Current and future perspectives for wastewater-based epidemiology as a monitoring tool for pharmaceutical use

Reference:
The science of the total environment - ISSN 0048-9697 - 789(2021), 148047
Full text (Publisher's DOI): https://doi.org/10.1016/J.SCITOTENV.2021.148047
To cite this reference: https://hdl.handle.net/10067/178500151162165141
Current and future perspectives for wastewater-based epidemiology as a monitoring tool for pharmaceutical use


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Key words

• Wastewater-based epidemiology
• Drug Utilization Research
• Pharmacoepidemiology
• Pharmaceutical (mis)use
Abstract

The medical and societal consequences of the misuse of pharmaceuticals clearly justifies the need for comprehensive drug utilization research (DUR). Wastewater-based epidemiology (WBE) employs the analysis of human metabolic excretion products in wastewater to monitor consumption patterns of xenobiotics at the population level. Recently, WBE has demonstrated its potential to evaluate lifestyle factors such as illicit drug, alcohol and tobacco consumption at the population level, in near real-time and with high spatial and temporal resolution. Up until now there have been fewer WBE studies investigating health biomarkers such as pharmaceuticals.

WBE publications monitoring the consumption of pharmaceuticals were systematically reviewed from three databases (PubMed, Web of Science and Google Scholar). 64 publications that reported population-normalised loads or defined daily doses of pharmaceuticals were selected.

We document that WBE could be employed as a complementary information source for DUR. Interest in using WBE approaches for monitoring pharmaceutical use is growing but more foundation research (e.g. compound-specific uncertainties) is required to link WBE data to routine pharmacoepidemiologic information sources and workflows. WBE offers the possibility of i) estimating consumption of pharmaceuticals through the analysis of human metabolic excretion products in wastewater; ii) monitoring spatial and temporal consumption patterns of pharmaceuticals continuously and in near real-time; and iii) triangulating data with other DUR information sources to assess the impacts of strategies or interventions to reduce inappropriate use of pharmaceuticals.

Graphical abstract

How can WBE be employed as a complementary information source in DUR?

Wastewater-based epidemiology (WBE)
1. Introduction

The development of new and more effective pharmaceuticals in the last decades has contributed to a significant decrease in mortality, an improved quality of life for people with chronic illnesses and reduced time in hospital (Lichtenberg, 2014; Poluzzi et al., 2016). Nevertheless, misuse and abuse of pharmaceuticals can also have negative consequences, such as increased emergency room visits, treatment admissions for prescription drug use disorders and overdose deaths (National Institute of Drug Abuse, 2018; Poluzzi et al., 2016). In addition, 20% of health spending is wasteful and can be reduced by preventing the misuse and mis- and overprescription of pharmaceuticals (Organisation for Economic Co-operation and Development, 2018). The medical consequences and economic burden of the inappropriate use of pharmaceuticals has encouraged comprehensive drug utilization research (DUR) over the past decades (Poluzzi et al., 2016). Currently, DUR relies on data from the sales, billing, prescription and movement through the distribution chain of pharmaceuticals. All of this information is necessary to ensure the availability of safe, high-quality and efficacious treatments (World Health Organization, 2003). These information sources can be used to establish utilization patterns for specific pharmaceuticals and may provide a proxy for the prevalence of the diseases treated by these drugs (Chen & Briesacher, 2011; World Health Organization, 2003). Definitions for DUR terminology can be found in Table S1.

Data on the illegal trade or clandestine manufacturing of pharmaceuticals are not covered by traditional DUR figures (Diamanti et al., 2019; European Monitoring Centre for Drugs and Drug Addiction, 2019b), which can lead to an underestimation of pharmaceutical consumption (van Nuijs et al., 2015). In some health care systems, incomplete coverage of these data sources might lead to gaps between the number of prescriptions and overall drug utilisation (i.e. scripts may not be filled, filled scripts may not be consumed, and pharmaceuticals may not be taken in the recommended doses or by the person for whom they were prescribed). Additionally, the locality where a prescription is filled may differ from where consumption occurs. Some patients may not be able to afford to fill their prescriptions, particularly when it comes to repeat prescriptions or due to associated costs or unwanted side effects. These data also do not always include information on the amounts of pharmaceuticals used in hospitals and so may only record the use of reimbursed pharmaceuticals. (Poluzzi et al., 2016; World Health Organization, 2003). Furthermore, a limitation of currently used methods for drug utilisation data is the lack of spatial specificity, the lag in data acquisition and the infrequency of data reporting (e.g. this is often only be done on a yearly basis). The resolution of the data is also dependent on the quality of the health care system and may differ between jurisdictions within the same country.
In order to provide community-health information on exposure to xenobiotics, wastewater-based epidemiology (WBE) measures biomarker concentrations in untreated wastewater and converts these to per capita mass load estimates using daily wastewater flow rates and population number in the catchment area (Fig. 1) (Boogaerts, Covaci, Kinyua, Neels, & van Nuijs, 2016; P. Choi et al., 2018; Daughton, 2018; Lai et al., 2013; van Wel et al., 2016; Zuccato, Chiabrando, Castiglioni, Bagnati, & Fanelli, 2008). Target analytes can be quantified at trace levels (ng/L) by applying specific, accurate and precise bioanalytical methods such as solid phase extraction and liquid chromatography mass spectrometry (LC-MS/MS) (Andrés-Costa, Andreu, & Picó, 2017; Baker & Kasprzyk-Hordern, 2011a; Botero-Coy et al., 2018; Fatta, Achilleos, Nikolaou, & Meriç, 2007). Although WBE is a relatively new scientific discipline, it has rapidly realised its potential to provide independent, timely, low cost/resource and complementary epidemiologic information on the exposure to and consumption of xenobiotics at high spatial and temporal resolutions (Banta-Green et al., 2009; Huerta-Fontela, Galceran, Martin-Alonso, & Ventura, 2008; Karolak, Nefau, Bailly, Solgadi, & Levi, 2010; Kasprzyk-Hordern, Dinsdale, & Guwy, 2009; Mari et al., 2009; Metcalfe, Tindale, Li, Rodayan, & Yargeau, 2010; Postigo, López de Alda, & Barceló, 2010; Terzic, Senta, & Ahel, 2010; van Nuijs et al., 2009; Zuccato et al., 2005). This is reflected in the increasing numbers of publications in this field (Fig. S1) (P. Choi et al., 2018). The majority of WBE research has focussed on back-estimating illicit drug consumption and only a few have investigated the use of pharmaceuticals (P. Choi et al., 2018; Gracia-Lor et al., 2017). In addition, most of the WBE applications on pharmaceuticals i) have used these data to estimate population size (P. Choi et al., 2018; Lai et al., 2011); ii) to evaluate the illegal use of specific pharmaceuticals (P. Choi et al., 2018; Thai, Lai, Edirisinghe, et al., 2016) or iii) to associate pharmaceutical loads with environmental stressors (P. Choi et al., 2018; Phung et al., 2017).
Fig. 1 Schematic overview of WBE for determining pharmaceutical consumption. Adapted from Choi et al (P. Choi et al., 2018).

