

Occurrence Profiling, Risk Assessment, and Correlations of Antimicrobials in Surface water and Groundwater Systems in Southwest Nigeria

Nathaniel B. Bolujoko^{1,2}, Damilare Olorunnisola^{1,2,3,6}, Sonika Poudel⁴, Martins O. Omorogie^{1,2}, Olumuyiwa O. Ogunlaja^{1,5*}, Chidinma G. Olorunnisola^{1,6}, Morenike Adesina^{1,6}, Esther Deguenon⁷, Victorien Dougnon⁷, Moses O. Alfred^{1,2}, Aemere Ogunlaja^{1,8}, Olumide D. Olukanni^{1,9}, Titus A. M. Msagati¹⁰, Emmanuel I. Unuabonah^{1,2*}

¹*African Centre of Excellence for Water and Environmental Research (ACEWATER), Redeemer's University, P.M.B 230, Ede, 232101, Osun State, Nigeria*

²*Department of Chemical Sciences, Faculty of Natural Sciences, Redeemer's University, P.M.B 230, Ede, Osun State, Nigeria*

³*University of Potsdam, Institute of Nutritional Science, 14558 Nuthetal, Arthur-Scheunert-Allee 114-116, Potsdam, Germany*

⁴*Department of Natural Resources and Ecology Management, Oklahoma State University, Stillwater, United States of America*

⁵*Department of Chemical Sciences, Faculty of Basic Medical and Applied Sciences, Lead City University, Ibadan, Nigeria*

⁶*Institute of Chemistry, University of Potsdam, D-14476 Potsdam, Germany.*

⁷*Research Unit in Applied Microbiology and Pharmacology of natural substances, Polytechnic School of Abomey-Calavi, University of Abomey-Calavi, Benin*

⁸*Department of Biological Sciences, Faculty of Natural Sciences, Redeemer's University, P.M.B 230, Ede, Osun State, Nigeria*

⁹*Department of Biochemistry, Faculty of Basic Medical Sciences, Redeemer's University, Ede, Nigeria*

¹⁰*Institute for Nanotechnology and Water Sustainability, College of Science, Engineering and Technology, University of South Africa, South Africa, The Science Campus, 1709, Roodepoort, Johannesburg, South Africa*

***Corresponding Author**

Unuabonah E. I. unuabonahe@run.edu.ng

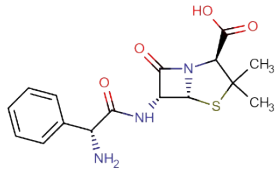
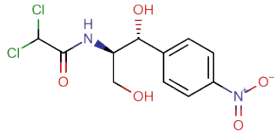
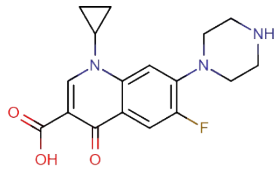
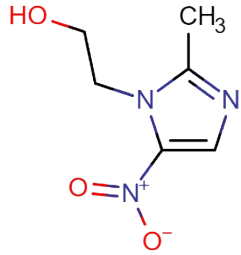
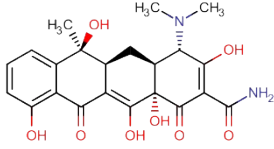
S 1.0 Sample Preparation

The selected analytes were extracted from water samples via a solid phase extraction (SPE) method using the OASIS HLB cartridges (500 mg, 12 mL). For this process, 200 mL of filtered water samples were spiked with 50 µg/L of the target analytes. Prior to loading the samples, the HLB cartridges were conditioned with 6 mL of methanol and ultrapure water. Subsequently, the spiked water samples and method blanks were loaded onto the SPE cartridges at a flow rate ranging from 5 to 10 mL/min and washed with 5 mL of ultrapure water. Afterward, the cartridges were drained of water for 5 min using a vacuum pump, and the analytes were eluted with 6 mL of methanol: acetonitrile (50:50, v/v). The eluents were concentrated in a vacuum oven at 50°C, reconstituted to a final volume of 0.5 mL in methanol and then filtered through a 0.22 µm syringe filter into a 2 mL amber glass vial for analysis.

