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Review

Occurrence and risk assessment of pharmaceuticals in surface waters of the Middle East and North Africa: A review

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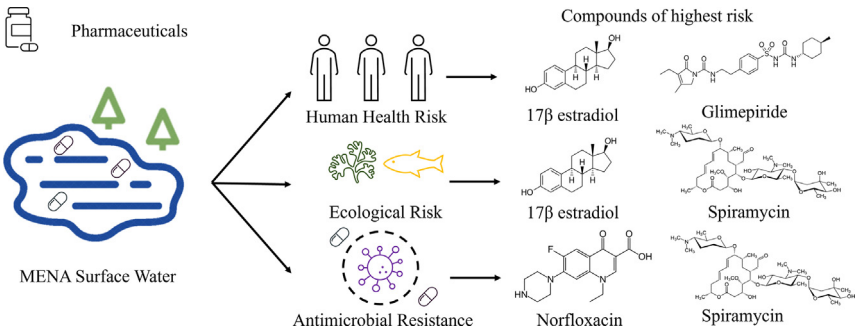
HIGHLIGHTS

- 151 out of 210 analyzed compounds were detected in MENA water matrices.
- 26 % of the detected pharmaceuticals in MENA waters posed a risk on aquatic life.
- Antibiotics posed the highest risk on the aquatic environment.
- 5 % of the detected pharmaceuticals in MENA waters posed a risk on human health.
- Hormones posed the highest risk on human health.

GRAPHICAL ABSTRACT



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ABSTRACT

Pharmaceutical compounds in surface water are perceived as contaminants of emerging concern due to their impacts on the aquatic environment and human health. The risk associated with these compounds has not been quantified in the Middle East and North Africa (MENA). This review identified that 210 pharmaceutical compounds have been analyzed in MENA water compartments between 2008 and 2022. In fact, 151 of these substances were detected in at least one of 13 MENA countries where occurrence studies had been conducted. Antibiotics claimed the highest number of pharmaceuticals detected with concentrations ranging between 0.03 and 66,400 ng/L (for Thiamphenicol and Spiramycin respectively). To investigate whether any of these compounds exert an ecological, human health, or antibiotic resistance risk, a screening-level risk assessment was performed in surface water matrices using maximum, median, and minimum concentrations. 39 and 8 detected pharmaceuticals in MENA surface waters posed a possible risk on aquatic ecosystems and human health respectively. Extremely high risk quotients (>1000) for six pharmaceuticals (17β estradiol, spiramycin, diclofenac, metoprolol, ethinylestradiol, and carbamazepine) were enumerated based on maximal concentrations implying an alarming risk on aquatic toxicity. Moreover, hormones posed the highest possible risk on human health whether ingested through drinking water or fish (e.g., 17β-estradiol had a health risk quotient of 2880 for children). Spiramycin showed a high risk of antibiotic resistance with a risk quotient of 133. This review serves as a basis for future prioritization studies and regulatory guidelines in the MENA region to minimize the risks of the identified compounds.

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Abbreviations

AC	acceptable concentration
ADI	acceptable daily intake
AF	assessment factor
AMR	antimicrobial resistance
AT	averaging time equivalent
BCF	bioconcentration factor
BW	median body weight
EC	emerging contaminants
EC_{50}	median effect concentration
ED	exposure duration
EF	exposure frequency
EMEA	European Medicines Evaluation Agency
ERA	environmental risk assessment
EU	European Union
FDA	Food and Drug Administration
HHRA	human health risk assessment
HRQ	health risk quotient
IR_{DW}	drinking water ingestion rate
IR_F	fish consumption rate
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOEC	lowest observed effect concentration
LTD	lowest therapeutic dose
MEC	measured environmental concentration
MENA	Middle East and North Africa
MIC	minimum inhibitory concentration
NOEC	no-observed effect concentration
NOEL	no-observed effect level
PhCs	pharmaceuticals
PNEC	predicted no-effect concentration
QSAR	quantitative structure activity relationships
RQ	risk quotient
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WWTPs	wastewater treatment plant

1. Introduction

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. These compounds have received a great deal of attention over the past decade, especially as pertains to their occurrence and the potential risk they pose to humans and different environmental compartments (Gani et al., 2021; Kovalakova et al., 2020). These pollutants linger in wastewater effluents due to inefficient removal in treatment plants, and thus re-enter surface and freshwater ecosystems. In cases where no wastewater treatment plants (WWTPs) exist, these compounds directly enter the water environment through municipal wastewater discharge as well as human and veterinary excretion (Avisar et al., 2009; Bavumiragira et al., 2022).

Over the past few years, a large body of research work has emerged establishing the occurrence of and reporting the concentrations of ECs in water bodies worldwide (Cizmas et al., 2015; Ebele et al., 2017; Wilkinson et al., 2022). ECs have been detected in the influents and effluents of WWTPs, rivers, lakes, seas, and groundwater with concentrations ranging from ng/L to μg/L (Azzi et al., 2021; Komori et al., 2013; Lee and Choi, 2019; Wilkinson et al., 2022). The U.S. Environmental Protection Agency and U.S. Geological Survey accounted for 118 pharmaceuticals in drinking water samples from 25 treatment plants across the nation (Furlong et al., 2017). Zhou et al. (2019) reported the occurrence of 284 (243 pharmaceuticals and 41 metabolites and transformation products) out of 477 studied substances (411 pharmaceuticals and 66 metabolites) in surface waters across 33 European countries.

However, some geographic areas have received more attention than others. In fact, the majority of review papers about occurrence studies of ECs target European and North American countries; very few apply to the developing world in Asia and Africa (aus der Beek et al., 2016; Lange et al., 2012). Hashim et al. (2016) identified the most common pharmaceuticals found in water bodies in developing countries in Southeast Asia (Malaysia, Philippines, Singapore, Thailand, Vietnam, Brunei, Cambodia, and Laos). However, they found a significant lack of ECs occurrence data in these countries compared to more developed areas in the region such as China, South Korea, and Hong Kong. That being said, more recent studies are emerging in countries like Sri Lanka, Vietnam, Thailand, and India (Goswami et al., 2022; Guruge et al., 2019; Sengar and Vijayanandan, 2022; Tran et al., 2019).

Similarly, Madikizela et al. (2020) found that while there are a few pharmaceutical monitoring studies in South Africa, there is no available data for most African countries.

This research topic is still comparatively new to the Middle East and North Africa (MENA) region. 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 discussing EC occurrence in the MENA region 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. Mansour et al. (2016) report that, as of 2016, a limited number of 12 investigation studies are found in the literature spanning six countries: Israel, Jordan, Lebanon, Palestine, Tunisia, and Saudi Arabia. These studies register the occurrence of 28 out of 42 compounds in the surface and groundwater compartments (Mansour et al., 2016).

