



Wastewater analysis reveals urban, suburban, and rural spatial patterns of illicit drug use in Dalian, China

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Abstract

Illicit drug use in rural and suburban areas of China has not been studied extensively, as most studies have focused on illicit drug use in urban areas. To compare the differences between urban, suburban, and rural drug use, we collected influent samples from 19 urban, 9 suburban, and 18 rural wastewater treatment plants in Dalian, respectively. A method using solid-phase extraction combined with derivatization for gas chromatography-mass spectrometry analysis was applied to detect biomarker concentrations. The concentrations of methamphetamine and morphine ranged from 3.12 to 605 ng/L and < 2.35 to 198 ng/L, respectively. Norketamine was found in only four samples (5.56 to 14.5 ng/L), while 3,4-methylenedioxymethamphetamine and benzoylecgonine were not detected in any samples. Methamphetamine use in rural areas (16.3 mg/day/1000 inhabitant (inh), prevalence: 0.06%) was significantly lower than those in urban (77.1 mg/day/1000 inh, prevalence: 0.23%) and suburban (234 mg/day/1000 inh, prevalence: 0.70%) areas. Heroin use in suburban areas (57.6 mg/day/1000 inh, prevalence: 0.10%) was significantly higher than that in urban (13.9 mg/day/1000 inh, prevalence: 0.02%) and rural (8.68 mg/day/1000 inh, prevalence: 0.02%) areas. The results indicate relatively low levels of illicit drug use in rural areas of Dalian, related to low incomes and outflow of the working-age population. Illicit drug use was most prevalent in suburban areas of Dalian, which may be influenced by large floating populations and few anti-drug efforts in suburban areas.

Keywords Wastewater-based epidemiology · Spatial patterns · Illicit drug use · Biomarkers

Introduction

Wastewater-based epidemiology (WBE) comprises the detection of excreted biomarkers including parent drugs or their metabolites in raw wastewater, which can be used for back-calculating drug use (Daughton 2001; Zuccato et al. 2008; Zuccato et al. 2005). As a powerful tool for assessing illicit drug use, WBE can accurately assess spatial patterns, on both small and large scales (Ort et al. 2014). Small-scale spatial patterns, in local communities, and cities (Croft et al. 2020; Mercan et al. 2019; Tschärke et al. 2015), university campuses (Gushgari et al. 2018; Heuett et al. 2015), prisons (Postigo et al. 2011; van Dyken et al. 2016), vacation areas (Lai et al.

2013a), and major event locations (Foppe et al. 2018; Gerrity et al. 2011; Lai et al. 2013b), have been observed. Large-scale spatial patterns (national- or international-level patterns) have been studied in Europe (Gonzalez-Marino et al. 2020; Ort et al. 2014; Thomas et al. 2012), North America (Banta-Green et al. 2009), Australia (Bade et al. 2019; Lai et al. 2016), and Asia (Du et al. 2015; Du et al. 2017; Khan et al. 2014; Kim et al. 2015; Shao et al. 2020). Cocaine is a popular drug in Europe, methamphetamine is a popular drug in Asia, and both cocaine and methamphetamine are widely used in North America and Australia. In China, the main illicit drugs are methamphetamine and heroin. Methamphetamine is widely used across the country (Du et al. 2015; Shao et al. 2020), while heroin is widely used in Western China (Du et al. 2017). The spatial patterns revealed in these studies are qualitatively consistent with United Nations Office on Drugs and Crime reports (UNODC 2020).

However, for cities with separate urban and rural wastewater systems, the results of drug use assessment in urban areas are not generalizable to the entire city or country. Therefore, some studies have focused on comparisons of differences in

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illicit drug use among different areas within cities. For instance, in Turkey, drug use in the city center was higher than those in the rural areas (Mercan et al. 2019). In the USA, cocaine use was higher in urban communities, while methamphetamine use was higher in rural communities (Banta-Green et al. 2009; Croft et al. 2020). In Australia, cocaine and 3,4-methylenedioxymethamphetamine (MDMA) use in urban areas were higher than those in rural areas, but methamphetamine use in urban areas was similar to that in rural areas (Lai et al. 2016). These studies have shown differences in drug use patterns in different areas within cities. Compared with those of developed countries, the differences in economic levels between urban and rural areas in China are highly significant, which may lead to greater differences in drug use (UNODC 2020). However, few studies have analyzed drug use in an entire city in China, especially in rural areas of a city, indicating that previously elucidated estimated drug use represents only urban residents. Some studies have reported that the analysis of drug consumption in small communities violates the ethical constraints of WBE (Hall et al. 2012; Prichard et al. 2014), while in China, this method has been used in drug-related criminal investigations.

In this study, we aimed to apply WBE to investigate the use of methamphetamine (METH), heroin (HER), ketamine (KET), MDMA, and cocaine (COC) in urban, suburban, and rural areas of Dalian, China. To achieve this objective, 19 urban, 9 suburban, and 18 rural wastewater treatment plants (WWTPs) were selected, covering the entire city of Dalian. Drug consumption and prevalence were derived based on the concentration of biomarkers in wastewater. We discuss the differences in drug use between urban, suburban, and rural areas and analyze correlations among the use of different drugs. Furthermore, a probabilistic Monte Carlo simulation was used to assess the uncertainty and variability of the estimation.

Material and methods

Reagents and materials

METH was purchased from Cerilliant (Round Rock, TX, USA). MDMA, morphine (MOR), norketamine (NK), and benzoylcegonine (BE) were purchased from A ChemTek, Inc. (Worcester, MA, USA). *N*, *O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS) and trifluoroacetic anhydride (TFA) was purchased from Aladdin (Shanghai, China). Naphthalene- d_8 (Nap- d_8) was obtained from Supelco Co., Ltd. (Bellefonte, USA). Methanol (MeOH), acetonitrile (ACN), and ethyl acetate (EAC) (HPLC $\geq 99.8\%$) were purchased from TEDIA Co., Ltd. (TEDIA, USA). 0.45- μm (33 mm) and 0.22- μm (33 mm) filter membranes were

purchased from Xinya Co., Ltd. (Shanghai, China). Ammonium hydroxide ($\text{NH}_3\cdot\text{H}_2\text{O}$) and sodium bicarbonate (NaHCO_3) (analytic reagent) were purchased from Kemiou Chemical Reagent Co., Ltd. (Tianjin, China). Oasis MCX (60 mg, 3 mL) solid-phase extraction (SPE) cartridges and vacuum pump manifold with twenty connections were acquired from Waters Corporation (Waters, USA).

