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Abstract

Global Trimethoprim (TMP) and Sulfamethoxazole (SMX) occurrences in raw wastewaters were systematically collected from the literature (*n*=140 articles) in order to assess the relevance of using the SMX/TMP ratio as a marker of the main origin of wastewaters. These two antibiotics were selected due to their frequent use in association (i.e. co-trimoxazole) in a 5:1 ratio (SMX:TMP) for medication purposes, generating a unique opportunity to globally evaluate the validity of this ratio based on concentration values. Several parameters (e.g. sorption, biodegradation) may affect the theoretical SMX/TMP ratio. However, the collected data highlighted the good agreement between the theoretical ratio and the experimental one, especially in wastewater treatment plant influents and hospital effluents. Only livestock effluents displayed a very high SMX/TMP ratio, indicative of the very significant use of sulfonamide alone in this industry. Conversely, several countries displayed low SMX/TMP ratio values, highlighting local features in the human pharmacopoeia.

This review provides new insights in order to develop an easy to handle and sound marker of wastewater origins (i.e. human/livestock), beyond atypical local customs.

Keywords: Antibiotics ; Wastewaters ; Marker ; Livestock ; Consumption

1. Introduction

The occurrence of numerous emerging contaminants in raw wastewaters has spurred the interest of the scientific community in further tracing the sources of the contamination of environmental compartments (Al Aukidy et al., 2012; Tran et al., 2014b; Verlicchi et al., 2010) and in back-calculating their use in the catchment area (Choi et al., 2018; Kasprzyk-Hordern, 2019; Van Hal, 2019). Several types of usage are therefore monitored in raw wastewaters such as illicit drug and pharmaceutical consumption (Baz-Lomba et al., 2016; Ort et al., 2014), industrial inputs (Kim et al., 2017; Rousis et al., 2017), and personal care product uses (Bressy et al., 2016; Nakada et al., 2017). This new scientific discipline, called wastewater-based (or sewage) epidemiology, has highlighted several patterns in the use/consumption of such compounds from the local to the worldwide scale (Causanilles et al., 2018; Thomas et al., 2012). Beyond the use of raw wastewaters as a source of information, their chemical composition is also of great concern in view of the insufficient removal of emerging pollutants in wastewater treatment plants (Grandclément et al., 2017; Patel et al., 2019; Rivera-Utrilla et al., 2013). As a result, the constant discharge of contaminated effluents leads to ubiquitous contamination within numerous environmental compartments such as rivers, groundwaters, sediments and seawaters (Burns et al., 2018; Gaw et al., 2014; Kümmerer, 2009; Thiebault et al., 2017a), and raises hard toxicological issues for living beings (Richmond et al., 2018; Saaristo et al., 2018). The fate of antibiotics within sewers is of particular concern due to the increase of the bacterial resistance and the spreading of antibiotic resistance genes (Le et al., 2018; Yi et al., 2017), mainly generated by both the increase in worldwide antibiotic consumption (Gelband et al., 2015; Klein et al., 2018) and the chronic exposure of bacterial communities to contaminated wastewaters (Baquero et al., 2008; Menz et al., 2019; Michael et al., 2013).

Several markers have been developed in order to easily obtain information about wastewater contamination of environmental compartments (Tran et al., 2019b; Warner et al., 2019). Among the targeted emerging contaminants, the use of the most resilient ones as markers has been assessed, i.e. Carbamazepine (Björlenius et al., 2018; Clara et al., 2004), Crotamiton (Nakada et al., 2008), Sucralose (Currens et al., 2019; Tran et al., 2019b) and Acesulfame (Buerge et al., 2009). The detection of these markers in environmental samples provides direct information about their contamination by wastewaters, and the extent of the contamination by raw wastewaters can be assessed through the use of ratio between labile (e.g. Acetaminophen, Caffeine) and conservative contaminants (e.g. Carbamazepine, Sucralose) (Kuroda et al., 2012; Tran et al., 2014a). However, this type of marker alone does not provide any deeper information, especially about the origin of the wastewater. The use of a chemical marker is therefore often performed through ratio calculation between organic contaminants. Among antibiotics, two of them are mainly consumed in association, namely Sulfamethoxazole (SMX) and Trimethoprim (TMP), which have been indeed mainly consumed in one medicine, co-trimoxazole, since 1968 (Salter, 1982), in a 5:1 ratio (SMX:TMP) allowing synergistic effects between the two compounds (Hitchings, 1973). Initially exclusively consumed in association with SMX, the consumption of TMP alone was authorized in the 1970s depending on the country (Tsakris et al., 1991). Currently, the global use of Sulfonamides and TMP in association (i.e. labelled J01E according to WHO) is the fourth highest after penicillins, macrolides and fluoroquinolones (Van Boeckel et al., 2014). This antimicrobial association is considered as an essential medicine by the World Health Organization (WHO, 2017), due to its use in the treatment of various infections such as pneumonia and urinary tract infection (Di Cocco et al., 2009; Guneysel et al., 2009). Briefly, TMP is a bacteriostatic antibiotic derived from trimethoxybenzylpyrimidine that belongs to a group of chemotherapeutic agents known as inhibitors of dihydrofolate reductase, whereas SMX belongs to sulfonamides, which act as a dihydropteroate synthase inhibitor. The use of co-trimoxazole was initially promoted following the development of antimicrobial resistance to older treatments, such as β-lactam antibiotics

(Warren et al., 1999), and due to its higher efficiency (Fischi et al., 1988; Fox et al., 1990). However, the current increase in antimicrobial-resistant bacteria to co-trimoxazole (in fact, to TMP and SMX separately) necessitates the development of new therapeutic solutions (Eliopoulos and Huovinen, 2001; Talan et al., 2004). Finally, this medicine appears to be appropriate in the treatment of opportunistic infections in HIV-infected people (Mermin et al., 2004; Walker et al., 2010), even if such use is currently not approved by health agencies such as the Food and Drug Administration (Kemnic and Coleman, 2019). Beyond their use in human medicine, SMX and TMP are also employed for veterinary purposes (Papich, 2016), with significant local variations (Boxall et al., 2002; Kemper, 2008; Sarmah et al., 2006).

The simultaneous analysis of SMX and TMP therefore represents a unique opportunity to better characterize raw wastewaters, due to the precise knowledge of the initial ratios consumed, and given that the consumption of co-trimoxazole is much higher than that of SMX or TMP alone.

2. Methods

2.1. Literature search and screening

Relevant studies for the purposes of this systematic review were identified by conducting a broad literature search on several databases such as Web of Science, Pubmed and Scopus, based on carefully selected keywords such as co-trimoxazole, sulfamethoxazole, trimethoprim, wastewater influents, hospitals, livestock and antibiotics. No geographical sorting or minimum publication date was used in order to maximize the number of publications. Only peer-reviewed articles (except one thesis) were selected.

2.2. Study evaluation

After the selection, raw data were extracted from publications provided that the following criteria were met: (i) both sulfamethoxazole and trimethoprim were analyzed in wastewater samples, (ii) both sulfamethoxazole and trimethoprim were quantified in wastewater samples (as the calculation of a ratio would be not possible if only one product was quantified), (iii) the analysis was conducted in untreated wastewaters, namely wastewater treatment plant influents in general (WI, Table 1), hospital effluents (HE, Table 2) and livestock farming wastewater effluents (LE, Table 3).

Consequently, studies dealing with other water compartments (i.e. river waters, ground waters) were not considered.

Each study that simultaneously analyzed SMX and TMP in the targeted matrixes was used in this review (n=140). No sorting was carried out on the minimum amount of samples or the specific sampling mode, as the calculation of a ratio is independent of external conditions. From the studies investigated, precise information was extracted such as the location (if the town was not-specified, the state or less precise information was given, Table 1-3), the flow, the sampling mode, the amount of samples, the number of installations analyzed (if $n > 1$ both flow and the population-equivalent capacity of each installation were summed), the origin of wastewaters (e.g. municipal, industrial, hospital or pharmaceutical industry for WI), in order to contextualize each ratio. It should be mentioned here that each single ratio (derived from SMX and TMP concentrations) was systematically evaluated from a site point of view rather than in terms of chronological evolution. For example, the seasonal effect was not specifically targeted in this work, unlike the geographical evolution of the ratio even within a specific country.

Statistical tests were performed to evaluate the significance of the observed variations using the Student t-test with chosen thresholds of 0.05, 0.01 and 0.001 (i.e. *, **, ***, respectively) for the resulting p-values.

3. Theoretical ratio in wastewater influents

3.1. Excretion

The calculation of the theoretical SMX/TMP ratio in raw wastewaters is mandatory for cross-comparison with the experimental data, and results from several drivers. Among them, the first one is the ratio in the medicine, which is, as already mentioned, 5:1 (SMX:TMP). After consumption, a significant proportion of the active principles is excreted through urine. Excretion rates have been evaluated in different studies in both humans and pigs (Table 4). However, the latter were not taken into consideration due to the small number of targeted animals, and the strong variation in the excretion rates obtained (Nouws et al., 1991).

As a result, only human excretion was used for the assessment of a theoretical excreted ratio. From the data published in the literature (Table 1), the median urinary excretion ratio of SMX and TMP in parent form is 20 ± 6 and 50 ± 11% respectively. By combining the extreme values of both, and taking into account the consumed ratio of SMX and TMP (i.e. 5:1, SMX:TMP), the theoretical ratio of SMX/TMP in raw wastewaters after excretion ranges between 1.1 and 3.3, with a value of 2.0 when using median excretion ratios.

3.2. Sorption

After excretion, the excreted fractions of drugs are collected as so-called raw wastewaters, which then enter a wastewater treatment plant or are released into the environment depending on the technological advance of the sewer system. Yet, raw wastewaters also contain solid fractions, mostly organic ones but potentially minerals especially in the case of non-separated sewers. This type of sewer collects stormwaters, which can erode roads and/or soil particles prior to collection. The solid fraction can therefore play a key role in the transport of organic contaminants especially if the organic molecules display particular affinity with inorganic/organic surfaces (i.e. hydrophobic contaminants) (Quesada et al., 2014; Xing et al., 2015). Organic and/or mineral suspended solids often present a significant cation exchange capacity (Barron et al., 2009; Hyland et al., 2012; Thiebault, 2019), therefore presenting a potential high affinity with cationic compounds.

Several studies have investigated the adsorption of both SMX and TMP onto suspended solids (Table 5). The resulting adsorption is generally presented as K_d for the solid/water partition coefficient (in $L.kg^{-1}$), which results from the ratio between adsorbed amount and dissolved concentration.

The solid/water partition coefficient values of SMX and TMP onto sludge are comparable and range from 3 to 427 (Table 5), corresponding to Log K_d values of 0.4 and 2.6. As a result, even if SMX and TMP display different speciations in raw wastewaters (i.e. SMX is mostly deprotonated, whereas TMP is partially neutral/protonated for pH values close to environmental conditions), their affinity for suspended solids appears to be limited, probably due to their weak lipophilicity (Log K_{ow} = 0.48 and 0.73 for SMX and TMP respectively, Table 5). A correction of the theoretical excreted ratio due to sorption onto suspended solids appears to be inappropriate because SMX and TMP can be considered as mostly dissolved molecules (da Silva et al., 2011), even if several batch studies have demonstrated a higher adsorption of TMP than SMX onto several adsorbents (de Oliveira et al., 2018; Nielsen and Bandosz, 2016a, 2016b). However, as these observations were not relevantly reported in environmental conditions, the theoretical ratio was maintained at 2.0 without considering any significant effect of the adsorption onto suspended solids.

3.3. Degradation and transformation products

Whereas adsorption onto suspended solids does not imply an alteration of the molecule structure, other mechanisms such as degradation (both bio- and photo-degradation) can alter these structures and generate transformation products (TPs), that are potentially more harmful than the parent compounds (Cwiertny et al., 2014; Stadler et al., 2012). First of all, even if photodegradation can induce molecular degradation of both SMX and TMP (Bahnmüller et al., 2014; Oliveira et al., 2019; Ryan et al., 2011; Trovó et al., 2009), this mechanism should not significantly impact SMX and TMP in raw wastewaters, as most sewer networks collect wastewater in pipes prior to wastewater treatment. However, the analysis of the degradation pathway of SMX under sunlight exposure exhibited the possibility of abiotic back-transformation from TP (i.e. acetyl-SMX) to SMX (Bonvin et al., 2013). This phenomenon may have a significant impact on the precise quantification of SMX in sunlight-exposed raw wastewaters.

Both TMP and SMX are considered as persistent molecules and moderately sensitive to biodegradation (Alexy et al., 2004; Lin and Gan, 2011), with biodegradability evaluated about 0.006 and 0.16 according to the MITI-test (i.e. a compound is considered biodegradable if biodegradability > 0.5, Tunkel et al. (2000)). Yet, even if several authors have reported significant removal of TMP and SMX during wastewater treatment, the biodegradation is mostly generated by nitrifying bacteria (Mulla et al., 2018; Pérez et al., 2005). Biodegradation may occur during sewer transport but to a much weaker extent than during the wastewater treatment process (i.e. longer hydraulic residence time, stronger occurrences of nitrifying bacteria). Therefore, it is preferable to analyze SMX/TMP ratios in wastewaters as close as possible to source of emission, i.e. raw wastewaters, in order to limit the impact of biodegradation. Also, the biological back-transformation of metabolites to parent products (e.g. acetyl-SMX to SMX) may alter the proper understanding of the SMX/TMP ratio, but requires at least 5 days to be initiated (Nödler et al., 2012; Radke et al., 2009), and other studies did not observe this phenomenon even in longer experiments (Harnisch et al., 2013; Poirier-Larabie et al., 2016). Therefore, the theoretical SMX/TMP/ ratio used remains unaffected by the potential biodegradation during in-sewer transport, as a precise assessment is not possible based on the literature data (Poursat et al., 2019), and appears to be less affected than the occurrence of both SMX and TMP.

