Electronic Supplementary Information

The Occurrence and Source Analysis of Selected Antidepressants and Their Metabolites in Aqueous System of Shanghai, China

Luo-dan Ma[a], Jian Li[a], Jia-jun Li[a], Min Liu[a], Dong-zhi Yan[a], Wen-yan Shi[a], Gang Xu[a] *

[a] Shanghai Institute of Applied Radiation, School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, P. R. China

* Corresponding authors

Tel.: +86 21 66137521; Fax: +86 21 66137787; E-mail address: xugang@shu.edu.cn (G. Xu).

School of Environmental and Chemical Engineering, Shanghai University, 99 Shangda Road, Shanghai 200444, P. R. China

Email address:

Luo-dan Ma: 1069403102@qq.com

Jian Li: 1486121872@qq.com

Jia-jun Li: 1175794485@qq.com

Min Liu: 1547558147@qq.com

Dong-zhi Yan: 122687549@qq.com

Wen-yan Shi: wyshi1981@shu.edu.cn

Table S1. Main operating parameters of the studied WWTPs

WWTP	Population served	Average flow (m^3/d)	SRT[a] (d)	Secondary treatment
WWTP1	88000	75000	10-12	A^2/O[b]
WWTP2	100000	60000	10	A^2/O
WWTP3	220000	40000	11.67	A^2/O
WWTP4	3560000	2800000	14.7	A^2/O

[a]:Sludge Retention Time

[b]: Anaerobic-Anoxic-Oxic

Table S2. Transition ions monitored, chromatographic retention time (t_R) and optimal tandem mass spectrometry (MS/MS) operational parameters for selected antidepressants and their metabolites analyzed by liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) in positive ion mode.

Analytes	Retention time (min)	Transition	Collision energy (eV)	Frogmentor (V)
ODV	3.06	264.2>58.2	18	109
VEN	5.79	278.2>58.2	18	111
CIT	7.72	325.2>109.1	27	144
PAR	8.38	330.2>192.2	19	138
NMI	9.23	264.1>233.1	11	111
NFLU	9.49	296.2>134.1	1	93
FLU	10.07	310.2>44.1	10	99
BUP	10.50	240.1>184.1	8	96
AMI	11.27	278.2>233.1	14	123
SER	12.43	306.1>159.0	27	90
AMI-d3	11.01	281.2>117.1	24	127

Table S3. The matrix effects of selected antidepressants and some of their metabolites in surface water, influent and effluent.

ME（%）	Surface water	Influent	Effluent
ODV	116	121	108
VEN	88	84	91
PAR	79	70	115
CIT	124	66	120
NFLU	83	72	90
NTRI	94	89	100
FLU	86	85	95
AMI	92	88	103
SER	85	73	91
BUP	79	68	83

Table S4. The liner correlation equation, correlation coefficient, concentration range and LOQ of the method

Analytes	Equation	Correlation coefficient	LOQ (ng/L)
VEN	y=25579.94x+27.97	0.99997	0.10
ODV	y=25375.29x-160.08	0.99997	0.10
CIT	y=17262.14x+1758.61	0.99993	0.50
PAR	y=2509.82x+652.26	0.99935	0.50
FLU	y=22827.96x+2045.36	0.99993	0.20
NFLU	y=3824.69x+983.34	0.99962	0.50
SER	y=6174.26x+373.18	0.99995	0.20
BUP	y=994.09x-18.06	0.99996	0.10
AMI	y=5797.29x-243.05	0.99995	0.10
NMI	y=7141.26x+667.67	0.99992	0.20

The liner range was from 0.1ppb to 100ppb.

Table S5. The concentrations of selected antidepressants from different regions in receiving waters and WWTPs

compound	Concentration (ng/L)	samples	region	reference
ODV	2600*	influent	Canada	
	1637*	effluent		1
	26-979	receiving water		
	310.10*	influent		
	276.25*	effluent		2
	21.00-68.70	receiving water		
	2703*	influent		3
	2487*	effluent		
	1138.43*	influent	Germany	4
	1101.87*	effluent		
	575*	influent		
	605*	effluent		5
	<LOQ-270	receiving water		
	653.18*	effluent		6
	<LOQ-743	receiving water		
	179.73*	effluent	Beijing	7
	971.50*	influent	The USA	
	1014.50*	effluent		8
	9-33	receiving water		
	ND-590000	receiving water	Israel	9
	87.22	influent	Shanghai	
	125.64	effluent		present
	0.15-4.53	receiving water		
VEN	1155*	receiving water	Canada	
	808*	effluent		1
	4-507	receiving water		
	204.35*	influent		
	195.25*	effluent		2
	12.90-45.90	receiving water		
	1343*	influent		3
	1087*	effluent		
	565.77*	influent	Germany	4
	539.00*	effluent		
	230*	influent		
	210*	effluent		5
	<LOQ-100	receiving water		
	157.36*	effluent		6
	<LOQ-122	receiving water		