Importantly, WBE cannot provide any information on the characteristics of the user and his personal consumption. That is, it cannot tell us about: the administration form, co-consumption, dose purity, dose frequency, individual compliance, drug use preferences, or the socio-demographic characteristics of individual patients. Nor can diversion and changes within the drug-using cohort be quantified by WBE. Specifically, if an increase was observed WBE cannot distinguish between the following possibilities i) more individuals are consuming at the same rate, ii) slightly more individuals consuming and at a higher rate each, iii) the same number of individuals consuming a higher total amount each, or iv) one group of individuals in the cohort consuming more than another group. Nevertheless, wastewater samples can be analyzed retrospectively to provide aggregated consumption estimates (Boogaerts et al., 2016; Burgard et al., 2019; Mackie et al., 2019) with easily adjusted spatio-temporal frequencies and short time-lags in gathering and reporting data. While specific socio-demographic features of individuals might not easily be obtained, WBE can provide a spatial comparison between different populations with different socio-economic status at a community level (P. Choi et al., 2019).

We review the current situation of applying WBE towards understanding pharmaceutical consumption and provide an overview of analytical information and biomarkers used to monitor pharmaceutical use in defined population groups. Our aim is to document state-of-the-art WBE applications on pharmaceutical consumption to give a better understanding on the future research that is needed to move forward WBE as a complementary epidemiological
information source in DUR. In this lights, this review aims to provide key insights and prospects where WBE can further contribute to DUR.

2. Literature search and eligibility criteria

Multiple literature searches were conducted (between July 2020 and March 2021) to identify all publications (i.e. research papers, short reports, letters,…) on WBE investigations of pharmaceutical consumption. PubMed, Web of Science and Google Scholar were queried as illustrated in Table 1. Since WBE was first applied in 2008, we only searched for publications between 2008 and March 2021. An updated search was performed on a monthly basis to identify new emerging WBE applications on pharmaceuticals.

Table 1 Applied search combinations during the advanced literature search

<table>
<thead>
<tr>
<th>Specified search terms</th>
<th>Search records</th>
</tr>
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<tbody>
<tr>
<td>(sewage OR wastewater OR &quot;wastewater epidemiology&quot;) AND (pharmaceuticals OR medicines)</td>
<td>6498</td>
</tr>
<tr>
<td>(((wastewater OR sewage OR &quot;wastewater based epidemiology&quot;) AND (&quot;pharmaceuticals&quot; OR &quot;medicines&quot;)) AND consum*)</td>
<td>350</td>
</tr>
<tr>
<td>(((((wastewater) OR sewage) AND influent) AND pharmaceuticals) NOT &quot;removal efficiency&quot;) NOT sludge</td>
<td>165</td>
</tr>
<tr>
<td>(((&quot;wastewater epidemiology&quot;) OR &quot;sewage epidemiology&quot;) OR &quot;wastewater based epidemiology&quot;) AND pharmaceuticals AND consum*</td>
<td>71</td>
</tr>
<tr>
<td>(sewage OR wastewater OR &quot;wastewater epidemiology&quot;) AND pharmaceutical AND &quot;influent wastewater&quot;</td>
<td>45</td>
</tr>
<tr>
<td>(((&quot;wastewater based epidemiology&quot;) AND (pharmaceutical OR medicines)) AND (consumption OR &quot;population normalised&quot;))</td>
<td>28</td>
</tr>
<tr>
<td>(&quot;wastewater epidemiology&quot;[Title/Abstract] OR sewage [Title/Abstract] OR wastewater[Title/Abstract]) AND (pharmaceuticals OR medicines) AND &quot;population health&quot;</td>
<td>26</td>
</tr>
<tr>
<td>wastewater AND influent AND pharmaceutical AND loads NOT effluent</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 1 describes the different keyword combinations that were applied to identify eligible studies for this review. After a preliminary screening against the eligibility criteria, 122 publications were selected from this wide range of search records. This initial search was further screened against the strict inclusion criteria defined below. This final screening resulted in 64 publications qualified for full text review. While the total number of WBE applications on pharmaceuticals is relatively small, interest in this field of research has grown for the last six years (~ 9 papers per year on average), as illustrated in Fig S1. Numerous other studies report concentrations of pharmaceuticals in influent wastewater (IWW) (Baker & Kasprzyk-Hordern, 2011b; Bodik, Mackulak, Faberova, & Ivanova, 2016). However, in WBE, concentrations are not suitable to estimate community-wide use of pharmaceuticals because of fluctuations in flow rates and population sizes. For this reason, it is imperative to normalize measured concentrations for varying population sizes and flow rates to allow reliable comparisons between locations. Additionally, these descriptive studies did not triangulate with other data of tested specific
hypothesis about the spatio-temporal patterns of use. Therefore, these studies were not included in this review. By normalizing to population sizes and flow rates, WBE offers the possibility to compare intra- and intercountry normalized-loads of pharmaceuticals (Ahmed et al., 2020; Bodik et al., 2016; Pereira, Silva, Meisel, Lino, & Pena, 2015). For these reasons, the selection of eligible cases goes beyond simply reporting of pharmaceutical concentrations in IWW.

We included (i) WBE studies that estimated population-normalised mass loads of excreted human metabolic pharmaceutical biomarkers (mg/day/1000 inhabitants) and (ii) WBE studies in which pharmaceutical doses were back-calculated using measured concentrations of the biomarkers (doses/day/inhabitant). For this purpose, we excluded wastewater studies on pharmaceuticals that focused exclusively on (i) method development and validation; (ii) evaluating removal efficiencies during wastewater treatment; (iii) investigating pharmaceuticals as a potential source of contamination in aquatic environments and (iv) evaluating the use pharmaceutical concentrations as population size markers. Citation tracking and searches in author’s bibliographies were performed to track down additional references. Detailed information on the applied analytical techniques and current WBE biomarkers is given elsewhere (Baker & Kasprzyk-Hordern, 2011a; P. Choi et al., 2018; Gracia-Lor et al., 2017; van Nuijs et al., 2011).

