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REVIEW ARTICLE

Nicotine consumption rate through wastewater-based epidemiology: a systematic review, meta-analysis and probabilistic risk assessment

Anvar Asadi[1,2] · Yadolah Fakhri[3] · Yahya Salimi[4] · Nebile Daglioglu[5] · Mina Tahmasebifard[6] · Maryam Aghajarinezhad[6]

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Abstract

Wastewater-based epidemiology (WBE), as a rapid tool, is used to measure and monitor illicit drug consumption in the population. This method is also used to bridge biomarkers of exposure, contaminants, and human health. Smoking cigarettes and tobacco use are everyday habits in nowadays community. This systematic review and meta-analysis aimed to calculate nicotine consumption globally. The related studies were retrieved within international databases including Scopus, Google Scholar, and Web of Science, up to February 2021. It included twenty-one articles containing 87 measurements covering 275.3 million people with total wastewater samples of 2250. Results showed that the highest and lowest nicotine consumption rate (mg/1000 inh./day) was in Portugal (5860) and Vietnam (1201), respectively. The global pooled nicotine consumption rate was 2476 mg/1000 inh./day (95% CI (2289–2663). Based on WBE results, the average daily cigarette smoked per smoker is 14 (95% CI: 10–18 cigarettes/inh./day), close to the value of 14.2 reported by the survey and interview studies. Risk assessment of the nicotine consumption rate through WBE was calculated by the margin of exposure (MOE) approach. In total, 82% of nicotine consumption measurements were located in the "risk" level (MOE < 100), and 18% of the MOE values were between 100–1000. The results reveal that nicotine consumption risks need immediate global and local action strategies. Finally, these findings are helpful for healthcare agencies and policy-makers to take action against tobacco use prevalence.

Keywords Cotinine · Wastewater-based epidemiology · Margin of exposure · Smoking cigarettes · Consumption rate

Responsible Editor: Lotfi Aleya

✉ Mina Tahmasebifard
tahmasemina94@gmail.com

Anvar Asadi
anvarasadi@sbmu.ac.ir

1 Department of Environmental Health Engineering, Faculty of Health, Kurdistan University of Medical Sciences, Sanandaj, Iran

2 Department of Environmental Health Engineering, School of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran

3 Food Health Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

4 Social Development & Health Promotion Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

5 Institute of Forensic Sciences, Department of Forensic Toxicology, Ankara University, Ankara, Turkey

6 Students Research Committee, Department of Epidemiology, Kermanshah University of Medical Sciences, Kermanshah, Iran

Introduction

Nicotine (NIC) is one of the most commonly used psychotropic substances. Consumption of NIC has a substantial role in the global burden of diseases and also injuries (Gao et al. 2020). About 15.2% of the European Union are daily tobacco smokers, which results in 7 thousand deaths each year and also 8 million people on a global scale (both direct and secondhand smoking) (Gracia-Lor et al. 2020). Three-quarters of cigarette smokers belong to low-income and middle-income countries (Jha et al. 2006).

Tobacco use is contributes to the top causes of preventable death and illness worldwide. Smoking deaths in 2016 exceeded 1.7 million, and more than 8 million are expected to die in 2030 (Mackie et al. 2019). According to the World Health Organization (WHO) global report, a tobacco-related disease caused about 8 million deaths in 2017 (WHO 2019). The tobacco industry produces about 5.5 trillion cigarettes yearly worldwide (Buerge et al. 2008), with an average NIC amount of 0.8 mg per cigarette (Gibson 1994).

NIC is the main psychoactive component in cigarette smoke, leading to addiction quickly (Lai et al. 2018). In addition, NIC is absorbed in the lungs at a high rate and comprehensively metabolized in the liver (Rodríguez-Álvarez et al. 2014a). The phase I metabolites of NIC as a complex route include the formation of many metabolites by oxidation, hydroxylation, and N-demethylation (Rodríguez-Álvarez et al. 2014b). Approximately 70–80% of the absorbed NICs are metabolized by the oxidation route to cotinine (COT). They are then hydroxylated to trans 3′-hydroxycotinine (OHCOT) and other minor metabolites (Tricker 2003; Yildiz 2004; Hukkanen et al. 2005). Glucuronide metabolites are produced in phase II through the binding with glucuronic acid, as in the case of cotinine-Nβ-glucuronide (COTGLUC) and trans-3'-hydroxycotinine-Oβ-glucuronide (OHCOT-GLUC) (Chen et al. 2012). Therefore, COT and OH–COT are used as an indicator to assess tobacco smoke exposure and tobacco use due to more extended stability and half-life of body fluids (e.g., plasma and urine) relative to NIC and other metabolites. Therefore, they are commonly used as a biomarker (Marclay and Saugy 2010; Miller et al. 2010; Jacob et al. 2011; Huang et al. 2013).

WHO has declared the need for effective tobacco control interventions. This program includes planning a monitoring program for the data collection on smoking rates, intensities, and trends in countries (Yavuz Guzel et al. 2021). Analyzing raw wastewater can monitor consumption and, thus, tobacco consumption at specific locations. This method has already been used to calculate the consumption of illegal drugs (Zuccato et al. 2005, 2008; González-Mariño et al. 2012; Thomas et al. 2012) and alcohol (Reid et al. 2011; Rodríguez-Álvarez et al. 2014c) in various countries.

The amount of tobacco consumption can be derived from its sales statistics. Still, such data is not always reliable, for example, because inventory levels, regions, and short-term figures are not usually available. More targeted action in this regard is measuring NIC and alcohol consumption through the WBE method (van Wel et al. 2016).

Wastewater can contain chemical pollutants such as heavy metals, pharmaceuticals, and biomarkers (Wong 2017; Ge et al. 2019; Moondra et al. 2020; Guan et al. 2021; Chen et al. 2022; Campos-Mañas et al. 2022). WBE was used at first in 2008 to study the consumption of illicit drugs in the three Italian cities (Zuccato et al. 2008), and subsequently to the consumption of alcohol (Reid et al. 2011; Rodríguez-Álvarez et al. 2015; Boogaerts et al. 2016; Daglioglu et al. 2020), tobacco (Castiglioni et al. 2015), caffeine (Senta et al. 2015), and selected pharmaceuticals (Hernández et al. 2014). Nowadays, the WBE application has been extended to licit materials such as alcohol, psychoactive drugs, NIC, caffeine, and even epidemiological outbreak like the COVID-19 outbreak (Pan and Chen 2021). Its recent application to measure the severe acute respiratory syndrome coronavirus 2 (SARS-CoVID-2) loads in neighborhoods, towns, and cities is an example of its usefulness (Vitale et al. 2021). WBE is currently fine-tuning as an environmental surveillance tool for the coronavirus disease 2019 (COVID-19) pandemic (Gagliano et al. 2023). Estimating the rate of NIC consumption by WBE is performed primarily by measuring its major metabolite COT in the raw wastewater and back-calculating the consumption rate of NIC by people served in the wastewater service (i.e., wastewater treatment or wastewater collection network) (Zheng et al. 2019).

