M. P., VALDES, M. E., BARCELÓ, D. & VALCÁRCEL, Y. 2020. Presence of pharmaceutical compounds, levels of biochemical biomarkers in seafood tissues and risk assessment for human health: Results from a case study in North-Western Spain. *International Journal of Hygiene and Environmental Health*, 223, 10-21.
- MASANABO, N., ORIMOLADE, B., IDRIS, A., NKAMBULE, T., MAMBA, B. & FELENI, U. 2022. Advances in polymer-based detection of environmental ibuprofen in wastewater. *Environmental Science and Pollution Research*, 30.
- MEMMERT, U., PEITHER, A., BURRI, R., WEBER, K., SCHMIDT, T., SUMPTER, J. P. & HARTMANN, A. 2013. Diclofenac: new data on chronic toxicity and bioconcentration in fish. *Environmental toxicology and chemistry*, 32, 442-452.
- MHEIDLI, N., MALLI, A., MANSOUR, F. & AL-HINDI, M. 2022. Occurrence and risk assessment of pharmaceuticals in surface waters of the Middle East and North Africa: A review. *Science of the Total Environment*, 851, 158302.
- MIRZAEI, R., YUNESIAN, M., NASSERI, S., GHOLAMI, M., JALILZADEH, E., SHOEIBI, S. & MESDAGHINIA, A. 2018. Occurrence and fate of most prescribed antibiotics in different water environments of Tehran, Iran. *Science of the total environment*, 619, 446-459.

- MOKH, S., EL KHATIB, M., KOUBAR, M., DAHER, Z. & AL ISKANDARANI, M. 2017. Innovative SPE-LC-MS/MS technique for the assessment of 63 pharmaceuticals and the detection of antibiotic-resistant-bacteria: A case study natural water sources in Lebanon. *Science of the Total Environment*, 609, 830-841.
- MORDECHAY, E. B., MORDEHAY, V., TARCHITZKY, J. & CHEFETZ, B. 2021. Pharmaceuticals in edible crops irrigated with reclaimed wastewater: Evidence from a large survey in Israel. *Journal of Hazardous Materials*, 416, 126184.
- MURADO, M. & PRIETO, M. 2013. NOEC and LOEC as merely concessive expedients: Two unambiguous alternatives and some criteria to maximize the efficiency of dose-response experimental designs. *Science of the Total Environment*, 461, 576-586.
- NAKADA, N., HANAMOTO, S., JÜRGENS, M. D., JOHNSON, A. C., BOWES, M. J. & TANAKA, H. 2017. Assessing the population equivalent and performance of wastewater treatment through the ratios of pharmaceuticals and personal care products present in a river basin: Application to the River Thames basin, UK. *Science of the total environment*, 575, 1100-1108.
- NASRI, E., DE LA VEGA, A. C. S., MARTÍ, C. B., BEN MANSOUR, H. & DIAZ-CRUZ, M. S. 2024. Pharmaceuticals and personal care products in Tunisian hospital wastewater: occurrence and environmental risk. *Environmental Science and Pollution Research*, 31, 2716-2731.
- NÖDLER, K., VOUTSA, D. & LICHA, T. 2014. Polar organic micropollutants in the coastal environment of different marine systems. *Marine Pollution Bulletin*, 85, 50-59.
- NRMMC-EPHC-AHMC, N. 2006. Australian guidelines for water recycling: managing health and environmental risks (phase 1). *National Water Quality Management Strategy, Canberra, Australia*.
- OSUOHA, J. O., ANYANWU, B. O. & EJILEUGHA, C. 2023. Pharmaceuticals and personal care products as emerging contaminants: Need for combined treatment strategy. *Journal of hazardous materials advances*, 9, 100206.
- OUDA, M., KADADOU, D., SWAIDAN, B., AL-OTHMAN, A., AL-ASHEH, S., BANAT, F. & HASAN, S. W. 2021. Emerging contaminants in the water bodies of the Middle East and North Africa (MENA): A critical review. *Science of the Total Environment*, 754, 142177.

- PETROVIC, M., PEREZ, S. & BARCELO, D. 2013. *Analysis, removal, effects and risk of pharmaceuticals in the water cycle: occurrence and transformation in the environment*, Newnes.