4. Results

4.1. Simultaneous occurrence of SMX and TMP in raw wastewaters

Several authors have highlighted the statistical correlation between SMX and TMP in raw wastewaters (e.g. Dan et al., 2013; Thiebault et al., 2019; Tran et al., 2018). This correlation can be clearly observed in Figure 1.

Their concentrations in raw wastewaters range from ng L^{-1} to mg.L^{-1} and the linear regression gives a correlation coefficient of 0.921 and a slope of 0.635 (i.e. SMX/TMP ≈ 1.57). Yet this correlation coefficient is strongly influenced by the most concentrated values of both SMX and TMP, analyzed in a unique study (i.e. K'oreje et al., 2016). Most of the concentrations of both SMX and TMP detected in raw wastewaters range from 0.1 to 10 µg.L^{-1}. In this range, the greatest dispersion is observed around the theoretical ratio (Figure 1).

In order to limit the impact of local features (e.g. strongly contaminated wastewaters) and due to the theoretical association of SMX and TMP in a single medication, most of the results are hereafter assessed through the SMX/TMP ratio rather than by raw concentrations of SMXand TMP. By distinguishing the three main types of raw wastewaters investigated here (i.e. WI, HE and LE) and the calculated SMX/TMP ratio in each compartment, a specific pattern is noticeable (Figure 2).

Whereas no statistically significant variation of the SMX/TMP ratio is visible between HE and WI, the ratio in LE is significantly different from both WI (p=0.026) and HE (p<0.001). Several drivers can lead to this result. First of all, LE is the least well investigated type of raw wastewater in the literature with only 8 values (Table 3). Second, the SMX/TMP ratio in these studies is significantly higher than in HE and WI (Figure 2). These higher values can be related to the specific use of sulfonamides alone in veterinary medicine, which will be investigated further. As a result, the ratios determined in LE will not be considered in the general assessment of the SMX/TMP ratios in raw wastewaters but will be used as an explanatory factor for some atypical values.

Between WI and HE, the lack of statistically significant variation of the SMX/TMP ratios (p=0.28) could indicate that the main source of the two antibiotics in these water compartments is the same, i.e. human consumption of co-trimoxazole. Even if a significant dispersion is visible in both WI and HE, most of the ratios are within the theoretical range of the SMX/TMP ratio, supporting the former hypothesis. The median SMX/TMP values in WI and HE are 1.93 and 1.64 respectively, in accordance with the determined range of the theoretical ratio. Beyond the median values, 128 data out of the total of 282 collected, i.e. 45%, were within the theoretical ratio. This confirms that in most of the studies investigated, the main source of SMX and TMP is human medication under "normal" operations, even if many values are not within the theoretical range.

4.2. Geographical features

Beyond the origin of raw wastewaters, geographical specificities can be of great importance regarding a local (Causanilles et al., 2018; O'Brien et al., 2019), a national (Kolpin et al., 2002; Nefau et al., 2013) or even a continental (Tran et al., 2018) pattern. From a continental point of view, the occurrence of micropollutants has mainly been studied in three continents (i.e. North America, Asia and Europe, Figure 3).

The occurrences of SMX and TMP in the raw wastewaters of Africa, South America and Oceania are less frequently reported in the current literature, with only 6, 6 and 7 SMX/TMP ratios respectively (Table 1-2). From a statistical point of view, only the statistically significant variations of the SMX/TMP ratio between the most frequently studied continents were therefore assessed (e.g. Africa is too strongly impacted by an isolated value, generating a statistically significant variation with the other continents). The SMX/TMP ratios are significantly higher in Asia than in Europe (i.e. $p<0.001$) and in North America ($p=0.014$), whereas no statistically significant variations were observed between Europe and North America ($p=0.35$).

Beyond these significant variations, it is however worth noting that the median SMX/TMP ratios are within the theoretical ratio whatever the continent studied (Figure 3). Hence, to better understand the dispersion of the SMX/TMP ratios within one continent, a refinement at a national scale was performed. As already mentioned at the continental scale, few countries recorded a sufficient number of data for statistical analysis to be performed. For example China (which is divided into China, Hong-Kong and Taiwan in this work) accounts for most data (52 out of 96) of the Asian continent and the United States for 44 out of 47 values for the North American continent. Hence, it is hard to obtain a correct assessment of the statistical variation in these two continents. In Europe, however, several countries display a significant number of data, and three of them have significantly different SMX/TMP ratios. The United-Kingdom (UK) and Sweden present significantly lower ratios (the ratios for Norway are not significantly different but systematically below the theoretical ratio) than the rest of Europe, whereas Greece displays significantly higher SMX/TMP values (Figure 4). The median values of other European countries (e.g. Germany, Portugal) are within the theoretical range.

Outside Europe, the only statistically significant variation is for China, which displays significantly higher SMX/TMP ratios than the rest of Asia (Figure 4).

4.3. Consumption data

Prior to discussing the results, consumption (both veterinary and human) data were gathered in order to better understand local features (Table 6). Several consumption data are reported in the scientific literature or through the release of annual reports at various scales. However, most of them provide the annual consumption of SMX and TMP in ddd (i.e. daily defined dose, even if the posology of SMX/TMP exists in various doses) or grouped under the general term "sulfonamides/trimethoprim derivatives" or J01E (Goossens et al., 2007; Grave et al., 2012; Wierup et al., 1987), for which the distinction between SMX and other sulfonamides or even TMP was not possible. Several articles also back-calculated the consumption of SMX and TMP through sewage epidemiology (Thiebault et al., 2017b; Zhang et al., 2019). Yet, the assessment of the consumption through sewage epidemiology derived from wastewater concentrations, which are the same data that are used for the calculation of SMX/TMP ratios. As a result, compare consumption and SMX/TMP ratios derived from the same data would be purposeless, that's why the consumption derived from sewage epidemiology will not be discussed hereafter. Accordingly, only reported data providing SMX and TMP use separately and specifically were used for the cross comparison (Table 6).

Whatever the country, most of the annual Human consumption data reported SMX/TMP consumed ratios between 3 and 5 (Table 6). This consumed ratio results in an excreted ratio between 1.2 and 2, within the theoretical range calculated in Table 4, thus confirming that in those countries, SMX and TMP are mostly consumed in association. However, several consumed ratios are outside this range.

This is systematically the case for veterinary consumption reports, in which the consumed SMX/TMP ratio is below 2, indicating that a significant amount of TMP is consumed alone (or in association with another sulfonamide such as sulfamethazine). Likewise, the reported consumed SMX/TMP ratios in human medication in Norway, Sweden, and the UK are very low (< 0.5), indicating a discrepancy between these countries and the rest of the world. Lastly, China displays an atypical pattern with an insignificant use of SMX in comparison to the use of TMP (Zhang et al., 2015). However, another study back-calculated a consumed SMX/TMP ratio of 2.93 in the Beijing region (Zhang et al., 2019), casting doubt on the former evaluation.

Conversely, the veterinary use data display low SMX/TMP ratios, ranging from 0 to 1.95 (Table 6). This may indicate that for veterinary purposes, another TMP/sulfonamide (such as TMP/sulfamethazine for example) association may be preferred (Jia et al., 2017; Kim et al., 2011).

5. Discussion

5.1. Comparison between LE and consumption data

As discussed above, LE present significantly higher SMX/TMP ratios than HE and WI (or even non-detectable TMP concentrations as in Ekpeghere et al. (2017) and Sim et al. (2013)). However, the annual use reports from various countries provide lower SMX/TMP ratios than expected (Table 6). Hence, there is a discrepancy between the observed occurrences of both TMP and SMX in LE and their uses according to annual reports. Several explanations can be put forward for this discrepancy.

The first major difference between human and veterinary assessment of SMX/TMP ratios can be the excretion ratios, which can differ between humans and livestock. For example, the only study reporting the excretion ratio of TMP and SMX in pigs found a TMP excretion ratio that was half that of the human values (Nouws et al., 1991). However, this explanation is not sufficient by itself to explain the variation between the theoretical use ratio (i.e. < 1) and the experimental ratios in LE (i.e. mean SMX/TMP value = 27.3).

It is therefore highly likely that SMX is used alone, especially in the countries in question (i.e. Asian countries, Table 3). It is worth noting that in general, the contamination by livestock itself (i.e. shrimp) is mostly generated by SMX and can lead to import refusals (Southern Shrimp Alliance, 2017).

The use of SMX alone has been discussed, for example in Vietnam (Le and Munekage, 2004; Thuy et al., 2011), in which not only SMX/TMP may be used. The illegal importation of antibiotics from neighboring countries was also documented (Chi et al., 2017), and can lead to significant errors in annual reported consumption, as well as the fact that antibiotics are readily available, without doctor prescription (Le et al., 2018; Tran et al., 2019a). Few studies have been conducted out of Asia on LE antibiotic contamination. Yet, although in those countries the reported SMX/TMP ratio is very low (Table 3), only SMX is significantly detected in LE as in the USA (Watanabe et al., 2010) or Germany (Bailey et al., 2015).

As a result, there is no clear explanation for the very significant SMX contamination of LE in comparison to TMP contamination, except the illegal and unrecorded use of SMX alone. As the latter antibiotic is mostly used for human purposes, it is highly possible that a portion of SMX is diverted from its original use for veterinary purposes. Also lacking in the current literature is a precise assessment of LE contamination in Europe and North America, which have, on the contrary, been extensively studied regarding WI and HE contamination levels. From the reported environmental occurrences of both TMP and SMX, it is possible that the mixing between LE and WI increases the SMX/TMP ratio of the latter.

5.2. Atypical SMX/TMP patterns in WI and HE

Several countries display statistically significantly different SMX/TMP ratios in comparison to their neighbors (Figure 4). Hence, before discussing the availability of the SMX/TMP ratio as a marker in raw wastewaters, it is necessary to contextualize these local features according to several drivers such as the national health system or the prophylactic recommendations.

5.2.1. SMX/TMP ratios in WI and HE below the theoretical value

Overall, 80 SMX/TMP ratios, i.e. 28% of the collected samples, were below the theoretical range (Figure 5). Some countries display significantly lower values than the theoretical ones, i.e. the UK and Sweden, and the values reported in Norway are systematically below the theoretical ones (Figure 4). It is worth noting that the reported ratios for the consumption of

SMX and TMP for those countries are in agreement with the ratios analyzed in WI and HE, as the consumed SMX/TMP ratios are 0.19, 0.16 and 0.32 in the UK, Sweden and Norway respectively (Table 6). These values can be explained by the fact that in these countries, TMP is not only consumed in association with SMX, but also alone (Ashton et al., 2004; Dolk et al., 2018; NORM/NORM-VET, 2017; Östholm-Balkhed et al., 2010). For example, in the UK, the use of TMP alone represents more than three times the use of SMX/TMP in combination (ECDC, 2018), even if the rapid growth of TMP resistant-bacteria (UK-VARSS, 2018) has modified the prophylaxis of uncomplicated urinary tract infection, nitrofurantoin being now preferred to TMP (Public Health England, 2018a, 2018b). Exactly the same pattern is currently in progress in Norway and Sweden as the use of TMP alone constantly decreasing while nitrofurantoin use is increasing. For example, the consumption of TMP alone decreased from 0.52 to 0.28 ddd.1000inh^{-1}.day^{-1} between 2001 and 2009 in Sweden, whereas the consumption of nitrofurantoin increased from 0.12 to 0.32 ddd.1000inh^{-1}.day^{-1} at the same time (Östholm-Balkhed et al., 2010). The same pattern is occurring in the Netherlands (NethMap, 2017), although in Norway, the consumption of TMP alone is constantly decreasing (i.e. from 0.74 to 0.38 ddd.1000inh^{-1}.day^{-1} between 2003 and 2016 according to NORM/NORM-VET (2017, 2012)) without any significant increase in nitrofurantoin consumption. These results highlight two drivers that are hard to address worldwide: first, the temporal change in antibiotic consumption behaviors, as it is not fixed in time, and second, the key role played by the health authorities in their recommendations for the use of a specific product. For example, SMX/TMP ratios in the USA are very variable and 18 ratios were below the theoretical range. Yet, the consumption of TMP alone was popular until 2012 since when the use of TMP alone has become marginal (ClinCalc Database, 2019). Before 2012, 52% (16 out of 31) of the collected ratios were below the theoretical value whereas this percentage fell to 15% after 2013 (2 out of

13). As a result, even if some precautions have to be taken at the scale of the USA, the switch in the consumption of TMP alone was recorded in the wastewaters.