3. WBE applications on pharmaceuticals: state-of-the-art applications

The final selection of 64 WBE applications can be categorized in different types including spatial and temporal comparisons, triangulating with sales and/or prescription statistics, monitoring pharmaceuticals as proxies of disease, correlations with socio-demographics, and evaluating illicit use of pharmaceuticals (Fig. 2). Table S2 summarizes all currently available WBE applications on pharmaceuticals. In this section, we will focus on the most prevalent applications.
3.1. Spatio-temporal analysis of pharmaceutical consumption

Population-normalized biomarker mass loads can be employed as a proxy for consumption of the parent compound. This normalization enables the comparison of consumption patterns across different locations and different time points. This proxy is more appropriate compared to per capita doses per day since less uncertainty is associated with the back-calculations (i.e. large uncertainties associated with excretion factors).

3.1.1. Spatial comparisons of pharmaceutical use

45 out of the 64 studies demonstrate the ability of WBE to investigate spatial differences in the consumption of pharmaceuticals (Ahmed et al., 2020; Australian Crime Intelligence Commission, 2020; Bade, Ghetia, White, & Gerber, 2020; Baker, Ocenaskova, Kvicalova, & Kasprzyk-Hordern, 2012; Baz-Lomba et al., 2016; Bodík et al., 2016; Boogaerts, Degreef, Covaci, & van Nuijs, 2019; Boogaerts, Quireyns, Covaci, De Loof, & van Nuijs, 2021; Burgard, Fuller, Becker, Ferrell, & Dinglasan-Panlilio, 2013; Castrignano et al., 2020; Causanilles, Emke, & de Voogt, 2016; Causanilles et al., 2018, 2017; P. M. Choi et al., 2018; P. Choi et al., 2019; Croft, Huffines, Pathak, & Subedi, 2020; Duan, Meng, Wen, & Chen, 2013; Escolà Casas et al., 2021; Fáberová, Bodík, Ivanová, Grabic, & Mackuľák, 2017; Fallati et al., 2020; Gao et al., 2016; Gomez-Canela, Sala-Comorera, Pueyo, Barata, & Lacorte, 2019; Gushgari, Driver, Steele, & Halden, 2018; Kim & Oh, 2020; Krizman, Senta, Ahel, & Terzic, 2016;
Mackulak et al., 2016, 2019; Mirzaei, Mesdaghinia, Hoseini, & Yunesian, 2019; Ort, Lawrence, Reungoat, Eaglesham, et al., 2010; Ostman, Fick, Nasstrom, & Lindberg, 2014; Pereira et al., 2015; Riva, Castiglioni, Pacciani, & Zuccato, 2020; Shao et al., 2021; Skees, Foppe, Loganathan, & Subedi, 2018; Subedi, Balakrishna, Joshua, & Kannan, 2017; Subedi & Kannan, 2015; Thiebault, Fougere, Destandau, Rety, & Jacob, 2017; Thomaidis et al., 2016; Venhuis, de Voogt, Emke, Causanilles, & Keizers, 2014; Xiao et al., 2019; J.-H. Yan et al., 2019; Q. Yan et al., 2014; Yargeau, Taylor, Li, Rodayan, & Metcalfe, 2014; Zhang et al., 2019, 2018. 34 studies indicate that WBE is sensitive enough to detect spatial variations in pharmaceutical use within countries (town/village level) and, therefore, able to identify locations that differ in pharmaceutical use. While some traditional DUR information sources may lack geospatial granularity, WBE can monitor consumption patterns at the scale of suburbs and regions within a metropolitan area. In contrast to the studies that focus on differences in pharmaceutical use within a specific country, only 8 studies provide a between-country spatial comparison (Baz-Lomba et al., 2016; Castrignano et al., 2020; Causanilles et al., 2018; Duan et al., 2013; Fallati et al., 2020; Gao et al., 2016; Subedi et al., 2017; Q. Yan et al., 2014). With traditional DUR information sources, it can be difficult to compare pharmaceutical consumption between jurisdictions when organization of the health care systems and therefore also data collection are completely different. In this light, Fallati et al. investigated the consumption of a broad range of pharmaceuticals in different therapeutic classes with WBE in Malé compared to Milan and Oslo (Fallati et al., 2020). Consumption in Malé could therefore be estimated through WBE as local prescription data were not available.

An under-explored area is the use of WBE within sub-catchments such as hospitals or university campuses, suburbs, or aged care facilities. Limited studies show the potential for WBE to monitor the consumption of pharmaceuticals in subsets of the population and during specific events (Burgard et al., 2019; Gomez-Canela et al., 2019; Gul, Gul, Stamper, Godfrey, & ElSohly, 2018; Gul, Stamper, Godfrey, Gul, & ElSohly, 2016; Gushgari et al., 2018; Kosma, Nannou, Boti, & Albanis, 2019; Mackulak et al., 2016; Ort, Lawrence, Reungoat, Eaglesham, et al., 2010; Stamper, Gul, Godfrey, Gul, & ElSohly, 2016; van Dyken et al., 2016). In this light, three WBE studies focused on the consumption of opioids and benzodiazepines during football games at the Mississippi University campus (Gul et al., 2018, 2016; Stamper et al., 2016) and found substantial increases in tramadol and hydrocodone while concentrations in the municipal IWW samples were unchanged.

3.1.2. Temporal analysis of pharmaceutical consumption

Due to its high temporal resolution, WBE can be employed to obtain useful information on the consumption patterns of pharmaceuticals over time. For instance, long-term trends can indicate whether pharmaceutical use is
stable, fluctuating, declining or on the rise. Additionally, seasonal patterns can highlight temporal changes with a
fixed frequency (e.g. between months of the year, between same months in different years). Furthermore, within-
week trends can reveal recreational pharmaceutical use versus habitual consumption (Tscharke, Chen, Gerber, &
White, 2016).

3.1.2.1 Within-week trends in pharmaceutical loads

To date, because sampling and analysis costs are typically relatively low, most studies have conducted 24-hour
composite sampling for multiple days. This allows for a temporal resolution that is difficult to obtain using other
methods. Differences in the mass loads measured on a daily basis can point to the recreational use of
pharmaceuticals on, for example, weekends as many pharmaceuticals, such as antihypertensives and
antidepressants, have low interdaily variability (Ahmed et al., 2020; Australian Crime Intelligence Commision,
2020; Been et al., 2015; Causanilles et al., 2016; Mastroianni, Lopez-Garcia, Postigo, Barcelo, & Lopez de Alda,
2017; Tscharke, Chen, Gerber, & White, 2015). Studies have thus found weekend differences in per capita
normalized mass loads for i) tramadol, methadone and possibly amitriptyline in the Czech Republic (Baker et al.,
2012), ii) tramadol, codeine and oxazepam in Slovakia (Mackulak et al., 2016) and iii) tramadol, diclofenac
(NSAID), methadone and antibiotics (sulfamethoxazole and trimethoprim) in France (Thiebault et al., 2017). Due
to the high frequency, analyses can also identify correlations between trends in the consumption of pharmaceuticals
that may be of concern.

