1 **The value of wastewater-based epidemiology in the estimation of alcohol consumption**

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Highlights

- Ethyl sulfate is measured in wastewater to back-calculate alcohol consumption
- WBE-data (local) are usually lower than WHO country-based data
- Main uncertainties are related to population-size estimates and ethanol metabolism
- Valid tool to rapidly derive changes in alcohol consumption patterns
- Advantages over traditional methods: fast, economic, objective and anonymous

Abstract

The present review discusses the value of wastewater-based epidemiology (WBE) to estimate alcohol consumption in a given population. It gives an overview of the works conducted in this respect to date, and the comparability of the WBE-derived data with official estimates provided by the World Health Organization, generated after survey and alcohol sales data. Finally, it provides insights to the main advantages and limitations of the WBE approach over traditional methods, and aspects/knowledge to be improved/investigated.

Keywords: sewage epidemiology, ethyl sulfate (EtS), alcohol consumption, ethanol metabolism

51 **1. Introduction**

52 Alcohol is one of the most used recreational substances in the world. According to the
53 World Health Organization (WHO), almost half of the worldwide population (43%)
54 consumed alcohol in the last 12 months in 2016. Alcohol consumption increased globally
55 between 2005 and 2010 from 5.5 L to 6.4 L per capita (aged over 15 years) and has
56 remained stable thereafter until 2016 [1]. Excessive alcohol consumption has been linked to
57 diverse social problems (suicides, homicides, robberies, violence, traffic accidents, etc.) and
58 health problems (digestive, infectious and cardiovascular diseases, cancer, etc.). Harmful
59 use of alcohol was the cause of 5.3% of all deaths worldwide in 2016 [1]. Thus, the
60 availability of tools to track alcohol consumption in time and evaluate the reliable
61 effectiveness of adopted measures to reduce its excessive use is important.

62 The prevalence of alcohol use is commonly estimated through population surveys [2, 3] and
63 sales statistics [4]. However, these methods are time-consuming and expensive. Moreover,
64 they do not always provide reliable data due to widespread under-reporting in surveys [5]
65 or unaccounted smuggled, stored and disposed alcohol in total sales volumes. Alternatively,
66 a novel approach known as wastewater-based epidemiology (WBE) has been applied in
67 recent years to assess alcohol use in a given population. WBE back-calculates alcohol
68 consumption from the concentration of an alcohol consumption indicator, most commonly
69 ethyl-sulfate (EtS), found in wastewater. Thus, WBE provides anonymous and objective
70 information in a fast and relatively economic way. However, this approach is also subject to
71 different sources of uncertainty. This review aims at (i) presenting the WBE approach to
72 estimate alcohol use by a specific population, (ii) discussing its utility based on the peer-
73 reviewed studies published so far on this topic, and (iii) highlighting its advantages and
74 limitations.

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76 **2. Basis for estimation of alcohol use using WBE**

77 WBE relies on the fact that wastewater is a diluted pooled urine sample of a specific
78 population that can provide valuable information if appropriate biomarkers are monitored.

After consumption of any alcoholic beverage, most of its ethanol content (~ 95%) is metabolized in the liver via oxidation to acetaldehyde and acetic acid. However, a very small fraction (< 0.1%) is converted to ethyl glucuronide (EtG) and EtS after conjugation with glucuronic acid and sulfate, respectively. These metabolites are excreted together with unaltered ethanol (5%). EtG and EtS are both good indicators of recent alcohol consumption, because they are excreted within a few hours after ingestion and are detectable in urine for 1 or 2 days, depending on the subject and the alcohol dose [6]. However, only EtS has been used as a biomarker of alcohol consumption because it is more stable in wastewater than EtG. Lab-scale experiments showed that EtS concentration in wastewater remained stable for at least one week at room temperature and for more than one month at -20°C [7]. On the contrary, EtG concentration decreased up to 50% after 18 h at room temperature [8]. In addition, EtS is not formed in wastewater through metabolization of unaltered ethanol by endogenous bacteria, and hence, its presence in wastewater can be only attributed to alcohol consumption [8]. This makes EtS an exclusive and unequivocal biomarker to be used in WBE for back-calculation of alcohol consumption according to Equation 1,