	0.80-250	receiving water	Poland	10
	41.93*	effluent	Beijing	7
	59.63*	effluent	Austria	11
	600-1000	receiving water	The USA	12
	375.50*	influent		13
	409.50*	effluent		
	596.50*	influent		
	600*	effluent		8
	1-390	receiving water		
	100-1003	receiving water	Spain	14
	22-387	receiving water		15
	1.90-41	receiving water	The Czech Republic	16
	290*	influent		17
	280*	effluent		
	ND-400000	receiving water	Israel	9
	59.49*	influent	Shanghai	
	86.70*	effluent		present
	<LOQ-3.03	receiving water		
	ND-4.10	receiving water		18
	ND-8.20	receiving water	Hunan Province	19
	304.84*	influent	Slovakia	20
CIT	223*	influent	Canada	
	203*	effluent		1
	ND-99	receiving water		
	52.45*	influent		
	52.30*	effluent		2
	3.40-11.5	receiving water		
	236*	influent		3
	173*	effluent		
	177.83*	influent	Germany	4
	212.43*	effluent		
	170*	influent		
	150*	effluent		5
	<LOQ-12	receiving water		
	ND-17	receiving water	Poland	10
	22.57*	effluent	Beijing	7
	67.08*	influent		21
	38.40*	effluent		
	110.63*	effluent	Austria	11
	40-90	receiving water	The USA	12
	96.20*	influent		13
	215*	effluent		
	3183*	influent		8
	2796.50*	effluent		

	<LOD-190	receiving water		
	156.00*	influent	Norway	22
	74.79*	effluent		
	256.67*	influent		23
	151.07*	effluent		
	<1-160	receiving water	Spain	14
	<LOQ-120	receiving water		15
	0.64-18	receiving water	The Czech Republic	16
	83*	influent		17
	73*	effluent		
	4.72*	influent	Shanghai	
	13.81*	effluent		present
	<LOQ	receiving water		
	ND-5.1	receiving water		18
	118.88*	influent	Slovakia	20
PAR	16*	influent	Canada	
	<LOQ	effluent		1
	ND	receiving water		
	4.95*	influent		
	4.75*	effluent		2
	1.30-3.00	receiving water		
	8.00*	influent		3
	5.60*	effluent		
	<LOQ	influent	Germany	4
	<LOQ	effluent		
	7.20*	influent		
	2.55*	effluent		5
	<LOQ	receiving water		
	2.10-3	receiving water	The USA	12
	322*	influent		
	315*	effluent		8
	<LOD-270	receiving water		
	9.10*	influent	Norway	22
	4.81*	effluent		
	5.23*	influent		23
	0.93*	effluent		
	<2	receiving water	Spain	14
	ND-7.76	receiving water		24
	<LOQ-225	receiving water		25
	<LOQ	influent	Shanghai	
	<LOQ	effluent		present
	ND	receiving water		
	ND-2.10	receiving water		18
NMI	3.80*	influent	Canada	2

	2.65*	effluent		
	0.41-0.73	receiving water		
	18*	influent		3
	11*	effluent		
	42.23*	effluent	Beijing	7
	<LOQ	influent	Shanghai	
	<LOQ	effluent		present
	<LOQ	receiving water		
NFLU	11*	influent	Canada	
	5*	effluent		1
	ND	receiving water		
	3*	influent		
	1.75*	effluent		2
	1.20-1.30	receiving water		
	9.10*	influent		3
	7.40*	effluent		
	<LOQ	influent	Germany	4
	<LOQ	effluent		
	9.05*	influent		
	0.95*	effluent		5
	<LOQ-9.10	receiving water		
	0.83-1	receiving water	The USA	12
	265*	influent		
	288*	effluent		8
	<LOD-260	receiving water		
	4.17*	influent	Norway	22
	1.39*	effluent		
	<LOQ	influent	Shanghai	
	<LOQ	effluent		present
	ND	receiving water		
FLU	191*	influent	Canada	
	122*	effluent		1
	ND-54	receiving water		
	3.30*	influent		
	2.85*	effluent		2
	0.42-1.30	receiving water		
	18*	influent		3
	11*	effluent		
	<LOQ	influent	Germany	4
	<LOQ	effluent		
	19.50*	influent		
	12*	effluent		5
	<LOQ-3.80	receiving water		
	ND-5.50	receiving water	Poland	10