Wastewater sampling

The sampling campaign was conducted during November to December 2019. A time proportional mode was applied during sampling with 60 mL collected every 30 min using an automatic sampler for 24-h composite influent wastewater. Two samples were collected from each of the 46 WWTPs in urban ($n = 19$), suburban ($n = 9$), and rural areas ($n = 18$). In the process of regional divisions, we investigated the attitude of local residents and referred to the administrative divisions of Dalian government departments. The main city and several satellite cities have high economic and urbanization level, and the WWTPs serving these areas are divided into urban areas. Suburban areas are developing areas outside the scope of urban areas, such as development zones and economic zones. Rural areas mainly include agricultural areas, remote mountain towns, and fishing villages. WWTP sampling locations are shown in Fig. 1, and information about the WWTPs is shown in Table S1. After collection, all samples were sent to the laboratory and stored at $-20\text{ }^\circ\text{C}$ until analysis. The time from sample collection to analysis was less than 3 days. The population served by WWTPs ranged from 600 (TLZ) to 0.57 million (CL2) people, for a total of 6.26 million: 4.94 million in urban areas, 0.73 million in suburban areas, and 0.59 million in rural areas. According to the Statistical Yearbook of Dalian, the permanent populations of the urban and rural areas in 2018 were 5.51 million and 1.49 million, respectively (Liaoning Province Bureau of Statistics 2019). As a tourist and port city, Dalian has large floating populations that cannot be reflected in census data. Considering these floating populations, the population size estimated in this study basically represents the entire urban population and part of the rural population in Dalian.

Extraction and analysis

The determination of the concentration of $\text{NH}_4\text{-N}$ was performed using standard method 350.1 from the United States Environmental Protection Agency (USEPA) with the Nessler method. The wastewater sample (100 mL) was passed through 0.45- μm and 0.22- μm filter membranes to remove solid particles. Each sample was divided into two parts (50 mL): one part was derivatized by TFA to detect METH, MDMA, and NK, and the other was derivatized by BSTFA to detect MOR and BE. Two filtered samples were extracted separately with

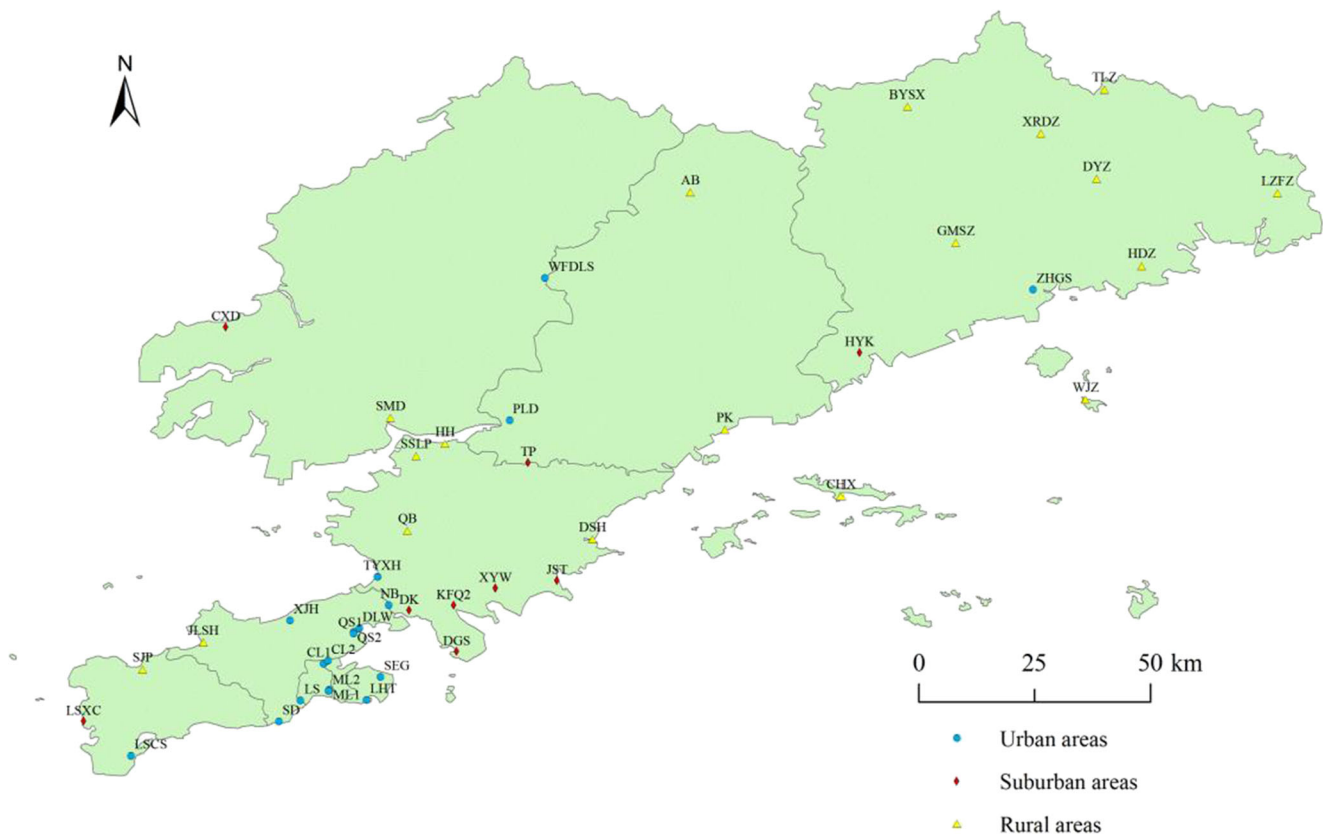


Fig. 1 Locations of WWTPs where wastewater samples were collected

two Oasis MCX SPE cartridges, which were preconditioned with 6 mL of MeOH and 9 mL of ultrapure water. After loading with wastewater, the cartridges were dried for 5 min under a vacuum to remove excess water. The column was eluted with 4 mL of MeOH and 4 mL of 5% NH₃·H₂O in MeOH and the eluate was dried under a soft stream of nitrogen. One part of the dried sample was redissolved using 200 µL of EAC and the other part was redissolved using 200 µL of ACN.

