Health Scope. 2023 May; 12(2):e132714. https://doi.org/10.5812/jhealthscope-132714.

Published online 2023 April 27. **Research Article**

Environmental Monitoring and Ecological Risk Assessment of Platinum Complex Drugs in Wastewater Effluent: A Case Study in Qom, Iran

Mohammad Reza Khaksar [1, 2], Yadollah Ghafuri [2, *] and Ahmad Reza Yari [2]

[1] Department of Occupational Health and Safety, Health School, Qom University of Medical Sciences, Qom, Iran

[2] Research Center for Environmental Pollutants, Qom University of Medical Sciences, Qom, Iran

[*] *Corresponding author*: Research Center for Environmental Pollutants, Qom University of Medical Sciences, Qom, Iran. Email: yadollahghafuri@yahoo.com

Received 2022 December 04; **Revised** 2023 March 04; **Accepted** 2023 March 19.

Abstract

Background: The presence of anticancer drugs in water sources has become critical in recent years. Anticancer drugs are used in controlled amounts and conditions in medical centers. Cancerostatic platinum complexes (CPC) like cisplatin, carboplatin, and oxaliplatin are used in oncology centers to treat many cancers.

Objectives: We determined the environmental risk of these compounds in municipal wastewater effluent of Qom, Iran.

Methods: The LC-MS/MS technique quantified platinum complex drugs in wastewater effluent. Based on the blank laboratory method, the limit of detection (LOD) was determined as 0.009 μg/L, 0.013 μg/L, and 0.017 μg/L for oxaliplatin, carboplatin, and cisplatin, respectively.

Results: The cisplatin, carboplatin, and oxaliplatin concentrations in wastewater effluent were 0.19 ± 0.098, 0.22 ± 0.094, and 0.12 ± 0.059 μg/L, respectively. Ecological risk assessment results indicated that *RQsw* for cisplatin, carboplatin, and oxaliplatin was 0.017, 0.013, and 0.02, respectively, showing that the platinum complex drugs had insignificant ecological exposure risk. Furthermore, ΣRQsw was estimated at < 1.

Conclusions: Managing cytotoxic waste from hospital oncology wards is vital for environmental pollution control. The use of other methods to remove these compounds, such as advanced oxidation processes and membrane systems, is inevitable.

Keywords: Risk, Toxicity, Platinum Compounds, Wastewater, Qom

1. Background

Carcinogenic compounds are a major cause of death worldwide, so 7,600,000 deaths occurred in 2008, and 13.1 million deaths are predicted by 2030, of which cancer is the main cause (1). Anticancer drugs are used in controlled amounts and conditions in medical centers. Platinum complex drugs, especially cisplatin, are used as platinum-containing chemotherapy drugs to decrease or stop the growth of cancer cells in various types of cancer (2). In general, it is desirable that such drugs act specifically by damaging the genetic resources of tumor cells, inhibiting their synthesis, and accelerating the induction of apoptotic cell death (3). In addition, the drugs have effective molecular mechanisms, including the induction of oxidative stress (OS), which increases the generation of reactive oxygen species (ROS) in tumor cells (4). Therefore, there is a possibility of lipid peroxidation and reduction of cellular antioxidant defense processes such as glutathione in healthy cells, which can have significant side effects such as nausea, diarrhea, vomiting, and nephrotoxic, neurotoxic, hematotoxic, hepatic, and cardiac effects (5-7).

The main environmental source of platinum complex drugs is the feces and urine of patients undergoing chemotherapy, which are excreted into municipal wastewater systems. Some findings suggest the presence of drug residues in aquatic environments. However, the specific effect of drug residues on the general population is unclear (8-10). Therefore, in recent years, measures have been taken to evaluate the risks of anticancer drugs in the environment (10). According to studies conducted in Iran (in medical centers in Qom and Urmia provinces), typically, 15 - 25% of the anticancer drugs used by patients admitted to the aforementioned centers were platinum-containing compounds. Thus, the high consumption of anticancer drugs in Iran and the plans of the Ministry of Health to develop oncology wards in medical centers must be taken into account, as must be the issue of the release of drug residues

into the environment due to the lack of a proper management system for collection, elimination, and disposal of residual drugs. Moreover, the lack of appropriate wastewater treatment systems to remove drug contaminants, the health consequences, the need to assess the rate of entry, environmental monitoring of platinum-containing compounds in municipal wastewater networks, prediction of drug concentrations in water sources, and studying the risk and environmental toxicity of drugs are of great importance (11).

2. Objectives

Considering the health and environmental toxicity aspects of the release of platinum anticancer drugs in the environment, this study aimed to monitor and evaluate the environmental risks of these compounds in the municipal wastewater effluent of Qom City.