	3.40*	influent	Beijing	21
	2*	effluent		
	12-20	receiving water	The USA	12
	8.40*	influent	Norway	22
	3.55*	effluent		
	1.37*	influent		23
	0.83*	effluent		
	<1	receiving water	Spain	14
	<LOQ-44	receiving water		15
	ND-14.50	receiving water		24
	<LOQ-23.80	receiving water		25
	0.60-66.10	receiving water		26
	1.03*	influent	Shanghai	
	2.73*	effluent		present
	<LOQ	receiving water		
	2.30–42.90	receiving water		18
	2.60*	influent		
	1.40*	effluent		27
	0.10-1.30	receiving water		
	ND-40.20	receiving water	Hunan Province	19
BUP	191*	influent	Canada	
	104*	effluent		1
	ND-96	receiving water		
	50-60	receiving water	The USA	12
	128.50*	influent		13
	50.75*	effluent		
	1458.50*	influent		
	1562*	effluent		8
	<LOD-220	receiving water		
	1.50	influent	Shanghai	
	1.56	effluent		present
	0.17-1.20	receiving water		
AMI	19.20*	influent	Canada	
	18.30*	effluent		2
	0.87-3.70	receiving water		
	138*	influent		3
	71*	effluent		
	<LOQ	influent	Germany	4
	17.23*	effluent		
	<1	receiving water	Spain	14
	2.39*	influent	Shanghai	
	3.87*	effluent		present
	0.12-0.64	receiving water		
	ND-4.80	receiving water		18

	3.00*	influent		
	1.20*	effluent		27
	<LOQ	receiving water		
SER	34*	influent	Canada	
	16*	effluent		1
	ND-6	receiving water		
	6.05*	influent		
	5.45*	effluent		2
	0.84-2.40	receiving water		
	20*	influent		3
	12*	effluent		
	<LOQ	influent	Germany	4
	<LOQ	effluent		
	28*	influent		
	8*	effluent		5
	<LOQ	receiving water		
	<LOQ	receiving water	Poland	10
	32.23*	effluent		7
	27*	influent	Beijing	21
	13.60*	effluent		
	33-49	receiving water		12
	61.95*	influent		13
	43.65*	effluent	The USA	
	792.50*	influent		
	805*	effluent		8
	<LOD-220	receiving water		
	12.53*	influent		22
	8.74*	effluent	Norway	
	2.10*	influent		23
	1.50*	effluent		
	12*	influent	The Czech Republic	17
	3*	effluent		
	5.00*	influent		
	7.37*	effluent	Shanghai	present
	<LOQ	receiving water		
	ND-5.00	receiving water		18

*: Mean concentrations of selected antidepressants in influents and effluents in WWTPs

Table S6. Concentrations of determined antidepressants in the mainstream and 3 of its tributaries of Huangpu River.

Category	Compound	Frequency（	Concentration(ng/L)

		%）	Min	Med	Max
SNaRIs	VEN	96	<LOQ	0.53	3.03
	ODV	100	0.15	0.88	4.53
SSRIs	FLU	4	<LOQ	<LOQ	0.24
	NFLU	0	ND	ND	<LOQ
	CIT	0	<LOQ	<LOQ	<LOQ
	PAR	0	ND	ND	<LOQ
	SER	0	ND	<LOQ	<LOQ
TCAs	AMI	100	0.12	0.19	0.64
	NMI	0	<LOQ	<LOQ	<LOQ
NaDaRIs	BUP	100	0.17	0.31	1.20

95

Table S7. PNEC values of six antidepressants from literature (ng/L)

Compound	Mollusc	Pseudokirchneriella subcapitata	Algae	Cladocerans	fish
VEN	313[a]	47580[b]		13000[c]	
CIT	405[a]	3030[b]	729000[d]	8000[c]	
PAR		630[b]	15699000[d]	2200[c]	
FLU		200[b]	345000[d]		100[c]
SER		150[b]	13086000[d]		
AMI		720[b]	246[c]		

[a]: PNEC from the effect concentrations (Fisher's Exact Test, $p < 0.0006$) for freshwater snails[28]

[b]: PNEC for freshwater for Pseudokirchneriella subcapitata[29]

[c]: PNEC from the concentrations resulting in 50% effect (EC50), which was calculated by uncertain factor[14]