Lastly, it appears that SMX/TMP ratios resulted from the consumption of both TMP alone and co-trimoxazole. as, Yet, it is possible to estimate the fraction of TMP consumed alone (Figure 6) based on the consumption data (Coenen et al., 2011) and the ddd of TMP and co-trimoxazole (WHOCC - ATC/DDD Index, 2019). A very good correlation was found (i.e., 0.86 Figure 6) using only those countries for which consumption data were available, highlighting the statistical link between the experimental ratio and the relative consumption of TMP alone.

5.2.2. SMX/TMP ratios in WI and HE over theoretical value

Overall, 74 SMX/TMP ratios, i.e. 26% of the collected samples, were over the theoretical range (Figure 4). Among these ratios, China and Greece are the two countries that exhibit significantly higher SMX/TMP ratios than both the theoretical value and the ratios in the neighboring countries. However, the drivers leading to these results are different. Greece is the largest consumer of antibiotics worldwide (Ferech et al., 2006; Machowska and Stålsby Lundborg, 2019), whereas the antibiotic consumption in China is "moderate" (in comparison with European countries), albeit rapidly growing (Van Boeckel et al., 2014).

The antibiotic consumption in Greece was also largely impacted by the economic crisis in the 2010s (Thomaidis et al., 2016), leading to a general decrease in antibiotic consumption. The crisis also generated an increase in illegal imports and self-medication (Kourlaba et al., 2016; Plachouras et al., 2010; Skliros et al., 2010). As a result of these misuses, antibiotic-resistant bacteria now represent a serious health problem as the occurrence of carbapanem-resistant bacteria is rapidly growing (Galani et al., 2018; Plachouras et al., 2010). According to Tsakris et al. (1991), SMX/TMP is the only product containing TMP that is consumed in Greece. Even if this study is quite old, this result is further confirmed by the ECDC antimicrobial consumption monitoring program, in which no consumption of TMP alone has been revealed in Greece since the beginning of this program in 1997 (ECDC Database, 2019). It is therefore highly possible that illegal imports and self-medication of unrecorded products are the best explanation of this atypical ratio, higher than the theoretical one.

China represents a particular case of antibiotic consumption as although some overuse for human medication is recorded (Hvistendahl, 2012), more than half of the yearly consumption of antibiotic is used for livestock production (Xie et al., 2018). Pigs are particularly concerned by antibiotic use, as half of the worldwide pig production and consumption is located in China (Larson, 2015). The massive use of antibiotics to prevent disease and promote growth currently generates critical issues of antimicrobial resistance in China (He et al., 2016; Hou et al., 2015). The transfer of antibiotic and antimicrobial resistance from food to people has for example already been demonstrated (Wang et al., 2019).

Focusing on the SMX/TMP ratio, its median value is higher than the theoretical value (Figure 4) even if the consumption data reported higher TMP consumption (Table 6). Hence, as is the case in Greece, there is a discrepancy between experimental data and consumption data. However, in the case of China, as the amount of livestock is very high, and the use of SMX alone in their treatment may be very extensive, the mixing between WI and LE may increase the SMX/TMP ratio determined in WI. Yet, several studies also reported very high SMX/TMP ratios in HE (Chang et al., 2010; Li et al., 2015), indicating that the use of SMX alone may also be significant in human medication only. As the consumption of antibiotics in China is not precisely monitored, further assumptions are necessarily speculative. Nevertheless, the huge use of antibiotics in livestock production could be one of the main drivers leading to the higher than theoretical SMX/TMP ratios, as in this study, 31% of the SMX/TMP ratios above the theoretical range were found to be located in China.

5.3. Potential of SMX/TMP ratio to be used as a marker

According to the general definition, a marker should meet two principal criteria, i.e. source specificity and a conservative behavior (Eganhouse, 1997). Beyond these two criteria, the definition has been enriched by a third one, quantification of the magnitude of the pollution (Kahle et al., 2009; Takada et al., 1997). Both the quantification of the occurrences of TMP and SMX and the use of the SMX/TMP ratio meet these criteria. TMP and SMX are found to be persistent within environmental compartments, i.e. from raw wastewaters to natural environments, and the use of the SMX/TMP ratio makes it possible to specify the main source of wastewaters. The collected data indeed highlighted that the median SMX/TMP ratio in each country in both HE and WI is close to the theoretical one except in several countries such as the UK, Sweden, Greece and China. In these countries, local features have been evidenced, such as particular medical use of TMP alone or contamination of WI by LE. Beyond these local features, the ratios in WI and HE are in most cases in agreement with the theoretical value, meaning that the SMX/TMP ratio can be used as a marker of the main origin of wastewaters. It should be pointed out that one of the main particularities of this ratio is that the proportion of SMX and TMP used in human medication is similar worldwide (if we except several European countries, in which the SMX/TMP ratios are found to be proportional with the use of TMP alone), allowing its use at a global scale. Hence, unlike other chemical markers that require in -depth knowledge of the catchment studied (McCance et al., 2018; Warner et al., 2019), the SMX/TMP ratio is suitable for the evaluation of the main origin of wastewaters by comparison to the theoretical value calculated here.

Based on the collected data, the following assumptions can be made. In the raw wastewaters sampled, (i) the main origin of SMX and TMP is human consumption/excretion of co-trimoxazole when the SMX/TMP ratio is between 1.1 and 3.3; (ii) for SMX/TMP values over this range, a mixing with livestock wastewaters is very likely, and the level of the ratio can indicate the extent of this mixing; (iii) for SMX/TMP ratios below the theoretical range, the consumption/excretion of TMP alone is present within the catchment, and can be estimated in comparison with countries with an atypical TMP consumption such as the UK and Finland (Coenen et al., 2011).

Finally, significant gaps in the literature have been found, especially concerning the occurrences of TMP and SMX in LE out of Asia. The discrepancy between the calculated ratios and the reported annual consumption represents a major challenge for the scientific community in that, beyond the two targeted antibiotics, the contamination generated by LE needs to be better characterized. Moreover, assessing the SMX/TMP ratio after wastewater treatment would is a matter of great concern, in order to estimate the suitability of this marker within environmental compartments.

6. Conclusion

This study evaluated the potential of the SMX/TMP ratio in raw wastewaters to act as a marker of their origin. From the results, it was highlighted that hospital effluents and wastewater treatment plant influents presented similar SMX/TMP footprints, whereas livestock effluents displayed higher SMX/TMP ratios, due to the use of SMX alone. This use of SMX or TMP alone was reflected in raw wastewaters of several countries, which presented atypical SMX/TMP values, outside the theoretical range, generated by the continuing of the use of TMP alone in the human pharmacopoeia (i.e. UK, Sweden) or by the overuse of illegal imports of SMX.

Therefore, the SMX/TMP ratio, due to its worldwide distribution, displays a significant potential to be used as a marker of the main origin of wastewaters especially the mixing with other sources, such as livestock effluents, and to characterize the extent of the consumption of TMP alone. Finally, in raw wastewaters, a SMX/TMP ratio between 1.1 and 3.3 signifies that human consumption/excretion of co-trimoxazole is the main origin of the wastewater contamination.

Acknowledgements

E. Rowley-Jolivet is warmly thanked for the improvement of the language of the manuscript. Two anonymous reviewers are gratefully acknowledged for their insightful comments.

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Table 1: Main characteristics of the reviewed WI, with Cont. the continent (N.Am. for North-America, S.Am. for South-America, Eur. for Europe and Oce. for Oceania), Town, the WWTP city or the state/region if the city was not available (*), n_{ins} the number of WWTPs investigated in each study, n_{samp}, the number of samples analyzed in each study, C_{SMX}, the mean concentration of SMX (for n_{samp}=1, C corresponds to the unique given data, and † for median concentration), C_{TMP}, the mean concentration of TMP (for n_{samp}=1, C corresponds to the unique given data, and † for median concentration), Ratio, the ratio between the concentration of SMX and TMP, Flow, the daily flow of WI, EH, the population-equivalent amount in the catchment of each WWTP, Samp., the sampling mode with F. for flow-enslaved composite, T. for time composites and G. for grab samples, Year, the year of sampling of WI and WW Origin, the given origins of wastewater, with Mun. for municipal, Dom. for domestic, Ind. for industrial and Hosp. for hospital. n.a. corresponds to non-available data.

Reference	Cont.	Country	Town/State	n_{ins}	n_{samp}	C_{SMX} µg.L^{-1}	C_{TMP} µg.L^{-1}	Ratio SMX/TMP	Flow 10^3 m^3.d^{-1}	EH 10^3 PE	Samp.	Year	WW Origin
(Göbel et al., 2004)	Eur.	Switzerland	Kloten	1	2	0.343	0.168	2.04	16	54	F.	03	Dom.+Airport
(Göbel et al., 2004)	Eur.	Switzerland	Altenrhein	1	2	0.641	0.110	5.83	21	40	F.	03	Dom.
(Bendz et al., 2005)	Eur.	Sweden	Källby	1	1	0.02	0.08	0.25	31	79	F.	02	n.a.
(Göbel et al., 2005)	Eur.	Switzerland	Kloten	1	3	0.126	0.085	1.48	16	55	F.	02/03	Dom.
(Göbel et al., 2005)	Eur.	Switzerland	Altenrhein	1	2	0.113	0.061	1.84	21	80	F.	02/03	Dom.+Airport
(Lindberg et al., 2005)	Eur.	Sweden	Stockholm	1	2	0.394	0.252	1.56	200	644	F.	02/03	Dom.+Ind.
(Lindberg et al., 2005)	Eur.	Sweden	Umeå	1	2	0.116	0.375	0.31	26	82	F.	02/03	Dom.+Ind.
(Lindberg et al., 2005)	Eur.	Sweden	Kalmar	1	2	0.169	0.924	0.18	15	50	F.	02/03	Dom.+Ind.
(Lindberg et al., 2005)	Eur.	Sweden	Floda	1	2	0.151	0.598	0.25	2.4	10	F.	02/03	Dom.
(Brown et al., 2006)	N.Am.	USA	Albuquerque	1	1	0.39	0.59	0.66	200	n.a.	T.	03	Mun.
(Brown et al., 2006)	N.Am.	USA	Hagerman	1	1	1	1.4	0.71	n.a.	n.a.	G.	03	Mun.
(Brown et al., 2006)	N.Am.	USA	Portales	1	1	0.4	1	0.40	n.a.	n.a.	G.	03	Mun.
(Gros et al., 2006)	Eur.	Croatia	n.a.	5	5	0.59	1.17	0.50	n.a.	n.a.	G.	n.a.	Mun.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	1.25	1.1	1.14	36	73	T.	01	Mun.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	0.17	0.58	0.29	110	150	T.	01	Mun.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	0.56	1.30	0.43	6.0	Sev 1.0	T.	01	Mun.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	0.13	0.05	2.6	4.0	4.7	G.	02	Mun.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	0.35	0.7	0.5	4.0	3.3	G.	02	Mun.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	0.45	0.12	3.75	2.0	2.6	G.	02	Mun.
(Vanderford and Snyder, 2006)	N.Am.	USA	Las Vegas	1	6	2.06	1.14	1.81	340	650	n.a.	n.a.	Mun.
(Batt et al., 2007)	N.Am.	USA	Amherst	1	2	2.8	7.9	0.35	114	n.a.	G.	n.a.	n.a.
(Batt et al., 2007)	N.Am.	USA	East Aurora	1	2	0.88	7	0.13	12	n.a.	G.	n.a.	n.a.
(Batt et al., 2007)	N.Am.	USA	Holland	1	2	0.75	2.3	0.33	0.3	n.a.	G.	n.a.	n.a.
(Batt et al., 2007)	N.Am.	USA	Lackawana	1	2	0.72	2.1	0.34	170	n.a.	G.	n.a.	n.a.
(Kim et al., 2007)	Asia	South Korea	n.a.	1	n.a.	0.194	0.021	9.24	0.001	n.a.	n.a.	04/05	Univ.
(McClure and Wong, 2007)	N.Am.	Canada	Edmonton	1	1	0.65	0.27	2.41	n.a.	700	T.	07	n.a.
(Martínez Bueno et al., 2007)	Eur.	Spain	n.a.	5	19	0.275	0.331	0.83	n.a.	n.a.	T.	07	Dom.+Ind.
(Ternes et al., 2007)	Eur.	Germany	Braunschweig	1	4	0.82	1.1	0.75	60	385	F.	03	Mun.
(Thomas et al., 2007)	Eur.	Norway	Slemmestad	1	7	0.125	0.835	0.15	317	440	T.	06	n.a.
(Watkinson et al., 2007)	Oce.	Australia	Brisbane	2	6	0.36†	0.34†	1.06	140	700	G.	06	Dom.+Hosp.
(Chang et al., 2008)	Asia	Japan	Saitama	1	1	0.007	0.042	0.16	n.a.	n.a.	G.	07	Dom.
(Chang et al., 2008)	Asia	Japan	Saitama	1	1	0.027	0.014	1.93	n.a.	n.a.	G.	07	Dom.
(Choi et al., 2008)	Asia	South Korea	TanCheon	1	3	0.560	0.151	3.69	1100	n.a.	G.	05	Dom.
(Choi et al., 2008)	Asia	South Korea	JungRan	1	3	0.524	0.220	2.38	1710	n.a.	G.	05	Dom.
(Choi et al., 2008)	Asia	South Korea	NanJi	1	3	0.409	0.040	10.13	1000	n.a.	G.	05	Dom.
(Choi et al., 2008)	Asia	South Korea	SeoNam	1	3	0.597	0.21	2.84	2000	n.a.	G.	05	Dom.
(Senta et al., 2008)	Eur.	Croatia	Velicka Gorica	1	1	4.664	2.038	2.29	n.a.	n.a.	G.	07	Mun.