Recently, the number of published studies reporting pharmaceutical contamination of aquatic compartments across the MENA region has risen considerably (Harrabi et al., 2018; Picó et al., 2019, 2020; Tahrani et al., 2017). Nonetheless, while this may be true in the region as a whole, there is still a severe lack of data in specific countries. To the authors' knowledge, no occurrence studies have been reported for Bahrain, Syria, Oman, Yemen, and Libya. This may be due to the lack of groundwork for routine trace analysis of emerging pollutants, the unavailability of specific machinery for water analysis, and the shortage of well-trained personnel for operating the equipment. Another key driver for the lack of data is the absence of environmental legislations in most of these countries.

As such, given that an in-depth compound analysis is costly and not readily available in many developing countries, an alternative risk quantification method is needed to preliminarily assess the potential threat such compounds pose. Consequently, many organizations worldwide have developed various environmental risk assessment guidelines to assess environmental and human health risk and frame safe target concentrations for water bodies. The European Medicines Evaluation Agency (EMEA) 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 et al., 2019). ERAs identify a safe threshold for the concentration of chemicals (PNEC) below which no adverse effect on ecosystem structure and functions is expected (Afsa et al., 2020; Dotan et al., 2017; Gredelj et al., 2018). Conducting ERA on human-released pharmaceuticals is a primary step to inform policymakers for the development of sustainable solutions for threat mitigation.

A range of experimental investigations, for both MEC and PNEC values, has been undertaken to assess the hazards and risks of pharmaceuticals in aquatic systems. Whereas MEC values are derived from extracted water samples, PNEC values are usually extrapolated from chronic toxicity data. In the absence of chronic data, acute toxicity data is used (Riva et al., 2019). However, there remains a large gap in the toxicity data available despite tremendous efforts to compile a comprehensive database of ecotoxicological effects of pharmaceuticals. Pure predictive models using Quantitative Structure Activity Relationships (QSAR) are widely used to fill in the gap. Nonetheless, the risk quotient (RQ) remains the prevalent indication of the ecotoxic effects expected at a certain concentration. This type of analysis has been frequently and effectively used over time as a means for quick and accurate assessment (Yi Chen et al., 2016; Komori et al., 2013; Rivera-Jaimes et al., 2018; Verlicchi et al., 2012; Ying Zhu et al., 2019).

This study aims to:

(i) review the occurrence of pharmaceutically active compounds in published studies across the water matrices in the MENA region (Section 3.1);
(ii) perform ecological (Section 3.2.1), human health (Section 3.2.2), and antimicrobial resistance (AMR) (Section 3.2.3) risk assessments of the pharmaceuticals that have been detected in MENA water compartments;
(iii) and evaluate the status of pharmaceutical occurrence, detection, and risk quantification in the MENA water compartments based on the aforementioned results (Section 4)

2. Materials and methods

For a more in depth understanding of the current state of pharmaceutical occurrence in water bodies in the MENA region, a database is compiled to include: (i) pharmaceuticals detected,

(ii) measured concentrations, and (iii) water body type. The data is then used to carry out a comprehensive environmental and health risk assessment.

2.1. Data collection

The concentrations of pharmaceuticals in the MENA water compartments were obtained from occurrence studies that analyzed samples collected from surface waters (mainly rivers, streams, lakes, and coastal seawater), influents and effluents of wastewater treatment plants, and groundwater. The data sources are peer-reviewed publications conducted in the MENA countries between 2006 and 2022. 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 like “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 collected is presented as ranges between the minimum and maximum concentrations measured for each pharmaceutical in each publication. Pharmaceuticals were then classified according to their therapeutic classes using the PubChem and World Health Organization (WHO) databases in addition to other publications (Tran et al., 2018; Zhou et al., 2019). The following compounds are excluded from the study: personal care products, metabolites, natural hormones, and stimulants (Table S2).

2.2. Environmental risk quotient (RQ)

In accordance with European Union (EU) legislations, the RQ is defined as the ratio between the predicted environmental concentration (PEC) and the PNEC (Tran et al., 2019). However, for the purposes of this study, measured concentrations, rather than predicted ones, are used as they provide a more accurate reflection of reality. As such, the RQ is then defined as the ratio of the MEC (ng/L) to the PNEC (ng/L) (Eq. (1)).

$$RQ = \frac{MEC}{PNEC} \tag{1}$$

PNEC values are calculated using measured chronic no-observed effect concentrations (NOECs), chronic lowest-observed effect concentrations (LOECs), short term median effective concentrations (EC_{50}), and short term median lethal concentrations (LC_{50}). 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). LC_{50} and EC_{50} refer to the concentration of a substance in an environmental medium expected to produce death or a certain effect, respectively, in 50 % of test organisms (Crowl and Louvar, 1990). An assessment factor (AF) is used to account for uncertainty in the PNECs, as presented in Eq. 2. The value of AF is specified based on the number of assays and species used to determine the toxicity data (Table S3). To further elucidate Eq. (2), the minimal values between NOEC, LOEC, EC_{50}, and LC_{50} for each of algae,

fish, and daphnia are divided by the suitable AF. Then, the minimal ratio between the three species is considered to be the PNEC.

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

Ecotoxicity data is obtained from the literature, mainly from the USEPA's ECOTOX database (United States Environmental Protection Agency, 2021), 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.

To assess potential ecological effects, three species were selected to represent different trophic levels in aquatic ecosystems: algae, fish and daphnid. The initial aim of the review was to assess RQ based on measured ecotoxicological data. However, due to scarcity of measured toxicity studies, acute toxicity values obtained from ECOSARv1.11 were used for compounds (or trophic levels) where no measured toxicity data was available. When more than one reference for the same species and the same pharmaceutical is observed, the lowest value is adopted to reflect the worst-case scenario. The toxicity data are presented in Table S3. The smallest value of PNEC for each pharmaceutical between the three trophic levels is used for the calculation of RQ. This reflects an overall worst-case scenario as any concentration above the lowest PNEC value is expected to pose a risk. 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.

In accordance with the EMEA methodology, a binary ecological classification for risk assessment is employed, where for an RQ < 1, the risk is unlikely whereas an RQ ≥ 1 implies appreciable risk (Tran et al., 2019).

