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REVIEW ARTICLE

Wastewater-based epidemiology in low Human Development Index states: bias in consumption monitoring of illicit drugs

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Abstract

Wastewater-based epidemiology is a promising approach worldwide, and its application is currently being developed in non-advanced economies. This technology, based on known toxicokinetic data initially used to detect illicit drugs in well-managed and maintained local sewer networks, has been extended to assess other products such as pesticides, alcohol, flame retardants, nicotine, and other substances. This technology is also used in countries with non-advanced economies. The present review aims to support future wastewater-based epidemiology in such countries by providing toxicokinetic data for locally used narcotic drugs that are expected or known to be emerging in developed countries, outlining the excretion differences due to human polymorphism, and summarising the practical obstacles due to the coverage, maintenance efficiency, or type of local sewage network.Case study feedback from Martinique is presented as an example; the Martinique field study complies with the Organisation for Economic Co-operation and Development standards for health issues, but not with regard to population and urban dynamics.

Keywords Global South countries · Sewer porosity · Pharmacokinetics · Crack · Ibogaine · Ayahuasca

Introduction

Wastewater-based epidemiology is a back-calculation approach used to estimate the consumption trends of chemicals among populations with access to a sewage network based on the chemicals released into wastewater. Currently, its main focus is assessing illicit drug consumption due to the illegal context and subsequent secrecy of this usage. The present review will chiefly focus on the wastewater-based epidemiology approach based on the back-calculation of illicit drug consumption, bearing in mind that these statements could also be transposed to other molecules.

Consumption Q is back-calculated as:

$$Q = Q_{\mathrm{day}}/U_{\mathrm{ex}} \times M_{\mathrm{ratio}} \times 1000/N_{\mathrm{inh}} \quad (1)$$

where Q_{day} is the load of the drug target residues (DTR) calculated from the flow measurement and raw wastewater concentrations, U_{ex} is the percentage of DTR urinary excretion, M_{ratio} is the parent drug/DTR molar ratio, and N_{inh} is the number of inhabitants in the catchment area. The correcting factor due to DTR degradation in the sewer network has been discussed in many articles (see Senta et al. 2014 and Devault et al. 2017a for a detailed study), although it should be noted that (i) DTR is selected as it is the least degradable molecule of the parent molecules and their metabolites; (ii) its transit in the sewer network is expected to be as short as possible; and (iii) its degradation could be integrated into corrected factors. Many reviews assessing such issues have already been detailed (Ort et al. 2010; Castiglioni et al. 2013; Van Nuijs et al. 2012; among many), and they support the conclusions of the present review. However, the specificity of low Human Development Index (HDI) countries leads to incomparably worse consequences compared to high HDI countries, as detailed below.

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This method calls for the measurement of the daily flux of chemicals, the pharmacokinetic characteristics of the monitored chemicals, and the size of the population connected to the sewage system. Pivotal data for wastewater-based epidemiology back-calculation include the illicit drug excretion rate, the fate of chemical tracers of illicit drugs contained in sewage in order to determine the most frequently excreted and/or the most persistent drugs, and the estimated size of the connected population based on water treatment plant data and biological oxygen demand over a 5-day period (considering a rate of 60 g of O_2/inhabitant/day; Andreottola et al. 1994). Such information is underpinned by field validation. However, after consulting field studies over the last decade with suitable ratios, these studies were found to be based on cities located in Australia, USA, Western Europe, and more recently, China.

By definition, the consumption of illicit chemicals cannot be directly assessed due to the clandestine nature of this market. Addictive molecules are indeed the first type investigated (Zuccato et al. 2005) to complete or improve epidemiology data obtained using written questionnaires (Tourangeau and Yan 2007). Since 2013, wastewater-based epidemiology has been applied in Martinique Island (French West Indies) following a protocol in the framework of the European Monitoring Centre for Drugs and Drug Addiction, in cooperation with the global "Sewage Analysis CORe group Europe" (SCORE) programme funded by the European Union (COST fund) (Devault et al. 2014).

This study raises numerous questions, and the application of wastewater-based epidemiology in such field studies notably highlights many obstacles: the room for improvement in both pharmacokinetics and sewer network coverage as well as the conditions for the application of wastewater-based epidemiology in the context of states with non-advanced economies (SNAEs), which are numerous in intertropical areas. SNAEs are defined as countries with a gross national income per capita of less than US$12,236 (World Bank 2016). The present article thus aims to assess the bias factors that may impact the application of wastewater-based epidemiology in tropical and/or seismic areas and their populations.

Wastewater-based epidemiology is based on the sewage concentration of DTR, i.e., the stable metabolite of the parent drug or targeted drug itself if it is sufficiently stable. Wastewater is mainly investigated at the entry of wastewater treatment plants (WWTPs). However, in SNAEs, one must bear in mind pharmacokinetic knowledge as well as the state of the existing monitoring devices and sewers:

1. A sufficient knowledge of the pharmacokinetics of DTR, including the alternative metabolic pathways in the case of the consumption of multiple drugs, including alcohol, as well as genetic variabilities due to gender, age, and interethnic origins.
2. There may be benign leaks in sewers or inexact data relating to the level of leaks and their impact. The need for the rapid transportation of wastewater between the point of emission (i.e., domestic, hospital, and/or industrial sources), and the sampling point must also be taken into consideration. In the case of a distant source and/or a slow sewage stream, the emission sources close to the sampling point will be relatively overestimated compared to distant ones. The sewer network coverage also has to ensure the representativeness of the population.

The evaluation of the direct impact of temperature and pH (i.e., degradation, biodegradation, adsorption, and flocculation putative enhancement) on DTR was detailed in a previous study (Devault et al. 2017a). This aspect will therefore not be detailed in the present article, although the results mentioned in Devault et al. (2017a) are cited.

These conditions have to be met in order to carry out wastewater-based epidemiology. However, considering the field conditions in the poorest states, meeting such conditions may prove challenging: it is not a matter of a given obstacle being present or absent, but rather a striking quantitative difference that could reach feasibility limits and demand particular attention in such a context. In the following review, the obstacles numbered above will be addressed in the sections enumerated below.

Wastewater-based epidemiology is increasingly performed in SNAEs (Bijlsma et al. 2016; Causanilles et al. 2017; Gao et al. 2017; Moslah et al. 2017; Wang et al. 2017; Zheng et al. 2017). These design briefs could be performed in SNAEs depending on the local conditions. The areas considered in these studies are developing and emerging states: a SNAE is defined by the International Monetary Fund in terms of HDI (International Monetary Fund 2008). The present review will focus more on states with a lower HDI, especially those located in warm conditions, including intertropical areas.

The present article will also highlight the amount of useful data obtained from questionnaires on addictive practices and consumers and studies on wastewater from homes connected to the sewer network. In other words, the present review discusses the potential biases linked to the use of wastewater-based epidemiology for illicit drug back-calculation. Information about sewer networks and physico-chemical conditions could be directly transposed to other molecules, while pharmacokinetics could be indirectly applied to other biomarkers.

In practice, wastewater-based epidemiology essentially uses WWTPs as well as sewage collecting points equipped with autosamplers that are capable of refrigerating at 4 °C a wastewater volume corresponding as much as possible to the representative daily loads. WWTP monitoring within the American and European framework is governed by legal directives and is a useful reference: WWTP managers have already calibrated autosamplers for a representative sampling at a daily cadence. Daily samples are then transported at 4 °C or frozen to the analytical laboratory. EMCDDA (2015)

proposed a detailed protocol to define the most propitious hour (around 8 am) to retrieve the daily sample considering metabolism and excretion duration.

Pharmacokinetics

The first bias is the pharmacokinetics of the illicit drugs under consideration: inappropriate excretion rates could be used, because the excretion rates for specific populations or routes of administration are unknown, or because administration routes present unusual proportions in states with a higher HDI. Moreover, some consumption trends emerging elsewhere are kept confidential in certain populations, while the corresponding excretion rates have never been summarised or even reported in wastewater-based epidemiology.

Wastewater-based epidemiology is based on human excretion rates, and therefore the compounds used for back-calculation will not be degraded in the sewer between the domestic excretion and the WWTP inlets where the autosamplers are located. Excretion rates used in international studies such as SCORE are based on European consumption, i.e., taking into consideration the proportion of each route of administration for illicit drugs, which can be used differently.

In the following section, local patterns of illicit drug use will be detailed, including excretion rates if available. Moreover, these data reflect the trend of drugs in remote places typically used for tribal ceremonies, which are currently being adopted by consumers in Europe and the USA (Nefau, pers. comm.); the concerned molecules are ibogaine and beta-carboline. In addition, the local route of administration of illicit drugs such as tetrahydrocannabinol (THC), cocaine (COC), cathinone, and opioids could present unusual modulations in terms of excretion patterns, with the best example being crack for COC.

