

Article

Quantifying the UK Online Interest in Substances of the EU Watchlist for Water Monitoring: Diclofenac, Estradiol, and the Macrolide Antibiotics

Amaryllis Mavragani ¹, Karla Sypsa ², Alexia Sampri ¹ and Konstantinos P. Tsagarakis ^{1,*}

¹ Business and Environmental Technology Economics Lab, Environmental Engineering Department, Democritus University of Thrace, 671 00 Xanthi, Greece; amavraga@env.duth.gr (A.M.); alexia93sab@gmail.com (A.S.)

² Department of Pharmacy and Forensic Science, King's College London, Fifth Floor, Franklin-Wilkins Building, Waterloo Campus, London SE1 9NH, UK; lamprini.sypsa@kcl.ac.uk

* Correspondence: ktsagar@env.duth.gr; Tel.: +30-2541-079-397

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Abstract: Due to the increased interest in micropollutants, this paper aims at quantifying and analyzing the UK online interest in Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin, substances included in the EU watchlist for monitoring, in order to examine if the public's online behavior and the use of these substances, in terms of issued prescriptions, are correlated. Using time series data from Google Trends from January 2004 to December 2014, an analysis of these substances in the UK, and in each UK region, i.e., England, Wales, Scotland, and Northern Ireland, is at first performed, followed by an analysis of interest by substance. The results show high interest in Diclofenac with a slight decline, while the Macrolides are significantly less popular though increasing. For Estradiol, the interest is low and declining throughout the examined period, in contrast to the scientific community, where Estradiol is the most studied substance. Prescription items and Google hits are highly correlated in the UK for Diclofenac, Azithromycin, and Clarithromycin, while no correlation is observed for Estradiol. Results from this study indicated that online search traffic data can be valuable in examining the public's online behavior towards the monitored micropollutants, and could assist with the evaluation and forecasting of their concentrations in the waste, surface, and ground water in the UK.

Keywords: azithromycin; big data; clarithromycin; diclofenac; erythromycin; estradiol; Google trends; macrolide antibiotics; online behavior; prescriptions

1. Introduction

The EU issued its first Directive for Water Policy, Directive 2000/60/EC, in 2000, where high risk substances were defined and prioritized [1], and Directive 2008/105/EC approved a list of 33 priority substances and their Environmental Quality Standards [2]. Following this, in Directive 2013/39/EU [3] a list of 45 priority substances was proposed, including Diclofenac, 17-Alpha-ethinylestradiol (EE2), and 17-Beta-Estradiol (E2) as recommended for monitoring. This was later implemented in Decision 2015/495 [4], issued on 20 March 2015, where the EU established a list of 10 substances to be monitored for Environmental Quality Standards in the field of Water Policy. This list consists of 17 organic compounds, namely 17-Alpha-ethinylestradiol, 17-Beta-estradiol Estrone, Diclofenac, 2,6-di-tetr-butyl-4-methylphenol, 2-ethylhexyl-4-methoxycinnamate, Macrolide Antibiotics (Azithromycin, Clarithromycin, and Erythromycin), Methiocarb, Neonicotinoids (Imidacloprid, Thiacloprid, Thimamethoxam, Clothianidin, and Acetamiprid), Oxadiazon, and

Triallate. These substances do not have a legal discharge limit, but need to be monitored as they are suggested to potentially be harmful for the environment.

Diclofenac is a widely used non-steroidal-anti-inflammatory drug (NSAID) [5], commonly administered orally or dermally, as well as intramuscularly and rectally. It has analgesic, anti-inflammatory, and antipyretic properties, and is mainly used in inflammatory diseases, such as rheumatoid arthritis, as well as for the treatment of short-term conditions, like migraines, fever, menstrual pain, and in postoperative pain [6]. Being a non-selective cyclooxygenase (COX) inhibitor, Diclofenac almost equally blocks both COX-1 and COX-2, with the inhibition of COX-1 being associated with gastrointestinal effects, such as gastric ulcers, and the inhibition of COX-2 causing atherosclerotic complications leading to myocardial infarction (MI) and stroke [7]. The increased risk of cardiovascular complications, such as acute MI, has been linked to both low and high doses of Diclofenac [8]. Despite being a non-selective inhibitor, Diclofenac has a similar atherosclerotic risk to that of selective COX-2 inhibitors, which, even though has not been fully understood, is probably due to a moderate COX-2 selectivity [9].

Oral Diclofenac is available as an over the counter medication in many European countries. However, due to the cardiovascular adverse effects caused by prolonged use of Diclofenac, some countries, including the United Kingdom, changed their policy and added high strengths of oral Diclofenac to the prescription-only medication list [10]. Despite the increased risk of cardiovascular complications being known for several years, Diclofenac is still one of the most popular NSAIDs, with its sales worldwide overriding those of less risky non-selective NSAIDs, like Naproxen [11].

Apart from risks towards human health, Diclofenac can also have a negative impact on the environment. Approximately 70% of an oral Diclofenac dose is excreted through the urine within three days of administration, mostly as conjugates of Diclofenac metabolites, and less than 1% is excreted as unchanged drug [12–14]. After their use by patients in the community, medicines can reach the aquatic environment via faeces and urine [15]. Diclofenac is not fully removed by wastewater treatment [14,16–18], with its removal through this process varying from 0% to 80% [18]. As Diclofenac is not highly biodegradable [14], it is detected in WWTP effluents [19], surface water, and groundwater [18], and unsuccessful treatment of water aiming to remove pharmaceutical residues has led to Diclofenac being traced in the tap water of several European countries in the past [20]. Diclofenac tends to remain in the aqueous phase once in the sewage system, as it is relatively water soluble and has a low tendency for absorption onto organic matter [20]. The presence of chlorine in the structure of Diclofenac has been linked to the failure of completely removing Diclofenac by conventional methods, such as applying activated sludge (CAS), and an increased persistence to more advanced treatments, such as membrane bioreactor (MBR) [20].

Additionally, the veterinary use of Diclofenac in cattle has caused a significant decline in the population of vultures in India, which after consuming the corpses of dead cattle that had been treated with Diclofenac, developed severe renal failure [15,21]. Several studies have been conducted in order to measure the extent of damage caused by Diclofenac to aquatic organisms. These studies have shown that Diclofenac can reduce the feeding rate and activity in the Japanese medaka fish [22]. Furthermore, Diclofenac has been shown to accumulate in the liver and kidney of the rainbow trout, indicating that subchronic exposure to Diclofenac can have a negative impact on the species' health, leading to tissue damage, as the lowest observed effect concentration for cytopathology for this species occurs at just 1 µg/L [15,23,24]. Another study has shown that the concentration of Diclofenac in the bile of bream and roach from a lake receiving municipal wastewater effluents was significantly higher than the concentration of Diclofenac detected in the lake water, indicating that it can accumulate in aquatic organisms [14].

Based on the above, it has been reported that Diclofenac can be harmful for environmental health [16] and, though there are no legal discharge limits, monitoring of its concentrations in the aquatic environment are required in order to preserve good quality of water [17].

The Macrolide Antibiotics, including Azithromycin, Clarithromycin, and Erythromycin, are a very commonly used group of antibacterial antibiotics [25]. Erythromycin was derived from the *Streptomyces* spp. in 1952, whereas Azithromycin and Clarithromycin were later derived from Erythromycin [26]. These antibiotics are frequently used in human and in veterinary medicine, mainly for the treating and preventing of bacterial infections [25,27].

As the Macrolides have a similar activity spectrum to that of the penicillins, they are commonly used in the treatment of penicillin allergic patients. They are mainly effective against Gram positive cocci apart from enterococci, against some Gram negative bacteria, as well as against atypical pathogens [28]. Despite most of the Macrolides having a relatively similar spectrum of activity, Azithromycin has a decreased activity towards Gram positive microorganisms and an enhanced activity towards Gram negative, including *Haemophilus influenza*, and Clarithromycin has a relatively increased activity, both in comparison to Erythromycin [29].

Clarithromycin is most commonly used alongside amoxicillin in the treatment of community acquired pneumonia and as part of the triple therapy used for the eradication of *Helicobacter pylori* [29,30], whereas Azithromycin and Erythromycin are used in the treatment of uncomplicated genital chlamydial infection and in acute non-specific urethritis [29]. The Macrolides have a relatively mild side effect profile, nevertheless, Erythromycin has been noted to have an increased prokinetic activity, causing gastrointestinal side effects more frequently than the other Macrolides, and in some rare occasions it has been linked to causing Torsades de pointes. However, this side effect is only important in patients with heart disease or other relevant comorbidities [31–33].