Interestingly, two out of four studies estimating population-normalized mass loads of sildenafil found no difference
between weekend and weekday in the Netherlands and in 8 European cities (Causanilles et al., 2016, 2018), whereas
two studies, in England and in the Czech Republic, that document such a difference (Baker, Barron, & Kasprzyk-
Hordern, 2014; Baker et al., 2012). Similarly, the ADHD medication methylphenidate, having possible stimulant
effects, showed increased use on weekends in some European cities (Baz-Lomba et al., 2016) while this effect was
not found on a university campus (Gushgari et al., 2018).

3.1.2.2 Seasonality and long-term temporal trends

Most of the studies included in this review focused on a period of 7 days or less and fewer than 10 pharmaceuticals
for only one or two WWTPs, as indicated in Table S2. About half of the publications that assessed pharmaceutical
population-normalised mass loads in wastewater sampled more than 7 days and reported long-term temporal data
(i.e. trends that occur over several months or years). The most investigated substances were opioids, antibiotics,
benzodiazepines and antidepressants. In contrast to illicit drugs, short-term variations in pharmaceutical
consumption are less expected since pharmaceutical treatment requires frequent dose intervals and fixed treatment schemes. For this reason, it is more interesting to monitor long-term consumption patterns in the use of pharmaceuticals.

Higher mass loads were found in the winter for antidepressants, antibiotics (Golovko, Kumar, Fedorova, Randak, & Grabic, 2014), tramadol and venlafaxine (Mackulak et al., 2016) while summer and autumn recorded higher mass loads of NSAIDs (Papageorgiou, Kosma, & Lambropoulou, 2016), antihistamines, lipid regulators (Golovko et al., 2014), codeine and oxazepam (Mackulak et al., 2016). For carbamazepine, oxazepam, methadone, citalopram, metformine and memantine, population-normalized mass loads were relatively consistent between seasons (Golovko et al., 2014; Mackulak et al., 2016; Xiao et al., 2019).

Pereira et al and Krizman et al (Krizman et al., 2016; Pereira et al., 2015) also highlighted that seasonal differences in consumption estimates may be due to tourism, as higher use of some pharmaceuticals was observed during summer periods at coastal tourist destinations, when compared with equivalent non-tourist destinations (Pereira et al., 2015). This seasonal effect was addressed in Phung et al. by directly investigating the link between temperature and consumption of a handful of pharmaceuticals (Phung et al., 2017). They found increased temperature associated with increased naproxen (NSAID) loads, while decreased temperature related to increasing atenolol consumption. No significant changes with temperature were observed for caffeine, codeine, carbamazepine and hydrochlorothiazide. The changes in consumption measured in that study could also be due to changing population demographics throughout the year, e.g. an efflux of older people during summer, making it more difficult to compare studies with multiple years of data from multiple locations. However, these studies may highlight seasonal effects on consumption of substances; changes that may be geographically or culturally specific.

Of the few long term studies available on pharmaceutical consumption key findings include a decreasing trends in methadone consumption and an increase in oxycodone and fentanyl in Adelaide between 2011 and 2015 (Tscharke et al., 2016). Sildenafil and metformin use increased in the Netherlands (Causanilles et al., 2016) and China (Xiao et al., 2019) respectively over more than 3 years. Notably, consistent use patterns of methadone, morphine and codeine were observed over time in Lausanne, Zagreb and Adelaide, respectively (Been et al., 2015; Krizman-Matasic, Senta, Kostanjevecki, Ahel, & Terzic, 2019; Tscharke et al., 2016).

3.2. WBE biomarkers for disease and disease outbreaks

The WBE approach demonstrates that urinary human biomarkers identified and quantified in wastewater can provide a perspective on a population’s health in (near)-real time (Daughton, 2018). Specific pharmaceuticals or
a combination of pharmaceuticals are generally prescribed to treat diseases (Thomas & Reid, 2011). Several WBE studies demonstrate the potential for WBE biomarkers to serve as a proxy measure for treated disease prevalence. By measuring at high spatio-temporal resolution, it will be possible to monitor the evolution of different diseases in specific locations and make area-specific assessments about their burden and monitor in near-real-time the evolution of specific diseases.

This can however be complicated by a number of factors such as underdiagnosis or undertreatment. Additionally, some diseases need a combination treatment while some pharmaceuticals are used to treat multiple diseases. Uncertainties as arise for some diseases (e.g. depressive disorders), where non-pharmacological treatment might be prioritized over pharmaceutical treatment. Furthermore a lack of compliance or recreational use should also be taken into account. Therefore, it is imperative to proceed with caution when using WBE as a proxy for specific disease prevalence.

To date, four Chinese WBE studies have used metformin as a proxy for type 2 diabetes (Shao et al., 2021; Song et al., 2020; Xiao et al., 2019; J.-H. Yan et al., 2019). While they successfully captured metformin consumption in Chinese communities, measurement of other antidiabetic drugs (e.g. sulfonylureas) would be necessary for a more comprehensive picture on the prevalence of this disease. Insulin has been a key component of management in patients with type 2 diabetes mellitus (T2DM), who require insulin therapy to maintain normal hemoglobin A1c (HbA1c) levels (Scheurer, Brauch, & Lange, 2009). While most diabetic drugs are excreted in sufficient amounts in urine (Gong, Goswami, Giacomini, Altman, & Klein, 2012; SHELDON, ANDERSON, & STONER, 1965), almost all insulin is reabsorbed in the kidney with only trace amounts found in urine (Hanefeld, 2014). Therefore, the use of WBE as a proxy for type 2 diabetes is not viable in the absence of suitable biomarkers for insulin and additional biomarkers for antidiabetic drugs.