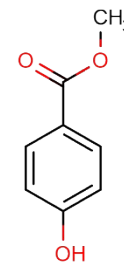
S 2.0 Data Analysis

Statistical analyses were done on data obtained using the Statistical Package for The Social Sciences (SPSS Statistics 23), with a significance level set at $p < 0.05$. The analysis of variance (ANOVA) was used to determine whether there was a statistically significant difference between the mean concentrations of antibiotics and paraben compounds. For this analysis, concentration values below the LOQ were replaced with half of the LOQ. Principal Component Analysis (PCA) was performed in SPSS 23[®] to extract factors (the process of obtaining the different principal components) and establish associations among the antibiotics and parabens. The site details were visualized through ArcGIS 10.8.2[®], while the plots were created in GraphPad Prism R Studio software[®].

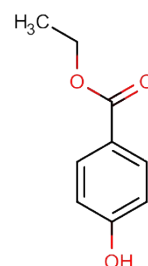
Table S1. Physicochemical properties of the targeted antibiotics and parabens

Compound	CAS	Molecular weight	pKa	logKow	Solubility (g/L)	Chemical structure
Ampicillin	69-53-4	349.4	2.5, 7.3	1.35	10.1	
Chloramphenicol	56-75-7	323.1	5.52	1.14	2.5	
Ciprofloxacin	85721-33-1	331.3	6.09	0.28	30	
Metronidazole	443-48-1	171.2	15.44	-0.02	9.5	
Tetracycline	60-54-8	444.4	3.3, 7.7, 9.7	-1.18	0.231	

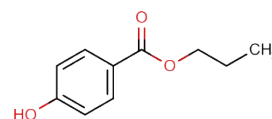
Methylparaben 99-76-3 152.2 8.17 1.66 5.98



Ethylparaben 120-47-8 166.2 8.22 2.19 0.96



Propylparaben 94-13-3 180.2 8.35 2.71 0.39



Butylparaben 94-26-8 194.2 8.37 3.24 0.21

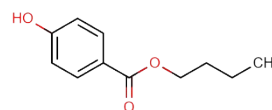


Table S2: Linear range, regression coefficient, limit of detection (LOD), limit of quantification (LOQ) of targeted antibiotics and parabens

Compound	Linear concentration (µg/L)	R²	LOD (µg/L)	LOQ (µg/L)	Spiked Conc. (µg/L)	Recovery (%)	RSD (%)
Ampicillin	0.5-500	0.9999	2.45	8.17	50	88.4	9.87
					125	83.4	6.72
Chloramphenicol	0.5-500	0.9916	5.30	17.7	50	97.8	8.66
					125	95.8	1.62
Ciprofloxacin	0.25-1000	0.9999	9.26	30.9	50	88.0	4.28
					125	92.9	6.97
Metronidazole	0.5-1000	0.9999	5.53	18.5	50	80.1	4.56
					125	79.7	5.12
Tetracycline	0.5-500	0.9996	7.17	23.9	50	83.5	11.9
					125	113	4.53
Methylparaben	0.5-500	0.9999	1.89	6.30	50	73.4	1.32
					125	91.5	0.83
Ethylparaben	0.5-500	0.9999	3.16	10.5	50	83.6	0.87
					125	87.5	0.70
Propylparaben	0.5-500	0.9999	3.66	12.2	50	91.1	1.62
					125	91.7	0.94
Butylparaben	0.5-500	0.9999	2.13	7.10	50	92.9	1.22
					125	92.7	0.91

Table S3: Predicted no effect concentration (PNEC) values (µg/L) for antibiotics and parabens for selected organisms