Moreover, some researche shows that continuing NIC uptake stimulates the progress of lung cancer cells and apoptosis (West et al. 2003; Baumung et al. 2016). In this context, we used the “margin of exposure” (MOE) method to assess the health risk of NIC through its consumption rate obtained from wastewater analysis (Mimmi 2021, Luo et al. 2022). MOE is a novel and preferred method for comparing the health risk of different compounds and taking managing actions for risk control. The MOE is the ratio between the point at which the toxicological threshold occurred (benchmark dose (BMD)) and the estimated human intake of the same compound (here the NIC consumption rate per person obtained from the WBE studies). The larger the MOE, the smaller the potential risk posed to the NIC consumers, and a MOE of 10,000 or more would not be considered of health concern and has low priority for risk management actions (Benford et al. 2010).

In this study, we will first provide a systematic review and meta-analysis to assess the consumption per capita per day (mg/1000 inh./day) of NIC through WBE studies on a global scale. Questionnaires, interviews, and self-report surveys compared the NIC and cigarette consumption in WBE studies. Data reported by official organizations like WHO, CDC-STATE, and Europeans survey. Then, the MOE approach estimated a comparative risk assessment of NIC consumption using probabilistic Monte–Carlo-type analysis). To the best of our knowledge, it is for the first time that the evaluation of NIC consumption rate on a global scale is provided by the WBE method, and also its risk is assessed using MOE.

Materials and methods

Search strategy

The study design and reporting used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement systematic review and meta-analysis (Liberati et al. 2009). The international databases, including Scopus, Google Scholar, and Web of Science searched up to February 2021. In addition, for any possible relevant article, check the bibliographies of the final included articles. The keywords used in this search were as follows: wastewater, nicotine, hydroxy cotinine, epidemiology, tobacco consumption, metabolite, and illicit drugs. The search steps were carried out according to PRISMA, as shown in Fig. 1 (Atamaleki et al. 2019).

The following terms were used as a search strategy for Web of Science and Scopus: Web of Science TS = (nicotine) OR TS = ("nicotine consumption") OR TS = ("Tobacco consumption") OR TS = ("hydroxy cotinine") OR TS = (cotinine) AND TS = (epidemiology) OR TS = ("sewage epidemiology") OR TS = ("wastewater epidemiology") OR TS = ("wastewater based epidemiology") OR TS = (sewage) OR TS = (wastewater) and Scopus ((TITLE-ABS-KEY (nicotine) OR TITLE-ABS-KEY ("nicotine consumption") OR TITLE-ABS-KEY ("hydroxy cotinine") OR TITLE-ABS-KEY ("cotinine") AND (TITLE-ABS-KEY (epidemiology) OR TITLE-ABS-KEY ("sewage epidemiology") OR TITLE-ABS-KEY ("wastewater epidemiology") OR TITLE-ABS-KEY ("wastewater based epidemiology") OR TITLE-ABS-KEY("back-calculation")) AND (TITLE-ABS-KEY (sewer) OR TITLE-ABS-KEY (sewage) OR TITLE-ABS-KEY (wastewater)) AND (TITLE-ABS-KEY (monitoring) OR TITLE-ABS-KEY(biomarker)). The researchers also conducted a manual search using Google Scholar. Additional studies were searched using the reference lists of identified studies.

Inclusion and exclusion criteria

Published articles that met the following criteria were included in this meta-analysis: (1) original articles that were peer-reviewed, (2) articles that measure the cotinine concentration in wastewater or calculate the consumption rate per capita of NIC through WBE, (3) articles published in English, (4) articles published up to February 2021. Each study contains the following variables: first author and year of publication, study location, population served by WWTP, number of sampling, year of measuring, mean and SD of per capita consumption of NIC (mg/inh./day), and tell mean of MOE (Table S1 (Supplementary Information (SI)). The reviewers were not blinded to the result of the study, author, and journal name. A third person resolved any disagreement.

Meta-analysis and statistical analysis

The consumption rate of NIC (based on mg/inh./day) was meta-analyzed using $SE = SD/N^{0.5}$ equation. Here, SE is the standard error of concentration, SD, standard deviation, and N is the number of the sample (Peck et al. 2015). The I^2 statistic and chi-square test were used to assess the heterogeneity of included studies. The pooled mean per capita consumption rate of NIC was estimated by the random effect model (REM). Publication bias was assessed using the Begg test. All statistical analysis was conducted using Stata version 14.0 software (Stata Corp, College Station, TX).

Health risk assessment

The MOE value measures the health risk of substance exposure and can be used to compare compounds in risk assessment (Lachenmeier et al. 2011; Mimmi et al. 2021). The approach is used to evaluate the risk of compounds. Due to their genotoxic and carcinogenic properties, they do not show a threshold in the dose–response curve (Lee et al.