Ahmed et al. measured oxypurinol as a disease biomarker in wastewater to estimate the prevalence of treated gout in Australia (Ahmed et al., 2020). Gout prevalence was estimated to be 2.7% in this study, which was comparable to estimates from other epidemiologic studies (Proudman et al., 2019; Robinson, Kempe, Tebbutt, & Roberts, 2017). However, while defined daily doses (DDD) provided a good basis for comparing the consumption of pharmaceuticals between different countries, it might be more challenging to use it to estimate the prevalence of disease because of variations in doses prescribed per patient. Additionally, compliance is also universally low in these patient groups which increases the uncertainty in these estimates (Silva et al., 2010).
Antibiotics have significantly reduced morbidity and mortality from many infectious diseases (Bérdy, 2012). Their total global consumption increased 65% while consumption per capita increased 39% between 2000-2015 (Klein et al., 2018). The excess or inappropriate use of antibiotics can lead to antibiotic resistance, as indicated by studies showing an association between high use of antibiotics and enhanced antimicrobial resistance (AMR) (Chambers, 2001; Llor & Bjerrum, 2014). Wastewater has been used to monitor antibiotic presence and consumption patterns. Zhang et al. measured loads of 23 antibiotics in wastewater from eight major WWTPs of Beijing (Zhang et al., 2018). In another WBE study, antibiotic consumption was correlated with the flu season and the housing price and population density of the catchment (Zhang et al., 2019). Another study in China assessed the use of six antibiotics using WBE because there were no other data (Yuan, Liu, Huang, Yin, & Dang, 2016). In Milan, Italy, antibiotic excretion was higher in winter than in summer, reflecting the higher rate of infections during winter (Castiglioni et al., 2006). As antibiotic resistance genes emerge and spread globally, wastewater can monitor sources of environmental antibiotic resistance. WBE can provide rapid information on community antibiotics consumption in different time frames. A recent WBE study showed the power of analysing the consumption of quinolones antibiotics and quinolones resistance genes in European wastewater. It found that higher daily load qnrS gene were associated higher quinolone loads (Castrignano et al., 2020).

3.3. Relationship between socio-demographic catchment parameters and pharmaceutical use

The WBE approach allows the study of the relationships between consumption of chemicals and sociodemographic features of catchment areas. This may extend the relevance of WBE in the social sciences to such fields as town planning or local policy evaluation. These studies find predicted relationships between socioeconomic factors and the consumption of legal and illegal compounds but they also uncovered novel relationships.

Changes in the socioeconomic composition of a population over time can be measured using WBE. In a 2016 study, Thomaidis et al. analysed a suite of pharmaceuticals and drugs in the wastewater from Athens (Greece) between 2010 and 2014, a period in which there was a severe economic downturn and the implementation of austerity measures (Thomaidis et al., 2016). It showed staggering increases in the per capita consumption of narcotic drugs such as methadone (7-fold) and psychiatric pharmaceuticals (35-fold), and antidepressants (11-fold). By contrast, the consumption of amphetamine, antibiotics and NSAIDs decreased. This study demonstrates how WBE can be used to document changes in drug consumption produced by large-scale socioeconomic disruptions. Recently, Reinstadler et al. also showed the potential to investigate temporal changes during the coronavirus disease 2019 (COVID-19) lockdown and quarantine in the catchment area of Innsbruck (Reinstadler et al., 2021). This study showed that consumption of medicines prescribed for chronic pharmaceutical treatment
(e.g. oxazepam, carbamazepine, venlafaxine, etc.) remained unaffected by the public health crisis. Contrastingly, the consumption of pharmaceuticals for short-term use (e.g. acetaminophen, codeine and trimethoprim) declined during the COVID-19 pandemic, potentially as a result of improved population health or a reduction in the number of consultations of medical doctors or pharmacies.

Housing prices and density have been shown to be associated with the consumption of pharmaceuticals. A 2018 study measured 37 pharmaceuticals from eight WWTPs in Beijing (China), and related these to the average housing price and population density for each WWTP catchment (Zhang et al., 2018). These measures were highly correlated ($r = 0.92 – 0.93$) with the total load of pharmaceuticals. Because of the sampling strategy in this study (where one wastewater sample was deemed representative of a WWTP), these results may reflect increased pharmaceutical consumption by transient residents (i.e. commuting workers) rather than residents. Nevertheless, the results imply that higher economic status in China is linked to higher pharmaceutical use.

Relationships between WBE biomarkers and socioeconomic measures also include measures of demographics, education and more. An Australian study measured a suite of mostly drug and pharmaceutical biomarkers from wastewater samples collected at the same time as a national Census in 2019 (P. Choi et al., 2019). Per capita loads of opioids, antipsychotics and antidepressants were significantly higher in catchments with older, lower socioeconomic status populations. The loads of antibiotics cephalexin, sulfamethoxazole, and trimethoprim were not associated with either age or socioeconomics of the catchments. Strong correlations were found between specific drugs and socioeconomic measures. There were for example correlations between: tramadol use and the percentage of labourers in a population ($r = 0.84$), amitriptyline and a lack of high school education ($r = 0.77$), and there was an inverse relationship between pregabalin and high income ($r = -0.77$) in Australia (P. Choi et al., 2019). However, these associations may be influenced by the way reimbursement systems are set up. While WBE studies examining socioeconomics are unable to distinguish between correlation and causation, they can uncover important insights into how drug and other chemical consumption patterns are associated with socioeconomic characteristics.

A WBE study in Milan (Italy) found a significant correlation between airborne particulate matter and salbutamol (Fattore et al., 2016). This study clearly demonstrated the association between environmental changes (i.e. air pollution, pollen season) and higher consumption of a pharmaceutical to treat respiratory disease. This study demonstrates the potential of applying WBE to investigate environmental diseases. It provides a direct comparison
between pharmaceutical consumption and pollution levels at the same day, which can be used to investigate the relationship between environmental exposure and disease.

4. Future perspectives and developments

4.1. WBE as a promising complementary information source for DUR

The current review demonstrates ways in which WBE can potentially be utilised as a complementary tool in DUR but additional research is needed on methodological issues (i.e. in-sewer stability, pharmacokinetics, etc.) and data triangulation. Nonetheless we observe an increasing number of WBE applications on pharmaceuticals. Fig. 3 indicates where WBE could be applied as a complementary strategy to aid in filling the current knowledge gaps in the field of DUR and address the strengths of the different data sources. By triangulating data from the different pharmacoepidemiologic information sources, it may be possible to estimate the prevalence of use of pharmaceuticals more accurately. This information can be employed by policy-makers in the design and evaluation of pharmaceutical regulations.