(Senta et al., 2008)	Eur.	Croatia	Cakovec	1	1	0.194	0.067	2.90	n.a.	n.a.	T.	06	Mun.
(Terzić et al., 2008)	Eur.	Balkans*	n.a.	17	24	1.18	0.781	1.51	n.a.	n.a.	G.	04/05	Mun.
(Gros et al., 2009)	Eur.	Spain	Catalonia*	3	n.a.	0.354	0.05	7.08	n.a.	n.a.	G.	n.a.	n.a.
(Kasprzyk-Hordern et al., 2009)	Eur.	UK	Colsech	1	n.a.	0.115	2.925	0.04	20	30	F.	07	Dom.+Ind.
(Kasprzyk-Hordern et al., 2009)	Eur.	UK	Cilfynydd	1	n.a.	0.029	2.192	0.01	30	110	G.	07	Mun.
(Li et al., 2009)	Asia	China (HK)	Shatin	1	2	0.147	0.129	1.14	232	600	G.	08	Mun.
(Li et al., 2009)	Asia	China (HK)	Stanley	1	2	0.356	0.161	2.21	8.0	27	G.	08	Mun.
(Radjenović et al., 2009)	Eur.	Spain	Terrassa	1	9	0.093	0.204	0.46	42	277	F.	07	Mun.
(Watkinson et al., 2009)	Oce.	Australia	Queensland*	5	19	0.25†	0.43†	0.58	n.a.	n.a.	T.	05/06	Dom.+Ind.
(Chang et al., 2010)	Asia	China	Chongqing	1	1	2.02	0.18	11.22	n.a.	n.a.	G.	04	n.a.
(Plósz et al., 2010)	Eur.	Norway	Oslo*	1	9	0.248	0.312	0.80	75	281	F.	07	Dom.+Ind.
(Rosal et al., 2010)	Eur.	Spain	Alcalá de Hen.	1	12	0.279	0.104	2.68	72	n.a.	T.	n.a.	Dom.+Ind.
(Behera et al., 2011)	Asia	South Korea	Ulsan	5	5	0.12	0.205	0.59	451	1100	T.	10	Dom.+Ind.
(Gerrity et al., 2011)	N.Am.	USA	n.a.	1	48	0.988	0.662	1.49	380	1000	T.	09/10	Mun.
(Hijosa-Valsero et al., 2011)	Eur.	Spain	Leon	1	5	0.26	0.1	2.6	123	330	T.	09	Mun.
(Li and Zhang, 2011)	Asia	China (HK)	Shatin	1	4	0.082	0.122	0.67	232	600	F.	09/10	Mun.
(Li and Zhang, 2011)	Asia	China (HK)	Stanley	1	4	0.220	0.155	1.42	7.9	27	F.	09/10	Mun.
(Matsuo et al., 2011)	Asia	Japan	Kumamoto	1	4	0.513	0.27	1.90	53	n.a.	F.	09/10	Mun.
(Murata et al., 2011)	Asia	Japan	Tokyo	5	9	0.119	0.047	2.56	n.a.	n.a.	T.	07/09	n.a.
(Sim et al., 2011)	Asia	South Korea	n.a.	12	30	0.254	0.230	1.10	n.a.	n.a.	G.	08	Mun.
(Sim et al., 2011)	Asia	South Korea	n.a.	4	8	166	62.9	2.64	n.a.	n.a.	G.	08	Ph.
(Wahlberg et al., 2011)	Eur.	Sweden	Stockholm*	3	30	0.25	0.19	1.32	500	1500	F.	n.a.	n.a.
(Yang et al., 2011)	N.Am.	USA	Gwinnette Coun.	1	12	2.6	0.61	4.26	227	n.a.	F.	08	Mun.
(Dinh, 2012)	Eur.	France	Limours	1	6	0.538	0.143	3.76	2.9	20	G.	10/11	Mun.
(Gracia-Lor et al., 2012)	Eur.	Spain	Castellon de la Pl.	1	14	0.45†	0.1†	4.50	36	265	T.	09	Mun.
(Gros et al., 2012)	Eur.	Spain	Girona	1	1	0.768	0.204	3.76	n.a.	206	T.	n.a.	Dom.+Hosp.
(Le-Minh et al., 2012)	Oce.	Australia	Sydney*	1	6	1.238	0.721	1.72	n.a.	3.8	G.	n.a.	Mun.
(Leung et al., 2012)	Asia	China (HK)	Stonecutters Isl.	1	2	0.11	0.095	1.16	1400	3500	T.	08	n.a.
(Leung et al., 2012)	Asia	China (HK)	Shatin	1	2	0.14	0.114	1.23	250	600	T.	08	Mun.
(Leung et al., 2012)	Asia	China (HK)	Tai Po	1	1	0.039	0.124	0.31	96	300	T.	08	n.a.
(Leung et al., 2012)	Asia	China (HK)	Central	1	1	0.128	0.307	0.42	108	305	G.	08	n.a.
(Leung et al., 2012)	Asia	China (HK)	Wan Chai East	1	1	0.145	0.228	0.64	110	237	G.	08	n.a.
(Leung et al., 2012)	Asia	China (HK)	Wan Chai West	1	1	0.293	0.555	0.53	27	70	G.	08	n.a.
(Leung et al., 2012)	Asia	China (HK)	North Point	1	1	0.183	0.428	0.43	90	370	G.	08	n.a.
(Teerlink et al., 2012)	N.Am.	USA	Boulder	1	24	1.54	0.809	1.90	50	125	T.	n.a.	Dom.+Ind.
(Teerlink et al., 2012)	N.Am.	USA	CO Sch. of Mines	1	24	11.2	5.69	1.97	0.015	0.4	T.	n.a.	Univ.
(Teerlink et al., 2012)	N.Am.	USA	Septic tank	1	24	0.11	0.012	9.17	0.00005	0.03	T.	n.a.	Univ.
(Blair et al., 2013)	N.Am.	USA	Oak Creek	1	6	0.311	0.160	1.94	379	n.a.	F.	09/10	Mun.
(Dan et al., 2013)	Asia	China	Guangzhou	1	12	0.141	0.084	1.68	n.a.	n.a.	T.	11/12	Univ.
(Gros et al., 2013)	Eur.	Spain	Girona	1	1	0.528	0.178	2.97	n.a.	206	T.	11	Dom.+Hosp.
(Gros et al., 2013)	Eur.	Spain	Castellon de la Pl.	1	1	0.18	0.067	2.69	36	265	T.	11	Mun.
(Khan et al., 2013)	Asia	Pakistan	Lahore	1	3	0.16	0.073	2.19	n.a.	n.a.	G.	12	Ph.
(Khan et al., 2013)	Asia	Pakistan	Lahore	1	3	4.7	1	4.7	n.a.	n.a.	G.	12	Ph.
(Khan et al., 2013)	Asia	Pakistan	Lahore	1	3	49	28	1.75	n.a.	n.a.	G.	12	Ph.
(Margot et al., 2013)	Eur.	Switzerland	Lausanne	1	37	0.34	0.235	1.45	95	220	T.	09/10	Dom.+Hosp.
(Santos et al., 2013)	Eur.	Portugal	Coimbra	1	7	0.912	0.124	7.35	31	213	T.	11	Dom.+Hosp.
(Senta et al., 2013)	Eur.	Croatia	Belisce	1	1	0.613	0.035	17.51	n.a.	35	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Bjelovar	1	1	0.826	0.365	2.26	n.a.	74	F.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Cakovec	1	1	0.293	0.481	0.61	n.a.	68	F.	05	Mun.

(Senta et al., 2013)	Eur.	Croatia	Karlovac	1	1	0.735	0.758	0.97	n.a.	117	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Novi Zagreb	1	1	11.56	2.555	4.53	n.a.	100	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Osijek	1	1	1.184	1.817	0.65	n.a.	285	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Rijeka	1	1	1.094	1.045	1.05	n.a.	275	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Sisak	1	1	0.858	0.347	2.47	n.a.	52	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	SlavonskiBrod	1	1	0.387	0.588	0.66	n.a.	93	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Split	1	1	0.675	0.776	0.87	n.a.	251	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Split-sewer	1	1	0.829	1.068	0.78	n.a.	251	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Varazdin	1	1	0.64	3.442	0.19	n.a.	143	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Velicka Gorica	1	1	1.944	2.706	0.72	n.a.	48	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Vinkovci	1	1	0.943	0.659	1.43	n.a.	55	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Zadar	1	1	2.033	2.318	0.88	n.a.	82	T.	05	Mun.
(Senta et al., 2013)	Eur.	Croatia	Zagreb	1	1	0.72	0.84	0.86	257	1000	T.	05	Dom.+Ind.
(Senta et al., 2013)	Eur.	Croatia	Zagreb	1	36	0.484	0.148	3.27	257	1000	T.	09	Dom.+Ind.
(Sim et al., 2013)	Asia	South Korea	Ulsan/Busan	2	3	0.28	0.089	3.15	3.8	n.a.	T.	10	Dom.
(Sim et al., 2013)	Asia	South Korea	Ulsan/Busan	8	13	0.108	0.261	0.41	1273	n.a.	T.	10	Mun.
(Tewari et al., 2013)	Asia	Thailand	Bangkok	5	15	0.017	0.06	0.28	348	2033	T.	11/12	n.a.
(Verlicchi et al., 2013)	Eur.	Italy	Po Valley*	1	4	0.446	0,058	7.69	28	120	T.	10	Dom.
(Zhou et al., 2013)	Asia	China	Guangdong*	1	4	0.474	0.154	3.09	74	425	T.	10	Mun.
(Zhou et al., 2013)	Asia	China	Guangdong*	1	4	0.228	0.090	2.54	96	380	T.	10	Mun.
(Birošová et al., 2014)	Eur.	Slovakia	Bratislava	1	6	0.103	0.1	1.03	33	125	T.	13	Mun.
(Birošová et al., 2014)	Eur.	Slovakia	Bratislava	1	6	0.186	0.171	1.09	150	350	T.	13	Mun.
(Camacho-Muñoz et al., 2014)	Eur.	Spain	Seville	1	48	0.32	0.12	2.67	n.a.	11	T.	11/12	Mun.
(Collado et al., 2014)	Eur.	Spain	Celra	1	3	0.07	0.054	1.30	2.1	20	F.	11/12	Ind.
(Du et al., 2014)	N.Am.	USA	Waco, TX	1	16	2.625	0.418	6.29	95	n.a.	F.	11/12	Mun.
(Golovko et al., 2014)	Eur.	Czech Republic	Ceske Budejov.	1	136	0.22†	0.32†	0.69	60	112	T.	11/12	Mun.
(Guerra et al., 2014)	N.Am.	Canada	n.a.	6	36	0.57†	0.24†	2.38	448	n.a.	T.	10-12	Dom.+Ind.
(Jank et al., 2014)	S.Am.	Brazil	Porto Alegre	1	8	0.473	0.989	0.48	21	170	G.	11	n.a.
(Kosma et al., 2014)	Eur.	Greece	Ioannina	1	4	0.904	0.132	6.84	25	100	T.	10/11	Dom.+Ind.
(Kosma et al., 2014)	Eur.	Greece	Arta	1	4	0.112	0.023	4.86	11	38	T.	10/11	Mun.
(Kosma et al., 2014)	Eur.	Greece	Preveza	1	4	0.120	0.016	7.38	7.0	25	T.	10/11	Mun.
(Kosma et al., 2014)	Eur.	Greece	Agrinio	1	4	0.016	0.017	0.98	14	90	T.	10/11	Mun.
(Kosma et al., 2014)	Eur.	Greece	Grevena	1	4	0.133	0.008	16.81	4.0	20	T.	10/11	Mun.
(Kosma et al., 2014)	Eur.	Greece	Kozani	1	4	0.227	0.034	6.74	10	70	T.	10/11	Mun.
(Kosma et al., 2014)	Eur.	Greece	Veroia	1	4	0.141	0.023	6.15	9.8	45	T.	10/11	Mun.
(Lindberg et al., 2014)	Eur.	Sweden	Holmsund	1	7	0.381	0.402	0.95	1.5	3.3	T.	13	Mun.
(Lindberg et al., 2014)	Eur.	Sweden	Obbola	1	7	0.309	0.401	0.77	0.8	1.4	G.	13	Mun.
(Lindberg et al., 2014)	Eur.	Sweden	Umeå	1	7	0.221	0.191	1.16	3.5	9.9	T.	13	n.a.
(Lindberg et al., 2014)	Eur.	Sweden	Umeå	1	7	0.711	0.305	2.33	16	62	T.	13	Dom.+Hosp.
(Lindberg et al., 2014)	Eur.	Sweden	Umeå	1	7	0.239	0.178	1.34	4.2	17	T.	13	n.a.
(Lindberg et al., 2014)	Eur.	Sweden	Umeå	1	7	0.073	0.027	2.70	5.9	9.5	T.	13	n.a.
(Lindberg et al., 2014)	Eur.	Sweden	Umeå	1	7	0.368	0.187	1.97	32	141	F.	13	n.a.
(Petrović et al., 2014)	Eur.	Serbia	Novi Sad	1	1	0.432	0.259	1.67	n.a.	n.a.	T.	12	Mun.
(Rossmann et al., 2014)	Eur.	Germany	Dresden	1	200	0.515†	0.186†	2.77	150	650	G.	n.a.	Dom.+Hosp.
(Singer et al., 2014)	Eur.	UK	Benson	1	24	0.057	0.332	0.17	1.4	6.2	T.	11	n.a.
(Singer et al., 2014)	Eur.	UK	Oxford	1	24	0.169	0.07	2.41	33	208	T.	11	n.a.
(Yan et al., 2014)	Asia	China	Tangiatuo	1	4	0.806	0.227	3.55	300	805	T.	12/13	Mun.
(Yan et al., 2014)	Asia	China	Jingkou	1	4	0.055	0.015	3.70	20	130	T.	12/13	Mun.
(Yan et al., 2014)	Asia	China	Lijiatuo	1	4	0.204	0.045	4.54	40	110	T.	12/13	Mun.