The environmental concerns regarding the impact of the Macrolides on the environment are mostly focused on the continuously increasing antimicrobial resistance. Antibiotics most commonly end up in the sewage system through excretion from humans, disposing of antibiotics in the toilet, as well as from runoff from agricultural facilities, and hospital waste. The excretion rate of the Macrolides can reach 60%, and they have been detected in wastewater treatment plants influents in the USA at very high concentrations (up to 1.5 µg/L) [34]. In specific, Clarithromycin has been detected in effluents worldwide in concentrations ranging from 12 to 536 ng/L [35–37].

A major issue in the removal of the Macrolide Antibiotics from wastewater is that conventional wastewater treatment plants fail to fully remove them, resulting in their detection in treated effluents, surface water, and groundwater [25]. Yet, secondary wastewater treatment with activated sludge has been proven to be more successful [27,34]. They are included in the EU list for monitoring, as they are regarded, even at low concentrations, as possibly harmful to environmental health [25]. Apart from concerns that the Macrolide Antibiotics in wastewater can contribute to increasing antimicrobial resistance, studies have shown that Clarithromycin and Erythromycin have an increased toxicity, causing growth inhibition against algae and other aquatic photoautotrophs with a no-observed-effect concentration (NOEC) for Clarithromycin at just 2.45 µg/L.

17 α -ethinylestradiol (EE2) is a synthetic steroid hormone produced from the natural hormone 17 β -estradiol (E2). EE2 is widely used as the estrogen component in combined oral contraceptives. It is also available as a transdermal patch and a vaginal ring for contraceptive purposes. Additionally, EE2 can be used for emergency contraception in combination with other hormones, for the treatment of acne, hirsutism, as well as for hormone replacement treatment in menopause [26]. The estrogen component of combined oral contraceptives has been linked to increased risk of venous thromboembolism, thus it is advised that the lowest effective concentration of estrogen is prescribed [38]. 17 α -ethinylestradiol is widely detected in surface waters worldwide, in concentrations at several ng/L, with EE2 being the most persistent in the aqueous environment [39]. The no effect concentration for E2 and EE2 has been estimated to be 2 ng/L and 0.1 ng/L, respectively [40]. The presence of EE2 in wastewater is very concerning as it has been linked to the feminization of certain aquatic species, such as the male Mediterranean swordfish, the rainbow trout, and the cyprinids [41].

As the need to further examine the impact that micropollutants have on the environment has increased [16], this study aims at exploring the public's interest in Diclofenac, Estradiol, Azithromycin,

Clarithromycin, and Erythromycin in the UK. In order to gain access to such vast amounts of information, namely Big Data, we use data from online search queries. One of the most popular tools to access these data is Google Trends [42], an open Google tool that shows what's trending.

Online search traffic data have been proven effective in analyzing online interest [43], and have been highly used in research over the last few years for analyzing online behavior. Data from Google Trends are suggested to be valid [44] and significantly contributing to forecastings [45] and in measuring public interest, subject to the careful selection of the terms to be examined [46]. Google Trends has the advantage of providing us with the revealed and not the stated data, so the public's online behavior is more accurately depicted, contrary to conventional methods of measuring public interest. Thus Google Trends is becoming all the more popular in various academic fields, especially in medical/health [47–62] and environmental issues [63–66]. Indicative examples include the detection of Tuberculosis outbreaks [48], the 2014 Ebola outbreak [49], flu predictions [61] and spreading [62], biodiversity [65], and interest in various environmental terms [63,66]. As indicated, the analysis of public interest is valuable in subjects concerning environmental and human health, thus, as the scientific interest in micropollutants is increasing, it is interesting to examine how the online searches are related to the use of these substances.

The aim of this paper is to quantify and analyze the public's online interest in Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin in the UK, and further compare the interest to the prescription volumes, and examine if any correlations between them exist. In showing that there is indeed a correlation between online interest and issued prescriptions, it is suggested that there exists a casual relationship between the interest in these terms and the actual usage of these substances. The rest of the paper is structured as follows: Section 2 consists of the data collection procedure and the method used to evaluate the online interest, Sections 3 and 4 consists of the results and discussion of our analysis, and Section 5 consists of the overall conclusions and further research suggestions.

2. Data and Method

Google Trends' [42] data from January 2004 to December 2014 are used to analyze the online interest in the terms 'Diclofenac', 'Estradiol', 'Azithromycin', 'Clarithromycin', and 'Erythromycin' in the UK. Data from Google Trends are downloaded online in '*.csv' format and are normalized over the selected time-frame as follows: "each data point is divided by the total searches of the geography and time range it represents, to compare relative popularity. The resulting numbers are then scaled to a range of 0 to 100" [67].

Let D_{t_i} , ES_{t_i} , A_{t_i} , C_{t_i} , and E_{t_i} be the weekly hits of the downloaded Google Trends' data for the terms 'Diclofenac', 'Estradiol', 'Azithromycin', 'Clarithromycin', and 'Erythromycin' of the i -th region, respectively. $D_{t_{pi}}$, $ES_{t_{pi}}$, $A_{t_{pi}}$, $C_{t_{pi}}$, and $E_{t_{pi}}$ denote the percentized weekly hits of their respective normalized Google searches, using Equations (1)–(5):

$$D_{t_{pi}} = \frac{D_{t_i}}{D_{t_i} + ES_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \quad (1)$$

$$ES_{t_{pi}} = \frac{ES_{t_i}}{D_{t_i} + ES_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \quad (2)$$

$$A_{t_{pi}} = \frac{A_{t_i}}{D_{t_i} + ES_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \quad (3)$$

$$C_{t_{pi}} = \frac{C_{t_i}}{D_{t_i} + ES_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \quad (4)$$

$$E_{t_{pi}} = \frac{E_{t_i}}{D_{t_i} + ES_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \quad (5)$$

The relative changes between the substances' Worldwide interest is examined for reference, followed by the change in online interest for each substance individually in England, Wales, Scotland, and Northern Ireland, in addition to a comparative analysis of the five substances in the UK.

Furthermore, the total prescriptions issued for all drugs consisting of the respective chemical substance per each examined term and the total cost per substance per year in England [68], Wales [69], Scotland [70], and Northern Ireland [71] over the examined period are examined, which are then compared and analyzed in relation to the change in online interest. In addition, the total scientific interest based on Scopus searches for published papers with UK affiliation and in total, consisting of these substances in the 'Article Title-Abstract-Keywords' field, is examined and then compared to the Worldwide and UK online interest. Note that the selected papers include 'Articles', 'Reviews', 'Letters', 'Notes', and 'Short Surveys'.

Based on our results, we examine if the relative interest can be a predictor of the use of these substances in the UK, and any potential harm in environmental health, and how data from online search queries can be valuable towards this direction.

3. Results

This Section consists of the analysis of (a) Worldwide's and UK's online interest in 'Diclofenac', 'Estradiol', 'Azithromycin', 'Clarithromycin', and 'Erythromycin' from January 2004 to December 2014; (b) the regional interest in these terms for the same period in England, Wales, Scotland, and Northern Ireland; (c) each individual term's change in online interest in the UK; (d) the yearly total prescription items and total cost (£) per substance in each region; (e) the scientific interest; and (f) the correlations between them.

3.1. Worldwide and UK's Online Interest

Figure 1 depicts the change in (a) the Worldwide and (b) UK's yearly averages of the percentized hits for the terms 'Diclofenac', 'Estradiol', 'Azithromycin', 'Clarithromycin', and 'Erythromycin' from January 2004 to December 2014. Tables 1 and 2 consist of the percentized hits' yearly averages in these terms in the same period Worldwide and in the UK, respectively.

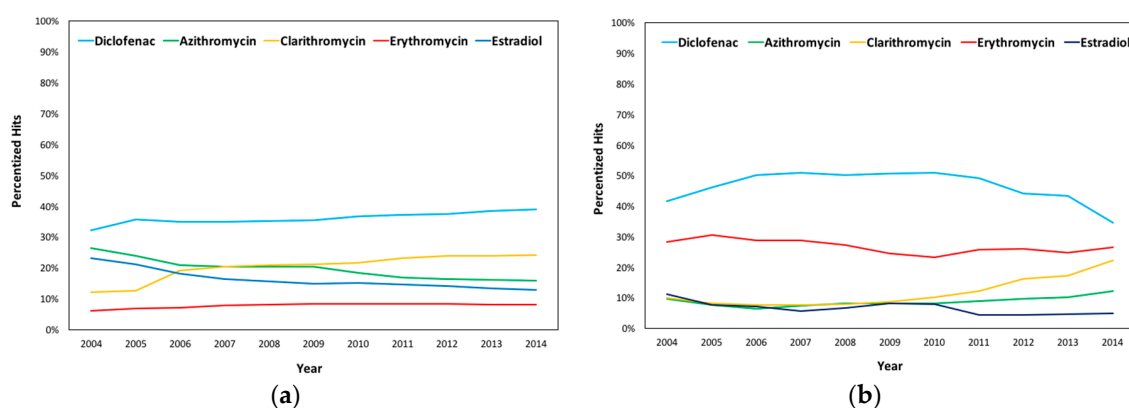


Figure 1. Yearly Averages of the (a) Worldwide and (b) UK Percentized Hits from 2004 to 2014.