PPCPs	Species	EC ₅₀ /LC ₅₀ (µg/L x10 ³)	NOEC (µg/L x10 ³)	PNEC-acute (µg/L)	PNEC-chronic (µg/L)
Ampicillin	Algae	-	26.76 ⁱ	-	267.6
	Daphnid	-	13.25 ⁱ	-	132.5
	Fish	-	50.9 ⁱ	-	509
Chloramphenicol	Algae	537.5 ^j	0.22 ⁱ	537.5	2.2
	Daphnid	81.2 ^j	47.61 ⁱ	81.2	476.1
	Fish	1000 ^j	15.46 ⁱ	1000	156.4
Ciprofloxacin	Algae	1620 ^h	455.22 ^h	1620	4552
	Daphnid	1240 ^h	81.27 ^h	1240	812.7
	Fish	13100 ^h	1550 ^h	13,100	15,500
Tetracycline	Algae	1890 ^g	474 ^g	1890	4740
	Daphnid	1060 ^g	59.9 ^g	1060	599
	Fish	13100 ^g	2490 ^g	13,100	24,900
Methylparaben	Algae	91 ^c	21 ^d	910	2100
	Daphnid	41.1 ^b	2.4 ^d	411	240
	Fish	160 ^a	0.16 ^d	1600	160
Ethylparaben	Algae	52 ^d	18 ^d	520	1800
	Daphnid	50 ^c	1.6 ^d	500	160
	Fish	34.3 ^a	0.08 ^d	343	80
Propylparaben	Algae	36 ^d	7.4 ^d	360	740
	Daphnid	23 ^e	1.1 ^d	230	110
	Fish	9.7 ^a	0.04 ^d	97	40
Butylparaben	Algae	9.5 ^f	0.8 ^d	95	80
	Daphnid	5.3 ^a	0.8 ^d	53	80
	Fish	8.2 ^d	0.03 ^d	82	30

a: ¹, b: ², c: ³, d: ⁴, e: ⁵, f: ⁶, g: ⁷, h: ⁸, i: ⁹, j: ¹⁰

Table S4: Acceptable daily intake of the targeted antibiotics and parabens

Compound	ADI (mg/kg/bw)	Reference
Ampicillin	0.0025	JECFA, ¹¹
Chloramphenicol	NE	
Ciprofloxacin	0.002	12
Metronidazole	30	13
Tetracycline	0.003	14
Methyl+ethyl+propylparaben	10	15
Butylparaben	NE	

NE: Not established

Table S5: ANOVA Data for mean concentrations of antibiotics in Surface water in Osun State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	13.366	4	3.341	30.366	.000
Within Groups	3.631	33	.110		
Total	16.997	37			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S6: ANOVA Data for mean concentrations of parabens in Surface water in Osun State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.978	3	.993	4.878	.007
Within Groups	6.309	31	.204		
Total	9.288	34			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S7: ANOVA data for mean concentrations of antibiotics in Surface water in Oyo State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	31578.204	3	10526.068	.861	.486
Within Groups	159000.538	13	12230.811		
Total	190578.742	16			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S8: ANOVA data for mean concentration of parabens in Surface water in Oyo State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	8505.438	3	2835.146	2.840	.106
Within Groups	7987.123	8	998.390		
Total	16492.561	11			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S9: ANOVA data for mean concentrations of antibiotics in Surface water in Lagos State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	53646.675	3	17882.225	.876	.472
Within Groups	367271.865	18	20403.992		
Total	420918.540	21			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S10: ANOVA data for mean concentrations of parabens in Surface water in Lagos State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	14008.881	3	4669.627	.811	.500
Within Groups	143929.817	25	5757.193		
Total	157938.698	28			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S11: ANOVA Data for mean concentrations of antibiotics in Groundwater in Osun State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5.822	3	1.941	8.450	.001
Within Groups	5.512	24	.230		
Total	11.334	27			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S12: ANOVA data for mean concentrations of parabens in Groundwater in Osun State.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.175	3	.058	.301	.824
Within Groups	2.902	15	.193		
Total	3.077	18			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S13: ANOVA data for mean concentrations of antibiotics in groundwater in Oyo State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.919	4	.730	3.245	.025
Within Groups	6.972	31	.225		
Total	9.890	35			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S14: ANOVA data for mean concentrations of parabens in Groundwater in Oyo State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	19344.067	3	6448.022	1.474	.243
Within Groups	122503.122	28	4375.111		
Total	141847.189	31			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S15: ANOVA data for mean concentrations of antibiotics in Groundwater in Lagos State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	4.755	2	2.377	13.408	.000
Within Groups	3.901	22	.177		
Total	8.655	24			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S16: ANOVA data for mean concentrations of parabens in Groundwater in Lagos State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	8518.592	3	2839.531	.794	.511
Within Groups	71492.205	20	3574.610		
Total	80010.797	23			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S17a: ANOVA data comparing antibiotics in Surface water and Groundwater in Osun State.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5948.317	1	5948.317	.343	.560
Within Groups	1177782.861	68	17320.336		
Total	1183731.178	69			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S17b: ANOVA data comparing parabens in Surface water and Groundwater in Osun State.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	55785.915	1	55785.915	7.776	.007
Within Groups	373045.688	52	7173.956		
Total	428831.603	53			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S18a: ANOVA data comparing antibiotics in Surface water and Groundwater in Oyo State.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	141.019	1	141.019	.013	.909
Within Groups	625382.167	58	10782.451		
Total	625523.186	59			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S18b: ANOVA data comparing parabens in Surface water and Groundwater in Oyo State.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5023.900	1	5023.900	1.333	.255
Within Groups	158339.750	42	3769.994		
Total	163363.650	43			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S19a: ANOVA data comparing antibiotics in Surface water and Groundwater in Lagos State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	3698.287	1	3698.287	.125	.725
Within Groups	1391620.430	47	29608.945		
Total	1395318.717	48			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S19b: ANOVA data comparing parabens in Surface water and Groundwater in Lagos State