[d]: PNEC from the tier of Structure-activity relationships(ECOSARs from the U.S. EPA's)[30]

References

1. C. D. Metcalfe, S. Chu, C. Judt, H. Li, K. D. Oakes, M. R. Servos and D. M. Andrews, Antidepressants and their metabolites in municipal wastewater, and downstream exposure in an urban watershed, *Environ Toxicol Chem*, 2010, **29**, 79-89.
2. C. G. A. Lajeunesse, and S. Sauve, Determination of Basic Antidepressants and Their N-Desmethyl Metabolites in Raw Sewage and Wastewater Using Solid-Phase Extraction and Liquid Chromatography-Tandem Mass Spectrometry, *Anal. Chem.*, 2008, **80**, 5325–5333.
3. A. Lajeunesse, S. A. Smyth, K. Barclay, S. Sauvé and C. Gagnon, Distribution of antidepressant residues in wastewater and biosolids following different treatment processes by municipal wastewater treatment plants in Canada, *Water Research*, 2012, **46**, 5600-5612.
4. R. Gurke, J. Rossmann, S. Schubert, T. Sandmann, M. Rößler, R. Oertel and J. Fauler, Development of a SPE-HPLC–MS/MS method for the determination of most prescribed pharmaceuticals and related metabolites in urban sewage samples, *Journal of Chromatography B*, 2015, **990**, 23-30.
5. M. P. Schlusener, P. Hardenbicker, E. Nilson, M. Schulz, C. Viergutz and T. A. Ternes, Occurrence of venlafaxine, other antidepressants and selected metabolites in the Rhine catchment in the face of climate change, *Environ Pollut*, 2015, **196**, 247-256.
6. P. C. Rua-Gomez and W. Puttmann, Impact of wastewater treatment plant discharge of lidocaine, tramadol, venlafaxine and their metabolites on the quality of surface waters and groundwater, *J Environ Monit*, 2012, **14**, 1391-1399.
7. L. H. Sheng, H. R. Chen, Y. B. Huo, J. Wang, Y. Zhang, M. Yang and H. X. Zhang, Simultaneous determination of 24 antidepressant drugs and their metabolites in wastewater by ultra-high performance liquid chromatography-tandem mass spectrometry, *Molecules*, 2014, **19**, 1212-1222.
8. P. Arnnok, R. R. Singh, R. Burakham, A. Perez-Fuentetaja and D. S. Aga, Selective Uptake and Bioaccumulation of Antidepressants in Fish from Effluent-Impacted Niagara River, *Environ Sci Technol*, 2017, **51**, 10652-10662.
9. G. G. A. Voloshenko-Rossin, K. Cohen, J. Gun, L. Cumbal-Flores, W. Parra-Morales, F. Sarabia, F. Ojeda and O. Lev Emerging pollutants in the Esmeraldas watershed in Ecuador: discharge and attenuation of emerging organic pollutants along the San Pedro-Guayllabamba-Esmeraldas rivers, *Environmental Science Processes & Impacts*, 2015, **17**, 41-53.
10. J. Giebułtowicz and G. Nałęcz-Jawecki, Occurrence of antidepressant residues in the sewage-impacted Vistula and Utrata rivers and in tap water in Warsaw (Poland), *Ecotoxicology and Environmental Safety*, 2014, **104**, 103-109.
11. M. Himmelsbach, W. Buchberger and C. W. Klampfl, Determination of antidepressants in surface and waste water samples by capillary electrophoresis with electrospray ionization mass spectrometric detection after preconcentration using off-line solid-phase extraction, *Electrophoresis*, 2006, **27**, 1220-1226.
12. M. M. S. a. E. T. Furlong, Trace Analysis of Antidepressant Pharmaceuticals and Their Select Degradates in Aquatic Matrixes by LC/ESI/MS/MS, *Anal. Chem.*, 2008,

80, 1756-1762.