3. Methods

3.1. Study Setting

Environmental monitoring and ecological risk assessment of platinum complex drugs in this study were designed and carried out in two stages. In the first stage, the concentrations of platinum complex drugs (oxaliplatin, carboplatin, and cisplatin) in the Qom City wastewater treatment plant effluent were determined. In the next stage, an ecological risk assessment was done. Part of the wastewater treatment system of Qom city, which utilizes biological treatment processes, is designed to receive urban and hospital wastewaters with a population of 250,000 people and a flow rate of Q = 0.7 m^3/s.

3.1.1. Sampling Process, Preparation, and Analytical Method

This study collected and analyzed 33 effluent samples from the municipal wastewater treatment plant based on 24-h composite sampling. The sampling sites of this research were in the Qomrud region of the studied province. Sampling sites were selected from the open canals carrying treated wastewater and raw urban wastewater along a length of 15 km in the vicinity of the Qomrud region (Figure 1).

Mass Chromatography-Mass Spectrometry (LC-MS/MS) determined the concentrations of platinum compounds in the samples. The calibration curves were drawn with 1, 5, 10, 25, and 50 ng/L concentrations of carboplatin, oxaliplatin, and cisplatin. The correlation coefficients > 0.9998, 0.9987, and 0.999 were obtained for oxaliplatin, carboplatin, and cisplatin, respectively. In all cases, the Relative Standard Deviation in percentage (RSD%) of platinum cytotoxic compounds (n = 5) was below 15%. The extraction recovery was determined by analyzing five concentrations (1.5, 10.25, and 50.00 ng/mL). In this study, required sensitivity by recovery of more than 50% was considered. The limit of quantification (LOQ) and limit of detection (LOD) were calculated using the following equation:

LOQ = 10σ/S, LOD = $3{:}3\sigma$/S,

Where σ is the standard error of the intercept, and S is the slope of the standard addition calibration curve. Multiple Reactions Monitoring (MRM) was used for the detection. For the platinum complex, $[M+H]^+$ ions were monitored at m/z as the product ion, and the result is shown in Table 1 (10).

3.1.2. Ecological Risk Assessment of Platinum Complex Drugs

In order to conduct an ecological risk assessment of cytotoxic drugs, the physicochemical properties contributing to the fate and transport of chemicals in the environment were considered by a theoretical model (EPI Suite 4.1). The characteristics and the environmental fate of Pt complex drugs are shown in Figure 2. The solubility factor, log (K_{ow}), and vapor pressure showed that the risk of platinum compounds in aquatic environments is critical (11).

Physicochemical parameters, such as the dissociation constant (pKa), the octanol-water dissociation coefficient (K_{ow}), solubility, Henry's coefficient, and vapor pressure, can be used for the drug risk analysis. The range of pKa values determines which compound dissociates at a given pH. An octanol-water dissociation coefficient of less than one ($\log K_{ow} < 1$) indicates that the chemical compound has high mobility in the aqueous medium and, therefore, exhibits the possible behavior of an anticancer compound with this characteristic, remains in the aqueous phase and is not absorbed by sediments or sludge in the environment. The risk assessment of a drug complex with $\log K_{ow} > 4.5$ should only be considered regarding degradability, biodegradability, and toxicity. In general, cytotoxic and anticancer drugs are mainly highly soluble in water with low $\log K_{ow}$ values, which is important in terms of increasing access and exposure to drug residues in drinking water sources because drugs have a low vapor pressure under normal conditions (25°C), and accordingly, cannot volatilize in the environment (12-14).

Ecological risk assessment of Pt compounds was done using the following diagram (Figure 3).

In the predicted environmental concentration (PEC) determination model (which predicts the concentration of drug compounds in the environment), according to quantities of platinum complex drugs in the treated wastewater effluent, the highest measured values of each platinum compound, including cisplatin, carboplatin,

Figure 1. Location of the study area

Table 1. Specific Multiple Reactions Monitoring Conditions for Determination of Platinum Cytotoxic Drugs by Mass Chromatography-Mass Spectrometry

Compound	Retention Time, min	Segment	ESI	Product Ion	MS/MS Transition
Cisplatin	5.3	2	ESI+	$[M+H]^+$	300 > 248
Carboplatin	5.3	1	ESI+	$[M+H]^+$	372 > 355.0
Oxaliplatin	5.3	1	ESI+	$[M+H]^+$	398 > 96.0

and oxaliplatin, with the worst case scenario were considered as PEC values. The reliability of the PEC value is based on the ratio of PEC/MEC estimated with an acceptable consistency for the ratio 0.2 - 4 (3).