As presented in Table 1, the yearly averages for the Worldwide interest show that the most popular amongst the examined substances is Diclofenac (36.05%), followed by Clarithromycin (20.27%), Azithromycin (19.61%), Estradiol (16.29%), and Erythromycin (7.77%) in that order.

In the UK, results showed that Diclofenac, though first amongst the five substances in terms of online searches, showed a slight decline in interest in 2014 compared to 2004, the same as Estradiol, though with variations throughout the examined period. In contrast, the Macrolides of the EU watchlist Azithromycin and Clarithromycin show an increased interest over the examined period, while Erythromycin shows a slight decrease from 2004 to 2014.

Table 1. Worldwide Yearly Averages of the Percentized Hits in the Five Examined Substances from 2004 to 2014.

Year	Diclofenac	Estradiol	Azithromycin	Clarithromycin	Erythromycin
2004	32.19%	23.08%	26.39%	12.19%	6.15%
2005	35.62%	21.04%	23.84%	12.70%	6.81%
2006	34.79%	18.05%	20.82%	19.18%	7.16%
2007	35.01%	16.40%	20.43%	20.35%	7.80%
2008	35.15%	15.61%	20.42%	20.75%	8.07%
2009	35.29%	14.91%	20.42%	21.13%	8.25%
2010	36.63%	14.98%	18.33%	21.71%	8.34%
2011	37.20%	14.58%	16.95%	23.03%	8.24%
2012	37.41%	14.21%	16.23%	23.86%	8.30%
2013	38.44%	13.46%	15.99%	23.95%	8.16%
2014	38.81%	12.89%	15.95%	24.14%	8.21%
Average	36.05%	16.29%	19.61%	20.27%	7.77%

Table 2. Yearly Averages of the Percentized Hits in the Five Examined Substances in the UK from 2004 to 2014.

Year	Diclofenac	Estradiol	Azithromycin	Clarithromycin	Erythromycin
2004	41.55%	11.07%	9.53%	9.76%	28.09%
2005	46.11%	7.66%	7.70%	8.18%	30.36%
2006	50.00%	7.06%	6.42%	7.69%	28.82%
2007	50.82%	5.61%	7.30%	7.49%	28.77%
2008	50.13%	6.55%	8.09%	7.92%	27.30%
2009	50.60%	8.05%	8.19%	8.69%	24.47%
2010	50.92%	7.78%	8.04%	10.12%	23.14%
2011	48.96%	4.40%	8.80%	12.08%	25.76%
2012	44.10%	4.33%	9.53%	16.03%	26.01%
2013	43.38%	4.55%	10.05%	17.25%	24.77%
2014	34.53%	4.91%	12.06%	22.19%	26.32%
Average	46.46%	6.54%	8.70%	11.58%	26.71%

Overall, in the UK, Diclofenac is the most searched substance out of the five, with Erythromycin, Clarithromycin, Azithromycin, and Estradiol following in that order. Interestingly enough, UK does not follow the Worldwide trend, with Erythromycin, though the second most searched term, being last in Worldwide interest.

3.2. Regional Online Interest

Table 3 consists of the percentage averages from 2004 to 2014 of the examined terms in England, Wales, Scotland, and Northern Ireland, while the yearly averages of each substance in the four regions can be found in Appendix A. Figure 2 depicts the change in the yearly averages of the percentized hits for the terms 'Diclofenac', 'Estradiol', 'Azithromycin', 'Clarithromycin', and 'Erythromycin' in (a) England; (b) Wales; (c) Scotland; and (d) Northern Ireland from 2004 to 2014.

Table 3. Percentage Averages from 2004 to 2014 for the five examined substances in England, Wales, Scotland, and Northern Ireland.

Region	Diclofenac	Estradiol	Azithromycin	Clarithromycin	Erythromycin
England	46.25%	6.67%	9.03%	11.59%	26.47%
Wales	37.29%	8.44%	11.03%	13.01%	30.22%
Scotland	39.66%	10.19%	11.29%	15.28%	23.58%
N. Ireland	35.63%	11.04%	12.26%	16.63%	24.44%

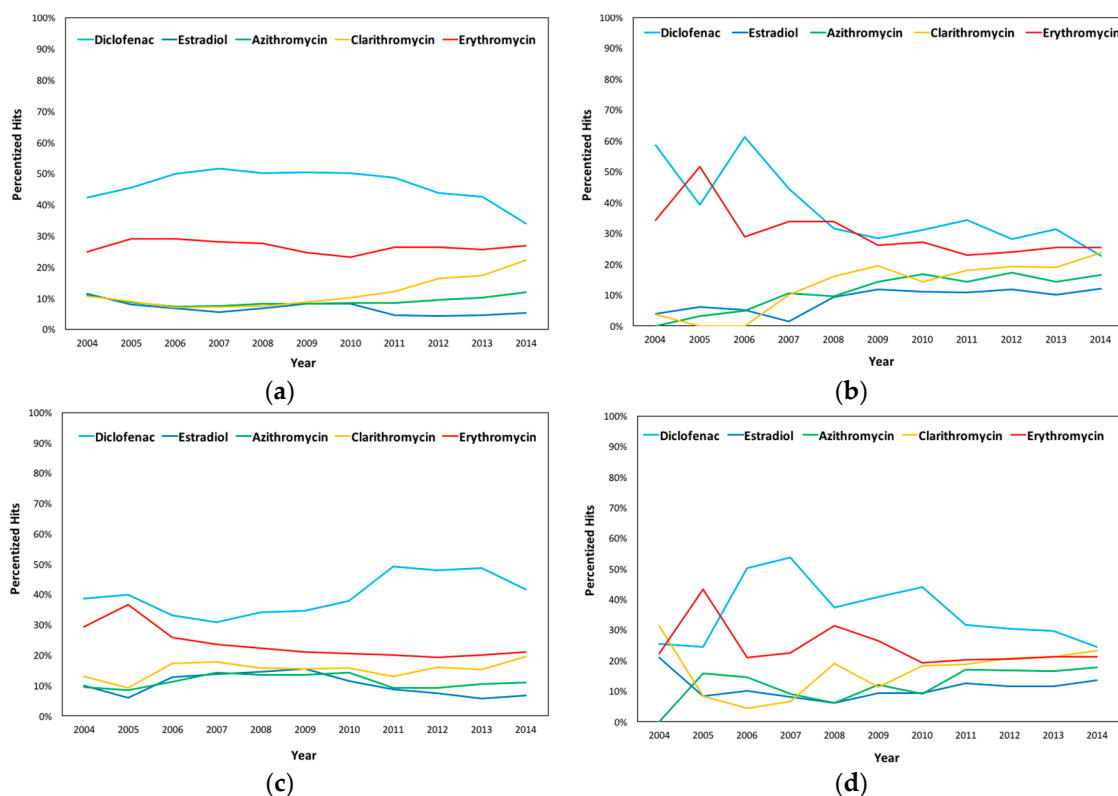


Figure 2. Yearly Averages of the Percentized Hits in (a) England; (b) Wales; (c) Scotland; and (d) Northern Ireland in Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin from 2004 to 2014.

Overall, the results showed that in each of UK’s regions, i.e., England, Wales, Scotland, and Northern Ireland, Diclofenac is the most searched term amongst the ones examined, followed by Erythromycin, Clarithromycin, Azithromycin, and Estradiol in that order, with Clarithromycin, Azithromycin, and Estradiol showing significantly less online interest.

More specifically, results revealed that in England Diclofenac is the most searched substance with an overall average of 46.25%, followed by Erythromycin (26.47%), Clarithromycin (11.59%), Azithromycin (9.03%), and Estradiol (6.67%) (Table 3). In Wales, Scotland, and Northern Ireland, the order of online popularity of the five substances is the same as in England, i.e., Diclofenac (37.29%, 39.66%, and 35.63%, respectively), Erythromycin (30.22%, 23.58%, and 24.44%, respectively), Clarithromycin (13.01%, 15.28%, and 16.63%, respectively), Azithromycin (11.03%, 11.29%, 12.26%, respectively), and Estradiol (8.44%, 10.19%, and 11.04%) (Table 3).