Fig. 3 The place of WBE in the myriad of pharmacoepidemiological information sources in the context of drug utilization research

A major advantage of WBE is that it may provide estimates of consumption for pharmaceuticals which are not recorded using other methods; either because they are consumed illegally, or that they are not recorded in existing data sets (e.g. the Pharmaceutical Benefit Scheme in Australia does not include private scripts or in-hospital use; some pharmaceuticals can be purchased without scripts) (Mellish et al., 2015). WBE can provide complementary
information on what proportion of pharmaceuticals that are sold, dispensed and/or prescribed are consumed by the population because it measures consumption through human metabolic excretion products in wastewater. Discrepancies between WBE and prescription data could indicate the degree of compliance to a medication regimen at a population scale. A pharmaceutical prescribed to a patient is not necessarily taken by the patient in prescribed amounts or the dispensed amounts (e.g. if some of the medicines are diverted to others).

Additionally, WBE may be a good alternative when prescription data are very difficult and sales data are too expensive. For countries with limited prescription and or sales data, WBE could provide cost effective measurements of the amounts of key compounds that are consumed. Additionally, many low income countries do not have a prescription system and allow many pharmaceuticals to be sold over the counter with poor record keeping (Borges, Chama, & Nilsson, 2016). WBE may be useful for surveillance of pharmaceutical regulation that are not captured through traditional datasets (e.g. for pharmaceuticals not subsidized or off-label indications not refunded by disability insurance). Some pharmaceuticals can also be obtained without prescription so their use will not be included in prescription data (e.g. online internet trades, import from neighbouring countries, over-the-counter sales, etc.).

The WBE approach can be especially helpful in monitoring the use of antibiotics (Zhang et al., 2019, 2018) and misuse of potentially addictive pharmaceuticals, such as opioids and benzodiazepines (Bade et al., 2020; Centazzo, Frederick, Jacox, Cheng, & Concheiro-Guisan, 2019; Croft et al., 2020; Duvallet, Hayes, Erickson, Chai, & Matus, 2020; Endo et al., 2020; Gushgari, Venkatesan, Chen, Steele, & Halden, 2019; Kim & Oh, 2020). Antibiotics are supplied in several countries without a prescription (e.g. previously prescribed courses, local markets or stores, diversion from families or friends) which facilitates the development and spread of antibiotic resistance (Bahta et al., 2020; Berendonk et al., 2015; Llor & Cots, 2009). A recent study by Castrignanò et al. found that higher total quinolone loads corresponded with a higher prevalence of quinolone resistance genes (measured through in-sewer investigation of \textit{qnrS} genes) in the catchment areas (Castrignano et al., 2020). If estimated antibiotic DDDs in wastewater are substantially higher or lower than prescribed DDDs, the community may not be compliant with therapy. It might be difficult to accurately estimate compliance to antibiotic treatment at a population scale due to lack of knowledge of the optimal treatment length and varied treatment regimens for different infections. Nonetheless, it is worth investigating trends in the discrepancies between prescribed amounts of antibiotics and measured amounts in wastewater. Knowledge of total antibiotic loads is helpful to policy makers because of the strong quantitative link between antibiotic use and antibiotic resistance (World Health Organization (WHO), 2018). Another critical component of this aspect is that WBE can capture uses of pharmaceuticals in animal
husbandry if the runoff from such facilities is connected to the WWTP. This is obviously of high relevance for identifying inappropriate use of antibiotics leading to antimicrobial resistance as this is a global challenge with particularly poor data on antibiotic use in the general community (World Health Organization (WHO), 2015).

Additionally, many non-antibiotic pharmaceuticals have shown ability to induce for antibiotic resistance (Berendonk et al., 2015; Singh et al., 2019).

4.2. Agreement between WBE data and other DUR information sources

Some efforts have already been done to triangulate WBE data with other DUR information sources. These WBE studies show reasonable relationships between WBE data on pharmaceuticals (e.g. oxazepam, atenolol, etc.) and prescription and sales data (Baker et al., 2014; Baz-Lomba et al., 2016; Been et al., 2015; Escolà Casas et al., 2021; He et al., 2020; Kasprzyk-Hordern et al., 2009; Rice, Kannan, Castrignanò, Jagadeesan, & Kasprzyk-Hordern, 2020; Riva et al., 2020; van Nuijs et al., 2015). For some pharmaceuticals (e.g. paracetamol, etc.), discrepancies were reported which may reflect over-the-counter pharmaceutical sales that are not included in prescription data (Baker et al., 2014; Crowley, White, Tschärke, & Gerber, 2017; van Nuijs et al., 2015). They could also reflect illegal sales of pharmaceuticals and import/export/diversion of pharmaceuticals to other geographical areas.

Additionally, these differences may also arise from methodological uncertainties associated with WBE such as the direct disposal of parent compounds in the sewer, poor accuracy of excretion rates used in WBE’s back-calculations and the complete/incomplete deconjugation of metabolites in the sewer (Escolà Casas et al., 2021).

As indicated by van Nuijs et al, predicted loads and measured loads from the analysis of biomarkers in IWW could potentially not match accurately because WWTP catchment areas and postal codes do not correspond and not all households may be connected to the sewer system (van Nuijs et al., 2015). Prescribed pharmaceuticals may not be consumed by patients and the locality between the location of consumption and excretion might be different due to commuting.

Riva et al. used WBE with four prescription medicines intended for chronic use, including citalopram, enalapril, losartan and ramipril (Riva et al., 2020) in an attempt to assess compliance at a population level. WBE estimates and prescription data showed good agreement for citalopram, enalapril and their metabolites but in other cases there was a poor match. Although these discrepancies could be related to poor compliance or overuse, the authors acknowledged that the disagreement may also be the result of methodological uncertainties associated with each data source. In back-calculating daily defined doses they had to use potentially inaccurate excretion factors found in pharmacokinetic and metabolism studies. These correction factors are often obtained from clinical trials performed within a small subset of patients which may not be representative for the catchment population.
Additionally prescriptions may be incomplete in some areas (e.g. combination formulations only included in national figures but not in the regional database) and local prescription data may not match completely with the catchment area. Therefore, uncertainties in extrapolating to actual consumption should be addressed for each individual compound.

4.3. Early-warning system for pharmaceutical misuse

The illegal use of pharmaceuticals cannot be monitored using conventional datasets. Data triangulation can highlight potential discrepancies in the amounts used (e.g. identifying potential shifts to illicit use of pharmaceuticals) and potentially estimate the number of users, at a local and national level. In order to enable this comparison, it will be necessary to first monitor fluctuations in population-normalised mass loads of pharmaceuticals to understand trends in consumption patterns at a population level. The high temporal resolution of WBE enables researchers to monitor the evolution of the illicit market continuously, and with short-time lag. This may enable policy-makers to counter more swiftly the spread of counterfeit medicines and the recreational use of pharmaceuticals. It should be noted that while WBE can provide valuable information on the extent of counterfeit medication it cannot provide data on the composition (i.e. impurities, lack of API, dose of API, etc.) of counterfeit pharmaceuticals. WBE is not limited to measuring specific APIs; it can also be used to monitor their by-products or precursors in communities. In addition, the effects of legal import and export of pharmaceuticals (i.e. cheaper prices across national borders) cannot be excluded. These complications highlight the need for data triangulation to obtain a comprehensive view of total consumption and to identifying the extent in which pharmaceuticals are used appropriately.