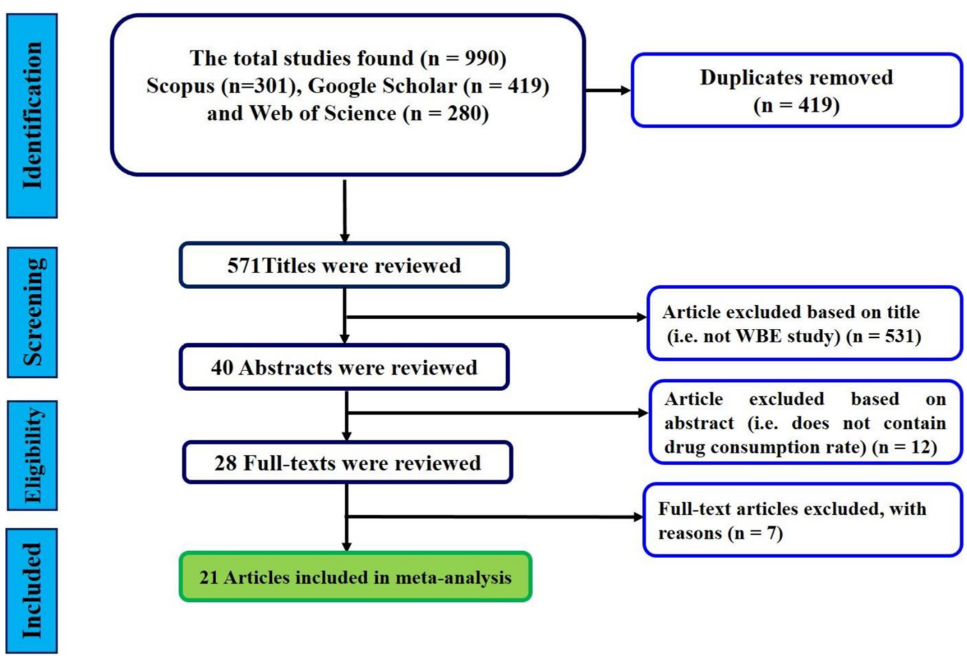

Fig. 1 Flow diagram of the study selection process

2019; Guo et al. 2021; Gao et al. 2022). In this study, we used Monte Carlo simulation to calculate MOE to obtain the quantitative risk assessment of NIC. (Lachenmeier and Rehm 2015) described the MOE as the ratio between the lower confidence limit of the benchmark dose (BMDL) obtained from the median lethal dose (LD50) and the estimated population exposure based on wastewater analysis. The $BMDL_{10}$ (BMDL for a 10% incidence of health effects) was used in this study. Extrapolating the animal LD50 obtained it (Lachenmeier and Rehm 2015). An estimated $BMDL_{10}$ is obtained from the mean LD50 of birds (17.8), dogs (9.2), mice (3.34), and rats (50) by division by 10.2 using method B of Gold et al. (2003). Therefore, the $BMDL_{10}$ of 1.96 mg per kilogram body weight per day (mg/kg-bw/day) was used for calculating MOE with an SD of 1.76 mg/kg-bw/day. The daily intake (ID) of NIC was calculated using Eq. (1):

$$\text{Daily exposure}\left(\frac{mg}{kg-bw.day}\right)=\frac{IR}{bw(kg)} \tag{1}$$

where ID is intake dose (mg/kg-bw/day), IR ingestion rate (mg/inh./day), and bw is body weight (kg). In addition, MOE was calculated using Eq. (2):

$$MOE=\frac{BMDL_{10}\left(\frac{mg}{kg-bw.day}\right)}{\text{The estimated daily exposure }(ID)\left(\frac{mg}{kg-bw.day}\right)} \tag{2}$$

where MOE is the margin of exposure (unitless) $BMDL_{10}$ benchmark dose level (mg/kg-bw/day), and ID intake dose (mg/kg-bw/day) (Lachenmeier and Rehm 2015).

Through simulation, the reputation number for MOE was at 50,000, and also mean of MOE was considered for the health risk benchmark. The distribution of NIC ingestion rate was considered lognormal, and the selected normal distribution was for BMDL10 and body weight (bw: 70 ± 7.0 kg). Monte Carlo simulation was conducted in Oracle Crystal Ball software (version 11.1.2.4).

Results and discussion

Study selection process

We searched Scopus, Google Scholar, and Web of Science up to February 2021 with the above-selected keywords and found 990 published articles. After a primary screening, removed 419 pieces because of the repetition. After that, 531 articles were excluded by reading and evaluation of titles. Then, 12 articles were excluded by reading abstracts. The full texts of the remaining 28 articles were downloaded, reviewed, and data from 21 reports were used in this systematic review and meta-analysis (see Fig. 1).

Characteristics of studies

This study evaluated community of NIC (mg/inh./day) using WBE studies. After tobacco use, NIC is excreted as urinary metabolites. It contains NIC as a parent compound (NIC) (about 19.5%), cotinine (COT) (about 32.3%), and trans-3′-hydroxy cotinine (OH-COT) (about 44.5%) (Zheng et al. 2017; Mackie et al. 2019). NIC is not used as a biomarker of NIC intake because cigarette ash and butts are directly disposed of in wastewater and contribute to the other sources of NIC (Rodriguez-Alvarez et al. 2014). On the other hand, OH-COT showed high variability in concentration and in-sewer instability (Mackie et al. 2019). Hence, COT is often used as a biomarker of NIC consumption due to its high in-sewer stability (Gao et al. 2020). This study used the COT concentration in wastewater for NIC intake, which did not mentione the NIC consumption rate in the results of included studies. The per capita consumption of NIC (in mg/person/day) is calculated using the back-calculation method by the following equation:

$$NIC\ consumption\ rate\ (mg/person/day)=\frac{COT_{concentration}\ (\mu g/L)\times Flow\ (L/day)\times EF_{NIC}\times 1000}{Population\times 10^{6}} \tag{3}$$

where EF_{NIC} is the excretion correction factor for COT after tobacco use, and a mean amount of 2.85 was used, which is presented in most included studies (Gao et al. 2020; Zheng et al. 2020, 2017). In some of the included studies, NIC consumption is given based on the number of cigarettes smoked. The amount of mg NIC absorbed per each cigarette smoked is different in included studies and values like (0.9 ± 15 mg) (Lai et al. 2018; Gao et al. 2020), (1 ± 0.36 mg) (Mackie et al. 2019), (1 – 1.5 mg) (Yavuz Guzel et al. 2021), 0.8 mg (Rodriguez-Alvarez et al. 2014), 1.2 mg (Gracia-Lor et al. 2020) are reported. However, we used a mean value of 1.25 mg NIC absorbed from one cigarette (denoted as D) for obtaining the NIC consumption rate in studies where NIC amounts are reported based on the number of cigarettes smoked per day. The number of cigarettes smoked per day by the population age above 15 (N_{15+}) for comparison of our results with other data sources was calculated using Eq. (4):

$$N_{15+}=\frac{NIC_{abs}}{D\times R_{15}} \tag{4}$$

The number of smokers aged 15+ (N_{smoker}) was also obtained using Eq. (5) which X_{smoker} is daily tobacco smokers among persons aged 15 years and over obtained from WHO report in 2015 (WHO 2015; Chen et al. 2019).

$$N_{smoker}=\frac{NIC_{abs}}{D\times R_{15}\times \chi_{smoker}} \tag{5}$$

The community consumption of NIC extracted from selected studies together with information like country, number study, ES or NIC consumption rate (mg/inh./day), lower rate, upper rate, weight, heterogeneity statistic, degree of freedom, *p* value, and I^2 are presented in Table 1.