- PICÓ, Y., ALVAREZ-RUIZ, R., ALFARHAN, A. H., EL-SHEIKH, M. A., ALOBAID, S. M. & BARCELÓ, D. 2019. Uptake and accumulation of emerging contaminants in soil and plant treated with wastewater under real-world environmental conditions in the Al Hayer area (Saudi Arabia). *Science of the Total Environment*, 652, 562-572.
- PICÓ, Y., ALVAREZ-RUIZ, R., ALFARHAN, A. H., EL-SHEIKH, M. A., ALSHAHRANI, H. O. & BARCELÓ, D. 2020. Pharmaceuticals, pesticides, personal care products and microplastics contamination assessment of Al-Hassa irrigation network (Saudi Arabia) and its shallow lakes. *Science of the Total Environment*, 701, 135021.
- PROSSER, R. & SIBLEY, P. 2015. Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation. *Environment international*, 75, 223-233.
- RIVA, F., ZUCCATO, E., DAVOLI, E., FATTORE, E. & CASTIGLIONI, S. 2019. Risk assessment of a mixture of emerging contaminants in surface water in a highly urbanized area in Italy. *Journal of Hazardous Materials*, 361, 103-110.
- RIVERA-JAIMES, J. A., POSTIGO, C., MELGOZA-ALEMÁN, R. M., ACEÑA, J., BARCELÓ, D. & DE ALDA, M. L. 2018. Study of pharmaceuticals in surface and wastewater from Cuernavaca, Morelos, Mexico: occurrence and environmental risk assessment. *Science of the Total Environment*, 613, 1263-1274.
- SCHRIKS, M., HERINGA, M. B., VAN DER KOOI, M. M., DE VOOGT, P. & VAN WEZEL, A. P. 2010. Toxicological relevance of emerging contaminants for drinking water quality. *Water research*, 44, 461-476.
- SCHWAB, B. W., HAYES, E. P., FIORI, J. M., MASTROCCO, F. J., RODEN, N. M., CRAGIN, D., MEYERHOFF, R. D., VINCENT, J. & ANDERSON, P. D. 2005. Human pharmaceuticals in US surface waters: a human health risk assessment. *Regulatory Toxicology and Pharmacology*, 42, 296-312.
- SEGURA, P. A., TAKADA, H., CORREA, J. A., EL SAADI, K., KOIKE, T., ONWONA-AGYEMAN, S., OFOSU-ANIM, J., SABI, E. B., WASONGA, O. V. & MGHALU, J. M. 2015. Global occurrence of anti-infectives in contaminated surface waters: Impact of income inequality between countries. *Environment international*, 80, 89-97.
- SEMERJIAN, L., SHANABLEH, A., SEMREEN, M. H. & SAMARAI, M. 2018. Human health risk assessment of pharmaceuticals in treated wastewater reused for non-

- potable applications in Sharjah, United Arab Emirates. *Environment international*, 121, 325-331.
- SEMREEN, M. H., SHANABLEH, A., SEMERJIAN, L., ALNISS, H., MOUSA, M., BAI, X. & ACHARYA, K. 2019. Simultaneous determination of pharmaceuticals by solid-phase extraction and liquid chromatography-tandem mass spectrometry: A case study from sharjah sewage treatment plant. *Molecules*, 24, 633.
- SENGAR, A. & VIJAYANANDAN, A. 2022. Human health and ecological risk assessment of 98 pharmaceuticals and personal care products (PPCPs) detected in Indian surface and wastewaters. *Science of the Total Environment*, 807, 150677.
- SHARMA, B. M., BEČANOVA, J., SCHERINGER, M., SHARMA, A., BHARAT, G. K., WHITEHEAD, P. G., KLÁNOVÁ, J. & NIZZETTO, L. 2019. Health and ecological risk assessment of emerging contaminants (pharmaceuticals, personal care products, and artificial sweeteners) in surface and groundwater (drinking water) in the Ganges River Basin, India. *Science of the Total Environment*, 646, 1459-1467.