Cocaine (snorted and consumed as crack) is among the most commonly used psychoactive drug worldwide. It is a psychostimulant alkaloid extracted from *Erythroxylum coca* leaves. The dose of snorted COC varies between 50 mg and 1 g (Ricordel and Ragoucy-Sengler 2012). Its bioavailability is around 85% when it is snorted and between 33 and 77% when it is smoked (Ricordel and Ragoucy-Sengler 2012). The main metabolite is benzoylecgonine (BZE) (30–50% of metabolites) followed by ecgonine methyl ester (20–40%) and norcocaine (around 9%) (Baselt 2004; Zuccato et al. 2008). Other metabolites have also been described. One of them, methylecgonidine, is created only when COC is smoked. Its half-life is about 20 min (Scheidweiler et al. 2003) but it can be found in the urine of crack consumers (Paul et al. 2005). It is demethylated into ecgonidine in about 3 h in the body. When COC is snorted with alcohol, between 2 and 10% of the dose is transformed into cocaethylene (COE). Table 1 presents the different molecules, their main metabolites, and the proportion reported in urine by Ricordel and Ragoucy-Sengler (2012). However, if we consider crack consumption, COE is under-excreted as reported by Devault et al. (2014, 2017b), despite the high prevalence and concentration of crack consumed in Martinique.

Table 1 Excretion rate of cocaine and its main metabolite

Molecule and metabolites	Proportion in urine (%)
Cocaine	1–14
Benzoylecgonine	16–60
Ecgonine methyl ester	7–49
Norcocaine	0.6
Cocaethylene	0.7–1.7
Ecgonidine methyl ester	0.02–0.3

Considering that the temperature in a crack pipe is approximately 250 °C during smoking (Perez-Reyes et al. 1982), 32% of the initial COC content remains, whereas the pyrolysis product is mainly (around 73%) ecgonidine methyl ester (Nakahara and Ishigami 1991). Thus, the inhaled COC dose is reduced to a third of the initial dose placed in the bowl, and the cocaethylene content is reduced threefold. With regard to monitoring in Martinique where crack consumption is prevalent, there was an inexplicably low level of COE of 5 ng/L (Devault et al. 2014, 2017b), whereas at least 40 ng/L for the ratio BZE/COE was found in wastewater elsewhere (Pal et al. 2013 and others). The urinary excretion rate depends on the route of administration: for example, BZE is about 39% for an intravenous route and 16% for a smoked route (Cone et al. 1998).

In Martinique, COC is both snorted and smoked (i.e., crack). Even though crack users are more frequent among all COC users (Costes 2010), they are the most visible proportion in public places or treatment centres. For example, according to the NEMO study, 98% of COC "problematic users" are crack consumers (Merle et al. 2007), although crack consumption is lower in populations in Europe, the USA, and Australia (UNODC 2015). To put things in perspective, the use of crack COC is predominant in the USA among those who report COC as their primary substance of abuse (73% of admissions to substance-abuse treatment programmes reported smoking to be their primary route of administering COC, SAMHSA 2007). In similar European populations, the reported smoking proportions are significantly less, with a suggested continental average of 31.6%, varying nationally from 0 to 45.9% (EMCDDA 2009). In Australia, the proportion of abusers smoking COC is minor, as crack is rarely available (NDARC, undated; Ross 2007).

COC is excreted by the human body in urine as two main metabolites, ecgonine methyl ester (7–50%) and BZE (16–55%), as well as a number of minor metabolites (0.3–20%) and in unchanged form (1–9%) (Baselt 2004). However, the BZE excretion rates of intranasal and smoked substances

(such as crack) are respectively 45% (Baselt 2004) and 14.8–28% (Cone et al. 1998; Huestis et al. 2007). Considering 21.4% as the mean value, the consumption of COC is at least twofold underestimated when using the Western population's mean ratio (45%). However, since 2013, results have also brought into question the ratio between COC and BZE. Bijlsma et al. (2016) found the COC/BZE ratio to be 0.42 in wastewater according to the SCORE annual surveys, with the 5 to 95 percentile values being 0.10 and 0.82, respectively; this was consistent with the findings of Ratola et al. (2012) and in line with results from China (Khan et al. 2014). However, the results published by Li et al. (2016) showed a COC/BZE ratio close to 1. On the contrary, since 2013, the median COC/BZE ratio of the 47 results taken from the Martinique population, which is 80% of African descent, has been less than 0.25, including an obvious direct input in 2014 as the result of a police raid. Of course, temperature, pH, oxygen content (Jelic et al. 2015), retention time in the sewer, route of administration, and many other parameters (Lens et al. 1998) should be taken into account to explain such results. Also, the duration of summer temperatures is inversely related to latitude. Metabolic differences due to human diversity are known (for example, Geisen et al. 2005; Kalow 1982; Loebstein et al. 2001; Scordo et al. 2002; Wadelius et al. 2004; Xie et al. 2014). This raises the question as to whether consumer variety has an impact on the BZE excretion rate and thus the COC back-calculation.

The impact of such a practice on the metabolisation of crack is unknown, but it led to a notable difference between the sewage results reported internationally and in Martinique: COE and norcocaine, two metabolites of COC, were never quantified or even detected. COE is known to be the metabolite of co-consumption of COC and alcohol (Baselt 2004) through COC transesterification, causing 0.7% of the COC dose (Baselt 2004) to be excreted as cocaethylene in urine after 24 h.

Rodríguez-Álvarez et al. (2015) estimated the average COE/BZE concentration ratio to be about 0.04, i.e., between 0.006 and 0.07. The same study estimated that a low COE/BZE ratio was due to low recreational alcohol consumption when COC was used during the weekend; however, alcohol and illicit drugs have a similar recreational context of use. The recreational use of COC in Martinique is quantitatively insignificant regarding the BZE flux detailed by Devault et al. (2014, 2017b) during normal weeks, i.e., weeks without a major festive event. Back-calculated COC consumption based on wastewater-based epidemiology, mainly due to crack use, does not distinguish between weekends and weekdays, regardless of the social level (Devault et al. 2014). One-third of COC consumers (i.e., crack consumers) are also alcoholics, with an alcohol intake equal to or greater than 1 L/day, whereas alcohol intake in Santiago and Milan was respectively estimated at an average of 13.6 L and 5.1 L ethanol/1000 individuals per day (Rodríguez-Álvarez et al. 2015). Alcohol consumption is not a limiting factor, and according to Rodríguez-Álvarez et al. (2015), the excretion of COE should be closer to the proposed upper than lower levels. Considering the average 0.04 ratio and the median concentration of BZE (i.e., 1100 to 2500 ng/L), the expected COE concentration should be between 44 and 100 ng/L. Regarding the limit of quantification of COE (5 ng/L), COE should have been quantified, but it has never been quantified. Considering the lowest median concentration of BZE (1100 ng/L) and the COE concentration close to limit of quantification (5 ng/L), the maximal COE/BZE ratio in the present study is 0.004, that is, 10 times lower than the average proposed by Rodríguez-Álvarez et al. (2015) and under the minimal value calculated by the authors.

There are two possible explanations in this respect. Firstly, we may note the rapid degradation of COE or sorption on particulate matter and biofilms in sewers, which is enhanced in the tropical context. The fate of COE in sewers has not been evaluated, even in temperate summer conditions. However, stability studies of blood and tissue samples (Moriya and Hashimoto 1996) suggest that COE will be more stable than COC in such samples, have a limited tendency to sorption, and be mainly excreted via urine (Khan and Nicell 2011).

Secondly, COE pharmacokinetics needs to be improved with regard to the consumption of crack. When COC is smoked as crack, the main pyrolytic product is methylecgonidine (anhydroecgonine methyl ester), which can form three main metabolites (Maurer et al. 2006), including ecgonidine (anhydroecgonine) that is measurable in wastewater. The change in BZE excretion is not the only parameter to change in the case of crack smoking. To our knowledge, the net fraction of urinary COE expected after co-administering COC through the commonly used route of smoking COC with oral ethanol has not been studied since the abovementioned report by Khan and Nicell in 2011.