Meta-analysis of nicotine consumption rate and comparison with survey statistics

NIC included 21 articles in this study with a total of 2250 samples size. The information such as country of measurement, pooled level of NIC consumption rate (mg/inh. / day), (95% CI), and percent of the weight of the studies are shown in Table 1. As can be seen, the order of NIC consumption rate (based on mg/1000 inh./day) between the included studies was as follows: Portugal (5860) > Slovakia (4390) > Belgium (4300) > Norway (4000) > Czech Republic (3949) > Switzerland (3291) > Turkey (2988) > Italy (2766) > USA (2600) > UK (2040) > Spain (2027) > Australia (1822) > China (1683) > Denmark (1300) > Netherlands (1300) > and in Viet Nam (1201). Generally, European countries showed much higher NIC consumption rates than other countries. The NIC consumption in China and Vietnam (located in South-Eastern Asia) was lower than in many European countries and the USA. However, in the WHO survey on the prevalence trend of tobacco use, in the year 2000, the Southeast Asia region poses the highest tobacco use at around 47% of people aged ≥ 15 years (Organization 2019). The global pooled level of NIC consumption rate through wastewater analysis was 2476 mg/1000 inh./day (95% CI: 2289–2663 mg/1000 inh./day). The results of the Begg test indicate that there is no publication bias ($p = 0.58$). By considering 85% of tobacco smokers as cigarette smokers (Organization 2019), the mean amount of 1.25 mg NIC per one cigarette (Gracia-Lor et al. 2020), and also around 20% of the catchment population with age under 15 years, the global pool rate of cigarette smoking for the whole population served by WWTPs is 2.5 cigarettes per person per day. Although this meta-analysis provided the geographical profiles of NIC consumption between nations, it cannot include the demographic properties of the population such as age distribution, consumption frequency, and prevalence of tobacco use and heavy users (Gao et al. 2020). The NIC consumption rate between nations is highly variable and cannot be easily pooled because it depends on several parameters like the route of NIC administration, cigarette price, cigarette accessibility, and frequency of cigarette usage. In addition, NIC consumption rates are not the same at different times of the year or even on days of the week in one location, which causes significant differences in NIC consumption rates. The primary source of heterogeneity among included studies season, time of sampling, number of samples, population served by WWTP, and the duration of monitoring were the primary source of heterogeneity among included studies. Moreover, wastewater sampling, stability of COT in samples, and trustability of analytical measurements. Its use of well-founded methods for recalculating. NIC consumption and different patterns of social and demographic habits in cities across countries and even within cities are the reasons for the difference in NIC consumption rates between countries (Zarei et al. 2020). The subject makes it challenging to generate homogeneous data for regional and international comparisons of sewage-based epidemiological estimates of NIC consumption (Castiglioni et al. 2013; Lai et al. 2011). Despite these limitations, the results of WBE measurements are generally comparable with data from traditional sources of substance use information (Chen et al. 2019).

Based on the attitudes of European countries (28 member states) towards tobacco survey, there are significant differences in tobacco consumption across the EU with higher rates of smoking in southern Europe including Greece (37%), Bulgaria (36%), France (36%), and Croatia (35%) (Eurobarometer 2015). Overall, the proportion of European smoking was 26% and countries like Sweden (7%), the Netherlands (16%), and the UK (17%) had the lowest proportions (Eurobarometer 2015). The results of this meta-analysis are from the European survey in which the Netherlands and UK had almost lower NIC consumption rates than other European countries. That confirms that the results of the NIC consumption trend through WBE agree with survey and interview studies. The average daily consumption was 13.7 cigarettes per day and, found the highest rates in Cyprus and Austria, with 18.1 and 18.9, respectively (Eurobarometer 2015). Considering the mean value of 1.2 mg NIC absorbed from one cigarette, the average amount of NIC consumption is 16.44 mg/person/day or normalized to a population of 16,440 mg/1000 smokers/day with 26% of smoker proportion is 4274.4 mg/1000 inh./day. The mean amount of 4274.4 mg/1000 inh./day in the European survey is near to the countries of Portugal, Slovakia, Belgium, and Norway in this meta-analysis which had NIC consumption rates of 5860, 4390, 4300, and 4000 mg/1000 inh./day, respectively. The pooled level of NIC consumption rate in European countries included in the meta-analysis was 3477.7 mg/1000 inh./day (95% CI: 2628.4–4326.9 mg/1000 inh./day) which is lower than the mean value of the European interview study (4274.4 mg/1000 inh./day). However, the mean amount of 4274.4 mg/1000 inh./day was for ages 15 years. Above, considering 15.1% of Europeans between 0 and 14 years, the total consumption will be 3628.9 mg/1000 inh./day for all ages, which entirely agree with the pool level of NIC consumption through WBE studies.

It also compared the NIC consumption rate and the number of smokers in countries involved in this meta-analysis with WHO survey data on prevalence trends of tobacco smoking in 2015 (WHO 2015). First, the daily number of cigarettes smoked per capita (cigarettes/inh./day) served

Table 1 Meta-analysis of nicotine consumption (mg/1000 inh./day) based on countries involved

Country	Number of locations/ measurements [a]	Pool level (mg/ inh./day)	Pool level (mg/1000 inh./ day)	Lower (mg/ inh./day)	Upper (mg/ inh./day)	Weight	Heterogeneity statistic	Degree of freedom	p value	I^2 (%)
Australia	30	1.822	1822	1689	1956	35.05	16,590.58	29	< 0.001	99.8
Belgium	2	4.300	4300	1949	6651	2.32	319.76	1	< 0.001	99.7
China	5	1.683	1683	1051	2315	5.68	255.69	4	< 0.001	98.4
Czech Republic	2	3.949	3949	3263	4635	2.34	128.89	1	< 0.001	99.2
Denmark	1	1.300	1300	1206	1394	1.17	0	0		
UK	1	2.040	2040	1887	2193	1.17	0	0		
Italy	15	2.766	2766	2394	3138	17.51	4629.13	14	< 0.001	99.7
Netherlands	1	1.300	1300	1218	1382	1.17	0	0		
Norway	1	4.000	4000	3749	4251	1.15	0	0		
Portugal	1	5.860	5860	3427	8293	0.39	0	0		
Slovakia	5	4.390	4390	1574	7365	5.41	336.39	4	< 0.001	99.2
Spain	4	2.027	2027	1241	2812	4.64	281.93	3	< 0.001	98.9
Switzerland	2	3.291	3291	2540	4041	2.15	3.95	1	0.047	74.7
Turkey	12	2.988	2988	1862	4114	14.01	14,550.71	11	< 0.001	99.9
USA	3	2.600	2600	2474	2726	3.51	11.54	2	0.003	82.7
Viet Nam	2	1.201	1201	1005	1397	2.33	3.07	1	0.08	67.5
Overall pooled	**87**	**2.476**	**2476**	**2289**	**2663**	**100.00**	**1.20E + 05**	**86**	**< 0.001**	**99.9**

[a]Number of locations (i.e., city) or repeated measurement of nicotine consumption over years in one country/city

by WWTPs ranged from 1.1 to 5.2 with an average of 2.5, which matched the NIC consumption trend between countries. Then, we assumed that 80% (national average) of the involved countries' population were 15 years old and over, and based on this we calculated the daily number of cigarettes smoked per smoker. These values were calculated by Eq. (5) using WHO data on daily tobacco smoking among persons aged 15 years and over and NIC consumption rate through wastewater analysis. The results are reported in Fig. 2.