In this light, Venhuis et al. highlighted the sale of sildenafil by online pharmacies in three Dutch communities (Venhuis et al., 2014). They compared estimates of sildenafil use based on WBE data with dispensing data on sildenafil that was legitimately sold. At least 60% of wastewater loads could not be explained by legal use of the drug. Causanilles et al. found also big discrepancies between WBE data and prescription data, if these were available (Causanilles et al., 2018) further documenting the power of WBE for documenting differences in local consumption patterns. However, a major limitation of this study is that prescription data was estimated by extrapolating the Dutch trend in prescription patterns, which might not be representative for other European countries.

Furthermore, historical WBE data could be used to quickly identify new consumption patterns at high spatio-temporal resolution early enough to avert an escalation in the use of pharmaceuticals. This approach can also be
used in specific locations to describe dissemination of a pattern of drug use of public health concern (e.g. increasing opioid consumption in rural areas in Australia).

4.4. Monitoring the effect of interventions and quality-control system in decision-making processes

In contrast to illicit drugs, tobacco and alcohol (Australian Crime Intelligence Commision, 2020; Mackie et al., 2019), WBE applications on pharmaceuticals have played a limited role in government strategies and decision-making. We propose several ways in which WBE may provide a complementary monitoring approach for governments and pharmaceutical policy makers.

The WBE approach provides a tool that can i) measure consumption of pharmaceuticals; ii) determine consumption patterns of pharmaceuticals at different spatial (e.g. local, regional, national, international) and temporal resolutions (e.g. daily, weekly, seasonally, yearly, etc.); and iii) by triangulating with other datasets, assess the impact that strategies or interventions have on consumption. These uses are not limited to a specific pharmaceutical, but could apply to a group of pharmaceuticals.

In this light, WBE may be particularly useful in monitoring the effect of an intervention or for assessing weekly or seasonal trends in pharmaceutical consumption. This could include an intervention such as a rescheduling or restricting of sale of a drug, a change in prescribing practice or regulations, or an education/advertising program to change the behaviours of prescribers or individuals consuming pharmaceuticals. As yet, fewer studies have done so reported this, however one notable example is Zhang et al, which evaluated a potential decline in antibiotic use following interventions to prevent their prophylactic use during flu season in China (Zhang et al., 2019). One limitation of their study was the absence of samples from the period before the change occurred, which necessitated the use of other data sources. Partnerships between researchers and government agencies may assist in undertaking evaluations of policy changes before, during and after they occur. Additionally, WBE studies of pharmaceuticals are not necessarily limited in their choice of pharmaceuticals, as may be the case for surveys of drug use. If researchers/policy advisors are interested in the effects of an intervention directed at one pharmaceutical, WBE may be used to assess how this intervention has influenced consumption of another pharmaceutical. WBE could quickly measure changes in the consumption of pharmaceuticals during public health crises. In this light, WBE can be employed to investigate the impact of large-scale lifestyle disruptions such as the COVID-19 pandemic, continuously and with a shorter time lag than prescription or sales data (Been et al., 2021; Reinstadler et al., 2021).

Additionally, WBE can provide location specific information for DUR, which could be used to set area-based health care priorities for policy-makers. Areas with a higher burden of pharmaceutical misuse may require more
policy attention e.g. public or prescriber education, or the prevention of opioid overdose deaths by distributing naloxone sprays (Endo et al., 2020). WBE can identify areas with a higher burden of both legal and illegal opioid use. By prioritising problematic areas, decision-makers can respond to an evolving public health problems and address the social determinants of a public health crisis. The EMCDDA has already shown the effectiveness of this approach in addressing the consumption of illegal drugs in different European communities (European Monitoring Centre for Drugs and Drug Addiction, 2019a).

In the same manner, WBE is also able to evaluate the effects of the promotional activities of pharmaceutical companies, government or other institutions. This would enable policy-makers to assess if these approaches are an efficient use of resources. If the measures don’t produce the desired effect, policy makers might look for different policies. WBE could be used, for example, to assess if statin compliance was adversely affected by exaggerated media reports about side effects (Nordestgaard, 2018).

Besides that, WBE can be used to quickly evaluate the effect of policy changes and to optimize prevention and harm reduction strategies targeting pharmaceuticals. Furthermore, by triangulating WBE data with other DUR data from different locations and information sources, decision-makers can identify and promote best practice. In this light, WBE can also be used to monitor and evaluate measures to ameliorate undesirable pharmaceutical use (e.g. over-use of antibiotics, benzodiazepines, Z-drugs, opioids etc.). This is especially helpful in situations where information on the consumption of pharmaceuticals needs to be obtained rapidly (e.g. socio-economic disruptions, health crises, epidemics, etc.). These interventions do not always have to be restricted to governments. Other organisations could potentially use WBE to assess the effects of their activities on the burden of pharmaceutical use (e.g. non-profit organisations that intervene to diminish addiction).

Furthermore, WBE can also provide an indicator of the extent of stockpiling of pharmaceuticals that have been removed from the market. WBE can complement DUR data source because sales and prescriptions of these pharmaceuticals are no longer available upon their removal from the market. It could also measure the extent of stockpiling after the sale and distribution of scheduled pharmaceuticals is prohibited. If these pharmaceuticals are still used in different communities, it would mean that they are acquired from other sources (e.g. online pharmacies, imported from other countries). WBE can also be applied to investigate if pharmaceutical reformulations (e.g. oxycodone reformulation in Australia to prevent injecting drug use) reduce consumption.

Two examples of governments that have used WBE for drug utilization research are the Australian National Wastewater Drug Monitoring Program (NWDMP) and the New Zealand National Wastewater Testing Programs.
These campaigns monitor an array of both illicit and licit drug metabolites (e.g., fentanyl and oxycodone) in a large proportion of the population. The Australian NWDMP demonstrated large spatial differences in per capita consumption of some pharmaceuticals such as fentanyl and oxycodone and that regional consumption for these was higher than in the capital cities, as well as changes in consumption over time (Australian Crime Intelligence Commission, 2020).