Delta-9-tetrahydrocannabinol (THC) is the main psychoactive product of *Cannabis sativa*. When it is smoked, the bioavailability of the psychoactive substance is between 15 and 50% (Coquerel and Lemaire-Hurtel 2012; Haney and Kutscheid 1973; Fairbairn and Liebmann 1974; Latta and Eaton 1975). Numerous metabolites exist, with the main ones being 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (TCH-COOH) created by liver cytochrome P450 2C9 (Goullé et al. 2008). Cannabis is mostly eliminated as acid and glucuronide conjugate (Kemp et al. 1995). The urine excretion rate is 20 to 35%, whereas it is between 65 and 80% in faeces (Wall and Perez-Reyes 1981). Less than 5% of the native drug is found in faeces (Halldin et al. 1982). The speed of elimination depends on the consumption habits, proportion of fatty tissue, and metabolism activity (Widman et al. 1985). Metabolites are present in urine for 12 days after a single dose and about 1 month for frequent doses (Grotenhermen 2003).

Considering cannabis, another bias could occur in the case of non-wastewater collection, diffuse porosity in saturated ground, and discharge of runoff waters into sewers (see below), because cannabis could potentially be cultivated on a large scale in these areas (Cruse and Figueira 2014). This is the case in North Saint Vincent, where large outdoor plantations of non-therapeutic cannabis are located (Griffith and Munroe 1995; Klein 2004; Labrousse 2002). Klein (2004) reported that among the Caribbean states, Saint Vincent has the most developed cannabis industry. While smaller than the Jamaican export sector, this industry in Saint Vincent plays a more important role in relation to the local economy (Klein 2004). Lavrieux et al. (2013) demonstrated that the retting process to separate the longer hemp fibres from the shorter ones for the textile industry left a natural tracer, cannabinol, which can still be measured in core sediment dating back to the ninth century. Thus, in surface water, it is necessary to consider that cannabis leaf maceration could induce, in a lotic environment, a quantifiable concentration of THC and its metabolites (Coffman and Gentner 1974). However, THC and its parent molecules are hydrophobic (K_{OW} around 5.5), meaning that these molecules tend to contaminate particulate fractions instead of remaining dissolved, which is a possible source of bias for the interpretation of THC and THC-COOH content in wastewater.

Opium normally contains about 10% morphine and 0.5% codeine (Yong and Lik 1977). In the case of opium consumption, the main metabolites excreted in urine are morphine and codeine glucuronides (Yong and Lik 1977). The urinary excretion of morphine from opium consumption is slower than that of medicinal morphine: the maxima in the hourly excretion pattern of morphine were found to be less pronounced and occurred 2–4 h after consumption (Yong and Lik 1977). The drug concentrations in urine are also incidentally lower (Yong and Lik 1977). However, the codeine/morphine ratio could theoretically be used to segregate opium addiction from morphine addiction: the codeine/morphine excretion ratio for opium addicts is 3:1 in the case of opium consumption and 1:2 in the case of morphine or heroin consumption (Yong and Lik 1977). However, in the context of a field study on medical codeine and the cleavage of morphine-glucuronide, bearing in mind the fate of micropollutants in the sewer, this could lead to confusion when segregating the parent consumption of heroin, morphine, and opium. Considering the current addiction trends, opium use is declining, with the remaining users mainly being elderly people (Yong and Lik 1977; Westermeyer 1983).

Cathinone and synthesis mephedrone are amphetamine-like drugs. This class of psychoactive drugs includes natural and synthetised molecules. Natural molecules (so-called cathinone and cathine) are found in *Catha edulis* leaves. Cathine is a biological metabolite of cathinone produced by the leaves. It is traditionally consumed in the Middle East and East Africa (UNODC 2015). Leaves are chewed, and molecules are absorbed by both the oral mucosa and gut (Geresu 2015). The first-pass effect is very significant (Geresu 2015). Cathinone is transformed into norephedrin and norpseudoephedrin in the body (Bouvet et al. 2012). Its body half-life is about 3 h (Hoffman and Al'Absi 2010): it disappears after 24 h in plasma. Considering the duration of a chewing session ranging from 2 to 10 h (Bouvet et al. 2012), the main cathinone excretion occurs during the chewing session. Urine is the main route of elimination: Toennes and Kauert (2002) and Toennes et al. (2003) estimated the cathinone urine excretion ratio (U_{ex}) to be less than 7%, while Sastre et al. (2014) provided a non-justified U_{ex} of about 2%. This low U_{ex} is counterbalanced by the amount chewed: around 100–500 g of leaves (Bouvet et al. 2012) contain between 0.9 and 3.3% of cathinone (Nencini and Ahmed 1989), or 0.9 to 16.5 g, which is an asset for wastewater-based epidemiology considering the analytical limit of quantification.

Many synthetised molecules are related to cathinone (López-Arnau et al. 2013). This category of illicit drugs is referred to as new synthetic drugs. The most widely used is mephedrone (4-methylmethcathinone) (Winstock et al. 2011). The route of administration is mostly intranasal or oral, and the dose rate is between 0.5 and 1 g (Zaitsu et al. 2016). Cytochrome p450 2D6 has been identified to play an important role in its metabolism (Linhart et al. 2016). Numerous metabolites are described, with the main ones being 4-carboxycathinone and 4-methylcathinone with three different conjugates (Linhart et al. 2016). Mephedrone and these two metabolites are found in urine at around 17%, 17%, and 30% of the dose, respectively (Linhart et al. 2016).

Ibogaine is a natural psychoactive chemical found in *Tabernanthe iboga* roots. This plant grows in West and Central Africa. This alkaloid has been used to combat hunger, thirst, and fatigue, and it could be an interesting option to suppress the withdrawal symptoms of opioid-dependent individuals (Glue et al. 2015). Ibogaine is o-demethylated in noribogaine and then noribogaine glucuronide (Glue et al. 2015). Their respective half-lives are about 28 to 49 h and 21 to 23 h. The main route of elimination is through the digestive tract (Zubaran 2000). Around 3.9% of noribogaine and 1.4% of noribogaine glucuronide are found in urine (Zubaran 2000).

Beta-carbolines are alkaloids that are widely distributed among plants and animals. Some produce psychodysleptic effects because of their strong and yet reversible action on monoamine oxidase (Herraiz and Chaparro 2005; Rommelspacher et al. 1994). Numerous plants such as *Banisteriopsis* sp. (used in South America as a beverage locally known as *ayahuasca*; De Smet 1985) and *Peganum* sp., (in the Middle East and Central Asia) are among the best known (Zhao et al. 2012). They are mainly used for shamanistic activities. Their hallucinogenic effect seems to be explained by their ability to bind the 5HT 2C and 5HT 2A serotonin receptors (Yu et al. 2003). Numerous molecules

have been identified, including harmaline and harmine (Yu et al. 2003; Zhao et al. 2012). They are mainly consumed in the form of beverages made from a mixture of aromatic plants. Cytochrome p450 (isoenzymes CYP 2D6, CYP1A2, CYP1A1, and CYP2C9) plays an important role in their metabolism, and many metabolites have been described (Zhao et al. 2012). Harmine is metabolised into harmol and harmaline into harmalol (Mulder and Hagedoorn 1974). They are sulfo-conjugated and glucuro-conjugated (Jorritsma et al. 1979). An in vivo study in rats carried out by Mulder and Hagedoorn (1974) found that 59% and 50% of harmol and harmalol doses, respectively, were eliminated in bile and urine within 3 h (Mulder and Hagedoorn 1974).

Causes of pharmacokinetic variations

Inter-individual and intra-individual variability can be explained by many factors that can influence absorption, distribution, metabolism, and elimination. These factors fall into two categories: internal factors relating to gender (Buccelli et al. 2016; Franconi and Campesi 2014), kidney, liver, or heart function (Coquerel and Lemaire-Hurtel 2012) and genetic disposition (Kalow 1982; Xie et al. 2014; Yasuda et al. 2008) as well as external factors as in the case of concomitant psychoactive drugs (Lukas et al. 1994; Sholar et al. 1994; Lukas and Orozco 2001).

Pharmakinetics depends on many factors, including metabolism, which is dependent on gender (known from Quinn et al. 1958; see also Becquemont et al. 2006), while other factors depend on the environment such as the healthcare provider–patient relationship.

Gender influences absorption, with gastric pH and gut motility differing between men and women. This has consequences on drug absorption and blood concentrations (Franconi and Campesi 2014). Gender influences distribution, as the ethanol concentration is lower in men than women for the same dose consumed. Metabolism is influenced by hormones. However, the relation between gender and pharmacokinetics is not systematic and seems dependent on both the molecule (Franconi and Campesi 2014) and route of administration. Furthermore, for the same molecule, the gender effect is unclear, and replicated studies have not led to the same results (Mendelson et al. 1999).