As shown in Fig. 2, the average daily cigarette smoked per smoker is 14 (95% CI: 10–18 cigarettes/inh./day). The average number of cigarettes smoked by adult smokers per day in this meta-analysis was almost the same as the 14.2 cigarettes reported by the Centers for Disease Control and Prevention (CDC) in the USA in 2015 (Jamal et al. 2016). Although Portugal showed the highest and Viet Nam the lowest number of cigarettes smoked per smoker, the trend does not match well with the NIC consumption rates. Generally, mean cigarette consumption is higher in European countries than in other nations. The movemen of daily tobacco smoking (right *Y*-axis) differs widely relative to cigarette consumption rates. Countries like China and the Czech Republic showed the highest daily smoking percentage of the total population 15 years and over, while cigarette consumption rates are low. It indicated that an individual city or lower population might not represent the entire state or country (Chen et al. 2019). However, a high correlation in the number of cigarettes smoked per day per 1000 smokers was observed (data not shown) in countries (i.e., Australia). The number of smokers in the WBE population is close enough to the estimated daily number of smokers of WHO surveys, indicating the ability of WBE to obtain actual consumption.

Health risk assessment

The higher the MOE, the lower risk for humans, and values < 10,000, < 100, and < 10 are used to define the "public health risks," "risk," and "high risk" categories, respectively (Lachenmeier et al. 2011, Lachenmeier and Rehm 2015). However, a MOE > 10,000 is not considered a risk management priority. Tornado diagrams of MOE and 95th percentile of MOE for individual NIC measurement (in Table S1) based on population-based exposure calculated from wastewater analysis are presented in Fig. S1 (Supplementary). The rank order of countries based on risk range (MOE < 100) was Belgium (100%) ~ Czech Republic (100%) ~ UK (100%) ~ Italy (100%) ~ Norway (100%) ~ Portugal (100%) ~ Slovakia (100%) ~ Spain (100%) ~ Switzerland (100%) ~ USA (100%) > Turkey (83%) > China (80%) > Australia (70%) > Denmark (0%) ~ Netherland (0%) ~ Vietnam (0%) (Fig. 3 and Table S2). Overall, 81.61% and 18.39% of the studies were in the "risk" range and "public health risk" range, respectively (Fig. 4).

Differences in health risks of NIC consumption in countries are due to differences in the intake of NIC

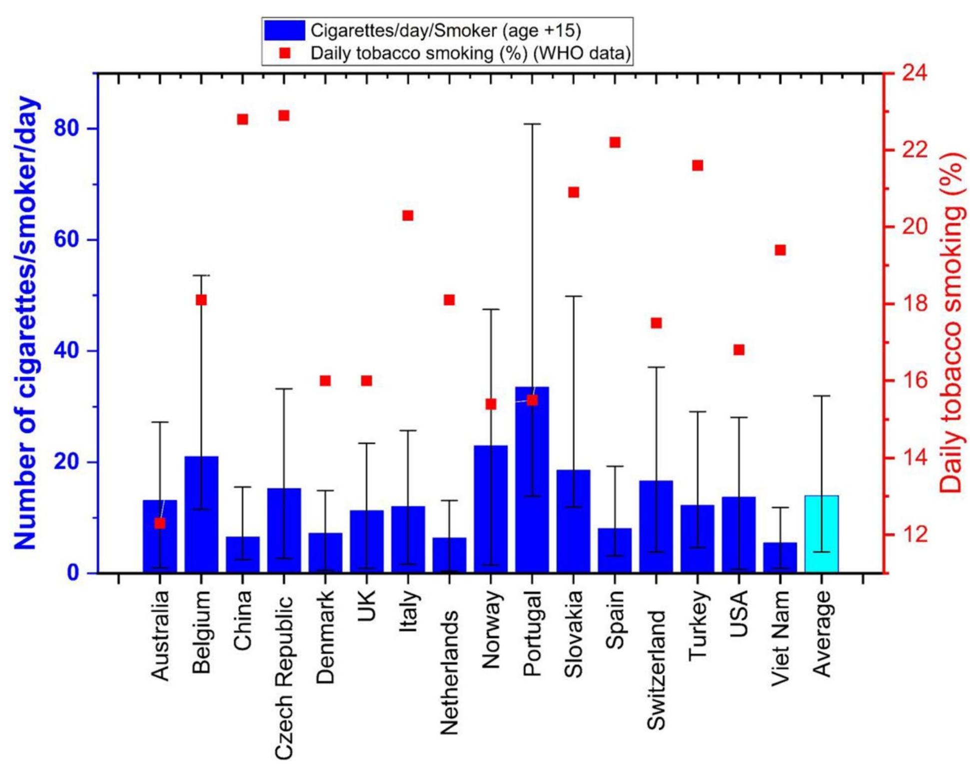

Fig. 2 Daily number of cigarettes smoked by smokers among involved countries (error bars are SD) and daily tobacco smoking (derived from WHO data in 2015)

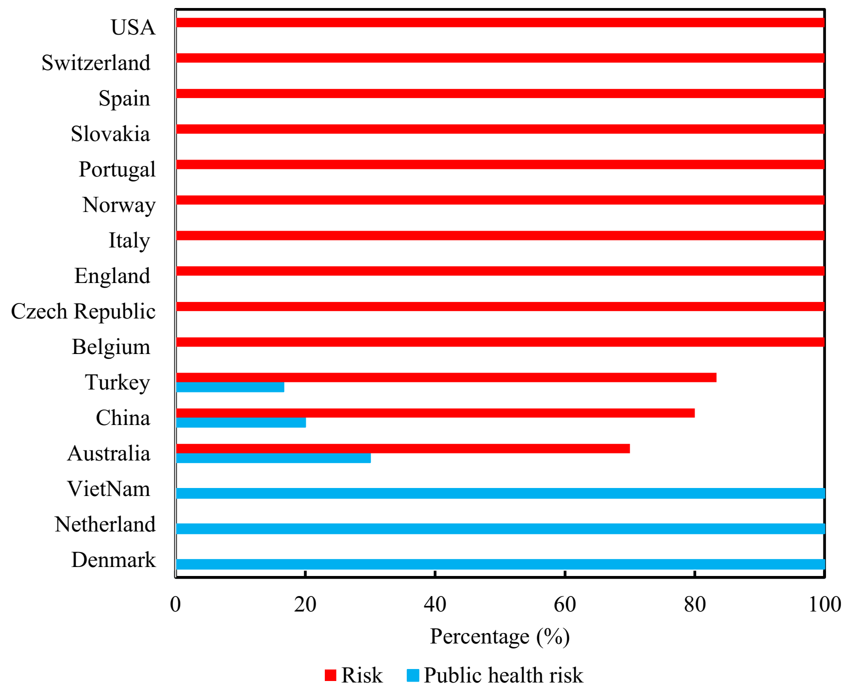

Fig. 3 The percentage of studies in countries based on classification of mean MOE