Risk estimate in the PEC model was used by risk quotients (RQ) or hazard quotients (HQ). This ratio is determined by calculating the PEC and determining the concentration at which we do not expect unacceptable adverse effects (predicted no-effect concentration, PNEC). The PNEC values are estimated through the toxicity threshold concentration ratio (LC50 or EC50) and the safety factor (f = 100). In this study, the PNEC of platinum complex drugs for aquatic animals was taken from literature data as 1.22 μg/L (3).

The present study calculated RQ for wastewater treatment plant effluent in surface water (RQsw).

RQ < 1.0 indicates very low and insignificant risk;

1.0 $\leq$ RQ < 10 indicates a low potential for adverse effects;

10 $\leq$ RQ < 100 shows the ability to create high adverse effects (15, 16).

Equations 1 and 2 demonstrate how to determine the

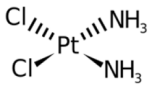
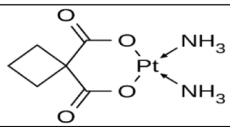
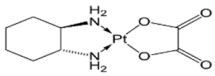
Compound	Structure	Physico-chemical properties					
		Molecular mass	Log_{kow}	Solubility	p_{ka}	Boiling point	Vapor pressure
Cisplatin		300	-2.19	14	7.2	575	1.16e - 0.19
Carboplatin		378	-1.78	11.7	6.6	772	4.59e - 0.19
Oxaliplatin		397	-1.65	7.9	6.1	780	4.8e - 0.19

Figure 2. Characteristics and environmental fate of platinum complex drugs

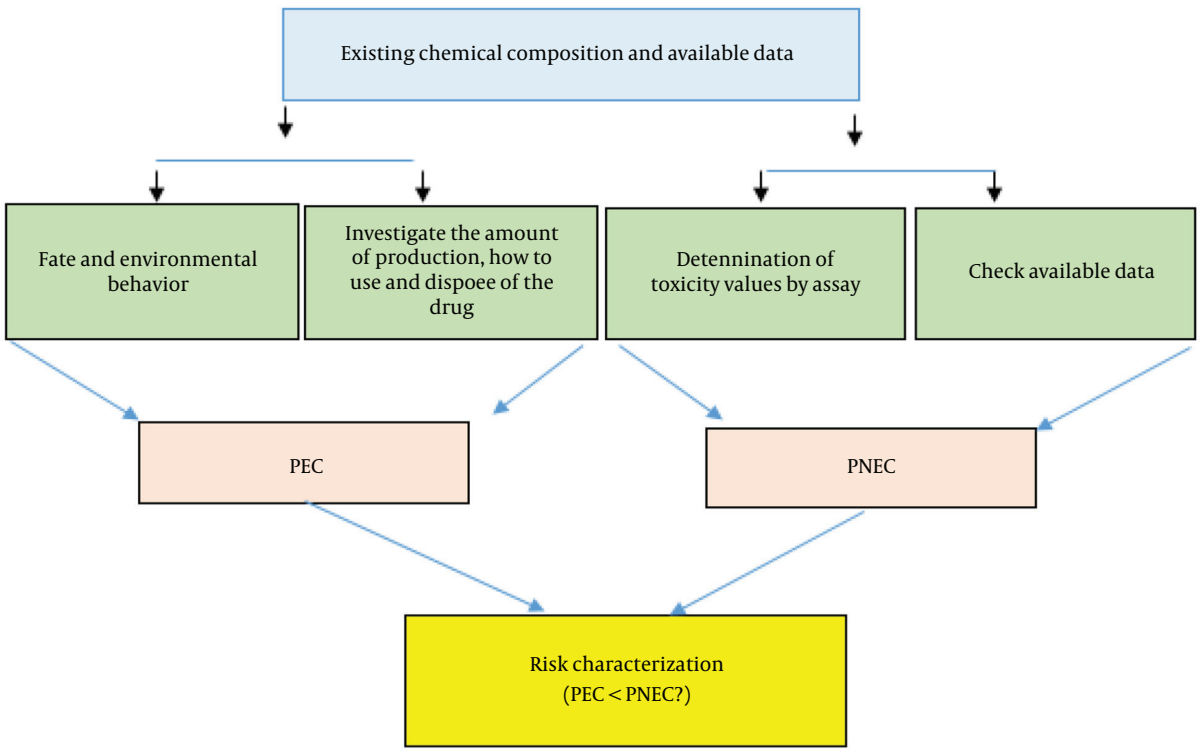


Figure 3. Diagram of ecological risk assessment steps

Table 2. Method Validation and Quality Control Parameters of Platinum Complex Drugs