As Franconi and Campesi (2014) summarised, in view of the numerous biological (sex) and psychosocial-cultural (gender) differences, women and men can be considered to be two different categories (Legato 2003) mediated by sex-specific mechanisms (Casey 2012). For example, β-adrenoceptor shows numerous sex–gender pharmacokinetic differences, which predominate in agents metabolised by CYP2D6 such as metoprolol and propanolol (Luzier et al. 1999). Notably, oral contraceptives increase the plasma concentration of metoprolol (Franconi et al. 2011).

Finally, some sex–gender differences are caused by social, educational, cultural, and lifestyle factors (e.g., smoking and alcohol habits), stress, and access to health care and services (Budesa et al. 2008; Glaser et al. 2000). In line with previous observations, poverty, low social status, domestic violence, and caregiver roles are related to the stress response and could directly interfere with health through stress-associated disease (Carney et al. 2001; Elovainio et al. 2011; Ghiadoni et al. 2000; Krantz et al. 1981; Muller et al. 1994; Veronesi et al. 2010). Overall, these considerations strongly suggest that gender and metabolism are closely and constantly associated (Marino et al. 2011; Springer et al. 2011).

Considering this from the perspective of wastewater-based epidemiology, the effects of male/female polymorphism necessitate the inclusion of sociological aspects such as the male/female distribution in the assessment of drug consumption in order to validate the results. In a male-dominated family context where the use of illicit drugs is forbidden and where women have a lower social status and limited access to healthcare, it is inappropriate to modify the assumption of consumption estimated for 1000 inhabitants as equivalent to 500 male inhabitants.

Polymorphism Some pharmacokinetic enzymes are polymorphic. Many isoforms exist, being characterised by slow or fast activity that influences the rate of metabolism (Bertilsson 1995). They can explain inter-individual variability and sometimes even interethnic variability. Among the most widely studied enzymes, cytochrome P450 plays a central role in the detoxification and catalysis of numerous reactions.

In the last decade, paleogenetics has highlighted the genetic consequences of human migration during the prehistoric period. From Li et al. (2008b), the literature focused on human genetic polymorphism has concluded non-intuitive results: regardless of the phenotypical differences between all Eurasian populations in the broadest sense of the word (including Native Americans and Oceanians), the entire non-sub-Saharan human population comes from tribes located in North-East Africa, close to the Isthmus of Suez, the crossing point to the Eurasian continent and beyond. Moreover, the Near and Middle East hosted Neanderthal populations, which interbred with Cro-Magnons until the non-sub-Saharan population reached a median 2.1% of the Neanderthal genetic heritage (maximum 4%); this legacy is absent from that of the sub-Saharan population (Green et al. 2010). Such results have two practical consequences. First, the Eurasian population has a relative genetic homogeneity. The intra-polymorphism of the sub-Saharan population is, broadly speaking, five times higher than that of the Eurasian population (Patin et al. 2006). Despite the fact that the founder effect allots genetic diversity stochastically and enhances (even if there is convergence) adaptive selection to the environment and cultural practices (Magalon et al. 2007), the Eurasian genetic heritage

can be considered to have, at least partly, a homo-inter legacy, i.e., independent of the genetic heritage common to early modern humans.

Could such heterogeneity have an impact on wastewater-based epidemiology? For example, there are nearly 100 polymorphisms for isoenzyme 2D6, and the combinations of different types of alleles fall into four categories (poor, normal, intermediate, and rapid metabolisers) (Marsousi et al. 2013). Numerous psychoactive drugs such as mephedrone (Linhart et al. 2016), opiates (Marsousi et al. 2013), ibogaine (Zubaran 2000), and harmine and harmaline (Yu et al. 2003; Zhao et al. 2012) are metabolised by this isoenzyme. Codeine is transformed into morphine, and its rate of excretion is influenced by this polymorphism (Gasche et al. 2004). In terms of ethnicity groups, around 8% of Caucasians, 1% of Asians, and between 1.9 and 7% of Africans are poor cytochrome P450 metabolisers (Bertilsson 1995), whereas 4.3% of Caucasians and 4.9% of Africans are rapid metabolisers (Yasuda et al. 2008).

The 2C9*2 isoform is characterised by reduced activity. This polymorphism is found in 8 to 11.9% of Caucasians, but only 1 to 3.6% of Africans. The metabolism rate of tetrahydrocannabinol may be higher in regions where Africans are numerous (Yasuda et al. 2008). However, 2C9 polymorphisms are still controversial, and *2 isoforms did not show any influence in the study of Sachse-Seeboth et al. (2009). By contrast, these authors found that 2C9*3 homozygotes had lower THC-OH and THC-COOH concentrations than heterozygotes and in people without this polymorphism.

The wastewater-based epidemiology approach is indeed based on the excretion coefficient, which is calculated mainly for Eurasian populations to measure illicit drug consumption. However, this raises the question as to whether human genetic polymorphism has an impact on chemical degradation pathways, durations, or excretion rates. While Eurasians appear to be genetically more homogeneous, Krämer and Testa (2008) performed a comprehensive review of inter-individual factors affecting drug metabolism to which we referred. Briefly, CYP2D6, CYP1A2, CYP1A1, and CYP2C9, cited above, are modulated when considering the ethnic origin of the population (Figs. 1 and 2). The CYP2D gene locus has been very active in human evolution, resulting in the near impossibility to gain a clear overall picture of CYP2D6 allele frequency, because new alleles and haplotypes are continuously emerging (Fig. 1). For example, the common null alleles of *4 and *5 with CYP2D6*4 have a frequency of around 20% in Caucasians, while Asian populations show a high percentage of allele *10, and Africans with alleles *17 and *41. While CYP2C8 variants mainly found in the African population are known to alter anti-malaria drug effectiveness (Gill and Berglund 2007), the impact of CYP2C9 polymorphisms (Fig. 2) is of even greater clinical relevance, with some (but not all) having a clearance that is at least four times lower (Kirchheiner and Brockmoller 2005). Caucasians have the highest levels of CYP2C9 and are thus safe; however, for non-Caucasian populations, there can be serious, even large-scale consequences, leading to severe episodes of bleeding, ataxia, and mental confusion (Kirchheiner and Brockmoller 2005).

Butyrylcholinesterase catalyses COC hydrolysis into BZE and is known to be polymorphic. The single nucleotide polymorphism rs1803274 is associated with a reduced activity of 30% (Negrão et al. 2013). This polymorphism is present in about 10 to 20% of the population, with little difference between populations (ensembl.org 2016).

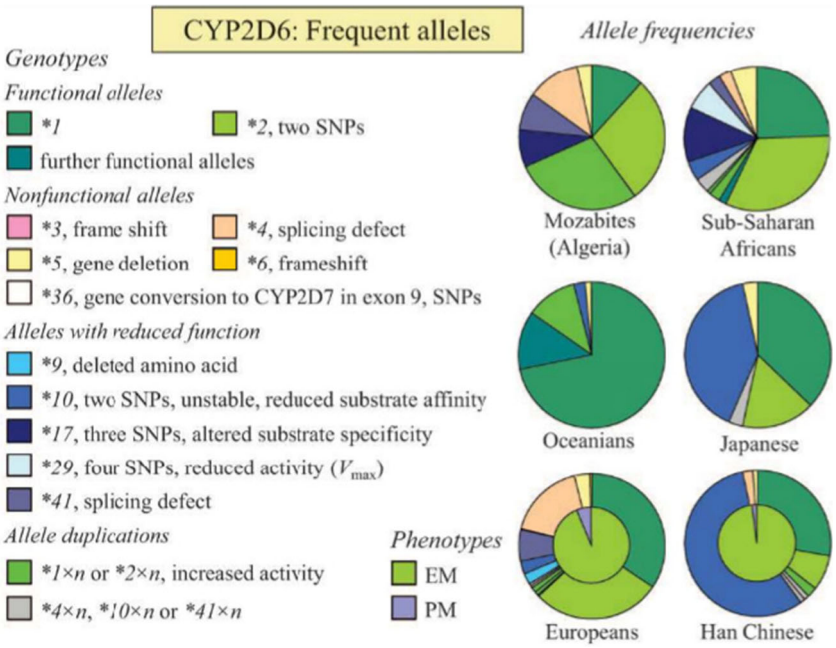

Fig. 1 Phenotype distribution of CYP2D gene locus diversity allele (*) corresponding to ethnic origin and impact of biochemical activity (from Krämer and Testa 2008)

CYP2C9: Frequent genotypes

Genotypes	Enzyme activities	Genotype frequencies [%]		
		Caucasians	Africans	Asians
*CYP2C9*1/*1*	Normal	65.3	87.0	96.5
*CYP2C9*1/*2*	Minor reduction (reduced V_{max})	20.4	8.7	0
*CYP2C9*2/*2*	Moderate reduction	0.9	0	0
*CYP2C9*1/*3*	Moderate reduction	11.6	4.3	3.5
*CYP2C9*2/*3*	Moderate reduction	1.4	0	0
*CYP2C9*3/*3*	Low (increased K_m, reduced V_{max})	0.4	0	0