2.3. Health risk characterization

Human health risk assessment (HHRA) is conducted on pharmaceuticals positively detected in surface water due to the diversity of its uses including drinking water, public use, and irrigation. A conservative and regulatory HHRA approach is adopted in this analysis, which consists of calculating a health risk quotient (HRQ) for each detected pharmaceutical. The worst-case scenario of the potential health risk is derived from the ratio of the maximum MEC in surface water to the corresponding acceptable concentration (AC) of said pharmaceutical (Eq. (3)). Moreover, median, mean, and minimum concentrations are used to explore other scenarios.

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

To determine the AC, acceptable daily intakes (ADIs) are combined with standard assumptions about potential exposure pathways. 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; National Health and Medical Research Council of Australia, 2008; 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. When not reported in the literature, ADIs are calculated based on the lowest therapeutic dose (LTD) (Eq. (4)), as the latter is typically lower than a dose that causes toxicity (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 (LD_{50}) and used as a point of departure (Eqs. (5) and (6)) (Walsh et al., 2013).

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

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

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

where ADI (μg/kg-day) is the acceptable daily intake, LTD (μg/day) is the lowest therapeutic intake, BW (kg) is the median body weight assumed to be 70 kg, SF is a safety factor of 1000, LD_{50} (μg/kg) is the median lethal dose, and NOEL (μg/kg) is the no-observed-effect-level.

For the ACs, the potentially exposed population is presumed to be age-dependent and includes healthy adults and children. Three categories of ACs are calculated as follows: i) exposure via drinking water (Eq. (7)), ii) exposure via fish consumption (Eq. (8)), and iii) combined exposure of both pathways (drinking water and fish consumption) (Eq. (9)).

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

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

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

where:

- ADI (μg/kg-day) is the acceptable daily intake that should not result in an appreciable effect in the health of directly exposed population
- BW (kg) is the median body weight of age-specific group (assumed to be 14 kg for children and 70 kg for adults)
- IR_{DW} (L/day) is the drinking water ingestion rate (assumed to be 1 L/day for children and 2 L/day for adults)
- IR_F (kg/day) is the fish consumption rate (assumed to be 0.0065 kg/day for children and 0.0175 kg/day for adults) based on previous similar human health risk assessment studies (de Jesus Gaffney et al., 2015; Schwab et al., 2005).
- BCF (L/kg) is the bioconcentration factor for fish obtained from EPI suite's BCFBAF
- EF and ED are the exposure frequency (350 days/year) and exposure duration (6 years for children and 30 years for adults) respectively
- AT (days) is the averaging time equivalent to ED, assumed to be 365 days
- 1000 is a conversion factor between ng and μg.

To assess the results, an HRQ value ≤ 0.2 means that the associated pharmaceutical does not pose an appreciable risk on human health. An HRQ > 1 indicates the possibility of a potential health risk and an HRQ value between 0.2 and 1 calls for more detailed assessment (Sharma et al., 2019). The HRQ values are provided in Tables S8, S9, S10, and S11 for maximum, minimum, median, and mean concentrations respectively.

2.4. Risk assessment for antimicrobial resistance (AMR)

In the case of antibiotics, there are major concerns associated with antibiotic persistence in water and the survival and proliferation of antibiotic-resistant bacteria (Al Maadheed, 2016; Craddock et al., 2020; Krzeminski et al., 2019). The AMR risk was indirectly calculated as the ratio of the MEC (maximum, median, mean, and minimum) of antibiotics to the lowest PNEC-Minimum Inhibitory Concentration (PNEC-MIC) reported in the literature, as 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). The results are tabulated in Table S12.

Out of the 56 antibiotics detected in the MENA, 38 had PNEC-MIC values published in the literature (Bengtsson-Palme and Larsson, 2016; Kümmerer, 2003; Zhang et al., 2020). These studies enumerated the PNEC-MIC for antibiotics 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). Then, the size-adjusted lowest MIC was found for antibiotics with <40 tested species using Eq. (11). If >40 species were tested, the lowest MIC was not adjusted (Zhang et al., 2020). This is done to ensure that 99 % of bacterial isolates would have a higher MIC 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). Finally, an AF of 10 is applied to obtain the PNEC-MIC. The above methodology was followed to derive the PNEC-MIC for ten antibiotics not previously reported in the literature (Table S13). Dapsone, metformin, and most of the compounds belonging to the sulfonamide family did not exist in either of the aforementioned databases which hindered the calculation of their PNEC-MIC, and hence their RQ_{AMR}.

3. Results

This section presents the occurrence of pharmaceuticals in the water compartments of the MENA countries and identifies the more prevalent compounds. In addition, the results of the risk assessment identify which pharmaceuticals pose a significant risk to the environment and humans.

3.1. Pharmaceutical occurrence in MENA region water bodies

Within the MENA region, occurrence studies of pharmaceuticals in aquatic ecosystems have been reported in 14 out of 19 countries: Algeria, Egypt, Iran, Iraq Israel, Jordan, Kuwait, Lebanon, Morocco, Palestine, Qatar, United Arab Emirates, Saudi Arabia, and Tunisia. To the authors' knowledge, a total of 69 monitoring studies are found in the literature across the MENA region spanning the years from 2006 to 2022.

Israel has the highest number of occurrence studies at 18, followed by Tunisia with 11 reported occurrence studies, and Jordan with 10 studies. Seven studies were performed in Iran, while six were reported for Lebanon and Saudi Arabia each. Fewer studies were conducted in Qatar (4) and Palestine (4), while two studies were performed for each of Algeria, Kuwait, Morocco, Egypt, and UAE. Only one study is conducted in Iraq. As previously mentioned, to the authors' knowledge, no studies on this topic were published for six countries in the MENA region: Syria, Yemen, Oman, Bahrain, and Libya. Overall, there has been a significant increase in the number of occurrence studies in the region, specifically in Tunisia where six studies about this subject were reported in the period from 2017 to 2022. Fig. 1 shows the number of pharmaceuticals detected in each country.