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1803.503	1	1803.503	.387	.537
Within Groups	237949.495	51	4665.676		
Total	239752.999	52			

* = The mean concentration difference is significant at $p < 0.05$ level

Table S20: Ecological risk quotient (RQ_E) for selected antibiotics and parabens in groundwater in Osun, Oyo, and Lagos States

	Osun						Oyo						Lagos					
	Acute			Chronic			Acute			Chronic			Acute			Chronic		
	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish
Amp	-	-	-	0.13	0.27	0.07	-	-	-	0.43	0.87	0.23	-	-	-	0.12	0.24	0.06
Chl	<0.01	0.02	<0.01	5.68	0.03	0.08	<0.01	0.03	<0.01	12.1	0.06	0.17	<0.01	0.02	<0.01	5.68	0.03	0.08
Cip	0.01	0.01	<0.01	0.04	0.22	0.01	0.01	0.01	<0.01	0.04	0.22	0.01	0.02	0.03	<0.01	0.07	0.39	0.02
Tet	<0.01	<0.01	<0.01	0.01	0.05	<0.01	0.01	0.01	<0.01	0.02	0.20	<0.01	<0.01	<0.01	<0.01	0.01	0.05	<0.01
Mep	0.05	0.11	0.03	0.02	0.20	0.29	0.13	0.28	0.07	0.06	0.49	0.73	0.09	0.19	0.05	0.04	0.33	0.49
Etp	0.10	0.10	0.15	0.03	0.31	0.63	0.10	0.11	0.15	0.03	0.33	0.66	0.15	0.16	0.23	0.04	0.49	0.99
Prp	0.04	0.06	0.15	0.02	0.13	0.36	0.16	0.25	0.59	0.08	0.52	1.44	0.17	0.27	0.64	0.08	0.57	1.56
Bup	0.59	1.05	0.68	0.70	0.70	1.86	0.96	1.72	1.11	1.14	1.14	3.04	1.24	2.23	1.44	1.48	1.48	3.93

Amp = Ampicillin; Chl = Chloramphenicol; Cip = Ciprofloxacin; Tet = Tetracycline; Mep = Methylparaben; Etp = Ethylparaben; Prp = Propylparaben; Bup = Butylparaben

Table S21: Ecological risk quotient for targeted PPCPs in surface water in Osun, Oyo, and Lagos States.

	Osun						Oyo						Lagos					
	Acute			Chronic			Acute			Chronic			Acute			Chronic		
	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish	Alg	Dap	Fish
Amp	-	-	-	0.18	0.36	0.09	-	-	-	0.44	0.89	0.23	-	-	-	0.20	0.41	0.11
Chl	<0.01	0.02	<0.01	5.68	0.03	0.08	0.01	0.03	<0.01	12.7	0.06	0.18	0.01	0.06	0.01	23.7	0.11	0.34
Cip	0.01	0.02	<0.01	0.04	0.23	0.01	0.01	0.01	<0.01	0.04	0.20	0.01	0.01	0.01	<0.01	0.03	0.20	0.01
Tet	<0.01	<0.01	<0.01	0.01	0.05	<0.01	<0.01	<0.01	<0.01	0.01	0.05	<0.01	<0.01	<0.01	<0.01	0.01	0.05	<0.01
Mep	0.17	0.37	0.10	0.07	0.64	0.96	0.06	0.13	0.03	0.03	0.22	0.33	0.15	0.32	0.08	0.06	0.55	0.83
Etp	0.29	0.30	0.43	0.08	0.93	1.85	0.15	0.16	0.23	0.04	0.49	0.99	0.16	0.17	0.25	0.05	0.53	1.06
Prp	0.09	0.14	0.33	0.04	0.29	0.81	0.04	0.06	0.15	0.02	0.13	0.36	0.23	0.36	0.86	0.11	0.76	2.08
Bup	0.80	1.43	0.92	0.94	0.94	2.52	0.84	1.51	0.98	1.00	1.00	2.67	0.82	1.47	0.95	0.97	0.97	2.59