$$\frac{\text{mL of EtOH}}{\text{day*person}} = C_{EtS} \left[\frac{\mu\text{g}}{\text{L}} \right] * 10^{-6} \left[\frac{\text{g}}{\mu\text{g}} \right] * Q \left[\frac{\text{m}^3}{\text{day}} \right] * 10^3 \left[\frac{\text{L}}{\text{m}^3} \right] * \frac{1}{P \text{ (persons)}} * F * \frac{1}{\rho_{EtOH} \left[\frac{\text{g}}{\text{mL}} \right]} \quad (\text{Eq. 1})$$

$$F = \left[\frac{M_{EtOH}/M_{EtS}}{\% \text{ excretion rate EtS}} * 100 \right] \quad (\text{Eq. 2})$$

where C_{EtS} is the concentration of EtS in wastewater at the entrance of a wastewater treatment plant (WWTP), Q is the water flow entering the WWTP during the sampling event, P is the population connected to the WWTP, F is a correction factor that takes into account the molar mass ratio between ethanol and EtS (0.365) and the excretion rate of EtS (see Table 1 and Equation 2), and ρ_{EtOH} is ethanol density (0.789 g/mL).

Two approaches have been used to estimate alcohol consumption, providing fully comparable results [8]. One is the classical average mass-flow method that is ideal for

compounds that have a long excretion half-life in urine or are consumed at a constant rate throughout the day and the night by many people in the studied area. The other one is based on the EtS excretion profile. This approach may provide more accurate consumption figures for compounds with short urinary excretion half-life, as it is the case for EtS (3 hours).

3. Applicability and value of WBE to estimate alcohol consumption

The first study that applied WBE to estimate alcohol use dates from 2011 [8]. Since then, various studies, summarized in Table 1, have been conducted in this line to explore i) the value of WBE to estimate alcohol consumption, and ii) the comparability of the data generated with this approach and traditional methods, i.e, official estimates provided by WHO and each country institutions. To date, WBE alcohol consumption figures have been derived from EtS loads entering 55 WWTPs spread in 13 different countries all over the world [8-19]. As shown in Table 1, most of the studies were conducted in major cities from different European countries.

Oslo was the first city where WBE was applied to estimate alcohol consumption. For this, samples were collected daily for 25 consecutive days at the entrance of one WWTP. In this study, two calculation methods to estimate alcohol use were evaluated and compared: the classical average mass-flow method and a novel method based on the EtS excretion profile. Equal alcohol consumption figures were obtained with both approaches (4,900 to 7,800 Kg/day). These data were in very good agreement with Norway sales statistics (6,750 Kg/day), which are among the most accurate in the world because of the strict control of import and sale of alcoholic beverages by the government [8]. In areas like the one investigated in this study, where alcohol is mostly consumed over a short period of time (usually during the evening), a limited number of samples can be used to derive alcohol use figures through the excretion profile integration method (morning peak of Et-S in wastewater associated with morning urination) [8].

Following this study, the average mass-flow method was applied to estimate alcohol use in Milan [17], the Spanish cities Santiago de Compostela [7] and Barcelona [14], and in multi-

city studies conducted at international [18] and European level [10]. In all of these studies, annual consumptions were derived from one-week sampling at one WWTP, except in the case of Milan where samples were collected for two weeks. The highest consumption rates (above 25 mL/day/inhabitant) were obtained for cities in Canada (Granby and Montreal), Denmark (Copenhagen) and Germany (Munich and Dresden). City based-WBE values were in good agreement ($< 15\%$) with country based-WHO data only in a few cases, i.e., Dresden, Munich, Castellón, Amsterdam, and Eindhoven. Mastroianni et al. [14] also reported a good agreement between wine consumption data derived from WBE and figures reported by the Spanish Ministry of Agriculture.

Overall, the low comparability of figures provided by WHO and WBE could be attributed to: i) the small geographic coverage of the WBE method (based on only one city or part of it) as compared to WHO data (based on nation-wide surveys and sales data), and to the fact that the area monitored by means of WBE may not be representative of country trends in alcohol consumption; ii) the short sampling periods used to derive WBE data (usually one “normal” week is selected to generate annual consumption data); iii) the uncertainty associated to the WBE methodology (see further discussion in section 5), and iv) imprecise estimates derived from surveys due to underreporting and sales data in areas where purchased alcohol may not be immediately consumed.