Based on the monitoring data, a total of 210 pharmaceuticals spanning 30 therapeutic classes were analyzed in MENA water bodies. Among these pharmaceuticals, 151 were positively detected in at least one water sample of all the compartments analyzed: WWTP influent or effluent, surface

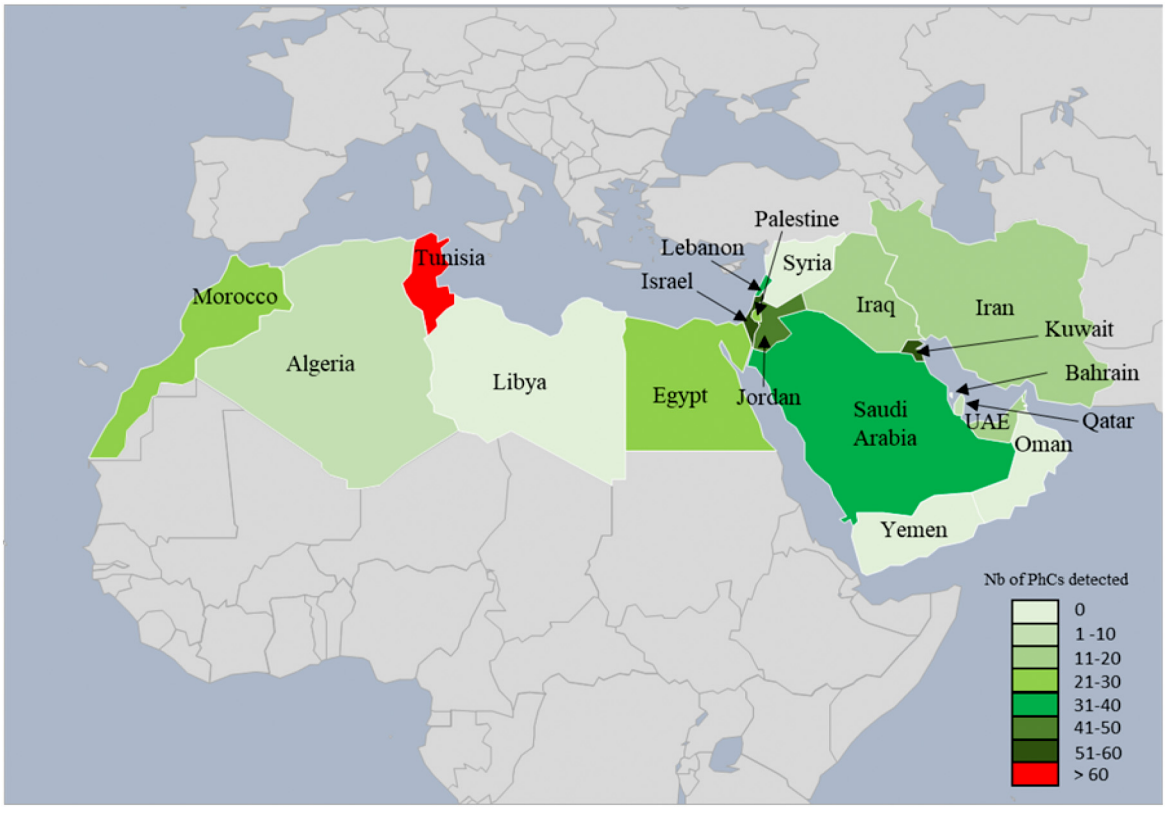

Fig. 1. Number of pharmaceuticals (PhCs) positively detected in different water compartments across each country of the MENA region given as groups.

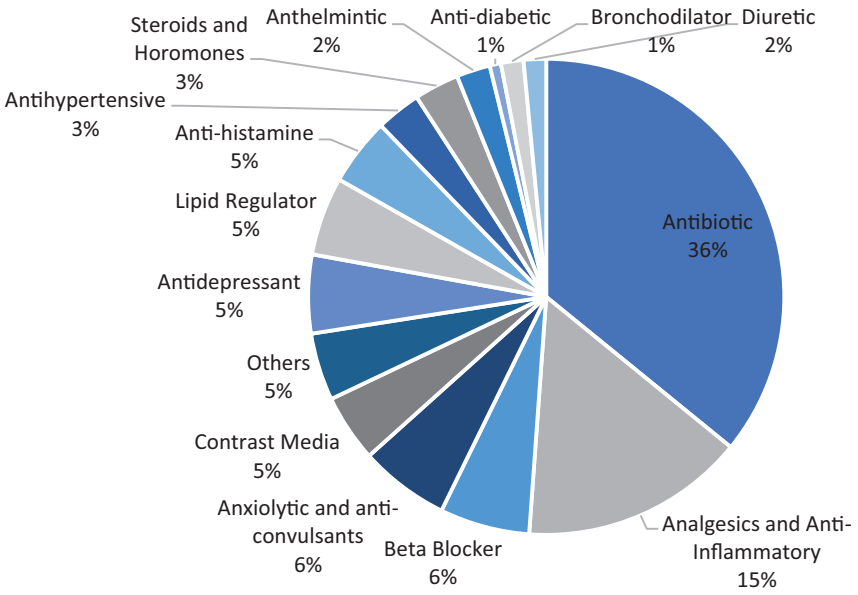

Fig. 2. The number of pharmaceuticals (given as a number and a percentage relative to the total number) positively detected in MENA surface waters classified into therapeutic groups.

water, or groundwater. The retrieved studies were distributed across the compartments as follow: 41 studies in WWTP effluents, 37 studies in surface water, 29 studies in WWTP influents, and 14 studied in groundwater. The entire database can be found in Table S1. The pharmaceuticals that were analyzed but not detected in can be found in Table S14. Moreover, Table S15 lists the number of pharmaceuticals detected according to therapeutic class.

Of the detected pharmaceuticals, 131 pharmaceuticals were found in surface waters. The corresponding therapeutic class distribution is presented in Fig. 2. Antibiotics are the most frequently detected therapeutic class (56 compounds) followed by the analgesics and anti-inflammatory (20 compounds). This is because these classes are the most frequently analyzed with 88 and 26 compounds respectively. The least detected groups are antidiabetics, bronchodilators, and diuretics. Similarly, these are the least analyzed therapeutic classes (Table S15).

Certain compounds had a high number of positive reports (i.e., in >10 data entries across the MENA), as summarized in Table S16. Fig. 3 is a box and whisker plot (logarithmic scale) showing the variation in concentration levels of such pharmaceuticals in MENA surface waters and WWTP effluents. The plot depicts the median values for the whole MENA region, the 25th and 75th quartiles in the data sets, 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 (39 out of 56 antibiotics).

Across all therapeutic classes, the highest concentration reported in the literature for water bodies in the MENA region is for steroids and hormones, specifically 17β estradiol in Egypt. The highest reported concentration of this compound is 1,029,000 ng/L (1 mg/L) in wastewater and 925,000 ng/L in the surface water in Egypt (Elnwishy et al., 2012). Moreover, 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).

Antibiotics claimed the highest number of pharmaceuticals detected across water compartments. The most frequently detected antibiotic is sulfamethoxazole, examined in 28 studies. Sulfamethoxazole was detected with a highest value of 68,700 ng/L in the effluent of a WWTP in Tunisia (Tahrani et al., 2017). It is followed by erythromycin which was detected in 19 studies. Its concentration ranges between 18.4 and 3900 ng/L in surface waters and a maximum of 14,700 ng/L in the effluent of WWTP (Tahrani et al., 2017; Wilkinson et al., 2022). Moreover, the highest concentration of an antibiotic recorded in surface water was for spiramycin (11,100–667,00 ng/L) in seawater in Tunisia (Tahrani et al., 2017).