Table 4 consists of the percentage differences of the yearly averages of the percentized hits between the years 2004 and 2014 for the terms ‘Diclofenac’, ‘Azithromycin’, ‘Clarithromycin’, ‘Erythromycin’, and ‘Estradiol’ in the UK, England, Wales, Scotland, Northern Ireland, and Worldwide.

Table 4. Worldwide, UK, and Regional Percentage Differences between the Years 2004 and 2014.

Region	Diclofenac	Estradiol	Azithromycin	Clarithromycin	Erythromycin
Worldwide	20.56%	−44.15%	−39.55%	98.02%	33.47%
UK	−16.90%	−55.69%	26.47%	127.34%	−6.28%
England	−19.64%	−54.78%	7.77%	109.02%	8.56%
Wales	−61.47%	224.48%	435.49% *	551.03%	−26.13%
Scotland	7.70%	−31.69%	18.77%	51.58%	−28.11%
N. Ireland	−3.52%	−35.87%	12.90% *	−26.22%	−5.26%

Note: * The differences are calculated based on the years 2005 and 2014.

In England, Diclofenac and Estradiol show significant decrease, in Wales a decrease is observed only in Diclofenac and Erythromycin, while in Scotland in Erythromycin and Estradiol. In Northern Ireland the interest in all substances apart from Azithromycin is decreasing, but minimal increase is observed in the case of Diclofenac and Erythromycin. Overall, the only substance that shows an increase in all regions, i.e., UK, England, Wales, Scotland, Northern Ireland, and Worldwide, is Clarithromycin.

3.3. Online Interest by Substance

This section consists of the individual analysis for each of the five terms' change in online interest in the UK in the selected period. Figures 3–7 depict the terms' (a) normalized hits in the UK from January 2004 to December 2014 and (b) the yearly averages of the percentized hits in England, Wales, Scotland, and Northern Ireland. Figures 3 and 4 depict the online change in interest in 'Diclofenac' and 'Estradiol', respectively, while Figures 5–7 depict the online change in interest in the Macrolides, i.e., 'Azithromycin', 'Clarithromycin', and 'Erythromycin', respectively.

In Diclofenac, as is observed in Figure 3, the online interest has relatively small variations throughout the selected period, where the peak in interest in the selected period is in June–July 2013.

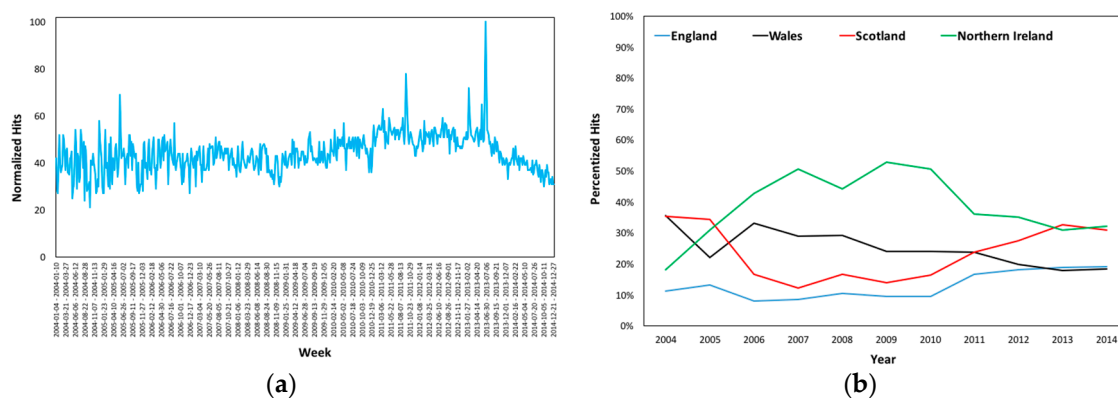


Figure 3. Diclofenac's (a) Normalized Hits in the UK and (b) Regional Percentized Hits Averages 2004–2014.

As intake of Diclofenac was suggested to have an increased risk for cardiovascular diseases, possibly even at small doses, and following the MHRA's concern on its availability in August 2013, Diclofenac was switched from being an over-the-counter drug to prescription only on 15 January 2015 [72]. This is indicative that incidence occurrence is instantly depicted in online searches.

Estradiol's online interest has decreased since 2004 in the UK, compared to other substances, as shown in Figure 4.

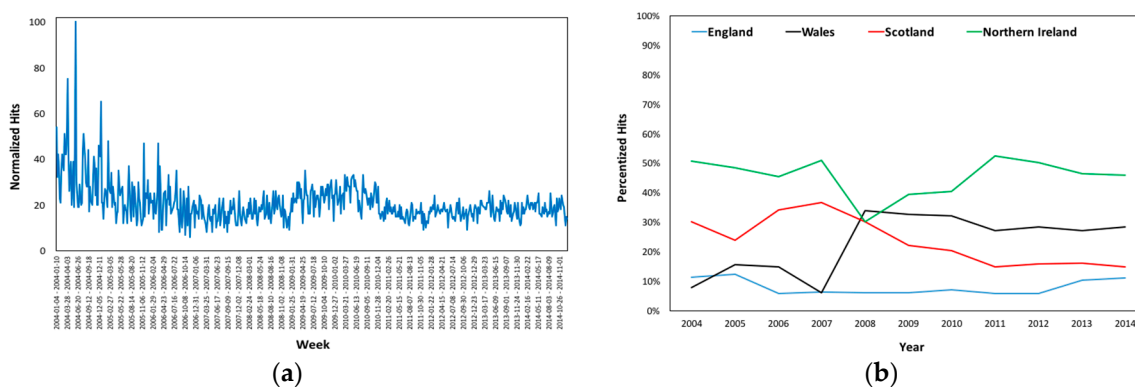


Figure 4. Estradiol's (a) Normalized Hits in the UK and (b) Regional Percentized Hits Averages 2004–2014.

Though the highest online interest is observed in Northern Ireland compared to the other regions, the only significant increase in the substance’s online interest is observed in Wales after 2008.

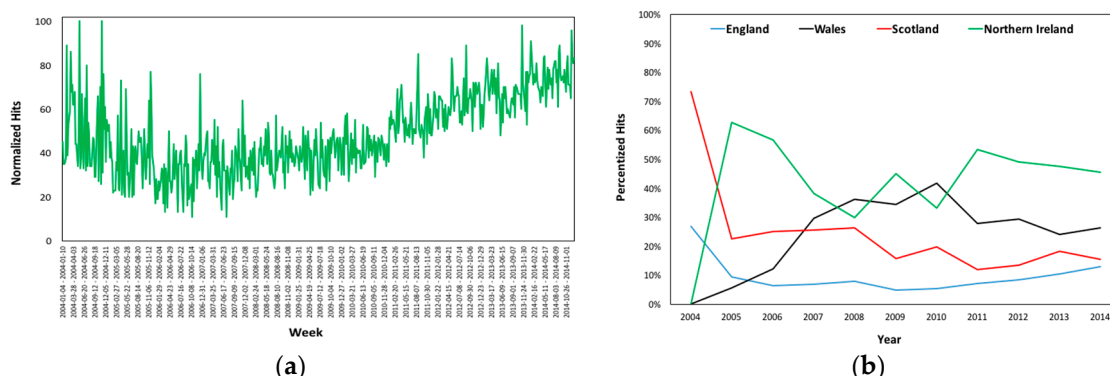


Figure 5. Azithromycin’s (a) Normalized Hits in the UK and (b) Regional Percentized Hits Averages 2004–2014.

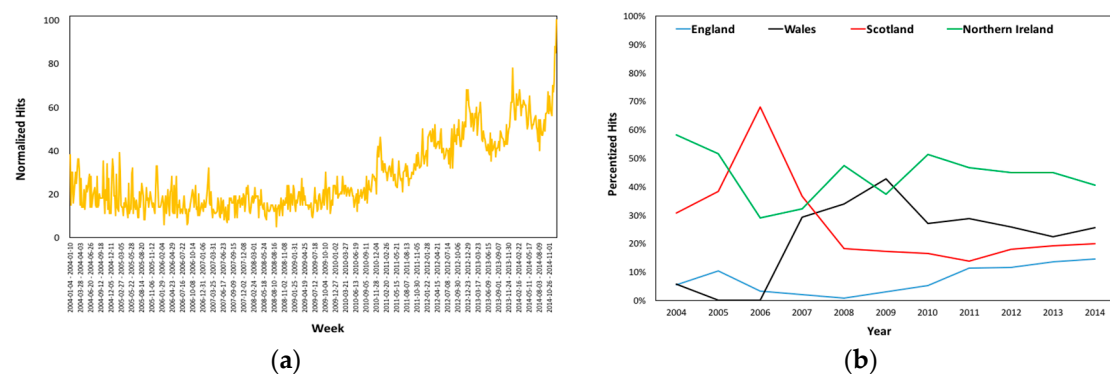


Figure 6. Clarithromycin’s (a) Normalized Hits in the UK & (b) Regional Percentized Hits Averages 2004–2014.