A couple of studies used EtS loads entering various WWTPs to derive national alcohol consumption figures. This was done by Boogaerts et al. in Belgium, [11], and by Lai et al. in Australia [13], who covered 12% and 45% of the country’s total population, respectively. In the case of Belgium, the WBE-derived figure was below the one reported by WHO. However, it was in agreement with alcohol use figures provided by the Belgian Scientific Institute of Public Health. In the Australian study, average alcohol consumption figures obtained were very similar to those reported by the National Drug Strategy Household Survey (NDSHS). However, contrary to NDSHS data, WBE figures revealed large differences in alcohol consumption between rural and urban communities.

The comparability between alcohol consumption estimates produced by WBE and surveys in a medium-sized Belgian city was investigated by van Well et al. [19]. The study showed

no correlation between WBE and survey data. However, authors attributed this to the small survey sample size (only 1% of survey response was obtained each study-week) [19].

Besides the comparison of WBE-data with survey data and official estimates, one of the main objectives of multi-city studies was investigating spatial differences in alcohol consumption. In addition to this, the collection of samples for seven consecutive days and the iteration of this exercise in consecutive years allowed investigating consumption patterns in time in each of the investigated cities throughout the week or throughout the years. As observed in the first study on this topic, conducted by Reid et al. [8], and several studies published afterwards, recreational use of alcohol resulted in higher EtS loads during the weekend than during weekdays [9, 11, 14, 15, 17-19]. In contrast, such profile was not observed in Lesbos Island (Greece), which could be attributed to the fact that alcohol drinking is a cultural aspect in Southern European countries [12].

The WBE approach also allows quantifying changes in alcohol consumption associated with special events, e.g., local festivities or festivals, when heavy drinking may take place. This was proved by Andrés-Costa et al. during the “Fallas” festivity in Valencia [9]. In this study, they found almost five and three times higher alcohol consumption during this festivity than during a normal week and weekend, respectively.

Recently, Chen et al. evaluated the WBE approach to estimate alcohol consumption in three different communities of the United States [20]. This study has been the longest conducted to date since samples were collected one weekday every month for 11 months. The average alcohol consumption obtained with the WBE approach was similar to those reported by the WHO and by the National Institute of Alcohol Abuse and Alcoholism (NIAAA). However, consumption figures were derived from samples collected on weekdays. In order to take into account weekend use, when alcohol use is presumably higher as compared to weekdays, they applied a correction factor (1.18) based on previously published studies. After correction, only one of the three investigated communities showed good agreement between the WHO and the WBE data.

4. Advantages of WBE for estimating alcohol consumption

The main advantages that WBE presents over traditional methods to estimate alcohol use are its capability of generating information on consumption habits in a fast, economic, objective, and anonymous way.

Contrary to traditional methods, the WBE approach allows obtaining patterns of alcohol consumption at a high spatial resolution. The coverage area of WBE-derived data is defined by the wastewater catchment (i.e., population connected to the same sewage network) where the sample is collected. Thus, consumption patterns in different size populations can be well defined (see studies carried out in Australia [13], Belgium [11], and Greece[12]). For instance, alcohol use in rural areas of Australia was three to four times higher than in urban zones. On the contrary, alcohol consumption estimates for large cities in Belgium and in Greece were higher than in small cities, although, in the case of Greece, differences were not significant.

Due to the high-throughput character of the WBE approach, consumption trends in time can be rapidly defined and changes in consumption patterns during special events can be detected. For the same reason, it could be used to evaluate the effectiveness of preventive measures (educational and sensibilization campaigns in schools or specific sub-populations) or the efficacy of certain regulations.

5. Limitations of WBE for estimating alcohol consumption

The WBE approach to estimate alcohol use presents also some limitations and therefore it has to be considered as a tool that complements traditional methods. The main limitation is the uncertainty associated with this method that has to be considered when interpreting WBE results. The sources of uncertainty of the WBE approach are well described [21]. They are related to the sampling protocol, the analytical measurement, the stability of the selected biomarker (EtS) in wastewater and in the sewer system, the metabolism of alcohol, and the estimation of the population contributing to the EtS loads measured. The amount of uncertainty associated with the WBE method is specific to each case study. This aspect has

221 been poorly addressed in most of the studies conducted so far, and needs detailed
222 characterization and deeper understanding in future studies.