Population frequencies of the above genotypes

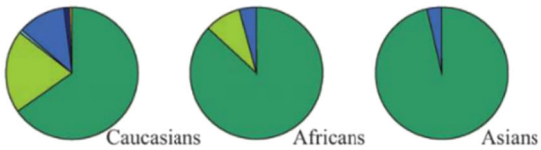

Fig. 2 Genotype distribution of CYP2C9 gene locus diversity allele (*) corresponding to ethnic origin and impact of biochemical activity (from Krämer and Testa 2008)

However, from genetic to practical studies, only nicotine has received appropriate monitoring, with a consequently abundant literature. Li et al. (2008a, b, 2016) demonstrated the genetic source of the significant difference in nicotine metabolisation, including excretion temporality, between Caucasian and African patients in the USA. The primary pathway of nicotine metabolism is conversion to cotinine (Patel et al. 2015). In general, 80% of nicotine is metabolised to cotinine via cytochrome P450 2A6 (CYP2A6)-catalysed C-oxidation. The other pathways of nicotine metabolism are N-oxidation and N-glucuronidation, with each typically contributing < 10% to the total metabolism. However, in African American patients, N-glucuronidation may account for > 40% of the excreted nicotine metabolites (Murphy et al. 2004; Yamanaka et al. 2004), even if global excretion rates are only slightly altered (Benowitz et al. 2016; Taghavi et al. 2017).

Adapting the wastewater-based epidemiology approach to the SNAE context involves, among others, monitoring connected districts where the population is not Caucasian. However, the available excretion rate data were mainly obtained from local patients in developed countries. In the very mixed scientific community, which supports the emergence of the wastewater-based epidemiology approach, working in a SNAE implies refining the excretion rates in order to study the effects of human genetic polymorphism, which could lead to severe modifications in drug metabolism according to the studied population. Moreover, for sub-Saharan populations, a critical effort must be made to manage the consequences of local high genetic heterogeneity (Magalon et al. 2007; Patin et al. 2006). Although pharmacokinetic and toxicokinetic studies should be conducted to help public health managers, the economic obstacle is considerable in such developing countries. Mazzitelli (2007) describes the "head-in-the-sand" policy observed in many such countries when considering the illicit drug issue, since other problems, even necessities, are prioritised. In this context, the international funding framework could compensate, but only supra-governmental administrations seem capable of doing this. Finally, the consequences of polymorphism impact pharmaceutical performances and could lead to severe complications, as the lack of polymorphism in a population is not taken into account (among many, Geisen et al. 2005; Kalow 1982; Loebstein et al. 2001; Scordo et al. 2002; Wadelius et al. 2004; Xie et al. 2014).

Cross effect Another important factor that influences metabolism is drug interaction, which is a complex process that can occur with pharmacokinetic enzymes. For example, concerning ethanol, in the case of chronic consumption, it induces cytochrome p450 2E1, leading to a greater rate of norcocaine formation, while in the case of acute consumption, it inhibits butyrylcholinesterase and reduces COC clearance by 20%. These interactions can be indirectly mediated by the pharmacological action of other drugs. If we consider the interaction between ethanol and cannabis, ethanol would increase THC bioavailability, while THC would reduce ethanol bioavailability by slowing gastric emptying (Lukas and Orozco 2001).

A high consumption of THC could have an influence on COC bioavailability. In their study, Lukas et al. (1994) found that smoking a 2.64% cannabis cigarette significantly increases the snorted COC plasma concentration. This could be explained by an inhibition of COC-induced vasoconstriction when it is snorted, whereas this effect is not found when COC is injected. Although this interaction is interesting, it was reported in only one study and is yet to be confirmed.

The route of administration influences the pharmacokinetics. When a drug is absorbed in the digestive tract, the first-

pass metabolism in the liver contributes to lowering its bioavailability. The intensity of the metabolism depends on the chemical structure, enzyme activity, and liver function. These phenomena are well described (Pond and Tozer 1984). This reaction exists regardless of whether the psychoactive drug is smoked, snorted, or injected, because of the pulmonary first-pass effect, although it is less influential. It seems to be significant for drugs with high clearance (Chiou 1979).

Another internal factor is organ dysfunction. The reduction of kidney clearance or liver fibrosis, for example, can impair drug metabolism and elimination rates. While this is not the subject of this article, it should be taken into account, because anybody can be affected, and chronic psychoactive drug consumption can lead to organ impairment.

Cannabis absorption is highly influenced by smoking behaviour (Hunault et al. 2010, among others). For details, please refer below.

Bias due to the sewer system: impact of porosity and extent of the sewer system

In tropical areas, temperature is not driven by the seasons, which only affect rainfall; it is instead influenced by altitude. In lowlands, the surface water temperature is 25–30 °C depending on the external temperature and distance from the source (Geijskes 1942; Vörösmarty et al. 1996, among many). Every increase of 100 m in altitude decreases surface water temperature by about 1 °C (Ward 1985).

If we consider wastewater-based epidemiology, air temperature has only a negligible impact due to the wastewater temperature. If temperature directly influences the poikilothermic species, the metabolism of species involved in chemical consumption (mammals or birds, thus homoeothermic species) is also affected (Hop et al. 2002 and Van Someren et al. 2002 for mammals; Hillman et al. 2013 for a metadata analysis of vertebrates from fish to mammals; Glazier 2015 for a critical overview of the interpretation of metabolisation limits; McCue 2010 for relativising the temperature concept in situ by behavioural strategies). Thus, wastewater-based epidemiology, being partly based on excretion rates U_{ex}, could be affected by the impact of heat on metabolism modifications, even for homoeothermic species. This latter effect has not yet been studied to date: in the present paper, the authors will consider it to be inexistent, but this potential effect should be mentioned, because it could partly explain the COC/BZE ratio variability highlighted by Bijlsma et al. (2016).

Sewage temperature, estimated between 25 and 30 °C in lowlands and about 26–28 °C in Martinique, should be compared to temperatures in temperate countries, where sewage temperature mainly fluctuates between 10 and 22 °C (Sanz and Fdz-Polanco 1990) with WWTPs being required to work between 5 and 40 °C (Pilukowski 1999). Temperature could have an impact on the chemical tracer concentrations used for wastewater-based epidemiology methods because of degradation, biodegradation, adsorption, and flocculation leading to sedimentation in sewers (Biggs et al. 2011; Thai et al. 2014). Considering high temperature conditions, only Bisceglia and Lippa (2014) proposed a 24-h experiment partly at 31 °C and highlighted the effect of temperature on illicit drugs at this temperature. For details, please refer to Devault et al. (2017a).

The main features of the urban sanitation cycle in SNAEs, mostly in tropical zones, can be analysed through its successive phases: wastewater production, collection, and treatment. However, wastewater production and collection are precisely the key points when considering wastewater-based epidemiology representativeness, as the raw material must be informative about the local population. In the present section, the authors wish to point out that the sewer systems in SNAEs rarely comply with the brief design required for the wastewater-based epidemiology approach. The considered states are mostly subject to rapid city growth as a result of massive rural flight, with limited resources and potentially inadequate professional training in the sanitation sector.

Since the United Nations (UN) International Year of Sanitation in 2008 in the context of the UN International Decade for Action known as "Water for Life 2005–2015," the situation has remained very alarming. In 2006, the UN estimated that "some 2.5 billion people are still without access to improved sanitation and 1.1 billion people practice open defecation. Some 1.6 million people, mostly children, die each year from water-related diseases and poor sanitation." A decade later, the indicators are equally alarming. In many urban areas of SNAEs, the sanitation infrastructure is also highly deficient or even non-existent (UN Habitat 2016). The indicator of the connection rate to a sewer network, whether at the city (Table 2) or country (Table 3) level, shows a very low rate of connection in almost all Sub-Saharan Africa. For example, it is less than 5% in Nouackchott and Addis Ababa (Van Rooijen and Taddesse 2009). These rates are even lower in the other major cities of the national urban network, with similar orders of magnitude also being found in Haiti. The rates are around 50% in India, while they exceed 70% in South Africa, Namibia, North Africa, and many cities in South America (UN Habitat 2016) (Fig. 3).