For METH, MDMA, and NK, 25 µL of TFA was added to the EAC phase and derivatized at 45 °C for 60 min. After the reaction, 250 µL of 10% NaHCO₃ solution was added to remove the remaining derivatizing agent and adjust the pH of the solution to around pH 7. The mixture was centrifuged at 2000 rpm for 3 min. Then, 50 µL of the obtained organic phase was transferred to the chromatographic bottle, and the internal standard Nap-d₈ (20 ng/mL) was used in the analysis.

For MOR and BE, 25 µL of BSTFA was added to the ACN phase and derivatized at 70 °C for 30 min. After the reaction, the remaining derivatizing agent was removed under a light stream of nitrogen, and the derivative was redissolved in 200 µL of ACN. The internal standard of Nap-d₈ (20 ng/mL) was added before analysis.

The samples were analyzed by gas chromatography-mass spectrometry (GC-MS) on an Agilent 7890B gas chromatograph connected to an Agilent 5977A mass spectrometer

(California, USA) equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 µm, J&W Scientific). The detection was performed in selective ion monitoring mode. The mass spectrometer was operated in the electron impact ionization source maintained at 70 eV at 230 °C and the quadrupole was maintained at 150 °C. The retention times and mass ions of compounds are listed in Table S2.

Different instrument settings were used for different target drug residues: For METH, MDMA, and NK, 1 µL of sample was injected and the injector temperature was set to 230 °C. The initial oven temperature was 90 °C and then increased to 230 °C at a rate of 10 °C/min and held at 230 °C for 1 min. For MOR and BE, 2 µL of sample was injected and the injector temperature was set to 280 °C. The initial oven temperature was 90 °C for 2 min and then increased to 290 °C at a rate of 20 °C/min and held at 290 °C for 5 min.

Quality control

The linearity of each derived substance was evaluated to obtain the calibration curve in the concentration range of 10–1000 ng/mL. The linear correlation coefficients of METH, MDMA, NK, MOR, and BE were 0.995, 0.999, 0.999, 0.993, and 0.999 respectively. Although the concentrations of biomarkers in some samples were below the minimum concentrations for linearity, the concentration range was based on the limit of quantification

(LOQ). The limit of detection (LOD) and LOQ were calculated as three times and ten times the signal-to-noise ratio, respectively. The LODs and LOQs are listed in Table S2. The recovery values of METH, MDMA, and NK using 50 mL of ultrapure water (100 ng/mL) were $98.4 \pm 4\%$, $122 \pm 17\%$, and $87.7 \pm 26\%$ ($n = 7$), respectively. The recovery of MOR and BE using 50 mL of ultrapure water (100 ng/mL) were $66.0 \pm 10\%$ and $75.3 \pm 3\%$ ($n = 7$), respectively. The recovery values of METH, MDMA, and NK using 50 mL of wastewater (25 ng/mL) were $106 \pm 9.8\%$, $97 \pm 7\%$, and $98 \pm 17\%$ ($n = 7$), respectively. The recovery of MOR and BE using 50 mL of wastewater (25 ng/mL) were $73.0 \pm 5\%$ and $92 \pm 12\%$ ($n = 7$), respectively. The final concentration was corrected by the recovery of biomarkers in the wastewater to ensure the accuracy of the results. A blank containing ultrapure water was run after every 20 wastewater samples and was subjected to the same pretreatment steps as the wastewater samples. All the target compounds were below the LODs for blanks. Chromatograms and MS spectrums of each substance at LOQ level are shown in Fig. S1.

Back-calculation of illicit drug consumption

The per 1000 inhabitant (inh) daily consumption of illicit drug ($m_{T,i}$) at specific WWTPs was estimated using the following equation:

$$m_{T,i} = \frac{C_{T,i} \times F_i \times f_T}{P_i} \quad (1)$$

where $C_{T,i}$ is the concentration of METH, MOR, NK, BE, and MDMA in a WWTP of i , F_i is the flow rate of raw wastewater in a WWTP of i , and P_i is the population served by a WWTP of i . f_T is the correction factor for each illicit drug; detailed data is shown in Table 1. $\text{NH}_4\text{-N}$ is used as a biomarker of the population. The population estimated by $\text{NH}_4\text{-N}$ was calculated as follows:

$$P_i = \frac{C_{\text{NH}_4\text{-N},i} \times F_i}{m_{\text{NH}_4\text{-N}}} \quad (2)$$

where $C_{\text{NH}_4\text{-N},i}$ is the concentration of $\text{NH}_4\text{-N}$ in a WWTP of i and $m_{\text{NH}_4\text{-N}}$ is the average amount of daily $\text{NH}_4\text{-N}$ production of each inhabitant. The value of $m_{\text{NH}_4\text{-N}}$ was determined to be 6 g/day/inh (Zheng et al. 2017). Therefore, Eq. (1) can be simplified as follows:

$$m_{T,i} = \frac{C_{T,i} \times m_{\text{NH}_4\text{-N}} \times f_T}{C_{\text{NH}_4\text{-N},i}} \quad (3)$$

As each WWTP serves a different population size, in order to obtain the average consumption of a region, the consumption of each WWTP needs to be corrected by population weight. Regional average consumption ($m_{T,\text{Mean}}$) can be calculated by Eq. (4).

$$m_{T,\text{Mean}} = \sum_{i=1}^n m_{T,i} W_i \quad (4)$$

where W_i is the weight of population served by a WWTP of i and the weight for each WWTP can be calculated based on the population served and the total population served by all WWTPs. n is the number of WWTPs in each region.

The prevalence of illicit drug use was based on the following equation:

$$PR(\%) = \frac{m_{T,\text{Mean}}}{D_T \times n_T \times R_{15-64}} \times 100\% \quad (5)$$

where D_T is the single dose of drug use, n_T is the frequency of drug use, and R_{15-64} is the proportion of the adult population aged 15–64 years old among the general population. D_T and n_T for each illicit drug are shown in Table 1.