223 Uncertainty associated to wastewater sampling and EtS analysis can be minimized and
224 controlled if best practice protocols are followed (collection of 24-hour flow or time-
225 proportional integrated samples, sample preservation during collection and transport in cool
226 conditions, use of deuterated surrogate standards for analysis, etc.) [21].

227 Regarding stability, EtS showed little or no significant degradation in wastewater at room
228 temperature for 18h [8] and even one week [7] (in-sample stability). However, two recent
229 studies conducted in both real sewer [22] and lab-scale sewer reactors (rising main and
230 gravity reactors) that mimic in-sewer conditions [23] have shown that EtS is degraded to
231 some extent in sewer systems (in-sewer stability). The study conducted in real sewer
232 systems demonstrated that the degradation rate of EtS is approximately 8% per hour and
233 this could vary from catchment to catchment [22]. The experiments done with lab-scale
234 sewer reactors showed that degradation of EtS in rising main sewer reactors is higher than
235 in gravity reactors and that 20% of EtS could degrade after 3 and 9 hours, respectively.
236 These aspects have to be taken into consideration when estimating alcohol consumption by
237 means of WBE, and also when comparing WBE-derived alcohol consumption data among
238 populations, as they could lead to underestimating the real alcohol consumption.

239 Alcohol metabolism has been scarcely explored and needs further investigation to reduce
240 the uncertainty associated. One of the studies conducted in this line showed that on a molar
241 basis, a median of 0.011% (range: 0.010-0.016) of the alcohol consumed was excreted as
242 EtS [24], while another study reported an EtS excretion rate of 0.022% [25]. Both studies
243 were conducted using very few individuals (ten individuals in the first one and one
244 individual in the second one), and consequently, they may not be representative of the
245 general population, since age, gender, race, and health conditions could also affect alcohol
246 metabolism. WBE alcohol consumption figures reported to date are based on different EtS
247 excretion rate values. As shown in Table 1, the median 0.011%, the range 0.011-0.016%, or
248 the people-weighted mean of the aforementioned studies 0.012% have been used for this
249 purpose. Based on this, ethanol metabolism needs to be further studied to define a single
250 and representative excretion rate of EtS.

The size of the population that contributes to the Et-S loads measured in wastewater is an important source of uncertainty. The method selected to estimate the population size (census data, WWTP design capacity, biomarkers, or water quality parameters) was shown in a multi-city study to affect illicit drug consumption rates to a different extent. Variations as low as 7 % or up to 55% were found in the different cities investigated [21]. Different water quality parameters, such as biological oxygen demand, chemical oxygen demand, total nitrogen and total phosphorus, and several human metabolites and pharmaceuticals and personal care products have been proposed and investigated as potential markers that can contribute to reduce uncertainty associated with the estimation of population size [21, 26, 27]. Ammonium (NH_4^+), an indirect marker of urine that can be measured online in wastewater, was reported to be an extremely useful marker to monitor fluctuations in population size in WBE studies [28]. The use of mobile device data has been recently proposed as a reliable tool to better estimate dynamic population size in a wastewater catchment [29]. However, since this type of data may be not easily accessible or may be costly, the most reliable estimation of population size has to be made in each case, after consulting WWTP experts (origin of wastewater, municipalities connected to the WWTP, and census data) and considering the population dynamics of each investigated area (presence of tourists, commuters, holiday periods, etc.). The latter has to be taken also into consideration when interpreting WBE results. For instance, the high alcohol consumption figures obtained by Chen et al. in one of the communities investigated in the US between June and September reflected the impact of tourist influx rather than increased consumption of alcohol by residents living in the area [20]. One major limitation of WBE is that, contrary to traditional methods, it does not provide alcohol consumption estimates for specific population groups, and thus, consumption patterns by age or by gender cannot be segregated.

6. Conclusions

The WBE approach is a very useful tool, complementary to traditional methods, to estimate the consumption of alcohol in a population. It allows obtaining timely estimates, in a fast, inexpensive, objective, and anonymous way. The uncertainty of this methodology can be

reduced by selecting the best method to estimate population size and increasing the knowledge on EtS stability in the catchment and alcohol metabolism. Data comparability with WHO annual estimates for the different countries could be also improved by using longer sampling periods and covering larger populations so that estimates obtained are representative of a whole country and a year period.