- SHARMA, R. & KUMAR, A. 2024. Human health risk assessment and uncertainty analysis of silver nanoparticles in water. *Environmental Science and Pollution Research*, 31, 13739-13752.
- SHIGEI, M., ASSAYED, A., HAZAYMEH, A. & DALAHMEH, S. S. 2021. Pharmaceutical and antibiotic pollutant levels in wastewater and the waters of the Zarqa River, Jordan. *Applied Sciences*, 11, 8638.
- SHRAIM, A., DIAB, A., ALSUHAIMI, A., NIAZY, E., METWALLY, M., AMAD, M., SIOUD, S. & DAWOUD, A. 2017. Analysis of some pharmaceuticals in municipal wastewater of Almadinah Almunawarah. *Arabian Journal of Chemistry*, 10, S719-S729.
- ŠKRBIĆ, B. D., KADOKAMI, K. & ANTIĆ, I. 2018. Survey on the micro-pollutants presence in surface water system of northern Serbia and environmental and health risk assessment. *Environmental research*, 166, 130-140.
- TAHRANI, L., VAN LOCO, J., ANTHONISSEN, R., VERSCHAEVE, L., BEN MANSOUR, H. & REYNS, T. 2017. Identification and risk assessment of human and veterinary antibiotics in the wastewater treatment plants and the adjacent sea in Tunisia. *Water Science and Technology*, 76, 3000-3021.
- TAHRANI, L., VAN LOCO, J., BEN MANSOUR, H. & REYNS, T. 2016. Occurrence of antibiotics in pharmaceutical industrial wastewater, wastewater treatment plant and sea waters in Tunisia. *Journal of water and Health*, 14, 208-213.

- THOMAIDI, V. S., MATSOUKAS, C. & STASINAKIS, A. S. 2017. Risk assessment of triclosan released from sewage treatment plants in European rivers using a combination of risk quotient methodology and Monte Carlo simulation. *Science of the Total Environment*, 603, 487-494.
- TIEHM, A., SCHMIDT, N., STIEBER, M., SACHER, F., WOLF, L. & HOETZL, H. 2011. Biodegradation of pharmaceutical compounds and their occurrence in the Jordan Valley. *Water Resources Management*, 25, 1195-1203.
- TRAN, N. H., HOANG, L., NGHIEM, L. D., NGUYEN, N. M. H., NGO, H. H., GUO, W., TRINH, Q. T., MAI, N. H., CHEN, H. & NGUYEN, D. D. 2019. Occurrence and risk assessment of multiple classes of antibiotics in urban canals and lakes in Hanoi, Vietnam. *Science of the Total Environment*, 692, 157-174.
- TRAN, N. H., REINHARD, M. & GIN, K. Y.-H. 2018. Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions—a review. *Water research*, 133, 182-207.
- VAN, D.-A., NGO, T. H., HUYNH, T. H., NAKADA, N., BALLESTEROS, F. & TANAKA, H. 2021. Distribution of pharmaceutical and personal care products (PPCPs) in aquatic environment in Hanoi and Metro Manila. *Environmental monitoring and assessment*, 193, 1-15.
- VERLICCHI, P., AL AUKIDY, M. & ZAMBELLO, E. 2012. Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment—a review. *Science of the total environment*, 429, 123-155.
- VERNOUILLET, G., EULLAFFROY, P., LAJEUNESSE, A., BLAISE, C., GAGNÉ, F. & JUNEAU, P. 2010. Toxic effects and bioaccumulation of carbamazepine evaluated by biomarkers measured in organisms of different trophic levels. *Chemosphere*, 80, 1062-1068.
- WALENG, N. J. & NOMNGONGO, P. N. 2022. Occurrence of pharmaceuticals in the environmental waters: African and Asian perspectives. *Environmental Chemistry and Ecotoxicology*, 4, 50-66.
- WALSH, A., OVAIS, M., ALTMANN, T. & SARGENT, E. V. 2013. Cleaning validation for the 21st century: acceptance limits for cleaning agents. *Pharmaceutical Engineering*, 33, 1-11.
- WALTER, S. & MITKIDIS, K. 2018. The risk assessment of pharmaceuticals in the environment: EU and US regulatory approach. *European Journal of Risk Regulation*, 9, 527-547.