Statistical analysis

The Shapiro-Wilk test was used to test the normality of the distribution of drug data as raw or log-transformed data. We used the independent samples t test and the non-parametric Kruskal-Wallis test for analyzing the differences of drug use between urban, suburban, and rural areas. Moreover, we used the Pearson and Spearman correlation analysis test to determine correlation. All calculations and statistical tests were performed using SPSS (Version 22) and Origin (Version 9.4) software, and a p value of < 0.05 was regarded as statistically significant. The Monte Carlo simulation (Oracle Crystal Ball software, Version 7.3.1) was used to evaluate the uncertainties of drug consumption and prevalence.

Results and discussion

Population estimation

The number of people served by a WWTP is an important parameter, used to calculate the per inhabitant consumption of drugs, but population estimates can be uncertain. In this study, we used $\text{NH}_4\text{-N}$ to estimate the population, which was proven to reflect the population changes during the survey period with low uncertainty (Been et al. 2014; Zheng et al. 2017). However, it is considered that some of the WWTPs that serve suburban and rural areas also process industrial wastewater, which affects the $\text{NH}_4\text{-N}$ concentration of wastewater. According to the proportion of domestic wastewater processed by WWTPs, we selected the most suitable population for each WWTP. If the domestic wastewater proportion was greater than or equal to 90%, the population was calculated based on $\text{NH}_4\text{-N}$ without considering the impact of industrial wastewater. When the proportion of domestic wastewater was less than 90%, the design service population was

Table 1 Estimated parameters of wastewater-based epidemiology

Drugs	Drug target residues (DTRs)	Excretion rate (%)	Molar ratio parent/DTR	Correction factor (f_T)	D_T (mg/dose)	n_T (dose/day/inh)
METH	METH	43% (Baker et al. 2014; Zuccato et al. 2008)	1	2.3	135 (Pei et al. 2016)	0.31 (Pei et al. 2016)
HER	MOR	71% (Khan and Nicell 2011)	1.29	1.82	30 (Gushgari et al. 2019; Zuccato et al. 2008)	2.4 (Wang 2018)
KET	NK	4% (Du et al. 2020)	1.06	26.5	75 (Yargeau et al. 2014)	0.33 (Wang et al. 2016)
COC	BE	30% (Baker et al. 2014)	1.05	3.5	100 (Yargeau et al. 2014; Zuccato et al. 2008)	0.31 (Waldrop et al. 2007)
MDMA	MDMA	20% (Baker et al. 2014; Khan et al. 2014)	1	5	100 (Yargeau et al. 2014; Zuccato et al. 2008)	0.43 (Wang 2018)

adopted (Table S3). The design service populations of all WWTPs were significantly correlated with the $\text{NH}_4\text{-N}$ populations ($r^2 = 0.42$, $p < 0.05$). According to the above classification, the correlation between the design service population and the $\text{NH}_4\text{-N}$ population became stronger after removing the WWTPs that processed industrial wastewater ($r^2 = 0.68$, $p < 0.05$), confirming the adverse impact of industrial pollution sources on the use of $\text{NH}_4\text{-N}$ to estimate the population (Fig. S2 and S3) (Rico et al. 2017).

Occurrence of target drug residues in wastewater

METH was detected in all the samples, and the concentrations ranged from 3.12 to 605 ng/L, with an average of 111 ng/L and a median of 38.7 ng/L. The concentrations of MOR ranged from < 2.35 to 198 ng/L, with an average of 56.2 ng/L and a median of 46.8 ng/L. NK concentrations were 1–2 orders of magnitude lower than those of METH and MOR, and NK residue was found in only four samples (5.56 to 14.5 ng/L). MDMA and BE were not detected in any samples (Table 2).

According to the service areas of WWTPs, the city was divided into urban, suburban, and rural areas (Fig. 2). The concentrations of METH and MOR in urban areas ($n = 19$) ranged from 15.6 to 449 ng/L and < 2.35 to 198 ng/L, respectively, and in suburban areas ($n = 9$) ranged from 3.43 to 507 ng/L and 20.3 to 190 ng/L, respectively, while in rural areas ($n = 18$), the concentrations of METH, MOR, and NK ranged from 3.32 to 605 ng/L, 2.89 to 136 ng/L, and < 0.35 to 14.5 ng/L, respectively.

Illicit drug use in urban, suburban, and rural areas

METH

METH was the most common drug detected, and the average amount was 89.7 mg/day/1000 inh (Table 2, Fig. 3), which was lower than those reported by Du et al. (2015) (156 mg/

day/1000 inh) and Shao et al. (2020) (102 mg/day/1000 inh) in Chinese cities (Du et al. 2015; Shao et al. 2020).

The average amounts of METH detected in urban, suburban, and rural areas were 77.1 mg/day/1000 inh, 234 mg/day/1000 inh, and 16.3 mg/day/1000 inh, respectively. Compared with a previous long-term study in urban areas in Dalian, it was lower than 144 mg/day/1000 inh, 256 mg/day/1000 inh, and 128 mg/day/1000 inh which were detected in 2015–2017, but higher than 33.6 mg/day/1000 inh, which was detected in 2018 (Wang et al. 2019). Compared with the data from nine of the same WWTP (SEG, ML1, ML2, CL1, CL2, QS, LHT, LS, and XJH), no significant differences were observed in these WWTPs ($p > 0.05$, Kruskal-Wallis test). METH use in urban and suburban areas was significantly higher than that in rural areas ($p < 0.05$, Kruskal-Wallis test) (Fig. 4); Mercan et al. (2019) found a similar pattern in Istanbul. Compared with those in urban areas, rural per capita disposable income, education levels, and expenditures are lower in rural areas (Table S4), and a large number of laborers travel from rural to urban and suburban areas (Liu et al. 2015). Due to the loss of the working-age population, the proportions of children and elderly individuals in rural areas are higher than those in urban areas, which may be one of the reasons for the low prevalence of illicit drug use in rural areas. Moreover, we found that METH use was higher in suburban areas than in urban areas, which was different from the results of previous studies in Australia and Beijing, China (Lai et al. 2013a; Li et al. 2014). This indicates that as anti-drug efforts by the government increase in urban areas, drug hotspots become more covert (NNCC 2020), such as in private locations or suburban areas. Moreover, there are many fast-developing areas in the suburban areas of Dalian, and these places have many factories and job opportunities. Most migrant workers live in suburban areas and work locally (Shen 2017). Overall, as a transitional area between urban and rural areas, suburban areas have large floating populations and are not primary targets for anti-drug efforts, which may contribute to a high level of drug use (Yang 2006).