With no doubt, the WBE approach is an already consolidated and valid tool to evaluate changes in alcohol consumption patterns and the effectivity of control and preventive measures applied in specific locations to reduce alcohol consumption.

Conflict of interest statement

Nothing to declare

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Table 1. Alcohol consumption estimates by means of the WBE approach

Level	City or country	Alcohol consumption (mL/day/inh.)		Normalized population	Period of time	Exc. rate (%) used	Ref.
		Average	Range				
Local	Oslo (NO)	16.1		Total population	2009 (3 weeks)	0.010-0.016	[8]
	Santiago (ES)	13.6	3.8-22.6	Total population	2012-2013-2014 (one week)	0.012	[7, 17]
	Barcelona (ES)	18	11-25	>15 years	2013-2014-2015 (one week)	0.011	[14, 15]
	Milan (IT)	5.1	3.2-10.5	Total population	2012-2013-2014 (two weeks)	0.012	[17]
	Valencia (ES)	4.3-17.0	1.1-56.1	>15 years	2014 (17 days in 3 WWTPs)	0.010-0.016	[9]
	Normal week	3.3-6.2	1.1-18.31				
	Festivity	6.4-42.7	4.4-56.11				
	Canberra (AU)	14.6	9.3-22.3	Total population	2014 (one week)	0.012	[18]
	Toowoomba (AU)	9.7	6.9-14.5				
	Montreal (CA)	29.2	21.8-38.8				
	Granby (CA)	44.3	27.3-59.3				
	Lugano (CH)	6.5	4.5-8.4				
	Dortmund (DE)	23.6	18.1-34				
	Dülmen (DE)	20.3	5.5-40				
	Dresden (DE)	29.4	15.1-91.7				
	Munich (DE)	29.5	0.5-47.4				
	Berlin (DE)	16.9	13.8-22.3				
	Copenhagen (DK)	40.2	24.6-74				
	Barcelona (ES)	11.7	5.7-17.6				
	Castellón (ES)	23.4	11.6-61.6				
	Milan (IT)	6.4	5.1-8.1				
	Amsterdam (NL)	22	14.3-30.5				
	Eindhoven (NL)	21.7	13.7-30.4				

Table 1 (cont.). Alcohol consumption estimates by means of the WBE approach

Level	City or country	Alcohol consumption (mL/day/inh.)		Normalized population	Period of time	Exc. rate (%) used	Ref.
		Average	Range				
	Utrecht (NL)	12.9	7.7-20.7	Total population	2014 (one week)	0.012	[18]
	Oslo (NO)	19.2	8.8-52.9				
	Almada (PT)	14.6	8.4-24.1				
	London (UK)	21.5	10.9-36				
	Brussels (BE)	21.6		Total population	2015 (one week)	0.012	[10]
	Zurich (CH)	14.7					
	Copenhagen (DK)	29.7					
	Castellón (ES)	6.6					
	Milan (IT)	6.6					
	Utrecht (NL)	10.8					
	Oslo (NO)	18.9					
	Bristol (UK)	16.2					
	Lier (BE)						
	Lesvos (GR)	5.4 / 3.4	2.2-11.2 / 1.7-7.2				
	Ho Chi Minh (Vietnam)	3.1-3.9					
	Midwestern and Northeastern region (U.S)	37		> 15 years	2015-2016 (one weekday every month for eleven months, 3 WWTPs)	0.012	[20]
National	Belgium						
	Australia	12-13	7-24				
				>15 years	2013-2015 (one week, 8 WWTPs)	0.012	[11]
				15-79 years	2014-2015 (one week, 18 WWTPs)	0.012	[13]

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* of special interest

** of outstanding interest

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References

Papers of particular interest have been highlighted as:

* of special interest

** of outstanding interest

8 – This is the first study that uses EtS concentrations in water to estimate alcohol consumption at the community level. (*)

9 – This study shows that the use of WBE allows detecting changes in alcohol consumption caused by a local festivity. (*)

13 – This is the first study that applies the WBE approach at the national level with very large population coverage (43% of total population). (**)

21 – Authors evaluate and quantitate the different sources of uncertainty associated with consumption estimates derived from the wastewater based epidemiology, and provide best practice protocols. (**)

28 – This study evaluates the use of ammonium level in wastewater as a marker of fluctuations in population size

29 – This study shows how population estimates may affect WBE-estimates and how population size can be accounted for using mobile devices data. (*)