- WEBB, S., TERNES, T., GIBERT, M. & OLEJNICZAK, K. 2003. Indirect human exposure to pharmaceuticals via drinking water. *Toxicology letters*, 142, 157-167.
- WILKINSON, J. L., BOXALL, A. B., KOLPIN, D. W., LEUNG, K. M., LAI, R. W., GALBÁN-MALAGÓN, C., ADELL, A. D., MONDON, J., METIAN, M. & MARCHANT, R. A. 2022. Pharmaceutical pollution of the world's rivers. *Proceedings of the National Academy of Sciences*, 119, e2113947119.
- WILLIAMS, E. S. & BROOKS, B. W. 2012. Human health risk assessment for pharmaceuticals in the environment: existing practice, uncertainty, and future directions. *Human Pharmaceuticals in the Environment: Current and Future Perspectives*, 167-224.
- YAMAMOTO, H., NAKAMURA, Y., KITANI, C., IMARI, T., SEKIZAWA, J., TAKAO, Y., YAMASHITA, N., HIRAI, N., ODA, S. & TATARAZAKO, N. 2007. Initial ecological risk assessment of eight selected human pharmaceuticals in Japan. *Environmental sciences: an international journal of environmental physiology and toxicology*, 14, 177-193.
- YANG, L. H., YING, G. G., SU, H. C., STAUBER, J. L., ADAMS, M. S. & BINET, M. T. 2008. Growth-inhibiting effects of 12 antibacterial agents and their mixtures on the freshwater microalga *pseudokirchneriella subcapitata*. *Environmental Toxicology and Chemistry: An International Journal*, 27, 1201-1208.
- YAZDANDOOST, F. 2020. Iran's Water Policy. *Water Policies in MENA Countries*, 63-84.
- YOON, Y., WESTERHOFF, P., SNYDER, S. A. & ESPARZA, M. 2003. HPLC-fluorescence detection and adsorption of bisphenol A, 17 β -estradiol, and 17 α -ethynyl estradiol on powdered activated carbon. *Water Research*, 37, 3530-3537.
- ZEMANN, M., WOLF, L., GRIMMEISEN, F., TIEHM, A., KLINGER, J., HÖTZL, H. & GOLDSCHIEDER, N. 2015. Tracking changing X-ray contrast media application to an urban-influenced karst aquifer in the Wadi Shueib, Jordan. *Environmental Pollution*, 198, 133-143.
- ZEMANN, M., WOLF, L., PÖSCHKO, A., SCHMIDT, N., SAWARIEH, A., SEDER, N., TIEHM, A., HÖTZL, H. & GOLDSCHIEDER, N. 2014. Sources and processes affecting the spatio-temporal distribution of pharmaceuticals and X-ray contrast media in the water resources of the Lower Jordan Valley, Jordan. *Science of the total environment*, 488, 100-114.
- ZHANG, S.-X., ZHANG, Q.-Q., LIU, Y.-S., YAN, X.-T., ZHANG, B., XING, C., ZHAO, J.-L. & YING, G.-G. 2020. Emission and fate of antibiotics in the Dongjiang River Basin, China: Implication for antibiotic resistance risk. *Science of the total environment*, 712, 136518.

- ZHOU, S., DI PAOLO, C., WU, X., SHAO, Y., SEILER, T.-B. & HOLLERT, H. 2019. Optimization of screening-level risk assessment and priority selection of emerging pollutants—the case of pharmaceuticals in European surface waters. *Environment International*, 128, 1-10.
- ZHU, Y., LIU, K., ZHANG, J., LIU, X., YANG, L., WEI, R., WANG, S., ZHANG, D., XIE, S. & TAO, F. 2020. Antibiotic body burden of elderly Chinese population and health risk assessment: A human biomonitoring-based study. *Environmental Pollution*, 256, 113311.
- ZHU, Y., SNAPE, J., JONES, K. & SWEETMAN, A. 2019. Spatially explicit large-scale environmental risk assessment of pharmaceuticals in surface water in China. *Environmental science & technology*, 53, 2559-2569.