In the anxiolytic and anti-convulsant class, specifically carbamazepine, prominent values were reported for WWTP influents (3020 ng/L in Jordan) (Shigei et al., 2021) and effluents (132,000 ng/L in Tunisia) (Khazri et al., 2019). This pharmaceutical was the most frequently studied pharmaceutical in MENA aquatic compartments covered by 43 out of the 69 observed studies. The highest concentration of a pharmaceutical in this class is for gabapentin found in an Israeli river at a concentration of 1060–6060 ng/L (Wilkinson et al., 2022).

As for the analgesic and anti-inflammatory pharmaceuticals, diclofenac was the most frequently detected compound appearing in 30 studies. It is followed by ibuprofen, acetaminophen, and naproxen at 21 studies each. The highest concentrations across all observed compartment are for acetaminophen recording 99,600 ng/L in WWTP influent and 90,500 ng/L in WWTP effluent in Saudi Arabia (Shraim et al., 2017). Moreover, it attained a concentration of 98,300 ng/L in the riverine compartment in Tunisia (Wilkinson et al., 2022) and 214,29 ng/L in seawater in Kuwait (Gevao et al., 2021). For the other classes, Table 1 presents a summary of the concentration ranges, by therapeutic group, found in the different water compartments.

3.2. Pharmaceutical risk assessment in water bodies

3.2.1. Risk assessment in surface waters

Table 2 presents the calculated RQ values for the 39 compounds (out of 151 compounds) with a value exceeding 1 and ranging between 1.2 and 562,500 in MENA region surface water. Six pharmaceuticals had extremely high RQ values: 17β estradiol (562,500 in Egypt), spiramycin (13,280 in Tunisia), diclofenac (10,221 in Saudi Arabia), metoprolol (5660 in Tunisia), ethinylestradiol (2500 in Morocco), and carbamazepine (1605 in Israel). The large RQ value for these compounds may be attributed to the high MECs of these compounds. In the case of ethinylestardiol, the large RQ is due to the low PNEC value resulting from the correspondingly low values for the toxicity parameters themselves. It is worth mentioning that all of these RQs were calculated based on measured toxicity data that had much lower values when compared with predicted ones. When using average concentrations, only two compounds still showed an RQ > 1000: 17β estradiol (150,058) and spiramycin (7750). The latter even exhibited an alarming RQ of 2200 at minimal concentrations.

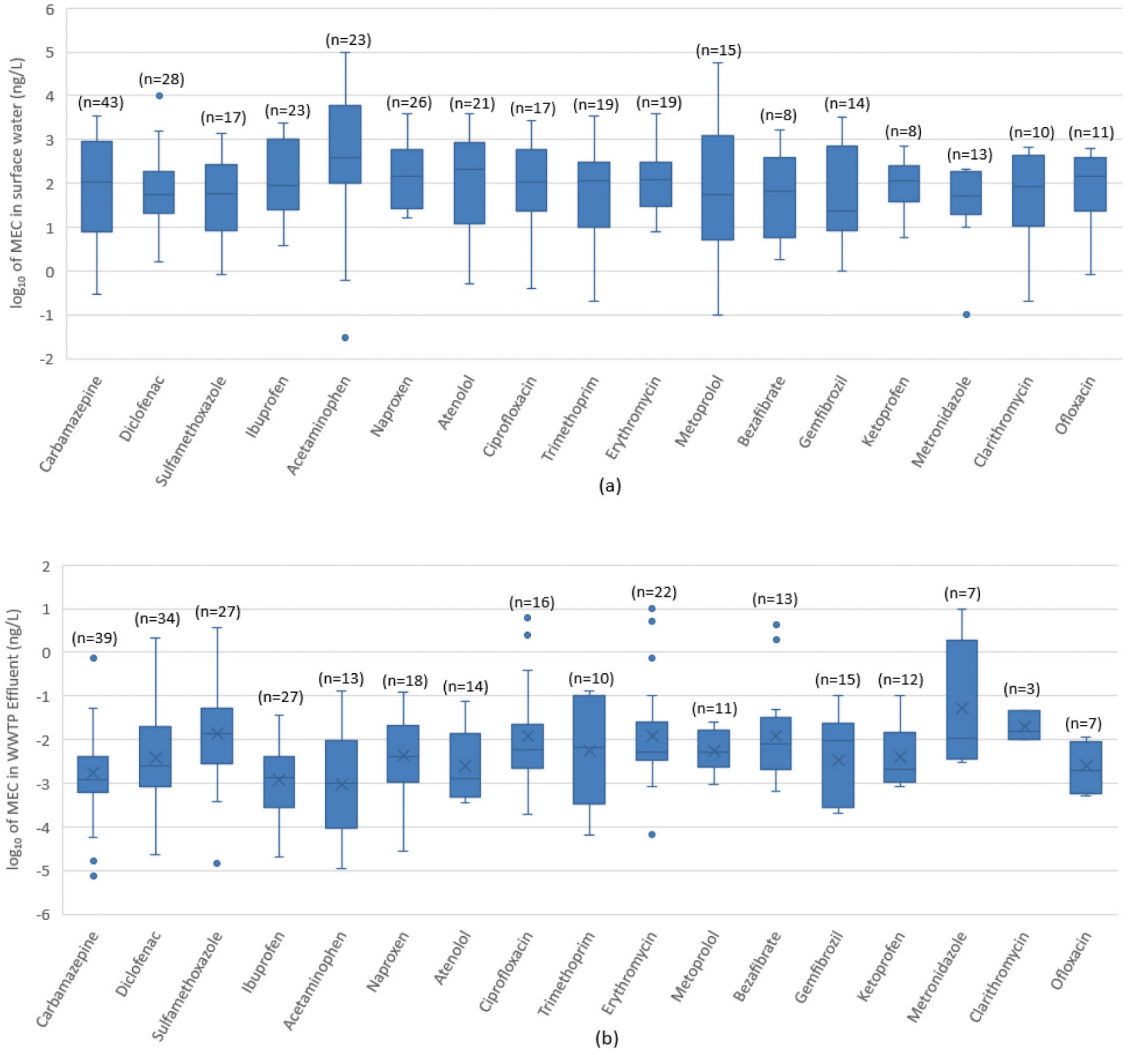

Fig. 3. Median values and variation in the concentration levels of the most frequently detected pharmaceuticals in MENA (a) surface water and (b) WWTP effluents (n = number of data entries).