Table 2 Drug concentration (C , ng/L) and consumption (m , mg/day/1000 inh) in 46 WWTPs (mean \pm SD)

Region	WWTPs	C_{METH}	C_{MOR}^a	C_{NK}^b	m_{METH}	m_{HER}	m_{KET}	
Urban areas	SEG	398 \pm 83.9	36.7 \pm 2.36	<0.35	180 \pm 37.9	9.06 \pm 0.84	–	
	LHT	193 \pm 6.60	95.2 \pm 33.9	<0.35	188 \pm 6.42	69.2 \pm 26.1	–	
	ML1	230 \pm 134	20.6 \pm 16.7	<0.35	115 \pm 66.6	4.06 \pm 6.20	–	
	ML2	50.0 \pm 26.0	24.7 \pm 2.65	<0.35	32.2 \pm 16.8	8.51 \pm 1.35	–	
	CL1	131 \pm 7.63	60.0 \pm 11.0	<0.35	127 \pm 7.37	41.8 \pm 8.44	–	
	CL2	37.6 \pm 35.6	<2.35	<0.35	18.3 \pm 17.3	–	–	
	LS	20.8 \pm 22.6	42.8 \pm 0.40	<0.35	10.7 \pm 11.6	13.3 \pm 0.16	–	
	SD	28.0 \pm 3.16	85.5 \pm 4.19	<0.35	9.60 \pm 1.08	19.2 \pm 1.14	–	
	DLW	205 \pm 17.8	198 \pm 12.3	<0.35	109 \pm 9.46	79.0 \pm 5.18	–	
	XJH	19.2 \pm 17.6	183 \pm 2.49	<0.35	8.13 \pm 7.45	57.1 \pm 0.83	–	
	QS1	78.1 \pm 6.66	8.28 \pm 0.42	<0.35	26.6 \pm 2.27	–	–	
	QS2	449 \pm 0.17	12.1 \pm 7.87	<0.35	153 \pm 0.06	–	–	
	TY	35.2 \pm 3.98	47.7 \pm 8.50	<0.35	16.2 \pm 1.83	13.3 \pm 3.10	–	
	XH	42.2 \pm 0.36	20.9 \pm 0.43	<0.35	20.3 \pm 0.18	3.93 \pm 0.16	–	
	NB	97.6 \pm 4.40	65.0 \pm 16.4	<0.35	135 \pm 6.08	66.9 \pm 18.0	–	
	LSCS	197 \pm 13.6	69.3 \pm 10.4	<0.35	81.8 \pm 5.64	18.8 \pm 3.44	–	
	PLD	15.6 \pm 1.36	43.7 \pm 4.88	<0.35	5.75 \pm 0.50	8.73 \pm 1.43	–	
	WFDLS	245 \pm 106	34.2 \pm 1.67	<0.35	305 \pm 132	29.5 \pm 1.64	–	
	ZHGS	16.3 \pm 1.62	10.1 \pm 1.79	<0.35	7.32 \pm 0.73	–	–	
	Mean	131 \pm 131	55.7 \pm 54.2	<0.35	81.5 \pm 83.9	23.3 \pm 26.3	–	
Suburban areas	DK	507 \pm 66.0	190 \pm 72.8	<0.35	322 \pm 41.9	91.5 \pm 36.6	–	
	KFQ2	46.9 \pm 41.8	32.4 \pm 8.35	<0.35	111 \pm 99.4	56.9 \pm 15.7	–	
	DGS	371 \pm 116	20.3 \pm 3.70	<0.35	1991 \pm 622	82.2 \pm 15.7	–	
	JST	274 \pm 95.7	78.1 \pm 27.1	<0.35	315 \pm 110	67.0 \pm 24.7	–	
	XYW	10.7 \pm 0.44	54.8 \pm 1.74	<0.35	11.2 \pm 0.47	41.4 \pm 1.45	–	
	LSXC	196 \pm 4.60	114 \pm 9.30	<0.35	110 \pm 2.59	46.8 \pm 4.14	–	
	TP	39.7 \pm 9.10	97.6 \pm 3.75	<0.35	27.4 \pm 6.28	49.2 \pm 2.05	–	
	CXD	11.7 \pm 0.53	48.3 \pm 3.25	<0.35	4.64 \pm 0.21	11.1 \pm 1.02	–	
	HYK	3.43 \pm 1.35	24.7 \pm 0.82	<0.35	1.13 \pm 0.44	2.37 \pm 0.21	–	
	Mean	162 \pm 186	73.4 \pm 54.5	<0.35	322 \pm 639	49.8 \pm 29.5	–	
	Rural areas	JLSH	234 \pm 31.4	37.5 \pm 7.14	<0.35	44.0 \pm 5.91	1.52 \pm 1.06	–
		SMD	12.9 \pm 12.4	4.31 \pm 1.22	<0.35	12.5 \pm 12.0	–	–
		QB	8.87 \pm 2.82	23.6 \pm 8.34	<0.35	1.53 \pm 0.49	–	–
DSH		3.12 \pm 0.58	2.89 \pm 1.99	<0.35	0.32 \pm 0.06	–	–	
HH		75.1 \pm 17.5	51.4 \pm 2.30	<0.35	25.0 \pm 5.84	9.50 \pm 0.61	–	
SSLP		5.27 \pm 0.19	49.8 \pm 13.3	<0.35	2.73 \pm 0.10	16.3 \pm 5.43	–	
SJP		65.1 \pm 3.33	92.7 \pm 6.14	<0.35	22.7 \pm 1.16	21.5 \pm 1.69	–	
AB		3.65 \pm 0.82	59.1 \pm 4.17	6.83 \pm 3.89	8.66 \pm 1.95	107 \pm 7.85	187 \pm 107	
PK		3.32 \pm 0.63	14.8 \pm 6.72	5.56 \pm 0.22	2.41 \pm 0.46	4.45 \pm 3.86	46.6 \pm 1.85	
DYZ		43.3 \pm 3.12	18.0 \pm 3.79	14.5 \pm 0.37	19.7 \pm 1.42	2.41 \pm 1.37	76.0 \pm 1.94	
BYSX		25.1 \pm 13.9	7.81 \pm 2.92	<0.35	30.2 \pm 16.7	3.36 \pm 2.77	–	
GMSZ		20.3 \pm 12.7	46.0 \pm 6.65	<0.35	10.1 \pm 6.37	14.1 \pm 2.62	–	
TLZ		4.60 \pm 0.18	76.6 \pm 16.7	<0.35	13.8 \pm 0.55	178 \pm 39.6	–	
HDZ		8.26 \pm 0.02	109 \pm 37.5	<0.35	2.26 \pm 0.01	19.5 \pm 8.11	–	
LZfZ		22.0 \pm 0.77	10.9 \pm 2.97	7.48 \pm 0	9.08 \pm 0.32	–	35.6 \pm 0	
WJZ		605 \pm 26.6	70.8 \pm 8.34	<0.35	244 \pm 10.7	18.5 \pm 2.66	–	
XRDZ		18.6 \pm 0.82	54.2 \pm 2.51	<0.35	7.58 \pm 0.34	13.5 \pm 0.81	–	
CHX	7.56 \pm 3.13	136 \pm 20.3	<0.35	1.89 \pm 0.78	22.9 \pm 4.01	–		
Mean	64.8 \pm 145	48.1 \pm 38.1	1.91 \pm 4.04	25.5 \pm 55.8	24.0 \pm 45.5	19.2 \pm 47.0		