(Yan et al., 2014)	Asia	China	Jiguanshi	1	4	2.935	0.077	37.94	600	1540	T.	12/13	Mun.
(Blair et al., 2015)	N.Am.	USA	Oak Creek	1	3	7.4	0.57	12.98	258	n.a.	T.	13	Mun.
(Dasenaki and Thomaidis, 2015)	Eur.	Greece	Athens	1	8	0.218	0.194	1.12	n.a.	3700	F.	11	Mun.
(Gurke et al., 2015b)	Eur.	Germany	Dresden	1	3	0.264	0.179	1.47	150	650	F.	14	Dom.+Hosp.
(Gurke et al., 2015a)	Eur.	Germany	Dresden	1	10	0.348	0.236	1.47	150	650	F.	15	Dom.+Hosp.
(Kuroda et al., 2015)	Asia	Vietnam	Yen So	1	2	2.35	0.235	10	120	n.a.	G.	13	Mun.
(Li et al., 2015)	Asia	China	Linan	1	3	0.645	0.439	1.47	60	300	T.	13	Mun.
(Li et al., 2015)	Asia	China	Linan	1	3	0.830	0.096	8.66	n.a.	3	T.	13	Dom.+Univ.
(Mackuľak et al., 2015)	Eur.	Slovakia	Bratislava	1	1	0.272	0.147	1.85	33	125	G.	13	n.a.
(Mailler et al., 2015)	Eur.	France	Colombes	1	14	0.613	0.054	11.46	240	900	F.	13	Dom.
(Marx et al., 2015)	Eur.	Germany	Dresden	1	n.a.	0.517	0.224	2.31	150	650	F.	12/13	Dom.+Hosp.
(Matongo et al., 2015)	Afr.	South-Africa	KwaZulu-Natal*	1	3	59.28	0.13	456	n.a.	n.a.	G.	13	Dom.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	0.98	0.43	2.28	2.6	1	T.	13	Dom.+Hosp.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	113.6	20.33	5.59	103	72	T.	13	Mun.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	3.68	0.65	5.66	1.3	0.8	T.	13	Dom.+Hosp.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	1.52	0.49	3.10	6.8	2.2	T.	13	Mun.
(Phan et al., 2015)	Oce.	Australia	Kangaroo Vall.*	1	35	2.036	0.376	5.42	0.15	1	G.	12-14	Dom.
(Rodriguez-Mozaz et al., 2015)	Eur.	Spain	Girona	1	3	0.331	0.088	3.77	51	n.a.	G.	11/12	Dom.+Hosp.
(Subedi et al., 2015)	Asia	India	Saidpur	1	1	0.195	0.033	5.91	19	350	G.	13	Dom.
(Subedi et al., 2015)	Asia	India	Beur	1	1	0.288	0.091	3.17	21	275	G.	13	Dom.
(Subedi et al., 2015)	Asia	India	Coimbatore	1	1	0.552	0.156	3.54	22	350	G.	13	Dom.
(Subedi et al., 2015)	Asia	India	Udupi	1	1	0.414	0.16	2.59	2.0	10	G.	13	Dom.
(Subedi et al., 2015)	Asia	India	Manipal	1	1	2.26	0.036	63.48	2.0	12	G.	13	Dom.
(Vergeynst et al., 2015)	Eur.	Belgium	Schilde	1	1	0.245	0.158	1.55	13	28	T.	13	n.a.
(Vergeynst et al., 2015)	Eur.	Belgium	Aalst	1	1	0.429	0.228	1.88	21	100	T.	13	n.a.
(Xu et al., 2015)	Asia	China	Beijing	1	1	0.263	1.955	0.13	n.a.	n.a.	n.a.	n.a.	n.a.
(Yuan et al., 2015)	Asia	China	Wuxi	1	3	0.224	0.047	4.81	200	820	F.	13	Mun.
(Yuan et al., 2015)	Asia	China	Wuxi	1	3	0.247	0.041	6.01	150	660	F.	13	Mun.
(Anumol et al., 2016)	Asia	India	Chennai	1	3	0.71	0.32	2.22	54	n.a.	G.	13/14	Dom.+Ind.
(Anumol et al., 2016)	Asia	India	Chennai	1	3	0.83	0.55	1.51	40	n.a.	G.	13/14	Dom.+Ind.
(Anumol et al., 2016)	Asia	India	Chennai	1	11	0.25	0.17	1.47	1.4	15	G.	14	Univ.
(Cardenas et al., 2016)	Oce.	Australia	South-Queensland*	1	4	3.57	2.35	1.52	45	180	G.	12	Mun.
(K'oreje et al., 2016)	Afr.	Kenya	Nairobi	1	2	10140	4250	2.39	445	600	G.	12	n.a.
(K'oreje et al., 2016)	Afr.	Kenya	Kisumu	1	2	54830	72850	0.75	6.6	50	G.	13	n.a.
(K'oreje et al., 2016)	Afr.	Kenya	Kisumu	1	2	23840	55750	0.43	6.8	50	G.	13	n.a.
(Mohapatra et al., 2016)	N.Am.	USA	South-East*	1	8	2.4	1	2.4	135	n.a.	T.	10	Mun.
(Mohapatra et al., 2016)	N.Am.	USA	South-East*	1	8	2.6	0.9	2.89	75	n.a.	T.	10	Mun.
(Papageorgiou et al., 2016)	Eur.	Greece	Volos	1	24	0.088	0.138	0.64	32	145	T.	13/14	Dom.Hosp.
(Paxéus et al., 2016)	Eur.	Sweden	Gothenburg	1	33	0.052	0.080	0.65	370	670	F.	06-15	Dom.+Ind.
(Petrie et al., 2016)	Eur.	UK	South-West*	1	3	0.113	0.672	0.17	n.a.	105	G.	n.a.	n.a.
(Prabhasankar et al., 2016)	Asia	India	Karnataka	1	3	0.392	0.176	2.23	1.5	11	G.	11/12	Dom.+Hosp.
(Prabhasankar et al., 2016)	Asia	India	Karnataka	1	3	0.402	0.094	4.27	2.0	11	G.	11/12	Dom.+Hosp.
(Prabhasankar et al., 2016)	Asia	India	Karnataka	1	3	0.023	0.01	2.33	2.0	9	G.	11/12	Dom.
(Thomaidis et al., 2016)	Eur.	Greece	Athens	1	8	0.229	0.243	0.94	n.a.	3700	F.	12	Mun.
(Thomaidis et al., 2016)	Eur.	Greece	Athens	1	11	0.142	0.106	1.33	n.a.	3700	F.	13	Mun.
(Thomaidis et al., 2016)	Eur.	Greece	Athens	1	8	0.156	0.106	1.47	n.a.	3700	F.	14	Mun.
(Tran et al., 2016)	Asia	Singapore	Ulu Pandan	1	4	1.141	0.224	5.09	n.a.	361	G.	15	Mun.
(Vatovec et al., 2016)	N.Am.	USA	Burlington	1	10	0.275	0.293	0.94	17	30	T.	14	Dom.+Univ.
(Afonso-Olivares et al., 2017b)	Eur.	Spain	Gran Canaria*	1	12	0.748†	0.201†	3.72	18	n.a.	G.	n.a.	Mun.

(Afonso-Olivares et al., 2017b)	Eur.	Spain	Gran Canaria*	1	12	0.019†	0.072†	0.26	n.a.	0.5	G.	n.a.	Dom.
(Afonso-Olivares et al., 2017a)	Eur.	Spain	Gran Canaria*	1	3	0.783	0.319	2.45	18	n.a.	G.	n.a.	Mun.
(Dinh et al., 2017)	Eur.	France	Fontenay-les-Briis	1	14	1.63	0.69	2.36	0.2	1.7	G.	09-11	Dom.+Hosp.
(Dinh et al., 2017)	Eur.	France	Fontenay-les-Briis	1	14	0.093	0.037	2.51	0.4	1.7	G.	09-11	Dom.
(Johnson et al., 2017)	Eur.	UK	Southern England*	1	10	0.230	0.733	0.31	163	38	T.	12-15	n.a.
(Johnson et al., 2017)	Eur.	UK	Southern England*	1	10	0.138	0.576	0.240	32	8	T.	12-15	n.a.
(Johnson et al., 2017)	Eur.	UK	Southern England*	1	10	0.163	0.588	0.28	11	2.4	T.	12-15	n.a.
(Johnson et al., 2017)	Eur.	UK	Southern England*	1	10	0.032	0.327	0.10	5.9	1.4	T.	12-15	n.a.
(Liu et al., 2017)	Asia	China	China*	12	24	0.039	0.008	4.94	2800	6000	G.	15	Mun.
(Mathenge et al., 2017)	Afr.	Kenya	Nairobi	4	12	0.079	0.026	3.08	n.a.	n.a.	G.	n.a.	Dis.
(Muter et al., 2017)	Eur.	Latvia	Riga	1	n.a.	0.173	0.29	0.60	4800	825	n.a.	16	Mun.
(Neyestani et al., 2017)	N.Am.	USA	Las Vegas	1	4	1.093	0.498	2.20	n.a.	n.a.	G.	16	Mun.
(Petrie et al., 2017)	Eur.	UK	South-West England*	1	17	0.192†	1.229†	0.16	43	106	G.	14	n.a.
(Pugajeva et al., 2017)	Eur.	Latvia	Riga	1	21	0.085	0.029	2.93	4800	825	n.a.	16	Mun.
(Reinholds et al., 2017)	Eur.	Latvia	Riga	1	n.a.	0.008	0.005	1.53	4800	825	T.	16	Mun.
(Subedi et al., 2017)	Asia	India	Udupi	1	7	0.22	0.18	1.22	14	150	n.a.	13	Mun.
(Subedi et al., 2017)	Asia	India	Mangalore	1	7	0.1	0.029	3.45	82	450	n.a.	13	Mun.
(Thiebault et al., 2017b)	Eur.	France	Orleans	1	84	2.30	0.819	2.81	4.5	78	F.	16	Mun.
(Yang et al., 2017)	Asia	China	Guangzhou	1	3	0.225	0.135	1.66	165	428	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Guangzhou	1	3	0.078	0.009	8.97	220	570	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Guangzhou	1	3	0.217	0.028	7.75	200	540	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Dongguan	1	3	0.032	0.002	16.05	47	130	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Dongguan	1	3	0.128	0.002	64.0	110	300	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Guangzhou	1	3	0.227	0.002	113.5	220	390	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Huizhou	1	3	0.072	0.037	1.92	88	380	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Huizhou	1	3	0.243	0.042	5.84	76	425	T.	15	Mun.
(Yang et al., 2017)	Asia	China	Guangzhou	1	3	0.416	0.021	19.90	100	130	T.	15	Mun.
(Ben et al., 2018)	Asia	China	China*	14	14	0.341†	0.046†	7.45	5123	n.a.	F.	15	Mun.
(Botero-Coy et al., 2018)	S.Am.	Colombia	Bogota	1	7	0.630	0.323	1.95	350	2500	T.	16	Dom.
(Botero-Coy et al., 2018)	S.Am.	Colombia	Medellin	1	7	0.299	0.075	3.98	150	n.a.	T.	16	Mun.
(Harrabi et al., 2018)	Afr.	Tunisia	Sfax	1	3	0.116	0.073	1.59	49	257	T.	16	Dom.+Ind.
(Le et al., 2018)	Asia	Singapore	Ulu Pandan	1	4	1.05	0.21	5	n.a.	361	G.	n.a.	Mun.
(Rivera-Jaimes et al., 2018)	N.Am.	Mexico	Cuernavaca	1	8	1.312	0.413	3.18	n.a.	n.a.	T.	15-16	Dom.
(Kibuye et al., 2019)	N.Am.	USA	Penn State	1	30	25.03	9.8	2.55	4	n.a.	T.	16/17	Mun.+Univ.
(Kumar et al., 2019)	Oce.	New Zealand	n.a.	1	32	0.713	0.59	1.21	25	<100	T.	16/17	Dom.+Ind.
(Sörengård et al., 2019)	Eur.	Sweden	Uppsala	1	1	0.14	0.096	1.47	42	180	F.	18	Mun.
(Vergili et al., 2019)	Asia	Turkey	Istanbul	1	1	0.24	0.14	1.71	0.8	1.2	G.	n.a.	Dom.
(Vergili et al., 2019)	Eur.	Germany	n.a.	1	1	2.6	0.29	8.97	10	30	G.	n.a.	Mun.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	3.590	0.123	29.28	115	2400	T.	16/17	Dom.+Ind.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	0.626	0.199	3.15	590	1900	T.	16/17	Dom.+Ind.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	0.967	0.438	2.21	575	2100	T.	16/17	Dom.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	0.254	0.256	0.99	204	500	T.	16/17	Dom.+Ind.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	0.221	0.154	1.44	85	400	T.	16/17	Dom.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	0.531	0.259	2.05	90	200	T.	16/17	Dom.
(Zhang et al., 2019)	Asia	China	Beijing	1	1	0.269	0.096	2.80	74	150	T.	16/17	Dom.+Ind.