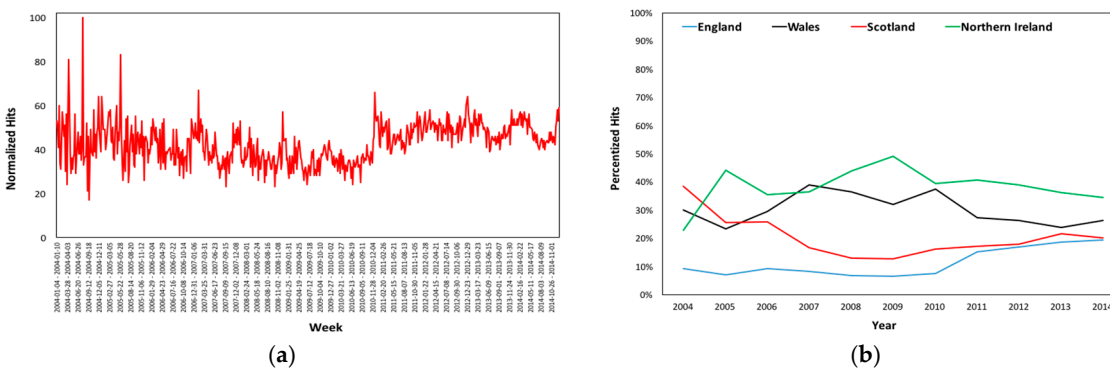


Figure 7. Erythromycin’s (a) Normalized Hits in the UK and (b) Regional Percentized Hits Averages 2004–2014.

For the Macrolides, Azithromycin and Clarithromycin showed an increase in online interest over the last years, while the interest in Erythromycin is relatively stable, compared to the other substances. More specifically, for Azithromycin, the regional interest is the lowest in England, followed by Scotland, Wales, and Northern Ireland in that order, though a significant increase is observed in Wales, the same as in Diclofenac. For Clarithromycin, the regional interest in England and Wales shows an increase over the examined period, while in Scotland a significant decrease is observed. For Erythromycin, regionally, the only significant increase is observed in England.

Overall, we observe that Wales shows an increase in online interest in all substances apart from Diclofenac and Erythromycin, while in England, an increase is observed in Diclofenac, Clarithromycin and Erythromycin. In Scotland, the online interest in all substances apart from Diclofenac is decreasing, while in Northern Ireland the only significant change in online interest (increase) is observed in Azithromycin.

3.4. Total Prescriptions and Costs per Substance

In Figures 8–11 we present (a) the total number of prescriptions (Pxs) and (b) total cost (Nic) per substance for each of the examined years in England [68], Wales [69], Scotland [70], and Northern Ireland [71], respectively. The detailed data can be found in Appendix B. In England, results revealed a high decrease in Diclofenac’s number of issued prescriptions from 2004 to 2014 starting in 2008, Estradiol and Erythromycin show a slight steady decrease in issued prescriptions over the examined period, while Azithromycin and Clarithromycin show a slight increase in issued prescriptions since 2004. The total cost (£) for all substances has overall decreased since 2004, apart from Azithromycin that shows a slight increase in the examined period.

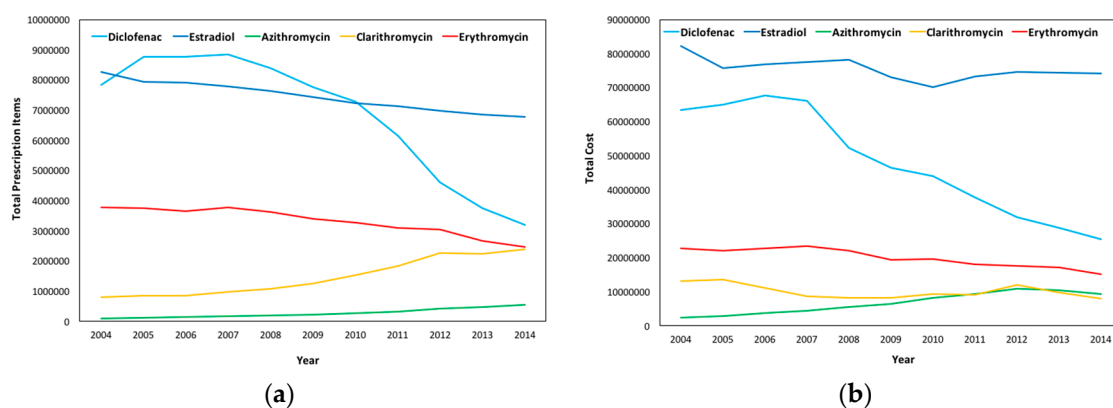


Figure 8. England’s Total (a) Prescription Items and (b) Cost (£) per substance from 2004 to 2014.

In Wales, a high decrease in issued prescriptions in Diclofenac and a significant decrease in Estradiol and Erythromycin are observed, while a slight increase in the number of prescriptions is observed for Clarithromycin and Azithromycin; a pattern similar to that of England. As demonstrated in Figure 9b, the total cost for the substances follows that of the number of prescriptions in Diclofenac, Estradiol, and Erythromycin, while for Azithromycin and Clarithromycin, though prescription items increased, the cost slightly decreased from 2012 to 2014.

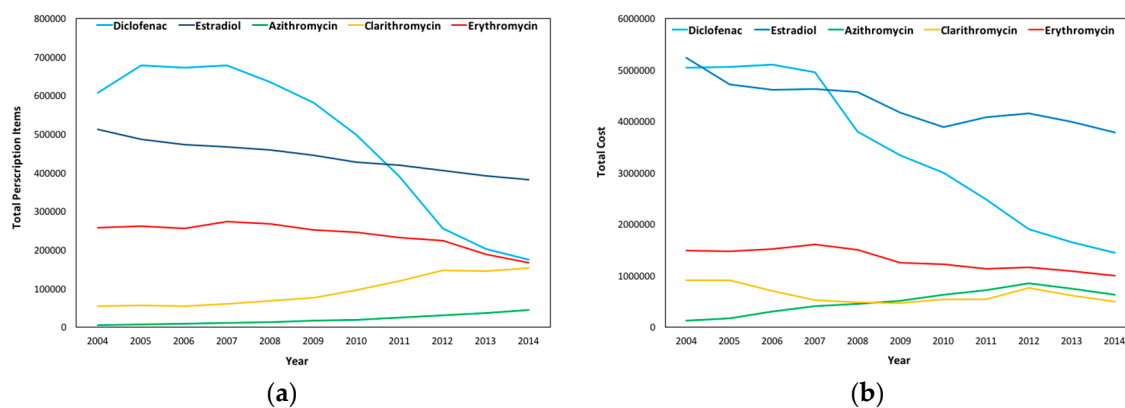


Figure 9. Wales’ Total (a) Prescription Items and (b) Cost (£) per substance from 2004 to 2014.

In Scotland, the prescriptions in Diclofenac, though increasing from 2004 to 2012, show a sudden decrease from 2012 to 2014, while the total cost shows a significant overall decrease from 2004 to 2014. For Estradiol, both prescriptions issued and total cost show a slight decrease over the examined period, the same as for Erythromycin. For Clarithromycin and Azithromycin, the issued prescriptions show an increase, apart for Clarithromycin from 2013 to 2014. The total cost for Clarithromycin has shown a decrease from 2006 to 2008, and a slight decrease since 2013, while for Azithromycin, the total cost has slightly increased over the examined years.