From a methodological point of view, it is important to bear in mind that in SNAEs, the weakness of the data forces researchers to retreat to second-order indicators (Durand and Jaglin 2012), meaning that in the absence of sufficiently reliable statistical data, analyses very often rely on orders of magnitude and field observations (Eawag 2016). The lack of reliable data is largely due to socio-economic characteristics. Indeed, the majority of the urban population lives in very precarious conditions in informal settlements. In SNAEs, 881 million urban residents were living in poor informal settlements in 2014 compared to 689 million in 1990. This

Table 2 Households in selected urban areas with piped water and connection to sewerage (UN 2016)

Country (year)	Location	Piped water (%)	Connection to sewer (%)	Country (year)	Location	Piped water (%)	Connection to sewage (%)	Country (year)	Location	Piped water (%)	Connection to sewage (%)
Angola	Luanda	28.4	19.4	Mauritania	Nouakchott	27.8	4.8	Peru (2012)	Lima	84.1	89.5
2011	Other towns	39	18.9	2001	Other towns	28.7	2.8	Armenia (2010)	Yerevan	98.7	99.1
Benin	Cotonou	67.5	4.7	Morocco	Rabat	89.7	99.7	Azerbaijan (2006)	Baku	89.6	90
2011	Other towns	23	1.2	2004	Other towns	83.6	96.3	Bangladesh	Dhaka	63.2	21.7
Burkina Faso	Ouagadougou	46.8	2.7	Mozambique	Maputo	81.3	?	2007	Other towns	7	1.3
2010	Other towns	19.6	1	2011	Other towns	46.1	?	Cambodia	Phnom Penh	86	86.5
Burundi	Bujumbura	69.7	18	Namibia	Windhoek	67.8	75.3	2005	Siem Reap	5.4	20
2012	Other towns	50.5	0.8	2013	Other towns	67.3	57.2	India	New Delhi	74.9	74.6
Cameroon	Yaoundé	46.8	20.6	Niger	Niamey	48.4	6.2	2006	Kanpur	37.4	38.3
2004	Other towns	27.9	9.2	2012	Other towns	31.7	0.9	Indonesia	Jakarta	29.7	23.1
CAR	Bangui	9.9	5.5	Nigeria	Lagos	4.5	7.6	2007	Palembang	16.8	22.4
1994	Other towns	1	0.1	2013	Other towns	5.1	10.7	Jordan	Amman	54.2	82.3
Chad	Ndjamena	27.6	10.3	Rwanda	Kigali	34.1	5.5	2009	Aqaba	95.2	88.6
2004	Other towns	12.5	2.7	2011	Other towns	10	0.1	Kazakhstan	Shymkent	100	100
Comoros	Moroni	33.8	9.1	Senegal	Dakar	85.6	39.9	1999	Other towns	84.9	80
2012	Other towns	66.9	7.9	2010	Other towns	67.3	3.7	Kyrgyzstan	Bishkek	95.7	11
Congo	Brazzaville	37.5	7.1	Sierra Leone	Freetown	36	0.3	2012	Other towns	87.9	45.6
2009	Other towns	32.5	7.1	2008	Other towns	6.1	0.2	Maldives	Male	52	99
Ivory Coast	Abidjan	87.3	24.5	South Africa	Pretoria	62.5	62.5	Moldova	Chisinau	89.1	91.4
2011	Other towns	43.5	2.4	1998	Other towns	89	77.8	2005	Other towns	55.5	43.6
DRC	Kinshasa	43.5	5.9	Swaziland	Mbabane	65.3	41.7	Nepal	Kathmandu	55.5	66.9
2013	Other towns	?	?	2006	Other towns	84.1	69.9	2006	Other towns	34.3	7.5
Egypt	Cairo	99	99.7	Tanzania	Dar Es Salaam	48.3	?	Pakistan	Islamabad	65.3	91.5
2014	Port Said	96.2	93.4	2010	Other towns	44.2	?	2012	Other towns	62.3	34.2
Ethiopia	Addis Ababa	68.3	4.9	Togo	Lome	13.8	0.2	Philippines	Manila	45.3	4.4
2010	Other towns	43.2	1.8	2013	Other towns	9.6	?	2008	Other towns	38.6	3.6
Gabon	Libreville	81.5	445	Uganda	Kampala	21.5	2.6	Timor-Leste	Dili	43.7	17.7
2012	Other towns	57.7	25.8	2011	Other towns	28.7	12.5	2009	Other towns	28.7	19
Gambia	Banjul	95.4	71.9	Zambia	Lusaka	44.9	28.8	Turkey	Ankara	80.2	98.5
2013	Other towns	64.3	0.7	2013	Other towns	28.7	15.2	2004	Istanbul	39.7	95.6
Ghana	Accra	37.3	?	Zimbabwe	Harare	34.3	15.2	Ukraine (2007)	Kyiv	67.6	67.4
2008	Other towns	22.3	?	2010	Other towns	61.2	68.3	Uzbekistan	Tashkent	98.7	81
Guinea	Conakry	82.5	7.4	Bolivia	La Paz	95	76.3	1996	Other towns	83.8	37.3
2012	Other towns	48	7.2	2008	Trinidad	60.7	21	Vietnam	Hanoi	84.8	97.6
Kenya	Nairobi	78.2	66.6	Brazil	Brasilia	89.8	71.2	2005	Other towns	58.3	69.6

Table 2 (continued)

Country (year)	Location	Piped water (%)	Connection to sewer (%)	Country (year)	Location	Piped water (%)	Connection to sewage (%)	Country (year)	Location	Piped water (%)	Connection to sewage (%)
2008	Other towns	46.3	18.8	1996	Other towns	79.4	42.2				
Lesotho	Maseru	55.3	3.8	Colombia	Bogota	98.3	99.4				
2009	Other towns	61.7	3.2	2010	Yopal	81.5	97.7				
Liberia	Monrovia	5	1.4	Dominican R. (2013)	Santo Domingo	2.4	88.2				
2011	Other towns	?	0.2	Guatemala (1995)	Guatemala City	58	71.7				
Madagascar	Antananarivo	26.6	0.5	Haiti	Port-au-Prince	28.5	26.9				
2013	Other towns	17	1.4	2012	Other towns	25.7	7.8				
Malawi	Lilongwe	34.2	10.9	Honduras	La Ceiba	32.4	37.6				
2013	Other towns	35.4	15	2011	Trujillo	24.5	19.2				
Mali	Bamako	34.9	9.7	Nicaragua	Managua	97.1	51.9				
2013	Other towns	35.9	3.4	2001	Jinotega	62.4	28.4				

represents an increase of 28% in absolute numbers of slum dwellers over the past 24 years. In 2000, 39% of the urban population in SNAEs resided in slums, although this declined to 30% in 2014 (UN Habitat 2016). These neighbourhoods are rarely or only partially taken into account in statistics. There is a lack of data proportional to household income level. Even if the water utilities in many countries do not currently organise customer data by income category, most of the urban space and urban population in SNAEs are not connected to a sewerage network. Indeed, Devault et al. (2014) demonstrated the effect of socio-professional categories and their impact on illicit drug use in the same spatial and temporal context.

When considering wastewater-based epidemiology, such an area would not even be taken into account because of the lack of sanitation or because the raw sewage flows directly into streams without an implanted monitoring system. There are numerous examples of SNAE cities, regardless of their size, in which the majority of wastewater is discharged into watercourses. However, large metropolitan areas and, even more so, megacities, concentrate large quantities of wastewater, which are directly dumped untreated into watercourses or the sea. The rivers that flow through the cities have for the most part become open sewers (Van Rooijen and Taddesse 2009).

Wastewater production is concentrated mainly in central districts, which correspond to the affluent neighbourhoods of most SNAE cities (Durand 2012). This spatial organisation opposing the centre and the periphery is found in most SNAE cities (Baron et al. 2016; Durand 2012; Durand and Jaglin 2012; Péné-Annette 2003; Reymond et al. 2016; UN Habitat 2016; WSUP 2014).

Socio-spatial segregation based on this centre-periphery model is also found for connections to the sewer system (Baron et al. 2016; Durand 2012; Péné-Annette 2011). Central residential neighbourhoods are generally well connected to the sewer system, dating back to the colonial period. Extensions of sewage systems, if they exist from the central districts (Eggimann et al. 2015), do not cover the entire urban territories. Quite often, technical sanitation networks, if existent, are inferior in size and efficiency to the water supply networks (Jaglin 2003). As a result, most of the wastewater that is not collected by a sewer system circulates or stagnates in the streets. This wastewater is evacuated during the rainy season and then flows down the streets of the affluent neighbourhoods. If the poorest districts are in an elevated position on hillsides surrounding the central districts of the middle or upper classes, the wastewater flows into the latter neighbourhoods, transforming them into a wastewater zone in rainy weather (Péné-Annette 2011). The sewage in the affluent neighbourhoods, which overflows from the sewers, mingles with the descending wastewater of the poor neighbourhoods. It is therefore difficult to estimate the actual amount of wastewater that is discharged without treatment.