Amp = Ampicillin; Chl = Chloramphenicol; Cip = Ciprofloxacin; Tet = Tetracycline; Mep = Methylparaben; Etp = Ethylparaben; Prp = Propylparaben; Bup = Butylparaben

Table S22: Human Health Risk Quotient (RQ_H) values for selected antibiotics in water samples from Osun, Oyo, and Lagos States.

	Osun					Oyo					Lagos				
	Infant	Toddler	Children	Teens	Adult	Infant	Toddler	Children	Teens	Adult	Infant	Toddler	Children	Teens	Adult
	Surface Water														
Amp	1.82	1.29	0.81	0.66	0.76	4.54	3.21	2.01	1.65	1.91	2.10	1.48	0.93	0.76	0.88
Cip	9.10	6.42	4.02	3.30	3.82	7.99	5.64	3.54	2.90	3.35	7.65	5.40	3.39	2.78	3.21
Met	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Tet	0.88	0.62	0.39	0.32	0.37	1.66	1.17	0.73	0.60	0.70	0.12	0.08	0.05	0.04	0.05
∑PBs	0.01	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	0.01	<0.01	<0.01	<0.01
	Groundwater														
Amp	1.37	0.97	0.61	0.50	0.57	4.43	3.13	1.96	1.61	1.86	1.24	0.88	0.55	0.45	0.52
Cip	8.66	6.11	3.83	3.14	3.63	8.71	6.15	3.85	3.16	3.65	15.4	10.8	6.79	5.57	6.44
Met	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Tet	0.38	0.27	0.17	0.14	0.16	3.75	2.65	1.66	1.36	1.57	0.38	0.27	0.17	0.14	0.16
∑PBs	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	<0.01	<0.01	<0.01	<0.01	0.01	<0.01	<0.01	<0.01	<0.01

Amp = Ampicillin; Cip = Ciprofloxacin; Met = Metronidazole; PBs = Parabens

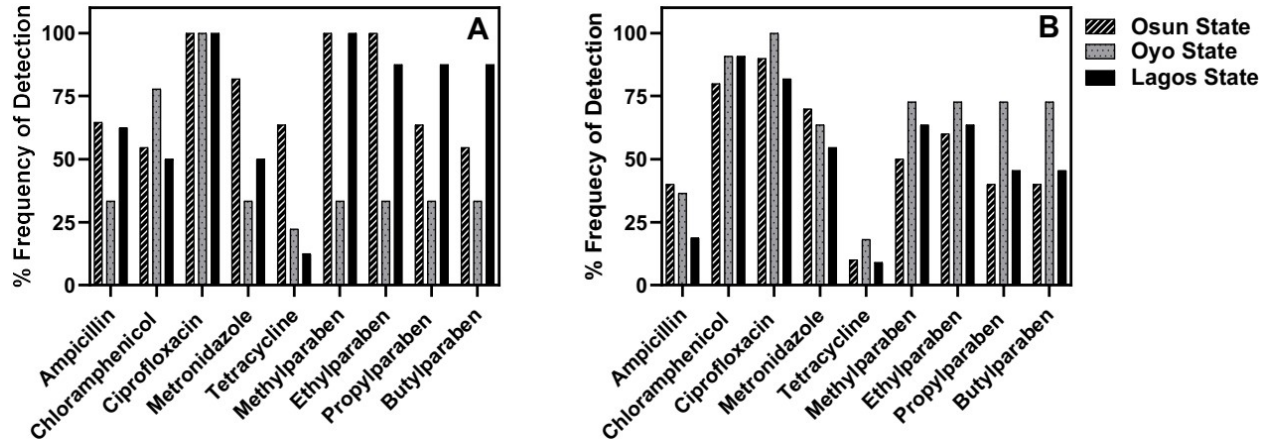


Figure S1. Percentage frequency detection of antibiotics and parabens in (a) surface water and (b) groundwater samples from Osun, Oyo, and