^a Concentrations were lower than the LOQ; half of the LOQ was used to calculate

^b Concentrations were lower than the LOD; 0 was used to calculate

HER

MOR is the primary urinary metabolite of heroin, but it is also a widely used prescription drug (Berterame et al. 2016). In wastewater, MOR is derived from illegal HER use, therapeutic MOR, and other therapeutic drugs such as codeine. Therefore, to accurately estimate the consumption of HER, this study deducted the contribution of therapeutic MOR

(1.96 mg/day/1000 inh) and therapeutic codeine (0.27 mg/day/1000 inh) from the MOR load in wastewater (Du et al. 2017). The deduction of other sources brings uncertainty to the estimation of heroin consumption, but the proportion of MOR load in wastewater from these sources is low, so it will not change the overall trend of heroin consumption. The HER average amount was 18.5 mg/day/1000 inh in Dalian (Table 2, Fig. 3), which was lower than those in 2017 (64.6 \pm 78.7 mg/

day/1000 inh) (Du et al. 2017) and 2019 (53.6 ± 67.6 mg/day/1000 inh) (Du et al. 2019) in Chinese cities.

The average amount of HER in urban, suburban, and rural areas was 13.9 mg/day/1000 inh, 57.6 mg/day/1000 inh, and 8.68 mg/day/1000 inh, respectively. The average value in urban areas of Dalian in 2019 was higher than that in 2015 (6.4 mg/day/1000 inh) (Du et al. 2017), but lower than those in the USA (1294 ± 296 mg/day/1000 inh, 1127 ± 163 mg/day/1000inh) (Gushgari et al. 2019) and Italy (92 mg/day/1000 inh) (Zuccato et al. 2016). HER use in suburban areas was significantly higher than those in urban and rural areas ($p < 0.05$, Kruskal-Wallis test). However, HER use was not significantly different between urban and rural areas ($p > 0.05$, Kruskal-Wallis test) (Fig. 4). HER use patterns in suburban areas were similar to METH use patterns, most probably because of large floating populations and few anti-drug efforts. HER may be the drug of choice in both suburban and rural areas (Deng et al. 2012; Faryar et al. 2018; Khan et al. 2014; Kuehn 2014). To investigate the potential simultaneous use of METH and HER, a correlation analysis was conducted. Spearman’s rank analysis showed that there was a positive correlation between the amounts of METH and HER in suburban areas ($r = 0.9$; $p < 0.05$), while in urban and rural areas, there was no significant correlation ($p > 0.05$). This indicates that METH use is linked to HER use in suburban areas, which may be due to mixed use by drug users (NNCC 2018).

KET

KET is used in surgery as an anesthetic, although it tends to be used less frequently in China and its concentration in wastewater can be ignored (Du et al. 2015). Moreover, NK is a product of human metabolism, so it is more suitable biomarker for estimating KET use and can reduce the uncertainty caused by the occasional direct disposal of KET. Therefore,

to accurately estimate the consumption of KET, this study used NK to estimate the use of KET. In this study, the average amount of KET was 0.82 mg/day/1000 inh (Table 2, Fig. 3) in Dalian, Northern China, which was lower than that in cities in Southern China (Shanghai: 45.5 mg/day/1000 inh, Shenzhen: 219 mg/day/1000 inh, and Guangzhou: 256 mg/day/1000 inh), indicating that there is a geographical difference in the consumption of KET; in Southern China, KET use is much higher than that in Northern China (Du et al. 2015; Zhang et al. 2019). Moreover, the average amount of KET was lower than those in Canada (267 mg/day/1000 inh) (Yargeau et al. 2014) and Italy (1.5–40 mg/day/1000 inh) (Castiglioni et al. 2015).

The KET amount was 8.70 mg/day/1000 inh in rural areas, but not found in urban and suburban areas. KET is mostly used as a recreational drug (NNCC 2020) but in this study only found in several rural areas (AB, PK, DYZ, and LZfZ).

Prevalence of drugs in urban, suburban, and rural areas

The prevalence was estimated based on the use of drugs and the proportion of adults (aged 15–64) in the population. Due to losses in populations in rural areas of China, the proportion of children and elderly individuals in rural areas is higher than those in urban and suburban areas. Therefore, in order to accurately estimate the prevalence of drug use among the adult population, according to the data of the sixth census in 2010, the proportion of the population aged 15–64 in China was calculated as 80.1% in urban and suburban areas, 70.8% in rural areas (National Bureau of Statistics of China 2010), and 71.2% in the entire city (National Bureau of Statistics of China 2019).