5. Methodological limitations

Despite the progress made through more than a decade of research, WBE has some intrinsic uncertainties related to sampling, biomarker stability, chemical analysis and real-time population that remain to be addressed (Castiglioni et al., 2013). Fig. 4 focuses on the different steps of WBE that should be checked when adopting this methodology. This flowchart also indicates the several sources of uncertainty associated with the different steps that need to be resolved when applying the WBE approach.

Efforts have been spent to evaluate these uncertainties and improve the accuracy of WBE estimations. In this sense, continuous flow-proportional sampling of the influent is recommended best practice for sampling (Ort, Lawrence, Reungoat, & Mueller, 2010), but in reality different sampling methods including time proportional or volume proportional sampling are used for logistical reasons. Most of the reported studies use fixed population numbers and it is difficult to verify if the fluctuations in population-normalized mass loads were due to variations in population size or changes in consumption patterns. Therefore, it would be more appropriate to use dynamic

Fig. 4 Criteria for implementing the WBE approach
population size numbers using either an anthropogenic biomarker or other data such as mobile phone data (Been et al., 2014; O’Brien et al., 2014; Thomas, Amador, Baz-Lomba, & Reid, 2017).

Metabolism and excretion of drugs are known to vary between individual or even within one individual under different health condition. Therefore, the excretion factor (EF), derived from these processes, contributes notably to the overall uncertainty of substance consumption estimation in WBE. EFs used in WBE applications are mostly derived from pharmacokinetic studies that had a limited number of participants and so may not reflect the average excretion profile in large populations (Kato, 1975; Klotz, 2011; Yasuda, Zhang, & Huang, 2008). Effort are being made to refine the EF of different drugs (Gracia-Lor, Zuccato, & Castiglioni, 2016). In recent years, some EF values derived from pharmacokinetics data were considered unsuitable for WBE application due to the large uncertainty involved. Therefore, estimation of absolute figures on back-calculated doses should be addressed more carefully. However, the primary focus of WBE has been to provide a complementary strategy to monitor spatial and temporal trends in consumption patterns of pharmaceuticals. For this purpose, a viable approach to uncertainty arising from EFs would be to use population-normalised mass loads and focus on the analysis of trends. Actually, back-calculating defined daily doses should only be considered when triangulation with other relevant DUR information sources is necessary. As an alternative, mass load of biomarkers in wastewater and prescription/sales statistics have been used to refine the EF for WBE applications. In some cases they have shown that these EFs can provide more accurate estimates of substance consumption in large populations (Thai, Lai, Bruno, et al., 2016).

Additional uncertainties can arise from the non-use and/or direct disposal of unused drugs or the formation from other chemicals or conjugated drugs (Bettington et al., 2018; Guirguis, 2010). This is especially an issue if the parent drug is used as biomarker and if the unused drugs are disposed directly into the sewers (Petrie, Barden, & Kaspryzk-Hordern, 2015). Most pharmaceuticals possess chirality and racemic analysis can be used to distinguish between dumping and consumption of pharmaceuticals.

Stability of biomarkers is another source of uncertainties in WBE. Several studies have been carried out to understand degradation/fate processes and evaluate and model the in-sample and in-sewer biomarker stability in order to improve our understanding of the degree of this uncertainty (P. Choi et al., 2020; Gao et al., 2019; Li et al., 2019; Ramin et al., 2017). Using preservatives such as HCl and storing the samples at low temperature (preferably <-20 °C) are appropriate ways to minimise biomarker transformation. However, preservatives can only be introduced at the point of collection and so do not account for any in-sewer degradation. For in-sewer stability, the uncertainty could be much higher due to the lack of control over the microbiota present in the sewer system,
especially the sewer biofilms. Overall, higher biofilm area to bulk water volume ratio, higher wastewater temperatures and longer hydraulic retention time promote biomarker transformation in the sewers (O’Brien et al., 2017).

For some chemicals, sorption to particulate matter and/or biofilm can also contribute to the overall uncertainty of the WBE approach, especially for biomarkers with high log $K_{ow}$ values such as methadone, fluoxetine and atorvastatin (Baker & Kasprzyk-Hordern, 2011c; Ramin et al., 2017).

6. Conclusion

Influent wastewater contains a wealth of information on population health and lifestyle and can be considered as a mirror of the society. The growing number of applications demonstrates how WBE can reduce current knowledge gaps in DUR. In the future, DUR could benefit from a better understanding of pharmaceutical use in the general population. In this light, WBE could provide information on pharmaceutical use not recorded using other methods (e.g. illegal use, imported pharmaceuticals,...) and could be employed as an alternative in countries with poor recordkeeping. Additionally, WBE has the potential to be used as an indicator on health aspects of populations which can be obtained with fast turn-around-times at high spatial and temporal resolutions and therefore to be used as early-warning system for more detailed investigations. However, knowledge of methodological issues and compound-specific uncertainties (i.e. biomarker excretion, in-sewer stability, population catchment size) will be needed to convert concentrations of human biomarkers to population-normalised loads and/or pharmaceutical consumption.

We also clearly emphasize the importance of triangulating multiple sources of information (e.g. prescription/sales/dispensing data, health interview survey data,...) to validate WBE measurements and obtain a multi-angled view on the use of pharmaceuticals in different locations. Additionally, the high spatio-temporal frequency of WBE enables correlation analysis to investigate association between pharmaceutical consumption and socio-demographics in specific communities. This adaptable sampling frequency also enables the investigation of the impact of interventions (e.g. pharmaceutical rescheduling, restricted sales, education initiatives,...) implemented by governmental agencies. It improves our understanding of pharmaceutical (mis)use for the location-specific allocations of health care resources made by policy-makers. Finally, WBE is one of the few data sources that can objectively measure the extent of illegal pharmaceutical consumption in the population. WBE and other DUR information sources have their strength and weaknesses but the combination promises to be yield more than the some of each.
Acknowledgements

None to declare

Declarations of conflicts of interest

We hereby declare that there are no conflicts of interest. This is an original study and the work has not been previously published as a whole or in part, and is not under consideration for publication elsewhere.

Funding information

Authors affiliated to the Toxicological Centre (University of Antwerp) were funded for this particular study by the European Union’s Justice Programme—Drugs Policy Initiatives, EuSeME (project number 861602). The Queensland Alliance for Environmental Health Sciences (QAEHS), The University of Queensland gratefully acknowledges the financial support of the Queensland Department of Health. Jochen F. Mueller is funded by an ARC Australian Laureate Fellowship FL 200100028. This manuscript is partly funded by an Australian Research Council (ARC) Discovery project (DP180101475).


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