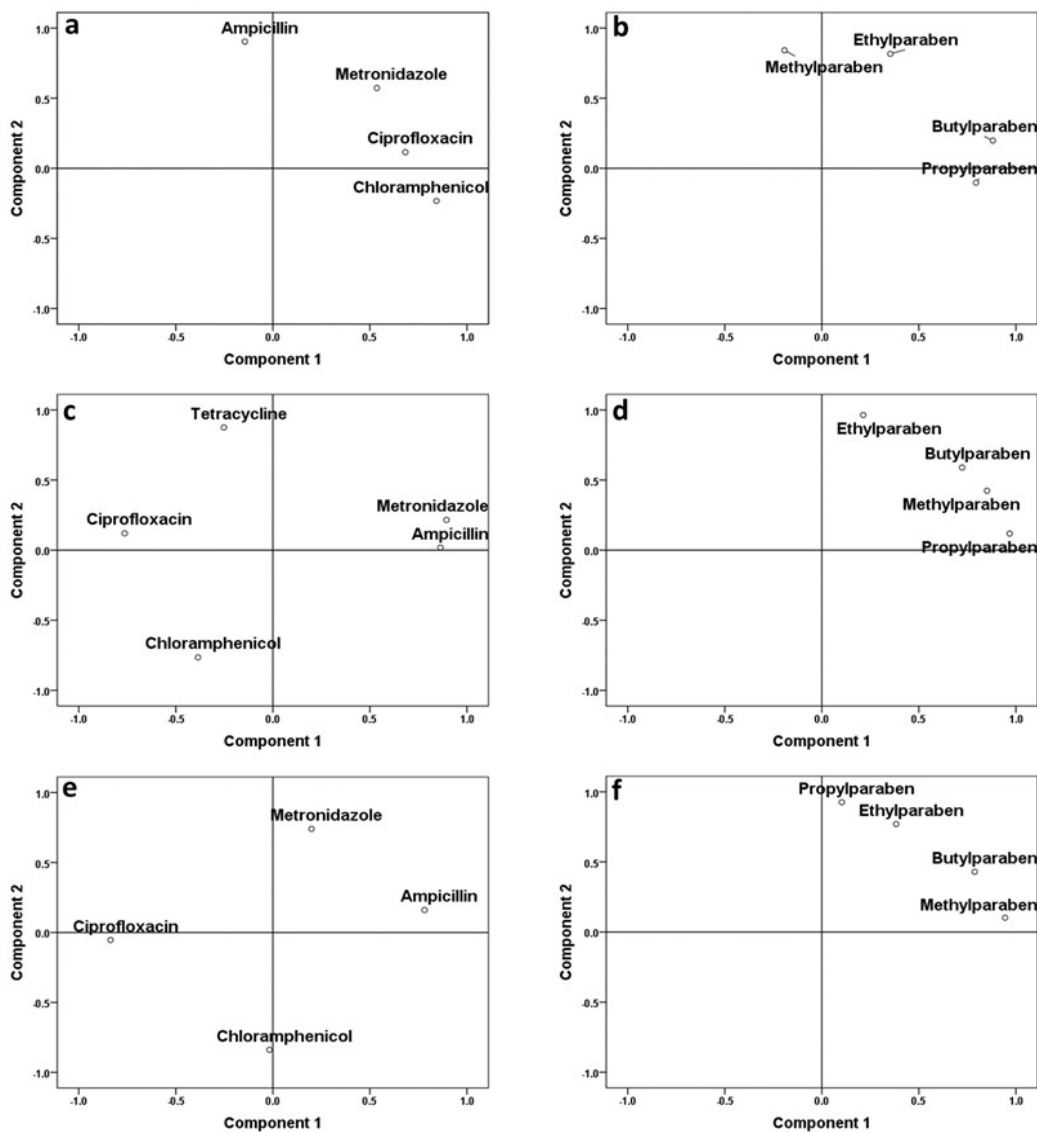


Figure S2: 3-D Plot of Principal Component Analysis (PCA) Loading (PC 1 vs PC 2) for (a) Antibiotics in aquatic systems in Osun State (b) Parabens in aquatic systems in Osun State (c) Antibiotics in aquatic systems in Oyo State (d) Parabens in aquatic systems in Oyo State (e) Antibiotics in aquatic systems in Lagos State (f) Parabens in aquatic systems in Lagos State