Table 3 Households with piped water and connection to sewerage by country (UN 2016)

Country	Year	Piped water (%)	Connection to sewerage (%)	Country	Year	Piped water (%)	Connection to sewerage (%)
Angola	2011	32.8	19.2	Togo	2013	51.3	21.5
Benin	2011	38.7	2.5	Uganda	2011	27.9	11.3
Burkina Faso	2010	31.4	1.7	Zambia	2007	39.7	25.2
Burundi	2012	62.2	11.3	Zimbabwe	2010	71	74.4
Cameroon	2004	34.7	14.1	Bolivia	2008	91.9	58.4
CAR	1994	4.9	2.4	Brazil	1996	84.3	62.4
Chad	2004	18.6	5.8	Colombia	2010	91.6	91.8
Comoros	2012	56.2	8.3	Dominican R.	2013	6.9	82.2
Congo	2011	38.7	2.4	Guatemala	1998	60.1	64.5
Ivory Coast	2011	61.4	13.5	Guyana	2009	28.5	11.4
DRC	2013	19.7	0.7	Haiti	2012	27.1	17.5
Egypt	2014	96	92.9	Honduras	2011	27.2	62.1
Ethiopia	2010	48.4	2.4	Nicaragua	2001	89.6	30.8
Gabon	2012	74	38.6	Peru	2012	82.4	80.9
Gambia	2013	65.9	4.3	Armenia	2010	97.1	95.5
Ghana	2008	27	–	Azerbaijan	2006	77.7	74
Guinea	2012	66.6	7.3	Bangladesh	2011	37.2	11
Kenya	2008	56	34	Cambodia	2005	37	30.8
Lesotho	2009	58.9	3.5	India	2006	50.7	27.8
Liberia	2013	1.9	1.8	Indonesia	2007	23	20.7
Madagascar	2013	17.3	1.3	Jordan	2009	58.4	69.3
Malawi	2012	35	13.7	Kazakhstan	1999	86.7	80.8
Mali	2012	35.4	6.6	Kyrgyzstan	2012	88.5	42.5
Mauritania	2001	28.1	4.1	Maldives	2009	52	99
Morocco	2004	85.2	97.8	Moldova	2005	72.9	68.3
Mozambique	2011	51.5	?	Nepal	2011	42.6	27.3
Namibia	2013	67.5	64.2	Pakistan	2012	50.4	69.8
Niger	2012	38.6	3.1	Philippines	2008	39.6	3.6
Nigeria	2013	5.5	9.2	Timor-Leste	2009	38.1	18.2
Rwanda	2011	23.7	3.2	Turkey	2004	66.6	92.7
Senegal	2010	77.1	23	Ukraine	2007	80.1	71
Sierra Leone	2013	10.9	0.7	Uzbekistan	1996	87.4	47.7
South Africa	1998	86.6	79.6	Viet Nam	2005	61.1	80.4
Swaziland	2006	72.6	49.7	Yemen	1991	87.2	53.7
Tanzania	2010	46.1	–				

Most of the urban areas in SNAEs are also characterised by very inadequate wastewater treatment systems, i.e., the amount of wastewater treated is strictly minimal. Moreover, it is difficult to assess this phenomenon due to the lack of reliable statistical data.

Notwithstanding, WWTPs are a useful support for wastewater-based epidemiology, because representativeness involves the adequate monitoring of the daily flux needed for such plants. Even when they do exist, most WWTPs operate at overcapacity and cannot meet the treatment needs of all the wastewater sent to the station (Péné-Annette 2003). In most cases, the high cost of wastewater treatment and management is a major obstacle to the implementation of such infrastructure (Chaplin 2011; Massoud et al. 2009). Governments also have more pressing concerns than wastewater management such as healthcare and food supply (Durand 2012; Durand and Jaglin 2012). Access to water in neighbourhoods is given priority by setting up water supply networks, or in the most precarious neighbourhoods, distributing drinking water in tanker trucks (Corcoran et al. 2010). The coupling of water and sanitation infrastructure is only rarely adequately carried out by the public authorities, despite the good intentions frequently expressed in

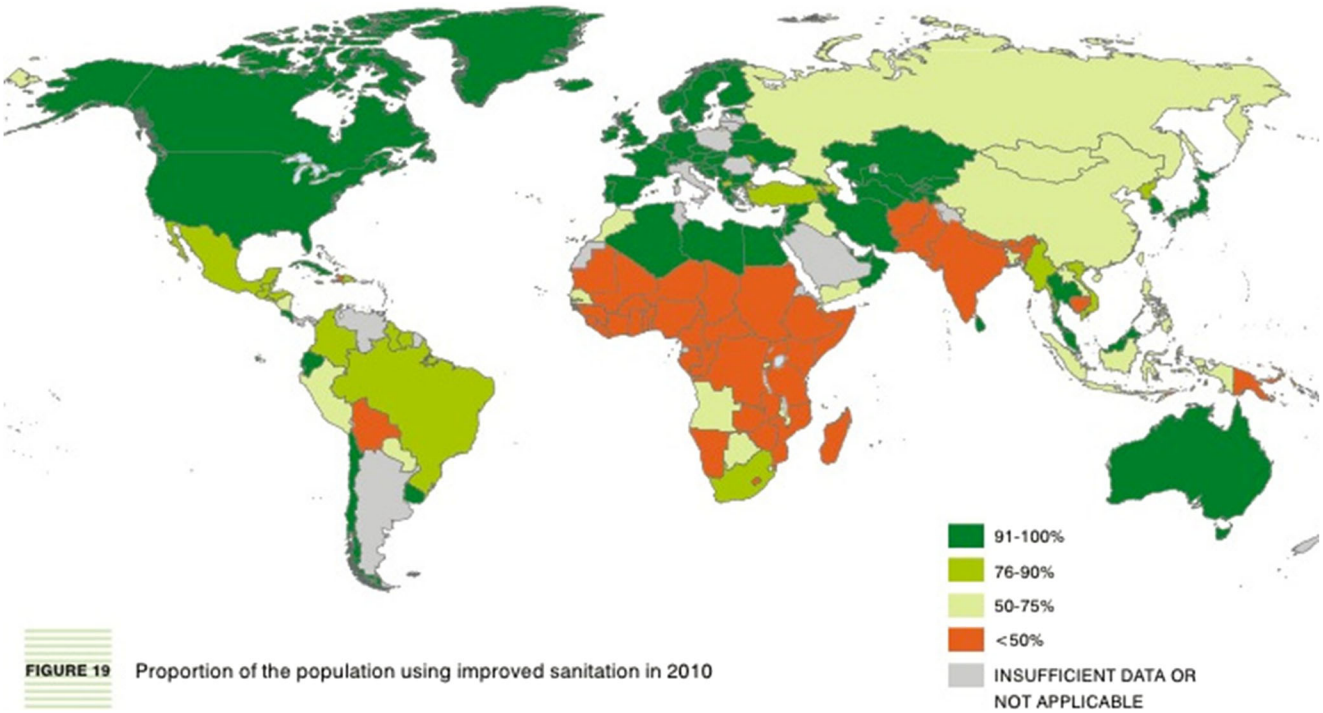

Fig. 3 Worldwide use of improved sanitation facilities in 2010, with an emphasis on the urgency of sanitation improvements in South Asia, Sub-Saharan, and Central Africa (Source: UNICEF WHO 2012)

urban plans (Baron et al. 2016; Chaplin 2011; Jaglin 2004, 2005; Jaglin et al. 2011; Péné-Annette 2003, 2011). Indeed, this service is often privatised, thus accentuating the socio-spatial segregation in favour of the wealthier neighbourhoods (de Gouvello 2001).

For the poorer neighbourhoods of neoliberal economies, NGOs or micro-enterprises are increasingly operators in a parallel economy, operating with micro-credit in particular, including for sanitary equipment (Crites and Tchobanoglous 1998). These solutions then become highly fragmented and individualised, operating outside of any urban planning. These alternative solutions suggest that it is important to consider these new heterogeneous management models and stop applying a Western management model that supports a universal system in which the objective is to achieve maximum coverage in sewage systems. Small-scale (for an apartment building) or even individual sanitary equipment could durably mask the socio-professional classes who live in these areas from the overview required for the wastewater-based epidemiology approach.

Ideally, a complete sewer system with pipeline networks reaching every home is needed for the wastewater-based epidemiology approach. However, the shortcomings of the sanitation policies have worsened, which means that the daily conditions of people are totally inadequate from a health perspective. Alternative sanitation solutions should therefore be more adaptable to the different contexts. Otherwise, the prevailing conditions will be those described by Chaplin (2011): "Unfortunately, this leads to the conclusion that the lack of sanitation in urban India will only be solved when the poor have sufficient political capacity to demand that services are provided by the State either through its institutions and agencies, through partnerships and private providers."