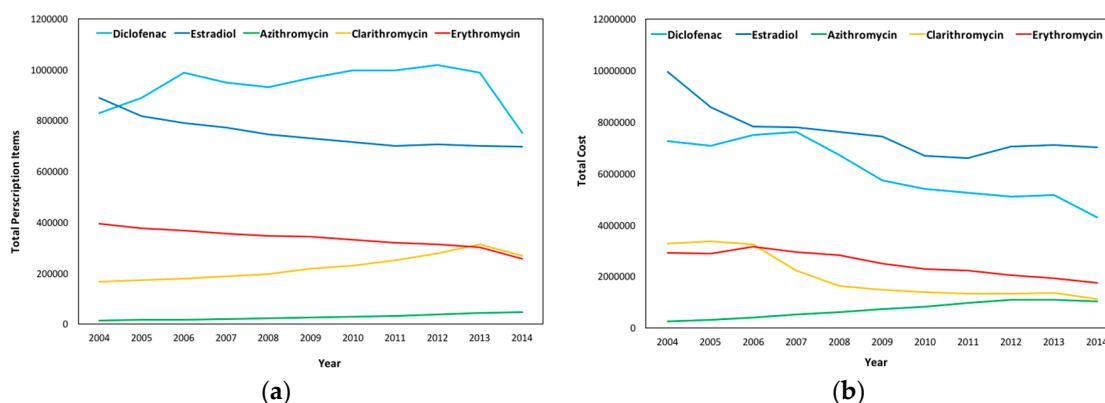


Figure 10. Scotland's Total (a) Prescription Items and (b) Cost (£) per substance from 2004 to 2014.

In Northern Ireland, as shown in Figure 11, the total prescriptions items for Diclofenac showed a slight increase up to 2010 and decreased significantly until 2014, the same as for the total cost. Estradiol's prescription items and cost are relatively stable throughout the examined period, while Erythromycin slightly decreases in both fields. For Clarithromycin, while the total prescriptions have increased since 2004, the cost shows a slight overall decrease, and for Azithromycin there is a small increase in both total prescriptions and cost over the examined period.

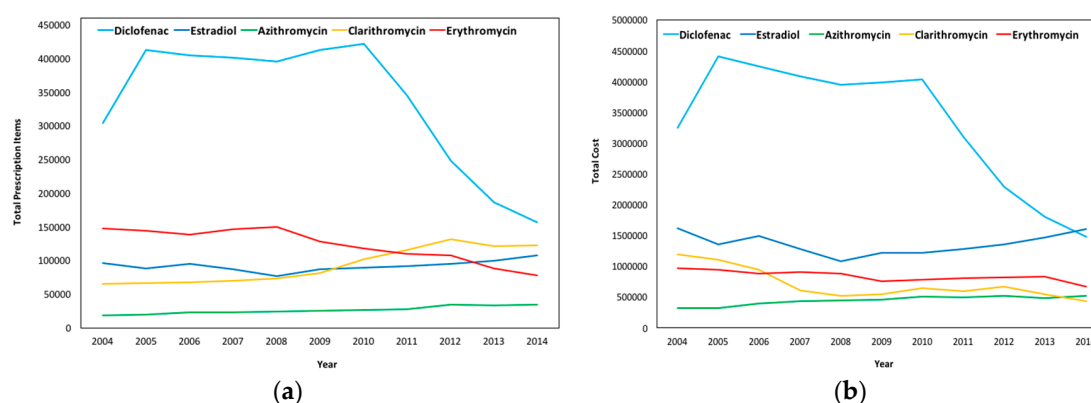


Figure 11. Northern Ireland's Total (a) Prescription Items and (b) Cost (£) per substance from 2004 to 2014.

Overall, we observe that Diclofenac is the substance with the most significant change out of the examined substances, with both prescription items and total cost from 2004 to 2014 decreasing.

3.5. Research Interest

In order to further examine the interest in the five examined micropollutants, we ran searches in the Scopus database [73] consisting of each of the substances' number of documents with the respective term for each year from 2004 to 2014 Worldwide (Table 5). In addition, we further limited the searches in Scopus to include only published papers from 2004 to 2014 with UK affiliation, as shown in Table 6.

Table 5. Total Scopus Number of Documents with the terms Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin from 2004 to 2014.

Year	Diclofenac	Estradiol	Azithromycin	Clarithromycin	Erythromycin
2004	1470	4203	1259	1582	2537
2005	1573	4342	1320	1593	2554
2006	1561	4384	1267	1445	2414
2007	1566	4278	1282	1443	2391
2008	1538	4453	1242	1422	2429
2009	1659	4364	1348	1493	2308
2010	1708	4376	1332	1401	2215
2011	1832	4447	1358	1334	2126
2012	1896	4507	1486	1356	2202
2013	1899	4469	1700	1465	2259
2014	1714	4316	1513	1249	2005
Total	18,416	48,139	15,107	15,783	25,440

Table 6. Scopus Number of Documents with UK Affiliation with the terms Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin from 2004 to 2014.

Year	Diclofenac	Estradiol	Azithromycin	Clarithromycin	Erythromycin
2004	147	244	96	97	233
2005	160	253	105	112	229
2006	163	256	93	74	220
2007	157	233	83	97	216
2008	166	263	92	112	217
2009	137	251	108	123	209
2010	121	244	132	104	182
2011	156	220	107	121	160
2012	133	205	116	115	161
2013	134	242	147	125	140
2014	108	188	129	98	117
Total	1582	2599	1208	1178	2084

We observe that the order of the substances in terms of published papers is Estradiol, Erythromycin, Diclofenac, Clarithromycin, and Azithromycin, are at no point similar to the Worldwide Google hits for the terms from 2004 to 2014. This shows that the scientific community and the public view these terms differently.

We observe that the number of published papers in Scopus with a UK affiliation is the highest for Estradiol, followed by Erythromycin, Diclofenac, Azithromycin, and Clarithromycin in that order. Thus we conclude that the scientific interest in the UK follows the Worldwide one.

3.6. Correlations amongst Prescription, Google Hits, and Scientific Papers

Table 7 consists of the Pearson correlations for the five examined substances between the percentized prescriptions (Pxs) and Google Trends (GT) percentized data in the UK, England, Wales, Scotland, and Northern Ireland, and between the Scopus' percentized number of documents and Google Trends hits in the UK and Worldwide.

As indicated by the results, prescription items and Google hits in the UK are highly correlated for Diclofenac, Azithromycin, and Clarithromycin, while no correlation whatsoever is observed for Estradiol. Correlations with high statistical significance ($p < 0.01$) are also observed in prescription items and Google hits in England in Diclofenac and Clarithromycin, in prescription items and Google hits in Wales in Clarithromycin, in the Scopus documents and Google hits for all substances Worldwide apart from Estradiol, and in the Scopus documents and Google hits in the UK in Azithromycin. Another interesting observation is that population seems to play a significant role in the regional results. For example, as shown in Table 7, for Diclofenac, though in the respective regions the correlations

between Google hits and prescriptions vary from high to none, in the UK as a total they exhibit a high correlation, the same as for Clarithromycin and Azithromycin, while, for Erythromycin in Wales, there is a weak negative correlation.

Table 7. Correlations amongst Prescriptions, Google Hits and Published Scientific Papers for Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin.

Substance	Pxs-GT (UK)	Pxs-GT (England)	Pxs-GT (Scotland)	Pxs-GT (Wales)	Pxs-GT (N. Ireland)	Scopus-GT (Worldwide)	Scopus-GT (UK)
Diclofenac	0.7814 ***	0.7903 ***	0.1358	0.6045 **	0.5843 *	0.8637 ****	0.3067
Estradiol	−0.2775	−0.3455	0.0369	0.4974	0.5189	−0.5293	0.371
Azithromycin	0.8287 ***	0.6395 **	−0.0642	0.7133 **	0.5783 *	−0.7569 ***	0.7778 ***
Clarithromycin	0.9531 ****	0.9384 ****	0.4014	0.7535 ***	0.4935	−0.9129 ****	0.6631 **
Erythromycin	0.5677 *	0.1295	0.7795 ***	−0.5847 *	0.3736	−0.7933 ***	0.609 **

Notes: * $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$; **** $p < 0.001$.

4. Discussion

Since 2004, there have been many studies that examined the micropollutants' occurrence and removal [16], in addition to their effects on environmental and human health. Out of the EU watchlist, the substances that have been studied the most are Diclofenac, Azithromycin, Clarithromycin, Erythromycin, Estradiol, and Estrone, contrary to the rest of the list, where the substances have not been extensively studied [16]. In the UK, comparing the examined substances, the results indicated that the online interest is mainly focused on Diclofenac, however, that interest has showed a slight decrease from 2004 to 2014. In contrast, the online interest in the Macrolide Antibiotics, specifically Clarithromycin and Azithromycin on a lower level, has showed a significant increase, whereas Erythromycin is the most searched for Macrolide, with its online interest maintained at similar levels throughout the years 2004–2014 compared to other substances. The online interest in Estradiol has remained at low levels throughout these 11 years.