References

1. L. L. Dobbins, S. Usenko, R. A. Brain and B. W. Brooks, Probabilistic ecological hazard assessment of parabens using *Daphnia magna* and *Pimephales promelas*, *Environmental toxicology and chemistry*, 2009, **28**, 2744-2753.
2. Y. Kamaya, Y. Fukaya and K. Suzuki, Acute toxicity of benzoic acids to the crustacean *Daphnia magna*, *Chemosphere*, 2005, **59**, 255-261.
3. T. Madsen, H. B. Boyd, D. Nylén, A. R. Pedersen, G. I. Petersen and F. Simonsen, Environmental and health assessment of substances in household detergents and cosmetic detergent products, *Environmental Project*, 2001, **615**, 221.
4. H. Yamamoto, I. Tamura, Y. Hirata, J. Kato, K. Kagota, S. Katsuki, A. Yamamoto, Y. Kagami and N. Tatarazako, Aquatic toxicity and ecological risk assessment of seven parabens: Individual and additive approach, *Science of The Total Environment*, 2011, **410-411**, 102-111.
5. M. Terasaki, M. Makino and N. Tatarazako, Acute toxicity of parabens and their chlorinated by-products with *Daphnia magna* and *Vibrio fischeri* bioassays, *Journal of Applied Toxicology*, 2009, **29**, 242-247.
6. H. Yamamoto, Y. Nakamura, C. Kitani, T. Imari, J. Sekizawa, Y. Takao, N. Yamashita, N. Hirai, S. Oda and N. Tatarazako, Initial ecological risk assessment of eight selected human pharmaceuticals in Japan, *Environmental sciences: an international journal of environmental physiology and toxicology*, 2007, **14**, 177-193.
7. R. Ma, B. Wang, L. Yin, Y. Zhang, S. Deng, J. Huang, Y. Wang and G. Yu, Characterization of pharmaceutically active compounds in Beijing, China: occurrence pattern, spatiotemporal distribution and its environmental implication, *Journal of Hazardous materials*, 2017, **323**, 147-155.
8. X. Guo, N. Ni, M. Shi, X. Zhang, Q. Yuan, N. Wang, S. Zhang and Y. Luo, The persistent, bioaccumulative, toxic, and resistance (PBTR) risk assessment framework of antibiotics in the drinking water sources, *Journal of Environmental Management*, 2023, **326**, 116776.
9. A. Sengar and A. Vijayanandan, Human health and ecological risk assessment of 98 pharmaceuticals and personal care products (PPCPs) detected in Indian surface and wastewaters, *Science of The Total Environment*, 2022, **807**, 150677.
10. H. W. Leung, T. Minh, M. B. Murphy, J. C. Lam, M. K. So, M. Martin, P. K. Lam and B. J. Richardson, Distribution, fate and risk assessment of antibiotics in sewage treatment plants in Hong Kong, South China, *Environment international*, 2012, **42**, 1-9.
11. W. H. Organization, Toxicological evaluation of certain veterinary drug residues in food: prepared by the eighty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2020.
12. Z. Fei, S. Song, J. Gao, Y. Song, X. Xiao, X. Yang, D. Jiang and D. Yang, Antibiotic residues in chicken meat in China: Occurrence and cumulative health risk assessment, *Journal of Food Composition and Analysis*, 2023, **116**, 105082.
13. C. Viscomi, A. B. Burlina, I. Dweikat, M. Savoiaro, C. Lamperti, T. Hildebrandt, V. Tiranti and M. Zeviani, Combined treatment with oral metronidazole and N-acetylcysteine is effective in ethylmalonic encephalopathy, *Nature medicine*, 2010, **16**, 869-871.
14. N. Bilandžić, B. S. Kolanović, I. Varenina, G. Scortichini, L. Annunziata, M. Brstilo and N. Rudan, Veterinary drug residues determination in raw milk in Croatia, *Food control*, 2011, **22**, 1941-1948.
15. E. F. S. A. EFSA, Advises on the safety of paraben usage in food, 2004.