13. B. Subedi and K. Kannan, Occurrence and fate of select psychoactive pharmaceuticals and antihypertensives in two wastewater treatment plants in New York State, USA, *Science of The Total Environment*, 2015, **514**, 273-280.
14. Y. Valcárcel, S. González Alonso, J. L. Rodríguez-Gil, A. Gil and M. Catalá, Detection of pharmaceutically active compounds in the rivers and tap water of the Madrid Region (Spain) and potential ecotoxicological risk, *Chemosphere*, 2011, **84**, 1336-1348.
15. S. González Alonso, M. Catalá, R. R. Maroto, J. L. R. Gil, Á. G. de Miguel and Y. Valcárcel, Pollution by psychoactive pharmaceuticals in the Rivers of Madrid metropolitan area (Spain), *Environment International*, 2010, **36**, 195-201.
16. G. Fedorova, T. Randak, O. Golovko, V. Kodes, K. Grabicova and R. Grabic, A passive sampling method for detecting analgesics, psycholeptics, antidepressants and illicit drugs in aquatic environments in the Czech Republic, *Science of The Total Environment*, 2014, **487**, 681-687.
17. O. Golovko, V. Kumar, G. Fedorova, T. Randak and R. Grabic, Seasonal changes in antibiotics, antidepressants/psychiatric drugs, antihistamines and lipid regulators in a wastewater treatment plant, *Chemosphere*, 2014, **111**, 418-426.
18. J. X. Minghong Wu, Fenfen Chen, Cao Fu, Gang Xu, Occurrence and risk assessment of antidepressants in Huangpu River of Shanghai, China, *Environmental Science & Pollution Research International*, 2017, **24**, 20291–20299.
19. R. Ma, B. Wang, S. Lu, Y. Zhang, L. Yin, J. Huang, S. Deng, Y. Wang and G. Yu, Characterization of pharmaceutically active compounds in Dongting Lake, China: Occurrence, chiral profiling and environmental risk, *Science of The Total Environment*, 2016, **557-558**, 268-275.
20. T. Mackulak, L. Birosova, M. Gal, I. Bodik, R. Grabic, J. Ryba and J. Skubak, Wastewater analysis: the mean of the monitoring of frequently prescribed pharmaceuticals in Slovakia, *Environ Monit Assess*, 2016, **188**, 18.
21. S. Yuan, X. Jiang, X. Xia, H. Zhang and S. Zheng, Detection, occurrence and fate of 22 psychiatric pharmaceuticals in psychiatric hospital and municipal wastewater treatment plants in Beijing, China, *Chemosphere*, 2013, **90**, 2520-2525.
22. T. Vasskog, T. Anderssen, S. Pedersen-Bjergaard, R. Kallenborn and E. Jensen, Occurrence of selective serotonin reuptake inhibitors in sewage and receiving waters at Spitsbergen and in Norway, *Journal of Chromatography A*, 2008, **1185**, 194-205.
23. T. Vasskog, U. Berger, P.-J. Samuelsen, R. Kallenborn and E. Jensen, Selective serotonin reuptake inhibitors in sewage influents and effluents from Tromsø, Norway, *Journal of Chromatography A*, 2006, **1115**, 187-195.
24. R. López-Serna, M. Petrović and D. Barceló, Occurrence and distribution of multi-class pharmaceuticals and their active metabolites and transformation products in the Ebro River basin (NE Spain), *Science of The Total Environment*, 2012, **440**, 280-289.
25. R. López-Serna, M. Petrović and D. Barceló, Development of a fast instrumental method for the analysis of pharmaceuticals in environmental and wastewaters

based on ultra high performance liquid chromatography (UHPLC)–tandem mass spectrometry (MS/MS), *Chemosphere*, 2011, **85**, 1390-1399.
26. C. Fernández, M. González-Doncel, J. Pro, G. Carbonell and J. V. Tarazona, Occurrence of pharmaceutically active compounds in surface waters of the henares-jarama-tajo river system (madrid, spain) and a potential risk characterization, *Science of The Total Environment*, 2010, **408**, 543-551.
27. M. Wu, J. Xiang, C. Que, F. Chen and G. Xu, Occurrence and fate of psychiatric pharmaceuticals in the urban water system of Shanghai, China, *Chemosphere*, 2015, **138**, 486-493.
28. P. P. Fong and C. M. Hoy, Antidepressants (venlafaxine and citalopram) cause foot detachment from the substrate in freshwater snails at environmentally relevant concentrations, *Marine and Freshwater Behaviour and Physiology*, 2012, **45**, 145-153.
29. L. Minguez, J. Pedelucq, E. Farcy, C. Ballandonne, H. Budzinski and M. P. Halm-Lemeille, Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France, *Environ Sci Pollut Res Int*, 2016, **23**, 4992-5001.
30. D. J. Johnson, H. Sanderson, R. A. Brain, C. J. Wilson and K. R. Solomon, Toxicity and hazard of selective serotonin reuptake inhibitor antidepressants fluoxetine, fluvoxamine, and sertraline to algae, *Ecotoxicology and Environmental Safety*, 2007, **67**, 128-139.