Table 2: Main characteristics of the reviewed Hospital effluents, with Cont. the continent (N.Am. for North-America, S.Am. for South-America, Eur. for Europe and Oce. for Oceania), Town, the Hospital city and the state/region if the city was not available (*), n_{ins} the number of Hospitals investigated in each study, n_{samp}, the number of samples analyzed in each study, C_{SMX}, the mean concentration of SMX (for n_{samp}=1, C corresponds to the unique given data, and † for median concentration), C_{TMP}, the mean concentration of TMP (for n_{samp}=1, C corresponds to the unique given data, and † for median concentration), Ratio, the ratio between the concentration of SMX and TMP, Flow, the daily flow of Hospital effluents, n_{beds}, the number of beds in the targeted hospitals, Samp., the sampling mode with F. for flow-enslaved composite, T. for time composites and G. for grab samples, Year, the year of sampling of Hospital effluents and WW Origin, the type of hospitals, with Gen. for general, Paed. for paediatric, Sen. for geriatric and Nurs. for nursing care services. n.a. corresponds to non-available data.

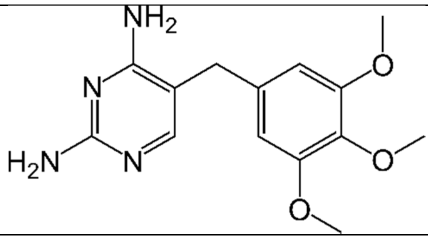
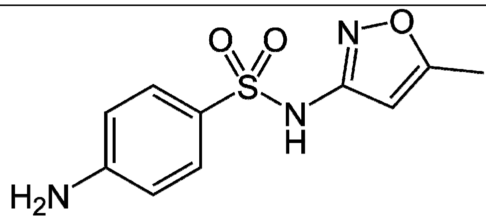
Reference	Cont.	Country	Town/State	n_{ins}	n_{samp}	C_{SMX} µg.L^{-1}	C_{TMP} µg.L^{-1}	Ratio SMX/TMP	Flow m^3.d^{-1}	n_{beds}	Samp.	Year	WW Origin
(Brown et al., 2006)	N.Am.	USA	Albuquerque	1	1	0.8	5	0.16	n.a.	n.a.	T.	03	Gen.
(Brown et al., 2006)	N.Am.	USA	Albuquerque	1	1	2.1	2.9	0.72	n.a.	n.a.	T.	03	Gen.
(Karthikeyan and Meyer, 2006)	N.Am.	USA	Wisconsin*	1	1	0.25	0.35	0.71	100	102	G.	02	Gen.
(Thomas et al., 2007)	Eur.	Norway	Oslo	1	7	0.404	4.302	0.09	n.a.	1200	T.	06	Gen.
(Thomas et al., 2007)	Eur.	Norway	Oslo	1	7	1.389	3.896	0.36	n.a.	n.a.	T.	06	Gen.
(Lin et al., 2008)	Asia	China(Taiwan)	n.a.	6	6	0.647†	1.04†	0.62	n.a.	n.a.	G.	08	n.a.
(Watkinson et al., 2009)	Oce.	Australia	Queensland*	1	3	0.1†	0.3†	0.33	n.a.	n.a.	T.	05/06	n.a.
(Chang et al., 2010)	Asia	China	Chongqing	1	1	0.613	0.174	3.52	n.a.	n.a.	G.	04	Gen.
(Chang et al., 2010)	Asia	China	Chongqing	1	1	0.195	0.092	2.12	n.a.	n.a.	G.	04	Gen.
(Chang et al., 2010)	Asia	China	Chongqing	1	1	1.06	0.061	17.38	n.a.	n.a.	G.	04	Gen.
(Sim et al., 2010)	Asia	South Korea	Busan	1	1	0.688	0.425	1.62	100	1129	T.	08	Gen.
(Brenner et al., 2011)	S.Am.	Brazil	Santa Maria	1	7	27.78	6.65	4.18	n.a.	n.a.	T.	n.a.	Gen.
(Sim et al., 2011)	Asia	South Korea	n.a.	4	12	25.3	1.62	15.62	1050	5417	G.	08	n.a.
(Kovalova et al., 2012)	Eur.	Switzerland	Baden	1	17	3.476	0.93	3.74	230	346	F.	09/10	Gen.
(Nagarnaik et al., 2012)	N.Am.	USA	Texas*	1	4	3.09	2.23	1.39	500	375	T.	08	Gen.
(Nagarnaik et al., 2012)	N.Am.	USA	Texas*	1	4	178	60.9	2.92	100	300	T.	08	Nur.
(Nagarnaik et al., 2012)	N.Am.	USA	Texas*	1	4	0.559	0.557	1.00	50	225	T.	08	Sen.
(Nagarnaik et al., 2012)	N.Am.	USA	Texas*	1	4	0.238	0.351	0.68	70	225	T.	08	Sen.
(Verlicchi et al., 2012)	Eur.	Italy	Northern Italy*	1	4	4.2	1.2	3.5	160	300	T.	09/10	Gen.
(Verlicchi et al., 2012)	Eur.	Italy	Northern Italy*	1	8	1.9	0.415	4.58	603	900	T.	09/10	Gen.
(Gros et al., 2013)	Eur.	Spain	Girona	1	2	0.133	0.133	1.00	n.a.	400	G.	11	Gen.
(Khan et al., 2013)	Asia	Pakistan	Lahore	1	3	4.6	2.2	2.09	n.a.	n.a.	G.	12	Gen.
(Santos et al., 2013)	Eur.	Portugal	Coimbra	1	9	3.015	1.849	1.63	883	1456	T.	11	Gen.
(Santos et al., 2013)	Eur.	Portugal	Coimbra	1	9	1.897	0.528	3.59	428	350	T.	11	Gen.
(Santos et al., 2013)	Eur.	Portugal	Coimbra	1	9	0.401	0.337	1.19	181	110	T.	11	Paed.
(Santos et al., 2013)	Eur.	Portugal	Coimbra	1	9	0.090	0.014	6.64	33	96	T.	11	Paed.
(Sim et al., 2013)	Asia	South Korea	Ulsan/Busan	3	3	21	8.14	2.58	173	n.a.	T.	10	Gen.
(Kosma et al., 2014)	Eur.	Greece	Ioannina	1	32	1.465	0.622	2.36	550	800	T.	10/11	Gen.
(Lindberg et al., 2014)	Eur.	Sweden	Umeå	1	7	2.751	1.802	1.53	720	600	F.	13	Gen.
(Li et al., 2015)	Asia	China	Linan	1	3	0.137	0.013	10.71	n.a.	200	T.	13	Paed.
(Li et al., 2015)	Asia	China	Linan	1	3	0.224	0.005	44.74	n.a.	600	T.	13	Gen.
(Li et al., 2015)	Asia	China	Linan	1	3	0.023	0.22	0.11	n.a.	30	T.	13	Paed.
(Li et al., 2015)	Asia	China	Linan	1	3	0.115	0.074	1.55	n.a.	30	T.	13	Gen.
(Li et al., 2015)	Asia	China	Linan	1	3	0.24	0.118	2.03	n.a.	600	T.	13	Gen.
(Li et al., 2015)	Asia	China	Linan	1	3	1.504	0.409	3.68	n.a.	250	T.	13	Gen.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	7	0.97	0.97	1	250	250	T.	13	Gen.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	7	2.17	1.32	1.64	250	250	T.	13	Gen.

(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	2.15	0.97	2.22	435	350	T.	13	Gen.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	0.49	0.38	1.29	435	450	T.	13	Gen.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	4	0.49	1.06	0.46	370	300	T.	13	Gen.
(Oliveira et al., 2015)	N.Am.	USA	Suffolk County*	1	8	1.52	0.93	1.63	568	600	T.	13	Gen.
(Rodriguez-Mozaz et al., 2015)	Eur.	Spain	Girona	1	3	0.752	0.594	1.26	1250	400	G.	11/12	Gen.
(Lien et al., 2016)	Asia	Vietnam	Hanoi	1	12	9.7	2.7	3.59	n.a.	520	T.	13	Gen.
(Lien et al., 2016)	Asia	Vietnam	Hanoi	1	12	9.8	7.7	1.27	n.a.	220	T.	13	Gen.
(Prabhasankar et al., 2016)	Asia	India	Karnataka*	1	3	0.060	0.031	1.95	50	200	G.	11/12	Gen.
(Prasertkulsak et al., 2016)	Asia	Thailand	Bangkok	1	8	22.76	25.75	0.88	n.a.	n.a.	n.a.	n.a.	Gen.
(Dinh et al., 2017)	Eur.	France	Fontenay-les-Briis	1	14	2.1	0.9	2.33	170	360	G.	09-11	Gen.
(Yilmaz et al., 2017)	Asia	Turkey	Istanbul	1	1	8.5	0.55	15.45	1500	1358	G.	14	Gen.
(Yilmaz et al., 2017)	Asia	Turkey	Istanbul	1	1	2.2	0.18	12.22	1166	1285	G.	14	Gen.
(Botero-Coy et al., 2018)	S.Am.	Colombia	Tumaco	1	3	0.572	0.9	0.64	200	122	T.	16	Gen.
(Thai et al., 2018)	Asia	Vietnam	Hanoi	1	12	2.246	0.645	3.48	n.a.	420	G.	16/17	Gen.
(Serna-Galvis et al., 2019)	S.Am.	Colombia	Tumaco	1	5	0.001	0.03	0.03	200	122	n.a.	n.a.	Gen.
(Sörengård et al., 2019)	Eur.	Sweden	Uppsala	1	1	1.5	0.74	2.03	0.96	n.a.	T.	18	Gen.

Table 3: Main characteristics of the reviewed Livestock farming effluents, with Cont. the continent, Town, the Livestock location, n_{ins} the number of livestock farms investigated in each study, n_{samp}, the number of samples analyzed in each study, C_{SMX}, the mean concentration of SMX in µg.L^{-1} (for n_{samp}=1, C corresponds to the unique given data, and † for median concentration), C_{TMP}, the mean concentration of TMP in µg.L^{-1} (for n_{samp}=1, C corresponds to the unique given data, and † for median concentration), Ratio, the ratio between the concentration of SMX and TMP, Flow, the daily flow of livestock farming effluents, Samp., the sampling mode with T. for time composites and G. for grab samples, Year, the year of sampling of livestock farming effluents and WW Origin, the type of livestock installations, with Sla. for slaughterhouse. n.a. corresponds to non-available data.