Approximately 56.5 % of the pharmaceuticals detected in Israeli surface waters pose an environmental risk, followed by 53.3 % in Iran and 50 % in Iraq. The maximum RQ calculated in Iran was 25 for diclofenac. Moreover, fifteen environmentally risky pharmaceuticals, corresponding to 40.5 % of the detected compounds, were found in Jordanian surface waters with a maximum RQ value of 1676 for carbamazepine. In contrast, lower RQ values were calculated for Kuwait (299.2), Lebanon (1055), and Palestine (1210) where 21.4 %, 38.7 %, and 30 % of the detected pharmaceuticals

Table 1
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	59–65
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	29–440
Antidepressant	0.3–11,720	2.8–11,340	0.2–18.9	1–1660	NA
Anti-diabetic	26–450,000	20–618,000	2–14.3	NA	NA
Antihistamines	230–9800	50–5200	0.2–1396	2.48–20,200	NA
Antihypertensive	5.8–11	2.2–594	0.3–568.3	1–104	NA
Anxiolytic/anti-convulsant	50–3020	6–132,000	0.3–109.6	1–6060	10.2–910
Beta blockers	1–4030	8–2900	0.2–1279.4	0.06–56,600	NA
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	NA
Lipid regulator	36–1000	0.23–7000	0.3–1620.6	1–3300	5–70
Steroids/hormones	1–1,029,000	0.07–684,000	36–184	0.2–900,000	NA
Others	129–1200	31–18,537	0.2–55.4	1.97–348	NA

Table 2
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	562,500.0	240,092	150,057.5	36	22.5
Spiramycin	5	66,400	13,280.0	38,750	7750.0	11,100	2220.0
Diclofenac	1	10,221	10,221.0	58.15	58.2	1.6	1.6
Metoprolol	10	56,600	5660.0	56.1	5.6	0.1	0.010[a]
Ethinylestradiol	0.02	50	2500.0	1.7	85.0	0.2	10.0
Carbamazepine	2	3353	1676.5	104.8	52.40	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]
Roxithromycin	100	18,537	185.4	1157	11.6	497	4.97
Norfloxacin	160	20,700	129.4	50	0.31[a]	19.36	0.12[a]
Erythromycin	40	3900	97.5	121	3.0	7.8	0.20[a]
Tetracycline	50	3900	78.0	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	108	2.2	0.4	0.0080[a]
Clarithromycin	20	677	33.9	83.55	4.2	0.2	0.010[a]
Gemfibrozil	150	3300	22.0	23	0.15[a]	1	0.0067[a]
Methotrexate	34,926	618,000	17.7	255,000	7.3	95,000	2.7
Amoxicillin	15.6	220	14.1	29.5	1.9	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]
Sildenafil	2910	18,537	6.4	18,537	6.4	18,537	6.4
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	2.0	755	1.5	510	1.0
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.

pose an environmental risk respectively. Detailed calculations for each country are provided in Table S3.

Carbamazepine, diclofenac, sulfamethoxazole, and ibuprofen show the highest number of positive reports in MENA surface waters. For carbamazepine and diclofenac, concentrations are 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.

3.2.2. Human health risk assessment

The HHRA identified 8 out of 151 detected pharmaceuticals posing a health risk to at least one age group via at least one mode of ingestion. Some compounds displayed an HRQ >100. The pharmaceutical 17β estradiol had the highest HRQ value of approximately 2880 for children (based on combined fish and drinking water exposure routes). This exaggerated value results from a very high MEC of 900 μg/L in an Egyptian Lake (Elnwishy et al., 2012). In fact, this was the only study that reported the measured concentrations in a higher order of magnitude (μg/L instead of ng/L). Hence, it is paramount to interpret the results of this study with caution. The authors used high-performance liquid chromatography (HPLC) coupled with fluorescence detector (FLD) to detect the hormone. They considered an excitation wavelength of 420 nm as opposed to 280 nm used in other studies detecting 17β estradiol using the same technique (De Liz et al., 2017; Yoon et al., 2003). Moreover, when it comes to quality assurance, Elnwishy et al. (2012) only considered precision and accuracy without accounting for other factors such as selectivity, linearity, and detection limits of the HPLC-FLD technique (De Liz et al., 2017). Hence, median and minimum concentrations were used to explore other scenarios and eliminate bias in the data. Nevertheless, 17β estradiol still showed a possible health risk at median concentrations. Table 3 presents the compounds with a HRQ exceeding 1 and posing a health risk to humans upon exposure.

Interestingly, three out of four hormones considered in this study have an HRQ > 1 (the exception being ethinylestradiol). The other compounds are anti-diabetics (2), antibiotics (1), anxiolytics and anti-convulsants (1), and others (1). All the compounds have a small ADI value which implies increased likelihood of adverse effects. It is worth mentioning that the pharmaceuticals tend to have higher HRQs in children due to their lower body weight, thereby decreasing the acceptable concentration and augmenting the HRQ value.

Twenty-two pharmaceuticals have HRQ values between 0.2 and 1, calling for a more detailed HHRA. Most of these compounds pose an uncertain risk to children with no risk to adults (e.g., bisoprolol, clarithromycin, diclofenac, diphenhydramine, florefenicol, gemfibrozil, glibenclamide, iomeprol, iopamidol, metoprolol, primidone, and venlafaxine). In fact, all the compounds, except for glibenclamide, pose uncertain risk via the drinking water and combined exposure pathways, but not through fish alone. Moreover, several compounds (e.g., dimetridazole, lorazepam, and sildenafil) 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.

3.2.3. Risk assessment for AMR selection

23 out of 56 antibiotics (around 41 %) detected in MENA surface waters showed a resistance risk based on the maximum MEC recorded. These

Table 3
Pharmaceutical compounds that pose a human health risk after exposure from surface water through (a) drinking water, (b) fish, and (c) combined source.

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	0.41[b]
Methotrexate	296	59.2	122.1	24.4	45.5	9.1
Sildenafil	4.2	0.85[b]	4.2	0.85[b]	4.2	0.85[b]
Compound	(b) 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
Methotrexate	6.1	3.3	2.5	1.4	0.94[b]	0.50[b]
Compound	(c) Human risk quotient – combined					
	Based on maximum MEC		Based on median MEC		Based on minimum MEC	
	Children	Adults	Children	Adults	Children	Adults
17β 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	1.0	2.3	0.93[b]
Methotrexate	302.1	121.7	124.6	50.2	46.4	14.7
Sildenafil	5.1	2.1	5.1	2.1	5.1	2.1

[a] The risk is unlikely.
[b] The risk is unknown.

antibiotics are displayed in Table 4 along with their corresponding RQ_{AMR}. Only spiramycin recorded an RQ_{AMR} higher than 100 (133 based on maximum MEC) due to its high environmental concentration in Tunisian seawater (Tahrani et al., 2017). The risk also persisted when using median, mean, and minimum MECs for the aforementioned antibiotic. Other alarming RQ_{AMR} values were calculated for ciprofloxacin (42.1) and norfloxacin (41.4) when adopting a worst-case scenario. In fact, norfloxacin no longer exhibited an appreciable risk once the median 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.