In summary, sanitation is the urban service that is least taken into account by alternative collective projects if the public authorities or private sector under contract does not intervene (Jaglin 2012; Massoud et al. 2009). Wastewater management is frequently low on the list of priorities. Even the most advanced technology should be supported by the appropriate institutions with enforced legislation to ensure maximum efficiency: nevertheless, sewer system coverage does not sufficiently develop to ensure a substantial increase in the connected percentage of the population. Moreover, it is focused on the central areas of the cities, i.e., mainly the old "colonial" quarters, where the sewers have been insufficiently renewed by private corporations to ensure public service concessions, leading to accrued leakage (Dubresson and Jaglin 2010; Duque Gómez and Jaglin 2017; Durand and Jaglin 2012).

In Martinique, as in many other intertropical areas, unbridled urbanism has led or is still leading to the construction of shantytowns where connection to the sewer network is not planned before population settlement. In the Caribbean, Martinique is one of the most well-equipped islands, because of the French standards of administration (i.e., Martinique is an overseas region of France, not an overseas territory), and as a result, construction, health, sanitation, and environmental

protection are governed by the same regulatory framework as applies to mainland France along with European directives. However, only 45% of the Martinique population is connected to the sewer system. Among the remaining 55%, 10% are not connected but have a suitable individually managed sanitation device complying to standards; 30% are not connected but have a suitable individual sanitation device that is not managed and does not comply to standards; 30% are not connected but are equipped with unsuitable individual sanitation (hollow device used as sceptic tank or even a hole) that does not comply to standards; and the final 30% directly discharges into surface water, that is, 16.5% of the total Martinique population (Devault et al. 2014). Is such a large non-connected and hence non-monitored population a bias in terms of wastewater-based epidemiology? In the Lesser Antilles, cities are not prosperous places as in Western society, and as a result, a partially non-connected population living in rural areas does not necessarily signify a population of low social level. However, there is a cultural specificity in the Lesser Antilles due to the local history, and the connection rate could be a pivotal parameter if connected and non-connected populations have significantly different standards of living.

Sewer porosity should be added to this issue, estimated to be about 50% in Martinique (Devault et al. 2014). Such porosity is due to many factors, but the main ones are the following:

- *Sewer oversizing*. In order to precede urbanisation or balance the effects of illegal connection during intense rainfall events (see below), sanitation authorities tend to overestimate the diameter of concrete-made sewers, leading to lentic flow that limits sewage oxygenation. As Coing (1998), Clarke et al. (2004), and Massoud et al. (2009) detailed, such a problem could arise due to political interference in environmental decisions such as site selection and other aspects related to construction and operation. In a warm context, oxygen concentration at saturation is less than in a cold climate: in sewers, the summer temperature (i.e., the effective temperature throughout the year in tropical areas) enhances the onset of anaerobic conditions (Willis et al. 2010). The crossing effect of temperature and oversizing was detailed by Devault et al. (2017a).
- *Leaks* can be partly due to illicit human connections associated with wastewater—mainly domestic sources—and partly to rainwater connections. Although the biological oxygen demand over a 5-day period allows for the stabilising of connected populations, including the illegal connection of wastewater, the rainwater connection could have a severe impact on WWTPs when considering the input of floods in the case of rainfall: the dilution factor limits the monitoring of low concentrated illicit drug tracers and could produce sewer overflowing and direct discharge, and thus weaken evaluation. During the 2013 sampling campaigns, standard rainfall induced a twofold dilution factor (Devault et al. 2014).
- Because of earthquakes and cyclonic rainfall, the occurrence of *landslides* is enhanced in the Caribbean as in other sloped tropical areas (Rad et al. 2013). On "slum-built" slopes, such landslides could occur more often than on natural slopes because of the human handling of soil without sufficient soil consolidation (Alimohammadlou et al. 2013; Izzo et al. 2010). Erosion worsening due to the waterproofing of urban surfaces and the lack of buffering effect due to foliage (Stokes et al. 2014) are the final factors that promote landslides. Ground movements exert pressure on sewers themselves and especially on their joints (Donnelly 2006).

Social and cultural bias

Bringing wastewater-based epidemiology together with local practices could be useful to understand the results and adjust them. Local taboos could have a consistent effect on the interpretation of wastewater-based epidemiology. However, such issues involve addictology, and this scientific field is scarcely represented in SNAEs (OGD 1998). The present review cannot list the wide variety of social and cultural biases, but it could serve as a reminder that for comparative purposes, the results of two populations should be weighed using the respective sex ratios of narcotic users and take into account the age distribution, while considering the potential family and traditional structures.

Many reasons, whether conscious or unconscious, could lead to underreporting. The stigmatisation of illicit drug use is known to discourage people from reporting their drug use. Thus, Chalmers et al. (2016) reported changes in the self-reported use of "ice" in general population surveys in Australia. Rapid increases in the quantum of media reporting the stigmatisation of the drug accompanied by growing public concerns may have increased the tendency to underreport lifetime use. In Martinique, crack and crack users are stigmatised. For example, crack can be "associated with the devil" (Charles-Nicolas 1998).

In Johnson and Fendrich 2005, Johnson and Fendrich published a review on the different sources of error in substance use prevalence surveys. Ethnicity should be highlighted in this respect. Some research suggests demographic variability in non-response rates to substance-use questions. Mead-Bennett (1992) found that African Americans were less likely to answer questions concerning their use of illicit drugs. Moreover, a literature review of 36 published studies conducted in the USA found consistent evidence of lower reliability and validity rates of substance use reporting among racial and ethnic minority populations (Johnson 2003). More recent

studies have reported similar findings (Fendrich 2005; Ledgerwood et al. 2008). The specific source of these differences is not clearly understood. Proposed models suggesting greater reporting errors among minority groups may be a consequence of differential group educational achievement and question comprehension, greater minority concerns about privacy, discrimination, and risk of prosecution, and/or stronger effects of social desirability pressures on minority groups to report behaviours that conform to majority cultural values. Internationally, cultural differences in normative patterns of alcohol consumption and other substance use may also influence the degree of response editing.

Toxicological findings from biological specimens (i.e., hair, saliva, and urine samples) usually indicate higher illicit drug use than in self-reports. Although hair testing has some limitations, especially for cannabis, a comparative study between hair or saliva testing and self-reporting should be conducted in Martinique to objectively assess the divergence between these two methods.

In Martinique, the use of intravenous illicit drugs such as heroin could be very limited due to a local taboo about syringes and injecting, because of metaphysical beliefs about blood and the risks of contamination. This aspect must be taken into account for wastewater-based epidemiology if the composite excretion rate U_{ex} combines multiple routes, including intravenous (i.e., COC), in order to correct the U_{ex}.

Conclusion

Applying wastewater-based epidemiology in tropical areas calls for greater precaution than in temperate areas due to field considerations such as the sewer system porosity, the limited extent of connections and capacity, and the physico-chemical conditions of wastewater. Consistent improvements must be performed on the pharmacokinetics of illicit drugs due to the prevalence of different routes of administration or the use of molecules less commonly found in Western societies. Many potential sources of bias exist, while many parameters calculated for other countries are not directly applicable to such an environment.

Notwithstanding, the key issue for scientists when applying wastewater-based epidemiology, whether in tropical or other environments, is to maintain close contact with the field operators working on the studied consumption or sanitation system in order to pragmatically determine the interpretation limits and best way to overcome obstacles.

However, the standards for wastewater-based epidemiology are rarely met in the SNAE context for numerous reasons: the insufficient coverage of the sewer network; the lack of sewer maintenance efficiency; the high proportion of wastewater discharge into rivers or other waterways compared to the volume of water treated at WWTPs, with the plants being set to sample a given proportion of the daily flux; the lack of toxicokinetic studies on the population under study; and the lack of toxicokinetic studies on substances of abuse and/or their routes of administration. The present review is a plea for all toxicological studies to provide details about drug metabolisation in understudied populations and provide an overview of human polymorphism; for wastewater-based epidemiology to be extended as an alternative for healthcare policies rather than expensive and difficult-to-interpret questionnaire campaigns; and for wastewater treatment to be promoted and expanded, because, while not a gratifying expense in impoverished regions, it does play a crucial role in the improvement of sanitation and hygiene standards. In short, the wastewater-based epidemiology approach is not an isolated practice but relies heavily on open collaboration with local scientists to properly assess the local conditions and adjust the back-calculation objectives.

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