Based on Eq. (5), the prevalence rates of METH and HER use in urban areas were 0.23% and 0.02%, and in suburban

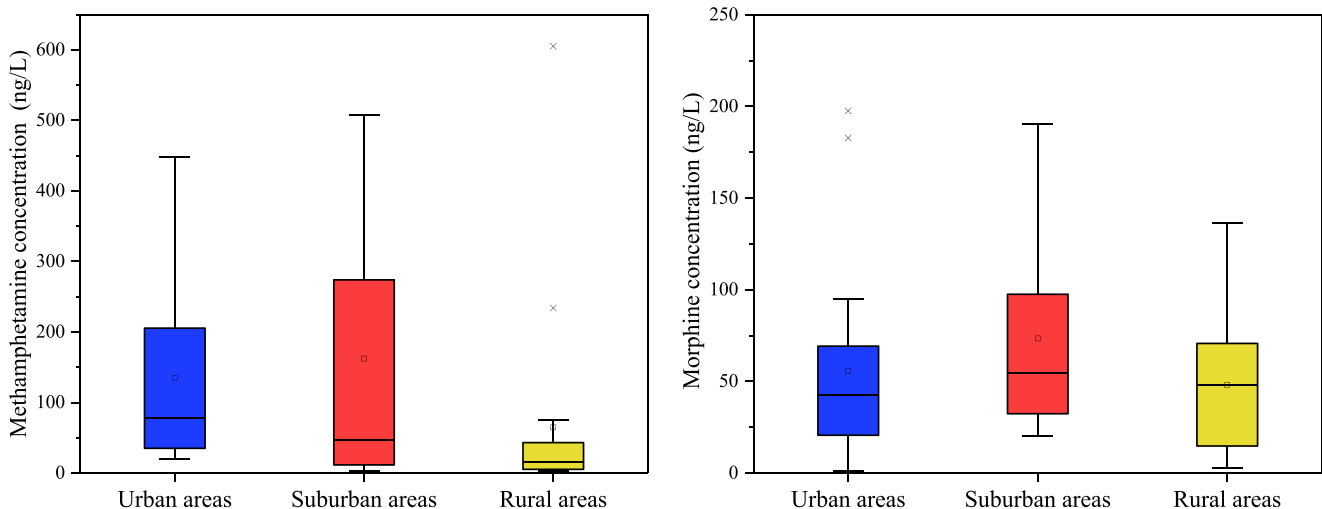


Fig. 2 Drug concentration in urban, suburban, and rural areas (Box = 25–75% interquartile range; Squares = mean values; Box inner line = median values; Whisker = interquartile multiplied by 1.5; Crosses = outliers, defined as values more than interquartile multiplied by 1.5)

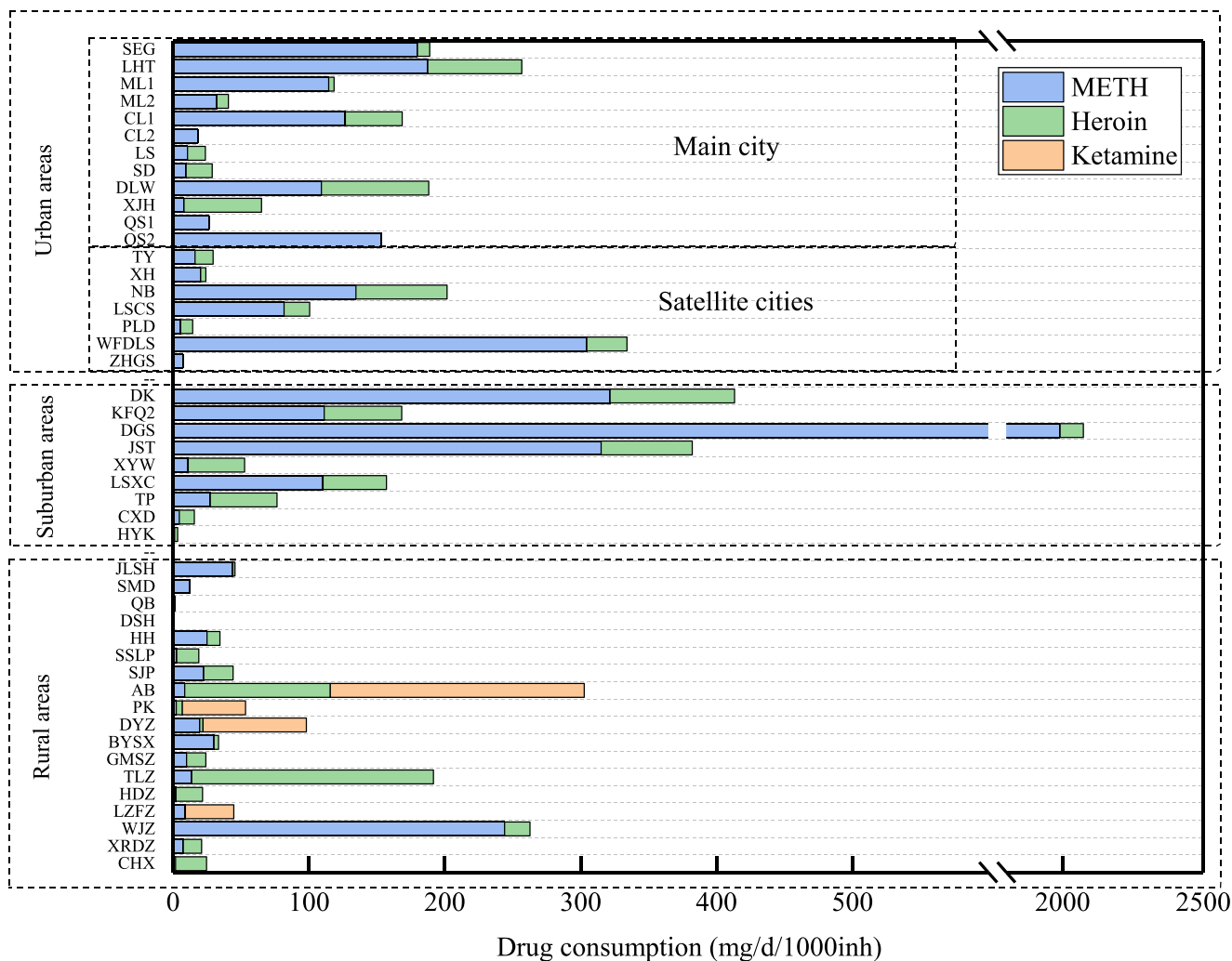


Fig. 3 Drug consumption in urban, suburban, and rural WWTPs

areas were 0.70% and 0.10%, respectively. The prevalence rates of METH, HER, and KET use in rural areas were