4. Discussion

4.1. Current status of occurrence studies in MENA region

An assessment of occurrence studies in the MENA region indicates that geographical coverage of such studies is predominantly biased to Israel, Tunisia, and Jordan. Israel, being the most scientifically advanced country in the region, has access to cutting edge technology and scientific methods that facilitate this type of research. Tunisia has a predominantly arid and semi-arid climate and has been characterized as a water stressed area, rendering water contamination of high concern. 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, Kuwait, and Libya.

Only a very small proportion (10 out of 69 studies) of published occurrence studies in the MENA region include groundwater. Most of the reviewed studies target surface water and WWTP effluent. For example, the studies performed in Tunisia focus on WWTP effluents and coastal waters more than surface water bodies (Belhaj et al., 2015; Cary et al., 2013; Fries et al., 2016; Tahrani et al., 2016, 2017) whereas those conducted in Jordan focus on surface water (Barel-Cohen et al., 2006; Tiehm et al., 2011; Zemann et al., 2014). This may be related to geographical differences as there are more rivers and lakes in Jordan than in Tunisia, which results in more attention to surface water quality. On the other hand, studies in Lebanon concentrate on surface water only due to the proliferation of surface water resources and the fact that very few WWTP are operational (Doummar et al., 2014; Doummar and Aoun, 2018b, 2018a). Meanwhile, studies in Saudi Arabia target WWTP effluent contamination probably due to their interest in wastewater reuse for agricultural purposes (Alidina et al., 2014; Cellamare et al., 2016; Picó et al., 2019). 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.

Table 4
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)
Spiramycin	500	66,400	132.8	38,750	77.5	11,100	22.2
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	16.0	2051.5	8.0	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	7.0	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	6.0	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]
Roxithromycin	1000	1839	1.8	1157	1.2	497	0.497[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.

This is concerning as groundwater is an essential source of potable water in numerous MENA countries (Mirzaei et al., 2018; Mokh et al., 2017). Similarly, more occurrence studies are needed in seawater due to the increasing reliance of some MENA countries on desalination as a source of drinking water, noting that it is uncertain whether the desalination pretreatment steps effectively remove ECs (Nödler et al., 2014; Ouda et al., 2021). Furthermore, the number of studies that analyze both surface water and groundwater is also very limited. In fact, for the purposes of consistency, it is best if a single study (using the same equipment and under the same climatic and testing conditions) analyzes samples from multiple water compartments; in this manner, experimental control is preserved. However, such collaboration within a single country is laden with difficulties, let alone across multiple countries.

As highlighted earlier, the pharmaceutical class most detected is the antibiotics therapeutic class. It is worth noting that most studies do not specify the reason for specifically selecting this class for analysis. The selection of the investigated pharmaceutical classes may be based on consumption, analytical data availability, or the expected degree of risk to the ecosystem and human health. In the case of antibiotics, there are major concerns associated with antibiotic persistence in water and the survival and proliferation of antibiotic-resistant bacteria (Al Maadheed, 2016; Craddock et al., 2020; Krzeminski et al., 2019; Zhang et al., 2020), which, in turn, highlights the importance of upgrading conventional WWTPs to more effective technologies for antibiotic removal. More comprehensive databases are needed to report quantitative data pertaining to the microbial selection to antibiotic resistance.

Nonetheless, the limited detection in antihistamines, bronchodilators, and antihypertensives does not necessarily indicate safe usage or efficient removal but may simply be a result of unfrequented analysis. Similarly, many studies tend to investigate specific compounds that have already been studied elsewhere. 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, recurring investigation into the occurrence of carbamazepine may be due to its high persistence in water (Andreozzi et al., 2002). The concentration of carbamazepine in MENA surface waters ranged between 0.3 and 3352 ng/L. 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). The frequent analysis of sulfamethoxazole may be due to the fact that it is regarded as an EC with potentially substantial adverse effects on the ecosystem and human health (Avisar et al., 2009). The concentrations of this pharmaceutical in MENA surface waters ranged between 0.8 and 1400 ng/L. This comparable to the results found by Van et al. (2021) where the concentration of sulfamethoxazole in the urban rivers of Metro Manila, Philippines was found to be between 16.66 and 1870 ng/L. 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. Thus, the lack of studies investigating a wider breadth of compounds emphasizes the need to go beyond traditional hotspots of therapeutic classes and compounds and consider others of potentially significant risk.

4.2. Pharmaceutical risk and health assessment

The risk assessment is primarily based on the measured concentrations of the pharmaceuticals. As expected, the minimum and maximum concentrations registered for the detected pharmaceuticals differ from one country to another. There are several reasons as to why this is the case and pinpointing the direct cause is not a straightforward manner. Such discrepancies may be attributed to: i) differing consumption patterns (which in and of itself is a major point that requires further in-depth research especially if one seeks a pre-emptive course of action that reduces consumption), ii) presence or absence of WWTPs, iii) removal efficiency in existing WWTP (the technologies used and the level of treatment applied), and iv) pharmaceutical characteristics (physicochemical properties and degradation rates).

For example, Iran has, as of 2019, 190 WWTPs whereas only seven in Lebanon are completed with two being operational (Karam et al., 2013; Yazdandoost, 2020). This leads to the increased likelihood of detecting pharmaceuticals typically removed by WWTP in Lebanese water (Kodom et al., 2021). Discrepancies between measured concentrations in different countries across the MENA region may also be due to dilution in the investigated water compartments. This is more likely to occur in places with frequent rainfall events or water bodies with tributaries. 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 of pharmaceuticals 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.

Furthermore, a key contributor to variation in MEC values is differing testing conditions. While LC-MS/MS is the most commonly used measuring technology across the studies considered (Álvarez-Ruiz et al., 2020; Ben Mordechay et al., 2021; Eslami et al., 2015; Semreen et al., 2019), and the measurement comparison is restricted to those within the same water compartments, the truth of the matter is that other environmental conditions such as temperature, season, and dilution also play a role in determining the final MEC value. Thus, given the experimental nature of these studies, it is nearly impossible to have identical conditions across the studies and there will remain a substantial margin of difference.