The declining online interest and prescribing of Diclofenac follows the results of a Europe-wide review regarding its cardiovascular complications, which led to the MHRA adding Diclofenac to the prescription-only-medication list in 2015 [72]. The MHRA suggests that Naproxen and low dose Ibuprofen can be used instead, as they have a safer cardiovascular profile [74]. However, Naproxen and Ibuprofen have been shown to accumulate in fish bile, as does Diclofenac [75]. Therefore, despite them having a better side effect profile for human use, they have the potential to cause harm to the aquatic environment.

The changes in the online interest and prescribing patterns of the Macrolide Antibiotics are due to various reasons. Initially Erythromycin was the most widely prescribed Macrolide, however during the course of these 10 years, Clarithromycin has gained ground over Erythromycin. This is justified by changes in the guidelines, which now state that Clarithromycin is the Macrolide of choice, as it has an improved side-effect profile and better patient compliance due to a less frequent dosage regiment [76]. Azithromycin ensures the maximum patient compliance by only requiring a once a day dosing for 3 days [29] and causing fewer interactions with other medications [32]. However, due to having a longer half-life than the rest, it provides a greater opportunity for resistance to develop, which could be an explanation on why it is not the Macrolide of choice in penicillin allergy [76]. Azithromycin is most commonly used for the treatment of sexually transmitted diseases, such as chlamydia and gonorrhea. The increase in Azithromycin prescribing can be linked to the increased rate of chlamydia and gonorrhea diagnosis during the past 10 years [77]. In addition, due to its anti-inflammatory action, it is also used in patients with deteriorating cystic fibrosis as part of an off-label 6-month treatment course [78]. In order to minimize the negative impact of Macrolide use to both humans and the aquatic environment, it is important to control their prescribing and use for farming purposes. The National institute for Health and Care Excellence has implemented certain guidelines in order to ensure the optimum use of antibiotics, also suggesting the minimum antibiotic prescribing in farming [79,80].

Estradiol has shown a rather minor online interest, compared to other substances; however, it is one of the most commonly prescribed substances out of those investigated. This is justified, as the Estradiol data work as an umbrella term covering both Estradiol and Ethinylestradiol prescribing data. Estradiol is mostly used in hormone replacement therapies in post-menopausal women as well as in conditions such as female hypogonadism and primary ovarian therapy. Ethinylestradiol is used in contraceptive pills and in emergency hormonal contraception, as well as in hormone replacement therapies and female hypogonadism [26]. The vast usage of these two substances can partially justify the increased research interest in Estradiol. It must be noted, that Estradiol, containing preparations such as contraceptive pills containing 17- α -ethinylestradiol, can be obtained from sexual health clinics without a prescription [81], and thus would not appear in the data analyzed by this study, which could be explaining why Estradiol is the only substance not to exhibit any correlation with Google hits in any region.

Though Diclofenac prescriptions have decreased over the past years, it is still a widely prescribed item (see Appendix B), that can cause environmental complications despite wastewater treatment. Diclofenac's removal through conventional wastewater treatment varies from 0% to 80% [18], and, as it is not always absorbed onto organic matter [20], it is detected in the aquatic environment [18,19] and in the tap water in EU countries [20]. This also applies to the Macrolide Antibiotics, where concerns are being raised on their effect on environmental and human health due to them not being completely removed through conventional treatment [25]. It has been shown that their detection in wastewater adds to the increased antimicrobial resistance, as well as toxicity due to Clarithromycin and Erythromycin. Estradiol is also not fully degraded, and its presence in surface waters [39] affects sea life [41]. As wastewater treatment is suggested to not completely remove the concentrations of these substances in the aquatic environment [14,16–18,39], the solution could be to manage the pollution at the source, which is the human, veterinarian, and agricultural intake and use. Steps towards this direction have been implemented, as for example in the case of Diclofenac, which is now a prescription-only drug in the UK [72].

This study, like any other study, has some limitations. At first, the analysis only takes into account the online interest of these substances in the UK, which could, however, provide ground for future research on the topic in other EU countries. In addition, the substances examined are limited to five, though this methodology can be applied in other substances included in the watchlist when more research has been documented. Furthermore, not each hit corresponds to only prescription issuing, as many of them could be for educational/academic searches or general interest on the subject, all the while not taking into account searches that are related to prescription issuing, e.g., due to incorrect spelling. Despite that, Google Trends' data have been suggested to be accurate for analyzing human behavior, which is further supported by previous studies indicating that Google Trends can indeed be a valid predictor of human behavior. In this study, it is observed that search queries are strongly correlated with three of the five substances' prescription volumes, further supported by the no observed correlation in Estradiol, which, as mentioned above, can be obtained directly through sex clinics. Nevertheless, as is presented by the correlations in Section 3 between the prescriptions issued and the hits in Google in the UK, we argue that the analysis of the online interest in micropollutants can assist with the prediction of the public's intake of these substances, in order to evaluate the steps that need to be taken towards the direction of decreasing these substances' use. In addition, as the amount of antibiotics found in wastewater is proportional to the prescribing trends of each country [34], the forecasting and monitoring of their concentrations in the aquatic environment is possible.

5. Conclusions

Given the increased interest in several micropollutants in the EU, and as they have been suggested to be possibly harmful for environmental and human health, their monitoring in the aquatic environment has been implemented with Decision 2015/495. This study analyzed the changes in online search queries, in order to examine how Google Trends' data can be used to evaluate the

public's interest in relation to the use of these drugs in the UK. Google Trends, being all the more used for examining the changes in interest in various medical, health, and environment-related terms, is a valid tool for evaluating online interest, as it uses the revealed and not the stated preferences of the users.

Normalized data from Google Trends were used in this study to examine the change in UK's online interest in Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin, included in the EU watchlist, from 2004 to 2014, the correlations between the public's interest and the prescriptions issued for these substances over the examined period, and the scientific interest in terms of published papers. Though it could not be argued that each search query corresponds to the respective prescription issuing, with any potential bias this may include, the results by the presented empirical relationships indicate that there indeed exists a strong correlation between prescription items and Google hits in the UK for Diclofenac, Azithromycin, and Clarithromycin, and a weak correlation for Erythromycin, while for Estradiol no correlation in any region is observed. The interest in Diclofenac is high, though declining, Estradiol exhibits lower and declining interest, while high but stable interest is observed for Erythromycin. Azithromycin and Clarithromycin, though searched for less, show a significant increase in online interest over the examined period. Estradiol's online interest is in contrast to the issued prescriptions, though, interestingly, it is the most popular out of the five examined substances in terms of scientific publications.

Further research could include more case studies of EU countries, and to also compare different states in terms of interest and Health Care System's performance. Furthermore, the possibility of exploring the relationship between online search queries from Google and concentrations of these substances in the aquatic environment could be examined, so as to develop an algorithm for forecasting these concentrations, and, subsequently, better monitor the degradation observed in the aquatic environment.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1 consists of the yearly averages of the percentized hits for the terms 'Diclofenac' (D), 'Estradiol' (ES), 'Azithromycin' (A), 'Clarithromycin' (C), and 'Erythromycin' (E) in England, Wales, Scotland, and Northern Ireland from 2004 to 2014.

Table A1. Yearly Averages of the Percentized Hits in Diclofenac, Estradiol, Azithromycin, Clarithromycin, and Erythromycin in England, Wales, Scotland & Northern Ireland, 2004–2014.

Year	England					Wales				
	D	ES	A	C	E	D	ES	A	C	E
2004	42.22%	11.40%	10.99%	10.61%	24.78%	58.46%	3.73%	0.00%	3.62%	34.19%
2005	45.53%	8.03%	8.67%	8.82%	28.95%	39.26%	6.03%	3.09%	0.00%	51.62%
2006	49.84%	6.84%	7.20%	7.07%	29.06%	61.19%	5.06%	4.88%	0.00%	28.86%
2007	51.67%	5.57%	7.52%	7.09%	28.15%	44.28%	1.48%	10.53%	10.04%	33.66%
2008	50.09%	6.68%	8.19%	7.55%	27.49%	31.47%	9.21%	9.51%	16.08%	33.74%
2009	50.32%	8.12%	8.25%	8.77%	24.55%	28.42%	11.74%	14.11%	19.53%	26.20%
2010	50.21%	8.27%	8.37%	10.05%	23.09%	30.93%	10.92%	16.72%	14.35%	27.08%
2011	48.70%	4.48%	8.54%	12.00%	26.28%	34.21%	10.85%	14.30%	17.88%	22.77%
2012	43.78%	4.30%	9.49%	16.18%	26.26%	28.09%	11.70%	17.30%	19.12%	23.80%
2013	42.44%	4.58%	10.22%	17.15%	25.61%	31.36%	10.04%	14.34%	19.00%	25.27%
2014	33.93%	5.16%	11.84%	22.17%	26.90%	22.53%	12.12%	16.55%	23.55%	25.26%

Table A1. Cont.