(Lachenmeier and Rehm 2015, Rodriguez-Alvarez et al. 2014) Following that, differences in the information about NIC can be due to cultural, racial, educational level, political, economic (Pearson et al. 2021; Fagan et al. 2007), weather conditions (Gyllerup et al. 1991), and per capita wastewater production in countries (Gao et al. 2020; Kahkha et al. 2019). On the other hand, this risk assessment is for only NIC compounds in tobacco and does not include toxic compounds such as hydrogen cyanide and acrolein that existing tobacco smoke. Therefore, long-term animal bioassay and toxicological studies for NIC are required considering all poisonous compounds.

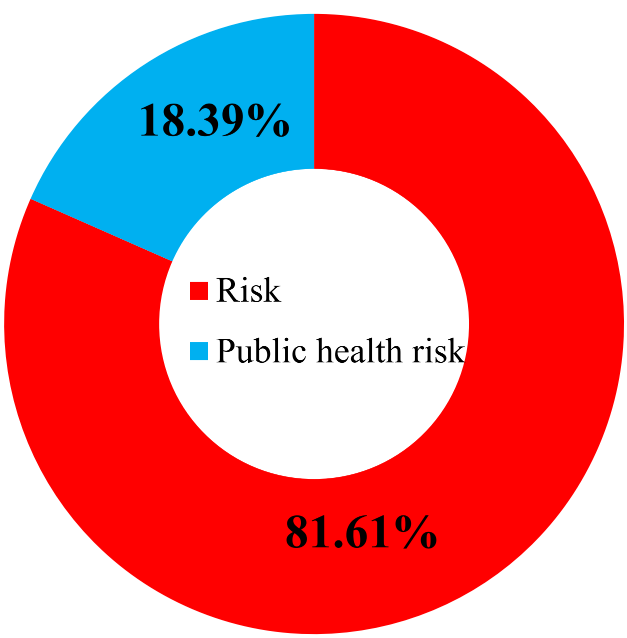

Fig. 4 The percentage of studies in the world based on classification of mean MOE

Conclusion

This study represents the first global-scale meta-analysis and systematic review of NIC consumption rate using WBE studies, conducted in various countries. The meta-analysis covered 275.3 million people from 16 countries, and the pooled NIC consumption rate was 2476 mg/1000 inh./day. The highest and lowest nicotine consumption rate was in Portugal and Vietnam, respectively. On average, every person (age + 15) served by the wastewater treatment plant consumes 2.5 cigarettes daily, and every smoker smokes 14 cigarettes daily. These results were in good agreement (through some calculations) with WHO data (WHO 2015); based on sales statistics and interviews, CDC-STATE (Jamal et al. 2016) system conducted questionnaires by a random-digit-dialing. They interviewed based attitudes of Europeans towards tobacco survey (Eurobarometer 2015). The subject indicates the potential of WBE as a promising tool for human biomonitoring and for providing complementary information on NIC consumption. However, WBE cannot include the demographic properties of the population such as age distribution, consumption frequency, and prevalence of tobacco use and heavy users. Moreover, high hetrogenity in number of wastewater samples and population under study in catchment area in each included study are the main limitations of this study. More efforts need to be made to decrease the uncertainties related to WBE estimation to improve the accuracy of the consumption rates. Risk assessment using a quantitative MOE approach revealed that most of the NIC measurements in this meta-analysis were in the "risk" category region (MOE less than 100) at the population level. Finally, necessary and practical action is felt to reduce the risk of NIC consumption. The result of this study is the most updated nicotine profile analysis and could be used for governments for different countermeasures.

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Data availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval This work was approved under ethical code # IR.KUMS.REC.1399.972.

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References

Atamaleki A, Yazdanbakhsh A, Fakhri Y, Mahdipour F, Khodakarim S, Mousavi Khaneghah A (2019) The concentration of potentially toxic elements (PTEs) in the onion and tomato irrigated by wastewater: A systematic review; meta-analysis and health risk assessment. Food Res Int 125:108518

Baumung C, Rehm J, Franke H, Lachenmeier DW (2016) Comparative risk assessment of tobacco smoke constituents using the margin of exposure approach: the neglected contribution of nicotine. Sci Rep 6:35577

Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc J-C, Renwick AG, Setzer W, Schlatter J, Smith B (2010) Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food Chem Toxicol 48:S2–S24

Boogaerts T, Covaci A, Kinyua J, Neels H, van Nuijs AL (2016) Spatial and temporal trends in alcohol consumption in Belgian cities: a wastewater-based approach. Drug Alcohol Depend 160:170–176

Buerge IJ, Kahle M, Buser H-R, Müller MD, Poiger T (2008) Nicotine derivatives in wastewater and surface waters: application as chemical markers for domestic wastewater. Environ Sci Technol 42:6354–6360

Campos-Mañas M, Fabregat-Safont D, Hernández F, de Rijke E, de Voogt P, van Wezel A, Bijlsma L (2022) Analytical research of pesticide biomarkers in wastewater with application to study spatial differences in human exposure. Chemosphere 307:135684

Castiglioni S, Bijlsma L, Covaci A, Emke E, Hernández F, Reid M, Ort C, Thomas KV, van Nuijs AL, de Voogt P, Zuccato E (2013) Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers. Environ Sci Technol 47:1452–1460

Castiglioni S, Senta I, Borsotti A, Davoli E, Zuccato E (2015) A novel approach for monitoring tobacco use in local communities by wastewater analysis. Tob Control 24:38–42

Chen G, Giambrone NE, Lazarus P (2012) Glucuronidation of trans-3'-hydroxycotinine by UGT2B17 and UGT2B10. Pharmacogenet Genomics 22:183–190

Chen J, Venkatesan AK, Halden RU (2019) Alcohol and nicotine consumption trends in three US communities determined by wastewater-based epidemiology. Sci Total Environ 656:174–183

Chen F, Ma J, Zhu Y, Li X, Yu H, Sun Y (2022) Biodegradation performance and anti-fouling mechanism of an ICME/electro-biocarriers-MBR system in livestock wastewater (antibiotic-containing) treatment. J Hazard Mater 426:128064