As regards the risk assessment calculations, the use of MECs is considered a reliable representation of environmental exposure given that it is based on experimentally collected data rather than predicted estimates (PECs). 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. Their presence at low values does not eliminate the possibility that, even at low concentrations, they may be highly toxic, and thus, hazardous to human and environment.

Moreover, the initial intention of the review was to base the calculation of PNECs on measured EC50s. However due to the insufficient data available for measured toxicity, estimates were substituted. 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). Most of the RQs exhibited discrepancies >90 %. Even with the use of theoretical values, there remained a lack of ecotoxicological data for some compounds that resulted in their exclusion from the analysis (Table S18). The exclusion of these compounds means that there may be additional unevaluated risk. This matter highlights the necessity of conducting additional toxicological analyses for less studied pharmaceuticals. Another worthy point of discussion is that PNECs, and thus RQs, were calculated for the surface water compartment only. Not only does this disregard the likelihood of appreciable risk in other important compartments like groundwater resources, but it also skews the results as all MECs, regardless of the compartment they were measured in, were compared to surface water based PNEC values.

The extremely high values of RQ calculated reflect an alarming risk to aquatic flora and fauna and necessitate additional rigorous assessment and 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 coincidence with other studies, diclofenac (which was calculated to have a value of 10,221) ranked among the pharmaceuticals with high RQ values, as in the case of European surface waters where it had a value of 18,740 (Zhou et al., 2019). The high RQ value is explained by the fact that diclofenac

highly bioaccumulates in fish and subsequently causes secondary poisoning within the aquatic food chain and to fish-eating birds (Memmert et al., 2013). Moreover, carbamazepine, which also possesses a high RQ value (1676), was found to physiologically and morphologically induce toxic effects on aquatic organisms when present in high concentrations (Ali et al., 2019; Vernouillet et al., 2010). Other studies reported pharmaceuticals with high risk in Sri Lanka (Guruge et al., 2019) and Vietnam (Van et al., 2021), yet with RQ values ranging 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 difference in specificity of sampling methods and the unique characteristics of each water body under study, it is also necessary to look at average MECs to better assess the risk.

Age-specific HRQs are estimated based on the maximum detected concentrations of pharmaceuticals in MENA surface waters as a worst-case scenario for human exposure. Eight pharmaceuticals, presented in Table 3, had an HRQ > 1. 17β-Estradiol exhibited the highest HRQ value across the three assessed pathways with higher risks marked for children. When it comes to world-wide studies, pharmaceuticals detected in Dutch drinking water (Houtman et al., 2014), Serbian surface water (Škrbić et al., 2018), and Chinese reservoirs (Yun 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. However, other studies conducted in India and China identified pharmaceuticals with potential human health risks (Dai et al., 2021; Sengar and Vijayanandan, 2022). Sengar and Vijayanandan (2022) stated that 11 out of 49 detected compounds pose a significant risk on human health in Indian surface waters. Moreover, Dai et al. (2021) reported that estrone, 17β estradiol, and estrogen detected in two Chinese river basins had an HRQ > 1 for children, which is comparable with this study. It is evident that the exposure by means of drinking water is the more significant exposure pathway for most of the studied pharmaceuticals. However, HRQs based on drinking water may be overestimated using the measured concentrations in surface water. One reason is that surface waters from river or sea reaches are not used as a direct source of drinking water. They undergo a set of water purification stages (e.g., carbon adsorption, ozonation, or reverse osmosis) that may markedly decrement the measured 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. It is still unclear whether a synergetic adverse health effect would arise due to this exposure (Sharma et al., 2019). It is noted that this evaluation assumes people are drinking water and consuming fish with the highest MECs detected. As such, the human health risk assessed in this review is a very conservative evaluation. Given the uncertainty associated with such method, more realistic scenarios using median and minimum MECs are conducted. As seen in Table 3, these calculations significantly reduce the risk. Nevertheless, 17β estradiol, glimepiride, and methotrexate are still to look out for as they pose a considerable risk at average and minimal concentrations.

Finally, when it comes to AMR risk, Tran et al. (2019) reported RQ_{AMR} values >1000 for erythromycin and >100 for amoxicillin and ciprofloxacin. This is significantly higher than the values found in this study where only spiramycin showed an RQ_{AMR} value >100. In Kenya, ciprofloxacin (RQ_{AMR} = 40.8) and norfloxacin (RQ_{AMR} = 5.8) had a high risk of resistance selection (Kairigo et al., 2020), which is comparable with our results, especially for ciprofloxacin. Overall, it has also been reported that these compounds belonging to the fluoroquinolones family are high-risk antibiotics when it comes to resistance selection (Sengar and Vijayanandan, 2022; Zhang et al., 2020).

5. Conclusion

This work, targeting the MENA region, reveals pharmaceutical detection levels in the ng/L–low mg/L concentration range. A conservative risk assessment method was applied where measured concentration values are used to determine pharmaceutical risk levels. Results showed that 26.5 % of detected pharmaceuticals pose a potential risk to the water ecosystems of MENA countries. Their RQs ranged between 1.2 and 562,500 with the most problematic pharmaceuticals being 17β-estradiol, spiramycin, diclofenac, metoprolol, ethinylestradiol, and carbamazepine. Moreover, eight compounds, namely from the hormones class, were found to pose a risk to human health. 17β estradiol had the highest HRQ value of approximately 2880 for children (based on combined fish and drinking water exposure routes). The occurrence data displayed a geographical bias with most studies being conducted in Tunisia, Israel, and Jordan. This work can serve as a basis for future prioritization studies in the MENA region. Specifically, further research should concentrate on other MENA countries to gain a better understanding of the hotspots of pharmaceuticals occurrence in MENA waters. Increasing population, increasing demands, unregulated access and increasing consumption of pharmaceuticals are all drivers for increased pharmaceutical occurrence and exposure. Hence, legislative regulatory guidelines are crucial to: i) directly address the human health and ecological risks, ii) implement strategies to decrease the potentially imposed risk, and iii) ensure treatment standards at WWTPs for efficient pharmaceutical removal. Given the uncertainty and scarcity surrounding toxicity, further investigation into the chronic effects of individual pharmaceuticals or in mixtures is needed to further improve the understanding of potential environmental effects.

CRediT authorship contribution statement

Nourhan Mheidli: Writing, data collection, methodology, formal analysis **Ali Malli**: Writing, data collection, methodology, formal analysis **Fatima Mansour**: Writing-original draft, methodology, review and editing, formal analysis. **Mahmoud Al-Hindi**: Conceptualization, writing-original draft, review and editing, methodology, formal analysis, supervision.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.158302.

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