Year	Scotland					Northern Ireland				
	D	ES	A	C	E	D	ES	A	C	E
2004	38.55%	9.88%	9.32%	12.91%	29.34%	25.36%	20.93%	0.00%	31.46%	22.25%
2005	40.00%	5.84%	8.32%	9.26%	36.58%	24.53%	8.26%	15.78%	8.26%	43.17%
2006	33.02%	12.69%	11.26%	17.21%	25.82%	50.27%	10.11%	14.55%	4.23%	20.83%
2007	30.86%	13.78%	14.13%	17.78%	23.45%	53.65%	8.12%	9.07%	6.63%	22.53%
2008	34.00%	14.39%	13.50%	15.72%	22.39%	37.28%	6.20%	6.20%	19.02%	31.29%
2009	34.53%	15.47%	13.52%	15.44%	21.05%	40.78%	9.41%	12.11%	11.25%	26.45%
2010	37.93%	11.42%	14.34%	15.80%	20.51%	43.88%	9.33%	9.16%	18.33%	19.29%
2011	49.15%	8.73%	9.15%	13.00%	19.97%	31.57%	12.58%	17.00%	18.65%	20.21%
2012	47.97%	7.56%	9.21%	16.02%	19.25%	30.48%	11.52%	16.67%	20.76%	20.57%
2013	48.72%	5.64%	10.34%	15.33%	19.97%	29.65%	11.51%	16.51%	21.16%	21.16%
2014	41.52%	6.75%	11.07%	19.57%	21.10%	24.47%	13.43%	17.82%	23.21%	21.08%

Appendix B

Tables B1–B4 consist of the total prescriptions issued and total cost per substance in England [68], Wales [69], Scotland [70], and Northern Ireland [71], respectively.

Table B1. Total Prescriptions Items and Total Cost per each Examined Substance from 2004 to 2014 in England.

Year	Diclofenac		Estradiol		Azithromycin		Clarithromycin		Erythromycin	
	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic
2004	7,835,083	63,478,356	8,251,847	82,173,534	103,963	2,362,482	795,270	13,225,502	3,766,953	22,679,369
2005	8,766,625	65,041,774	7,941,468	75,777,693	123,291	2,939,084	852,806	13,603,648	3,748,994	21,987,699
2006	8,764,671	67,572,195	7,899,767	76,832,218	139,963	3,652,018	853,852	11,156,286	3,646,943	22,700,296
2007	8,851,377	66,137,104	7,772,486	77,574,221	164,441	4,498,897	973,997	8,723,270	3,763,697	23,421,676
2008	8,388,693	52,224,959	7,642,773	78,099,605	191,842	5,446,935	1,077,097	8,294,989	3,630,628	22,108,822
2009	7,748,234	46,427,799	7,434,276	72,950,292	225,109	6,456,947	1,257,967	8,242,025	3,395,881	19,482,448
2010	7,271,070	43,885,658	7,215,934	70,045,022	274,706	8,203,889	1,541,129	9,352,900	3,279,767	19,505,861
2011	6,145,755	37,721,617	7,129,956	73,214,245	326,009	9,429,128	1,823,774	9,077,182	3,098,773	17,956,893
2012	4,595,666	31,811,877	6,983,092	74,604,834	410,781	10,998,016	2,258,788	12,040,359	3,050,915	17,696,503
2013	3,742,673	28,798,913	6,841,917	74,364,235	476,529	10,369,500	2,245,430	9,833,664	2,673,169	17,052,495
2014	3,191,910	25,334,219	6,767,640	74,071,656	543,986	9,296,368	2,397,752	8,030,665	2,451,888	15,181,583

Table B2. Total Prescriptions Items and Total Cost per each Examined Substance from 2004 to 2014 in Wales.

Year	Diclofenac		Estradiol		Azithromycin		Clarithromycin		Erythromycin	
	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic
2004	607,248	5,042,779	511,028	5,236,612	4568	117,091	53,652	903,849	256,824	1,481,228
2005	678,484	5,046,112	485,694	4,716,870	5699	172,899	55,902	900,822	261,533	1,469,651
2006	671,812	5,093,644	472,642	4,613,931	7941	294,818	53,439	698,619	255,790	1,519,369
2007	678,105	1,067,870	466,309	4,617,357	10,364	398,855	60,221	521,634	272,313	1,600,360
2008	635,085	3,793,644	459,422	4,569,660	12,630	455,641	67,349	478,072	266,925	1,504,670
2009	580,770	3,338,177	443,828	4,163,532	15,805	511,380	75,638	460,939	251,236	1,249,129
2010	498,367	2,989,491	427,581	3,883,315	19,028	620,973	94,390	530,313	245,055	1,215,885
2011	388,495	2,472,713	419,273	4,080,473	24,305	719,482	119,245	539,206	230,841	1,133,924
2012	254,997	1,901,062	404,993	4,145,176	30,320	843,584	146,134	764,544	222,667	1,159,973
2013	201,798	1,647,361	390,974	3,984,881	36,997	743,283	145,506	610,597	188,956	1,092,414
2014	173,686	1,440,695	381,413	3,781,056	44,190	633,734	153,445	495,161	166,866	994,933

Table B3. Total Prescriptions Items and Total Cost per each Examined Substance from 2004 to 2014 in Scotland.

Year	Diclofenac		Estradiol		Azithromycin		Clarithromycin		Erythromycin	
	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic
2004	828,315	7,240,001	888,889	9,945,074	13,510	251,295	165,909	3,276,480	392,270	2,895,902
2005	888,239	7,064,040	816,091	8,562,827	14,625	295,412	170,758	3,369,381	375,763	2,872,755
2006	988,181	7,488,552	790,058	7,825,990	16,726	388,981	177,455	3,229,276	366,113	3,149,333
2007	947,237	7,598,272	769,913	7,790,662	19,231	512,789	186,086	2,234,031	355,662	2,932,906
2008	930,227	6,706,394	743,438	7,590,806	21,053	595,080	197,300	1,621,024	346,642	2,821,866
2009	966,564	5,709,160	729,726	7,412,799	25,109	729,715	215,696	1,483,031	341,418	2,483,633
2010	996,611	5,400,387	712,913	6,688,184	28,035	818,739	229,736	1,371,893	329,611	2,278,828
2011	996,967	5,231,754	698,473	6,582,956	31,215	956,196	250,527	1,336,948	317,831	2,223,376
2012	1,016,319	5,097,518	705,705	7,048,774	36,229	1,098,991	275,497	1,330,449	313,722	2,041,729
2013	986,949	5,156,256	700,361	7,092,274	41,638	1,090,442	313,086	1,341,904	301,406	1,937,615
2014	750,888	4,298,521	694,916	7,011,775	44,818	1,039,360	266,637	1,121,077	255,645	1,736,324

Table B4. Total Prescriptions Items and Total Cost per each Examined Substance from 2004 to 2014 in Northern Ireland.

Year	Diclofenac		Estradiol		Azithromycin		Clarithromycin		Erythromycin	
	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic	Pxs	Nic
2004	303,754	3,243,777	96,509	1,617,714	18,353	321,834	65,089	1,197,697	147,641	969,240
2005	412,903	4,402,937	88,408	1,351,945	19,548	321,170	66,880	1,107,689	143,967	936,716
2006	404,206	4,241,150	94,915	1,491,020	22,380	392,940	67,440	940,586	137,832	874,958
2007	401,661	4,081,595	86,548	1,276,070	23,380	435,724	70,131	607,166	146,797	898,771
2008	394,935	3,949,307	77,148	1,084,687	24,536	442,670	72,918	520,957	150,073	884,860
2009	413,144	3,981,120	86,468	1,219,970	25,491	460,367	81,595	541,349	128,384	754,316
2010	421,552	4,036,778	89,379	1,214,298	26,312	499,738	101,820	645,725	117,861	778,011
2011	345,627	3,102,062	91,519	1,276,442	27,760	493,735	115,077	593,917	109,444	806,347
2012	247,985	2,289,123	94,837	1,349,398	34,649	522,087	131,903	667,656	107,395	814,308
2013	186,076	1,799,736	99,058	1,463,963	32,788	479,013	120,734	545,088	88,419	829,671
2014	156,732	1,477,050	107,500	1,602,230	33,831	517,421	122,544	433,467	78,104	668,663

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