Reference	Cont.	Country	Town/State	n_{ins}	n_{samp}	C_{SMX} µg.L^{-1}	C_{TMP} µg.L^{-1}	Ratio SMX/TMP	Flow 10^3 m^3.d^{-1}	Samp.	Year	WW Origin
(Chang et al., 2010)	Asia	China	Chongqing	1	1	0.216	0.028	7.71	n.a.	G.	04	Sla.
(Watanabe et al., 2010)	N.Am.	USA	California*	2	10	1.379	0.288	4.79	n.a.	G.	06-08	Cow
(Hoa et al., 2011)	Asia	Vietnam	Hanoi	3	6	0.307	0.019	15.84	n.a.	G.	07	Fish/Pig
(Murata et al., 2011)	Asia	Japan	Tokyo	1	?	50.13	0.378	132.6	n.a.	T.	06	Pig
(Shimizu et al., 2013)	Asia	Vietnam	Hanoi	5	13	0.158	0.015	10.31	n.a.	G.	07/08	Pig
(Shimizu et al., 2013)	Asia	Vietnam	Hochimin	2	2	0.114	0.057	1.99	n.a.	G.	06	Pig
(Shimizu et al., 2013)	Asia	Vietnam	CanTho	9	9	0.442	0.022	20.30	n.a.	G.	09/10	Pig
(Choi et al., 2016)	Asia	South Korea	Nonsan	1	5	5,505	225	24.47	n.a.	G.	12	Pig

Table 4: Physico-chemical properties of the targeted antibiotics, with M_w the molecular weight in $g.mol^{-1}$, pK_a, the acid dissociation constant, Log K_{ow}, the octanol/water partition coefficient, Sol_w, the solubility in water at 25°C, Exc. R., the excretion rate in unchanged form in % following human consumption († for pig) ± the standard deviation, Theoretical ratio, the theoretical ratio (SMX/TMP) based on the median excretion rate and considering only consumption of SMX and TMP in association

Abbreviation	TMP	SMX
Structure		
Formula	$C_{14}H_{18}N_4O_3$	$C_{10}H_{11}N_3O_3S$
CAS-Number	738-70-5	723-46-6
M_w	290.32	253.28
pK_a	7.2	6.16-1.97
Log K_{ow}[p]	0.73	0.48
Sol_w[p]	400	459
Exc. R. (†in pig)	48[a];46[b];50[d];43[e];45[f];60[h];80[i];50[j]; 50[k];69[m];64[n];†32[o]	15[a];30[b];10[c];18[d];23[e];20[f];20[g];15[h]; 30[i];20[j];10[k];20[l];10[m];11.5[n];†16[o]
Median Exc. R.	50 ± 11	20 ± 6
Theoretical ratio	SMX/TMP: Min. = 1.1; Mea. = 2.0; Max = 3.3	

Data from: [a](Schwartz and Rieder, 1970), [b](Dollery, 1991), [c](Vree and Hekster, 1987), [d](Huschek et al., 2004), [e](Carballa et al., 2008), [f](ter Laak et al., 2010), [g](Lienert et al., 2007), [h](Hirsch et al., 1999), [i](Kasprzyk-Hordern et al., 2009), [j](Lindberg et al., 2006), [k](Göbel et al., 2005), [l](Radke et al., 2009), [m](Flores-Murrieta et al., 1990), [n](Örtengren et al., 1979), [o](Nouws et al., 1991) and [p](drugbank.ca)

Table 5: Sludge/water partition coefficient (K_d) of SMX and TMP reported in the literature

$K_{d\,(SMX)}$	$K_{d\,(TMP)}$	Sludge Type	Reference
45	165	MBR	(Abegglen et al., 2009)
3	427	Primary Sludge	(Radjenović et al., 2009)
256	208	Secondary Sludge	(Göbel et al., 2005)
<30	251	Primary Sludge	(Stevens-Garmon et al., 2011)
11	10	Primary Sludge (Batches)	(Hyland et al., 2012)
48	76	Nitrifying Act. Sludge	(Fernandez-Fontaina et al., 2014)
10	14	Primary Sludge	(Blair et al., 2015)
9	25	MBR	(Fernandez-Fontaina et al., 2013)
320	390	Primary Sludge (Batches)	(Hörsing et al., 2011)

Table 6: Available annual use data of SMX and TMP (recorded separately) in kg.y^{-1} for human (Hum.), hospitals (Hosp.) and Veterinary (Vet.) purposes; atypical ratios (i.e. outside the theoretical ones) are bolded

Year	Country/zone	Use	SMX	TMP	Ratio	Reference
1992-2003	Australia	Hum.	89,000	26,000	3.42	(Watkinson et al., 2009)
1992-2003	Australia	Vet.	0	21,000	**0**	(Watkinson et al., 2009)
1995	Germany	Hum.	49,920	9,984	5.00	(Hirsch et al., 1999)
1995-1999	Kenya	Vet.	365	577	**0.63**	(Mitema et al., 2001)
1998	Germany	Hosp.	3763	758	4.96	(Kümmerer and Henninger, 2003)
1998	Germany	Hum.	44,352	9,152	4.85	(Kümmerer and Henninger, 2003)
2003	Spain	Hum.	12,700	3,700	3.43	(Carballa et al., 2008)
2004	France	Hum.	16,730	3,346	5.00	(Besse et al., 2008)
2004	USA	Hum.	109,000	22,000	4.95	(Palmer et al., 2008)
2005	Norway	Hum.	218	534	**0.41**	(Thomas et al., 2007)
2005	South-Korea	Hum.	15,334	4,350	3.53	(KEI, 2007)
2005	South-Korea	Vet.	14,791	7,572	**1.95**	(KEI, 2007)
2006	UK (Wales)	Hum.	115	722	**0.16**	(Kasprzyk-Hordern et al., 2009)
2007	Switzerland	Hum.	2,079	700	2.97	(BAFU, 2009)
2007	Norway	Hum.	n.a.	n.a.	**0.32**	(Grung et al., 2008)
2008	Kenya (Nairobi Region, Hosp)	Hum.	6,528	1,306	4.99	(K'oreje et al., 2012)
2009	Switzerland	Hum.	2,427	486	4.99	(BAFU, 2011)
2009	Saudi Arabia (local data)	Hum.	1,663	333	4.99	(Shraim et al., 2017)
2009	Sweden	Hum.	45	279	**0.16**	(Wahlberg et al., 2011)
2010	Greece	Hum.	2,111	3,224	**0.65**	(Iatrou et al., 2014)
2010	Spain	Hum.	10,297	69	**149.9**	(Ortiz de García et al., 2013)
2013	China	Hum.	2,000	500,000	**0.004**	(Zhang et al., 2015)
2013	China	Vet.	310,900	246,300	**1.26**	(Zhang et al., 2015)
2013	Vietnam (local data)	Hosp.	1.000	0.200	5.00	(Lien et al., 2016)
2014	UK	Hum.	2,255	11,599	**0.19**	(Johnson et al., 2017)
2014	France (local data)	Hosp.	4.05	0.81	4.99	(Dinh et al., 2017)
2018	Belgium	Vet.	96	11,136	**0.01**	(Belvet-SAC, 2018)

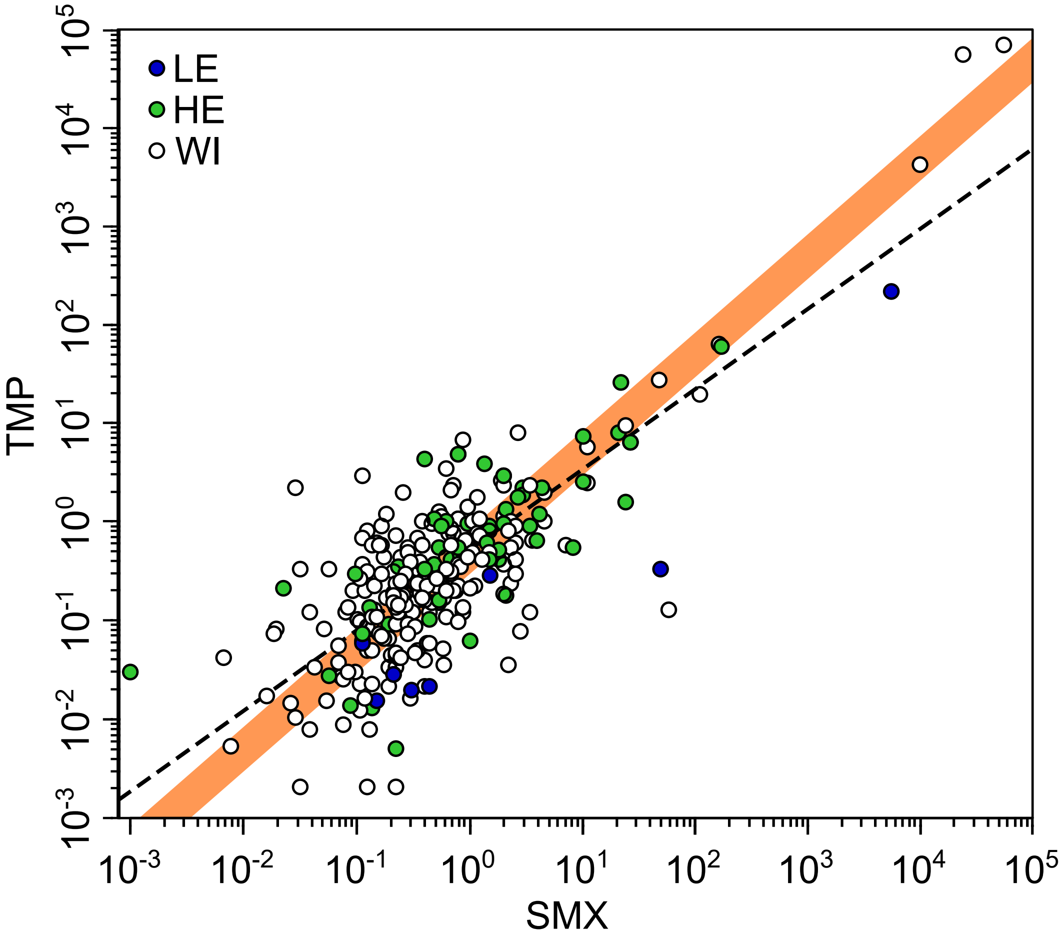


Figure 1: Linear regression between the concentration of SMX and TMP (in µg.L^{-1}) with WI for wastewater influents (white circles), HE for hospital effluents (green circles) and LE for livestock effluents (blue circles). The dashed dark line marks the linear regression fit and the orange area marks the theoretical ratio value.

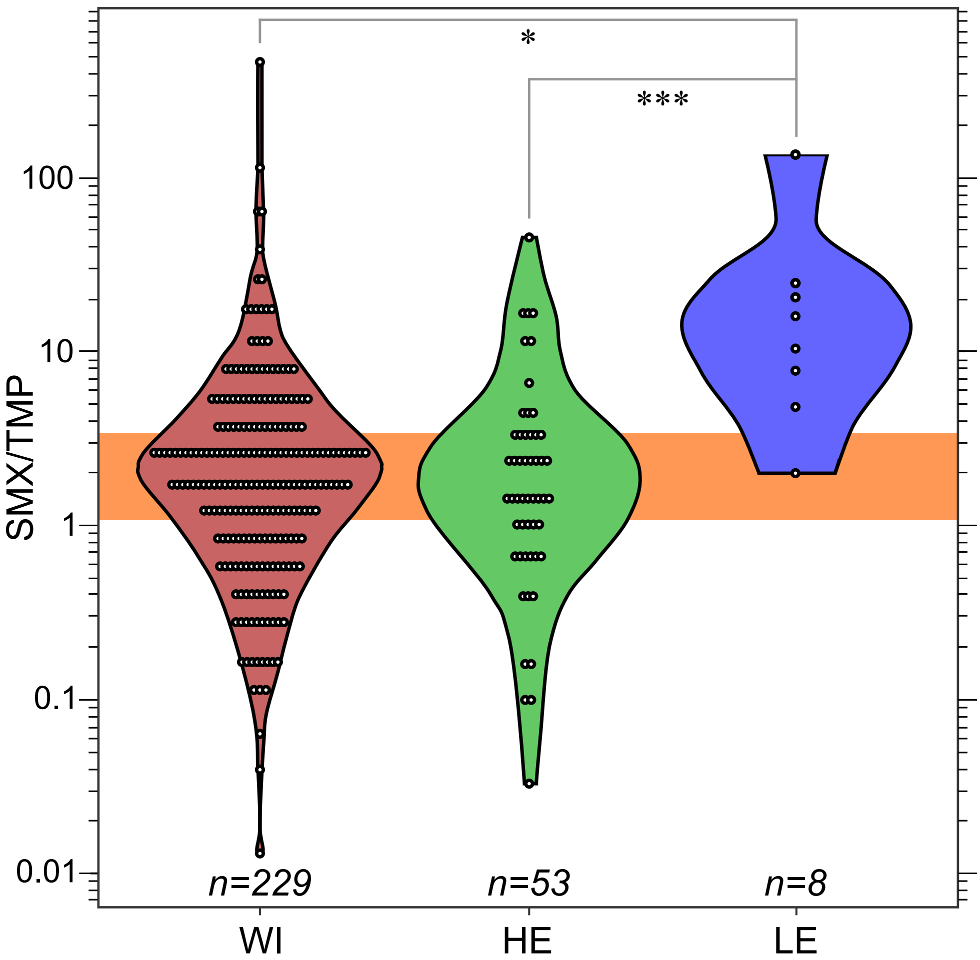


Figure 2: Violin plots of the SMX/TMP ratios as a function of the targeted matrix, with WI for wastewater influents, HE for hospital effluents and LE for livestock effluents, *n* is the amount of individual data (see Table 1-3 for further details), gray lines mark statistically significant variations with *p*-values < 0.05, 0.01 and 0.001 for *, ** and *** respectively and the orange area marks the theoretical ratio.