Daglioglu N, Atasoy A, Asadi A, Guzel EY, Dengiz H (2020) Estimating alcohol consumption by using wastewater-based epidemiology in Adana Province, Turkey. Environ Sci Pollut Res 27:31884–31891

Eurobarometer S (2015) Attitudes of Europeans towards tobacco and electronic cigarettes. TNS Opinion Social 429:1–42. https://doi.org/10.2875/670456

Fagan P, Moolchan ET, Lawrence D, Fernander A, Ponder PK (2007) Identifying health disparities across the tobacco continuum. Addiction 102:5–29

Gagliano E, Biondi D, Roccaro P (2023) Wastewater-based epidemiology approach: The learning lessons from COVID-19 pandemic and the development of novel guidelines for future pandemics. Chemosphere 313:137361

Gao J, Zheng Q, Lai FY, Gartner C, Du P, Ren Y, Li X, Wang D, Mueller JF, Thai PK (2020) Using wastewater-based epidemiology to estimate consumption of alcohol and nicotine in major cities of China in 2014 and 2016. Environ Int 136:105492

Gao L, Huang X, Wang P, Chen Z, Hao Q, Bai S, Tang S, Li C, Qin D (2022) Concentrations and health risk assessment of 24 residual heavy metals in Chinese mitten crab (Eriocheir sinensis). Qual Assur Saf Crops Foods 14:82–91

Ge D, Yuan H, Xiao J, Zhu N (2019) Insight into the enhanced sludge dewaterability by tannic acid conditioning and pH regulation. Sci Total Environ 679:298–306

Gibson GG (1994) Nicotine and related alkaloids. Absorption, distribution, metabolism, excretion, edited by JW Gorrod and J. Wahren, Chapman and Hall, London, pp. 304, Taylor & Francis

Gold LS, Gaylor DW, Slone TH (2003) Comparison of cancer risk estimates based on a variety of risk assessment methodologies. Regul Toxicol Pharmacol 37:45–53

González-Mariño I, Quintana JB, Rodríguez I, Gonzalez-Diez M, Cela R (2012) Screening and selective quantification of illicit drugs in wastewater by mixed-mode solid-phase extraction and quadrupole-time-of-flight liquid chromatography–mass spectrometry. Anal Chem 84:1708–1717

Gracia-Lor E, Rousis NI, Zuccato E, Castiglioni S (2020) Monitoring caffeine and nicotine use in a nationwide study in Italy using wastewater-based epidemiology. Sci Total Environ 747:141331

Guan Q, Zeng G, Song J, Liu C, Wang Z, Wu S (2021) Ultrasonic power combined with seed materials for recovery of phosphorus from swine wastewater via struvite crystallization process. J Environ Manage 293:112961

Guo W, Chen Y, Jiao H, Hu D, Lu P (2021) Dissipation, residues analysis and risk assessment of metconazole in grapes under field conditions using gas chromatography–tandem mass spectrometry. Qual Assur Saf Crops Foods 13:84–97

Gyllerup S, Lanke J, Lindholm L, Schersten B (1991) Smoking habits, sales of fat and antihypertensives fail to explain the high coronary mortality in cold regions of Sweden. Scott Med J 36:165–168

Hernández F, Ibáñez M, Bade R, Bijlsma L, Sancho JV (2014) Investigation of pharmaceuticals and illicit drugs in waters by liquid chromatography-high-resolution mass spectrometry. TrAC, Trends Anal Chem 63:140–157

Huang R, Han S, Li XS (2013) Detection of tobacco-related biomarkers in urine samples by surface-enhanced Raman spectroscopy coupled with thin-layer chromatography. Anal Bioanal Chem 405:6815–6822

Hukkanen J, Jacob P, Benowitz NL (2005) Metabolism and disposition kinetics of nicotine. Pharmacol Rev 57:79–115

Jacob P 3rd, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL (2011) Determination of the nicotine metabolites cotinine and trans-3’-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography-tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. J Chromatogr B Analyt Technol Biomed Life Sci 879:267–276

Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM (2016) Current cigarette smoking among adults—United States, 2005–2015. Morb Mortal Wkly Rep 65:1205–1211

Jha P, Chaloupka FJ, Corrao M, Jacob B (2006) Reducing the burden of smoking world-wide: effectiveness of interventions and their coverage. Drug Alcohol Rev 25:597–609

Kahkha MRR, Kaykhaii M, Sargazi G, Kahkha BR (2019) Determination of nicotine in saliva, urine and wastewater samples using tantalum metal organic framework pipette tip micro-solid phase extraction. Anal Methods 11:6168–6175

Lachenmeier DW, Rehm J (2015) Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. Sci Rep 5:1–7

Lachenmeier DW, Kanteres F, Rehm J (2011) Epidemiology-based risk assessment using the benchmark dose/margin of exposure approach: the example of ethanol and liver cirrhosis. Int J Epidemiol 40:210–218

Lai FY, Ort C, Gartner C, Carter S, Prichard J, Kirkbride P, Bruno R, Hall W, Eaglesham G, Mueller JF (2011) Refining the estimation of illicit drug consumptions from wastewater analysis: co-analysis of prescription pharmaceuticals and uncertainty assessment. Water Res 45:4437–4448

Lai FY, Gartner C, Hall W, Carter S, O’Brien J, Tscharke BJ, Been F, Gerber C, White J, Thai P (2018) Measuring spatial and temporal trends of nicotine and alcohol consumption in Australia using wastewater-based epidemiology. Addiction 113:1127–1136

Lee J-G, Suh J-H, Yoon H-J (2019) Occurrence and risk characterization of polycyclic aromatic hydrocarbons of edible oils by the Margin of Exposure (MOE) approach. Appl Biol Chem 62:1–11

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62:e1-34

Luo C, Sun J, Tan Y, Xiong L, Peng B, Peng G, Bai X (2022) Comparison of the health risks associated with exposure to toxic metals and metalloids following consumption of freshwater catches in China. Qual Assur Saf Crops Foods 14:1–12

Mackie RS, Tscharke BJ, O’Brien JW, Choi PM, Gartner CE, Thomas KV, Mueller JF (2019) Trends in nicotine consumption between 2010 and 2017 in an Australian city using the wastewater-based epidemiology approach. Environ Int 125:184–190

Marclay F, Saugy M (2010) Determination of nicotine and nicotine metabolites in urine by hydrophilic interaction chromatography-tandem mass spectrometry: potential use of smokeless tobacco products by ice hockey players. J Chromatogr A 1217:7528–7538

Miller EI, Norris HR, Rollins DE, Tiffany ST, Wilkins DG (2010) A novel validated procedure for the determination of nicotine, eight nicotine metabolites and two minor tobacco alkaloids in human plasma or urine by solid-phase extraction coupled with liquid chromatography-electrospray ionization-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 878:725–737