0.06%, 0.02%, and 0.05%, respectively. According to the World Drug Report, the prevalence rates of amphetamines,

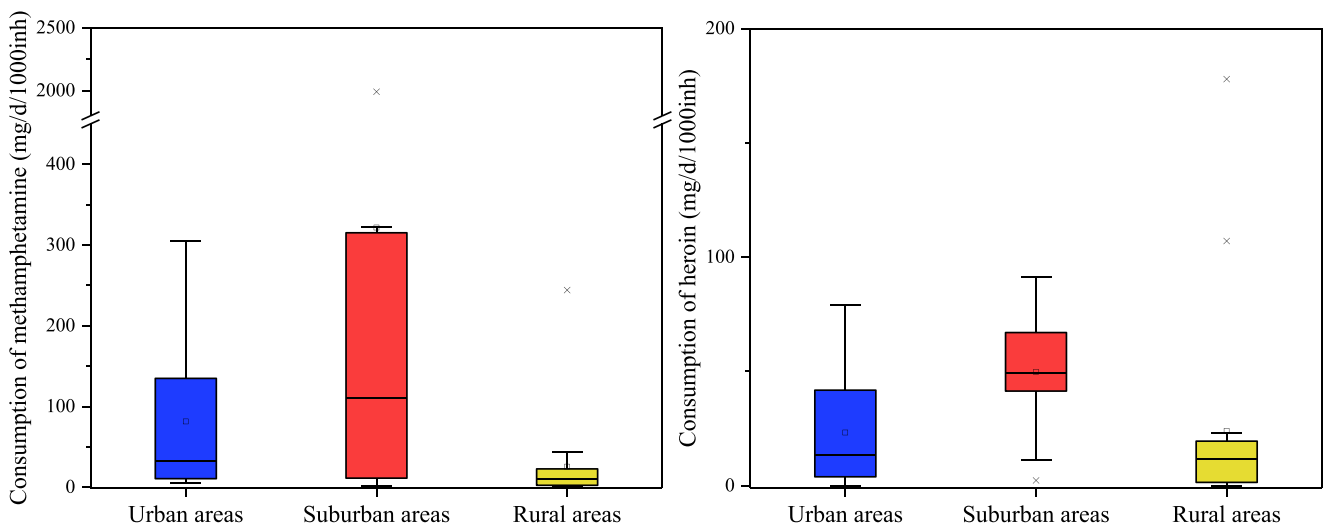


Fig. 4 Comparison of drug consumption in urban, suburban, and rural areas (Box = 25–75% interquartile range; Squares = mean values; Box inner line = median values; Whisker = interquartile multiplied by 1.5; Crosses = outliers, defined as values more than interquartile multiplied by 1.5)

opiates, ecstasy, and cocaine use in East and Southeast Asia were 0.62%, 0.21%, 0.31%, and 0.04%, respectively, and the ketamine use prevalence was 0.05% in Hong Kong (UNODC 2016, 2020). The prevalence of drug use in Dalian (METH: 0.30%, HER: 0.02%, and KET: 0.004%) was lower than that in the World Drug Report. The results were consistent with the drug use situation in China, with high levels of methamphetamine, and relatively low levels of heroin, ketamine, MDMA, and cocaine use (NNCC 2020). It is worth noting that the prevalence of METH use in suburban areas was higher than those reported in the World Drug Report and many previous WBE studies, including studies conducted in Beijing (0.58%) (Pei et al. 2016), another Chinese city (0.55%) (Shao et al. 2020), and South Korea (0.04–0.42%) (Kim et al. 2015). The results indicate that the prevalence of drug use in suburban areas is high and that additional attention should be paid by government departments.

Uncertainty analysis

Each step in the estimation of drug use can cause uncertainties. These steps include sample collection, population estimation, and determination of correction factors (Castiglioni et al. 2013; Lai et al. 2011). In this study, we used auto-samplers that were programmed to imbibe 60 mL of wastewater every 30 min. Samples collected in this way may cause errors in drug concentration estimations. However, since each composite sample contained a mixture of 24 separate hourly samples collected during a particular sampling day, we suspect that compared to those associated with continuous and proportional sampling, the uncertainties associated with our sampling method are not significant. This study selected the most suitable population from the NH₄-N population and the design population through a comparison of wastewater types to reduce uncertainty in population estimations.

In order to reduce the uncertainty caused by the use of mean-based input parameters in the estimation, Monte Carlo simulation was used to analyze the uncertainty of consumption and prevalence. The characteristics of input parameters are listed in Table S5. For analyzing, the mean, mode, and median values, as well as the 2.5% and 97.5% percentiles, i.e., 95% confidence interval (CI), were extracted and presented. Fig. S4 and S5 show the result of Monte Carlo simulation of the probability distribution density of the consumption and prevalence in urban, suburban, and rural areas of Dalian, China.

Conclusion

We found differences in illicit drug use among urban, suburban, and rural areas. METH use in rural areas was significantly lower than those in urban and suburban areas, and HER use

in suburban areas was significantly higher than those in urban and rural areas, indicating that simply assessing drug use in urban areas to represent use throughout an entire city or country is inaccurate and problematic. This study investigated only Dalian and cannot be generalized to other cities in China; additional studies are needed. To better reflect the overall situation of a city or even a country, future WBE studies should consider not only urban areas but also suburban and rural areas.

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Data availability All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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