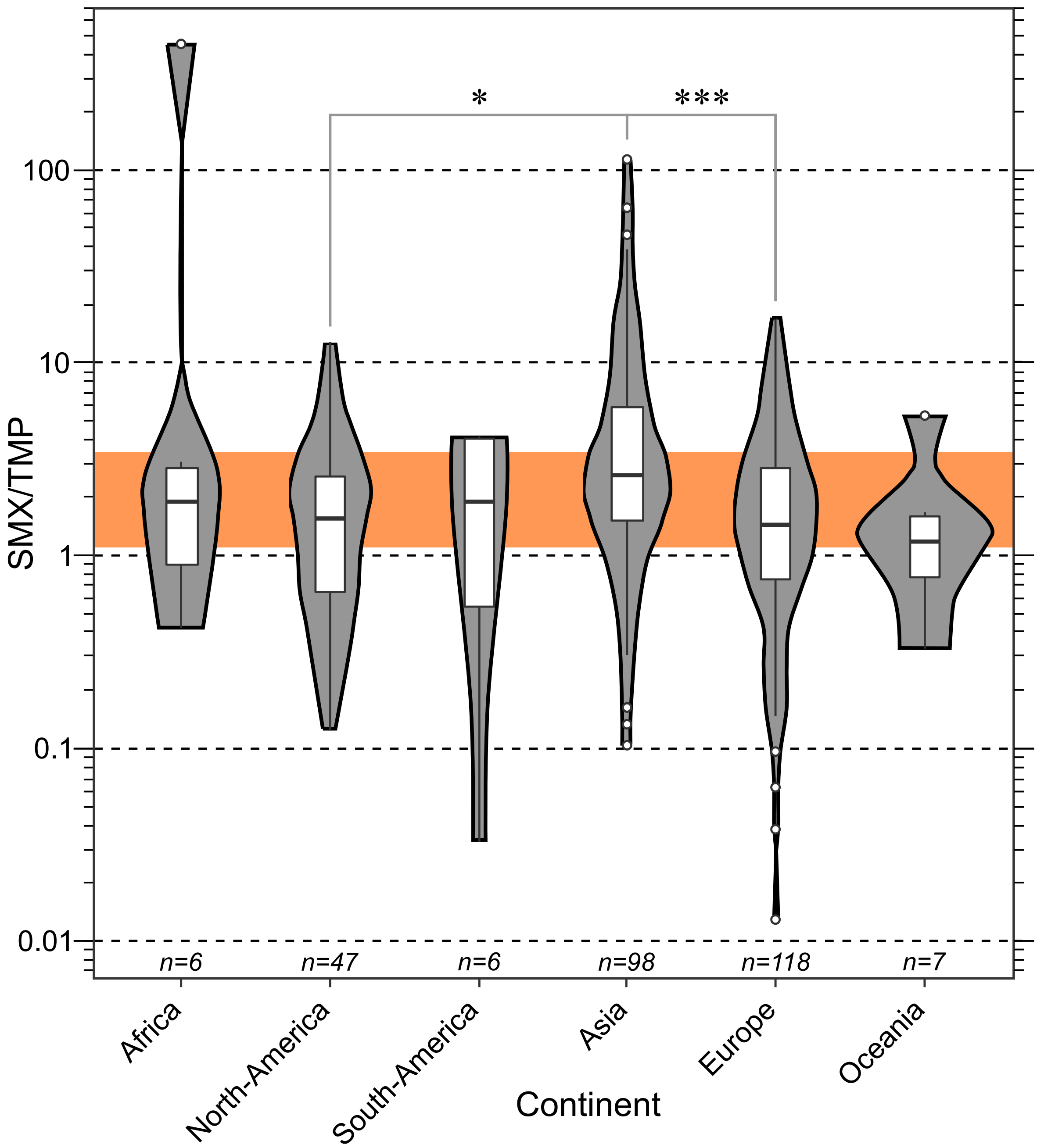


Figure 3: Violin plots of the SMX/TMP ratios in WI and HE as a function of the continent with *n* the amount of individual data. The line within the box (white boxes) marks the median, boundaries indicate the 25th and 75th percentiles, error bars indicate maximum and minimum values in ± 1.5 σ variations and white circles indicate values outside this range, gray lines mark statistically significant variations with *p*-values < 0.05, 0.01 and 0.001 for *, ** and *** respectively and the orange area marks the theoretical ratio value.

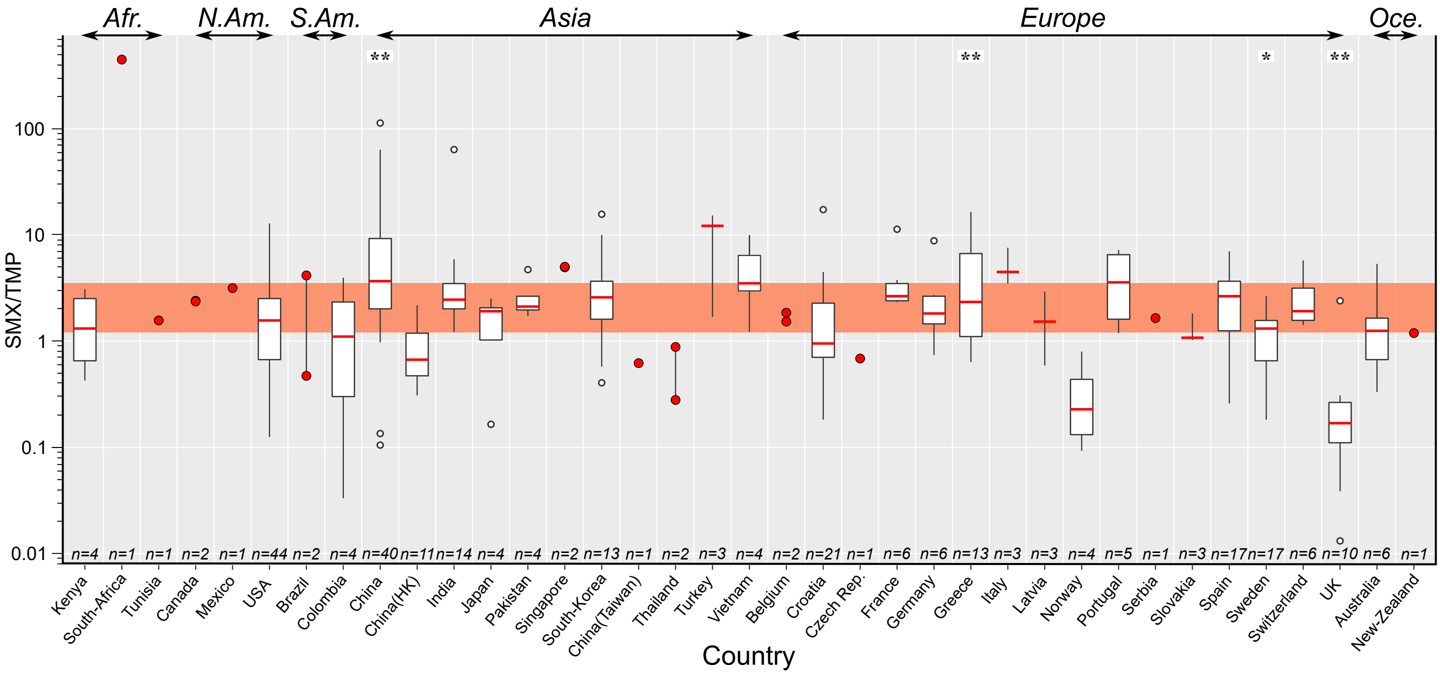


Figure 4: Boxplots of the SMX/TMP ratios in WI and HE as a function of the country with *n* the amount of individual data. The red line within the box marks the median, boundaries indicate the 25th and the 75th percentiles, error bars indicate maximum and minimum values in ± 1.5 σ variations and white circles indicate values outside this range, red circles indicate individual values and the orange area marks the theoretical ratio. Boxplots are represented only if *n* > 3.

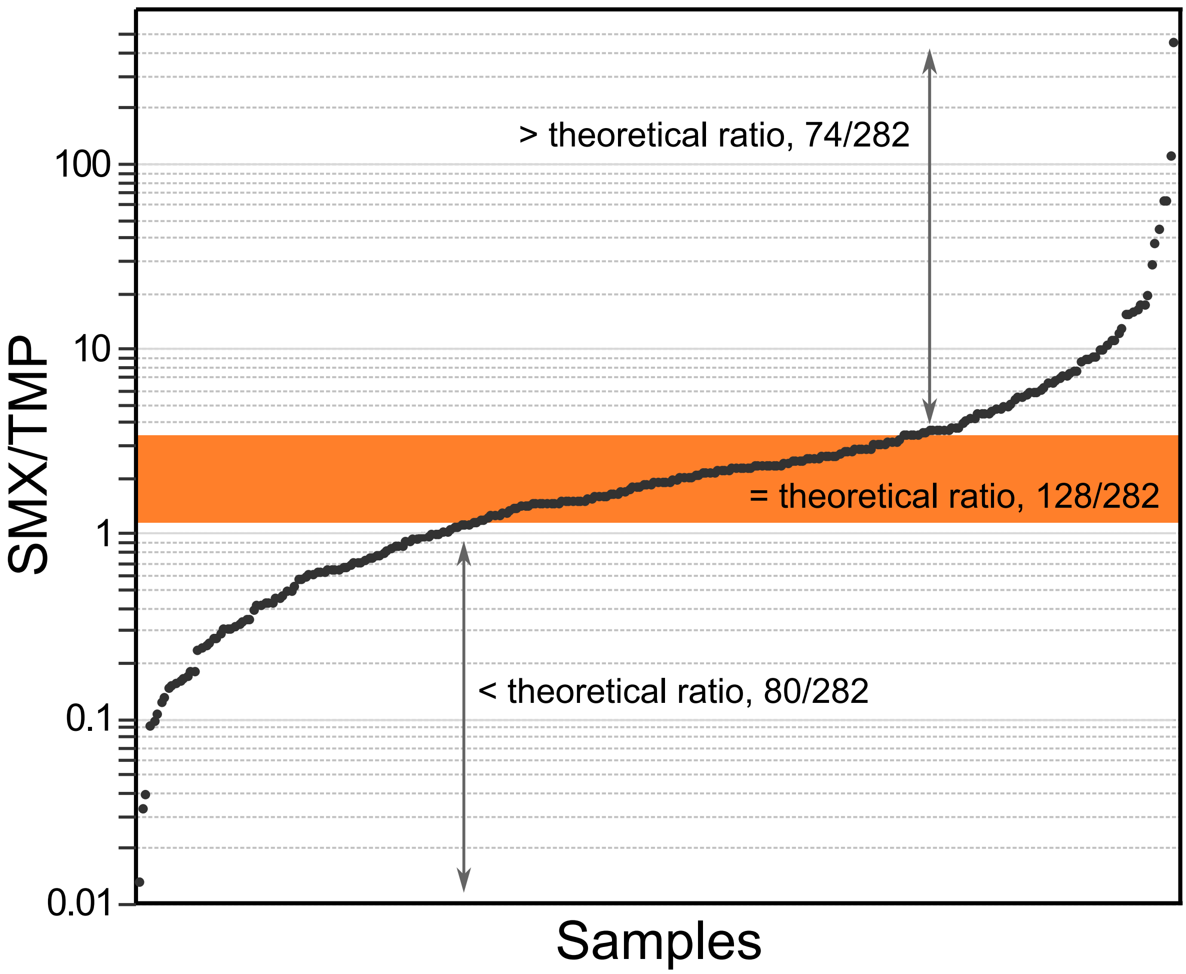


Figure 5: SMX/TMP ratios sorted from the smallest to the largest, *n*=282

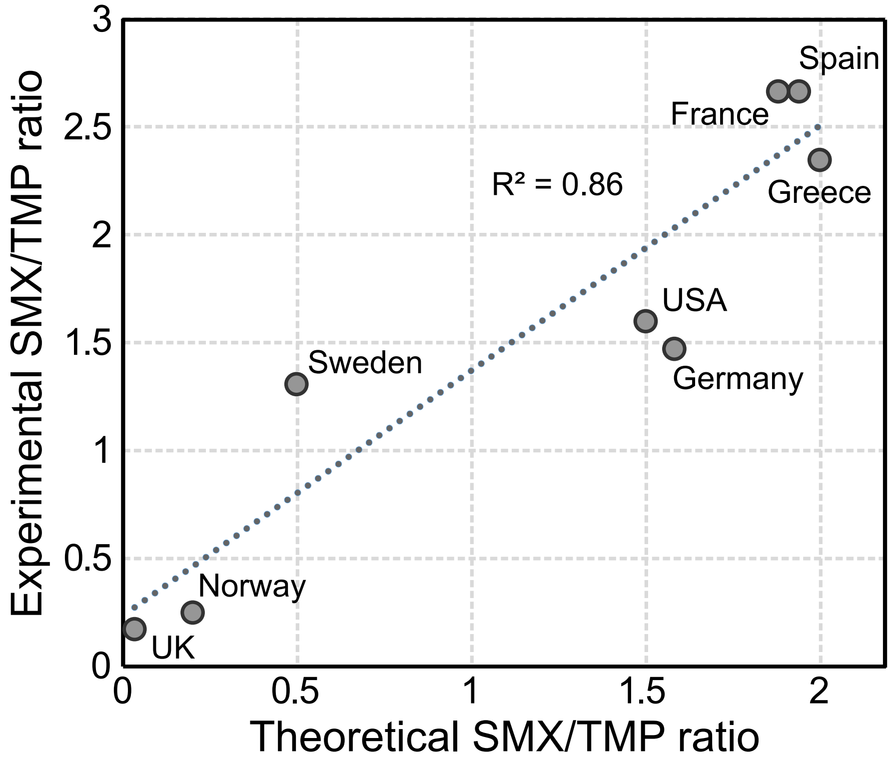


Figure 6: Comparison between the experimental median SMZ/TMP ratio in several countries with the theoretical ones, based on the consumption data (Coenen et al. (2011); ClinCalc Database (2019))