Mimmi SFH, Islam A, Islam A (2021) A comparative study of environment risk assessment guidelines for genetically engineered plants of developing and developed countries including Bangladesh. Sci Herit J 5:21–28

Mimmi SFH (2021) A comparative study of Environment Risk Assessment (ERA) guidelines of developing and developed countries including Bangladesh, Brac University

Moondra N, Jariwala ND, Christian RA (2020) Microalgal-bacterial consortia: an alluring and novel approach for domestic wastewater treatment. WCM 4:51–56

Organization WH (2019) WHO global report on trends in prevalence of tobacco use 2000-2025. World Health Organization

Pan D, Chen H (2021) Border pollution reduction in China: the role of livestock environmental regulations. China Econ Rev 69:101681

Pearson JL, Waa A, Siddiqi K, Edwards R, Nez Henderson P, Webb Hooper M (2021) Naming racism, not race, as a determinant of tobacco-related health disparities. Oxford University Press, US, pp 885–887

Peck R, Olsen C, Devore JL (2015) Introduction to statistics and data analysis. Cengage Learning

Reid MJ, Langford KH, Mørland J, Thomas KV (2011) Analysis and interpretation of specific ethanol metabolites, ethyl sulfate, and ethyl glucuronide in sewage effluent for the quantitative measurement of regional alcohol consumption. Alcohol Clin Exp Res 35:1593–9

Rodriguez-Alvarez T, Rodil R, Rico M, Cela R, Quintana JB (2014) Assessment of local tobacco consumption by liquid chromatography–tandem mass spectrometry sewage analysis of nicotine and its metabolites, cotinine and trans-3′-hydroxycotinine, after enzymatic deconjugation. Anal Chem 86:10274–10281

Rodríguez-Álvarez T, Rodil R, Cela R, Quintana JB (2014a) Ion-pair reversed-phase liquid chromatography-quadrupole-time-of-flight and triple-quadrupole-mass spectrometry determination of ethyl sulfate in wastewater for alcohol consumption tracing. J Chromatogr A 1328:35–42

Rodríguez-Álvarez T, Rodil R, Rico M, Cela R, Quintana JB (2014b) Assessment of local tobacco consumption by liquid chromatography–tandem mass spectrometry sewage analysis of nicotine and its metabolites, cotinine and trans-3′-hydroxycotinine, after enzymatic deconjugation. Anal Chem 86:10274–10281

Rodríguez-Álvarez T, Rodil R, Rico M, Cela R, Quintana JB (2014c) Assessment of local tobacco consumption by liquid chromatography-tandem mass spectrometry sewage analysis of nicotine and its metabolites, cotinine and trans-3’-hydroxycotinine, after enzymatic deconjugation. Anal Chem 86:10274–10281

Rodríguez-Álvarez T, Racamonde I, González-Mariño I, Borsotti A, Rodil R, Rodríguez I, Zuccato E, Quintana JB, Castiglioni S (2015) Alcohol and cocaine co-consumption in two European cities assessed by wastewater analysis. Sci Total Environ 536:91–98

Senta I, Gracia-Lor E, Borsotti A, Zuccato E, Castiglioni S (2015) Wastewater analysis to monitor use of caffeine and nicotine and evaluation of their metabolites as biomarkers for population size assessment. Water Res 74:23–33

Thomas KV, Bijlsma L, Castiglioni S, Covaci A, Emke E, Grabic R, Hernández F, Karolak S, Kasprzyk-Hordern B, Lindberg RH (2012) Comparing illicit drug use in 19 European cities through sewage analysis. Sci Total Environ 432:432–439

Tricker AR (2003) Nicotine metabolism, human drug metabolism polymorphisms, and smoking behaviour. Toxicology 183:151–173

van Wel JH, Gracia-Lor E, van Nuijs AL, Kinyua J, Salvatore S, Castiglioni S, Bramness JG, Covaci A, Van Hal G (2016) Investigation of agreement between wastewater-based epidemiology and survey data on alcohol and nicotine use in a community. Drug Alcohol Depend 162:170–175

Vitale D, Morales Suárez-Varela M, Picó Y (2021) Wastewater-based epidemiology, a tool to bridge biomarkers of exposure, contaminants, and human health. Curr Opin Environ Sci Health 20:100229

West KA, Brognard J, Clark AS, Linnoila IR, Yang X, Swain SM, Harris C, Belinsky S, Dennis PA (2003) Rapid Akt activation by nicotine and a tobacco carcinogen modulates the phenotype of normal human airway epithelial cells. J Clin Invest 111:81–90

WHO (2015) WHO global report on trends in prevalence of tobacco smoking 2015. World Health Organization

WHO (2019) WHO global report on trends in prevalence of tobacco use 2000–2025. World Health Organization

Wong A (2017) Natural treatment technology for cleaning wastewater. Water Conservation and Management

Yavuz Guzel E, Atasoy A, Gören İE, Daglioglu N (2021) Estimation of alcohol and nicotine consumption in 11 cities of Turkey using wastewater-based epidemiology. Drug Test Anal 13:853–861

Yildiz D (2004) Nicotine, its metabolism and an overview of its biological effects. Toxicon 43:619–632

Zarei S, Salimi Y, Repo E, Daglioglu N, Safaei Z, Güzel E, Asadi A (2020) A global systematic review and meta-analysis on illicit drug consumption rate through wastewater-based epidemiology. Environ Sci Pollut Res 27:36037–36051

Zheng Q-D, Lin J-G, Pei W, Guo M-X, Wang Z, Wang D-G (2017) Estimating nicotine consumption in eight cities using sewage epidemiology based on ammonia nitrogen equivalent population. Sci Total Environ 590–591:226–232

Zheng Q, Tscharke B, O'Brien J, Gerber C, Mackie R, Gao J, Thai P (2019) Uncertainties in estimating alcohol and tobacco consumption by wastewater-based epidemiology. Curr Opin Environ Sci Health 9:13–18

Zheng Q, Gartner C, Tscharke BJ, O'Brien JW, Gao J, Ahmed F, Thomas KV, Mueller JF, Thai PK (2020) Long-term trends in tobacco use assessed by wastewater-based epidemiology and its relationship with consumption of nicotine containing products. Environ Int 145:106088

Zuccato E, Chiabrando C, Castiglioni S, Calamari D, Bagnati R, Schiarea S, Fanelli R (2005) Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ Health 4:1–7

Zuccato E, Chiabrando C, Castiglioni S, Bagnati R, Fanelli R (2008a) Estimating community drug abuse by wastewater analysis. Environ Health Perspect 116:1027–1032