Compound	Linearity (R2)	LOD (ng/L)	LOQ (ng/L)	Recovery%	RSD% (n = 5)				
					1 ng/mL	5 ng/mL	10 ng/mL	10 ng/mL	50 ng/mL
Cisplatin	0.999	0.1	0.3	0.70	6.5	8.2	5.8	5.6	9.1
Carboplatin	0.999	0.013	0.4	0.78	6	6.4	7.8	6.9	8.9
Oxaliplatin	0.999	0.09	0.027	0.74	7.5	7.7	9.9	8.8	7.9

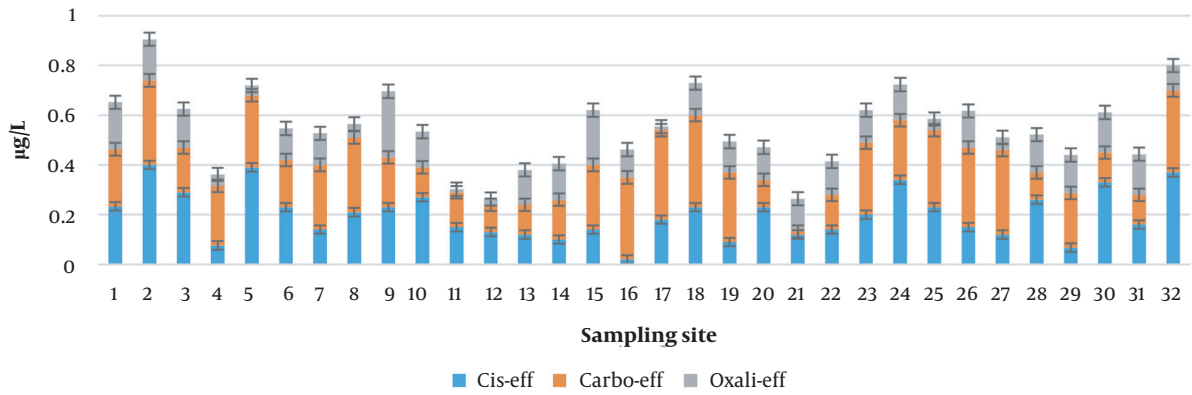


Figure 4. Concentrations of platinum complex drugs in municipal wastewater treatment plant effluent (μg/L) by mass chromatography-mass spectrometry

Table 3. Ecological Risk of Exposure to Platinum Complex Drugs

Drug Compound	MEC (μg/L)	PEC (μg/L)	PEC/MEC	PNEC(μg/L)	RQSw
Cisplatin	0.19	0.4	2.1	122	32 E-4
Carboplatin	0.22	0.36	1.63	122	29 E-4
Oxaliplatin	0.12	0.26	2.16	122	21 E-4

risk ratio.

Equations 1: RQ=PEC/PNEC

Equations 2: RQ=PEC/EC50/f

4. Results

Statistical analysis results are presented in Tables 2 and 3 and Figures 4 and 5.

5. Discussion

As described in the materials and methods section and based on the results presented in Table 2, the instrumental LOQ and LOD for cisplatin, carboplatin, and oxaliplatin were determined. According to these results, the LODs of cisplatin, carboplatin, and oxaliplatin were calculated to be 0.1, 0.013, and 0.09 μg/L, respectively. Similarly, the LOQs of cisplatin, oxaliplatin, and carboplatin were 0.3, 0.027, and 0.4 μg/L, respectively. Figure 4 indicates the concentration of platinum complex drugs in the municipal wastewater treatment plant effluent. According to this figure, the concentrations of oxaliplatin, carboplatin, and cisplatin in the effluent of the wastewater treatment plant were 0.12 ± 0.059, 0.22 ± 0.094, and 0.19 ± 0.098 μg/L, respectively. The results show that the pattern of changes in the concentration of platinum pharmaceutical compounds in the municipal wastewater treatment plant effluent is the same at the sampling points. Figure 5 shows the box plot of cisplatin, carboplatin, and oxaliplatin in the effluent samples, in which the labeled bars indicate significant differences among samples ($P < 0.05$).

Ecological risk of exposure to platinum complex drugs and RQsw calculated for cisplatin, carboplatin, and oxaliplatin (32E-4, 29E-4, and 21E-4, respectively) show that these platinum complex drugs could have no significant risk on aquatic organisms. In this study, ΣRQsw was estimated at < 1 (Table 3). In a study of the ecological risk assessment of 98 pharmaceuticals, including platinum drugs, in Indian surface water and wastewater, anticancer drugs were detected in domestic wastewater effluent at ng/L (17). The difference in the concentrations of platinum compounds be-

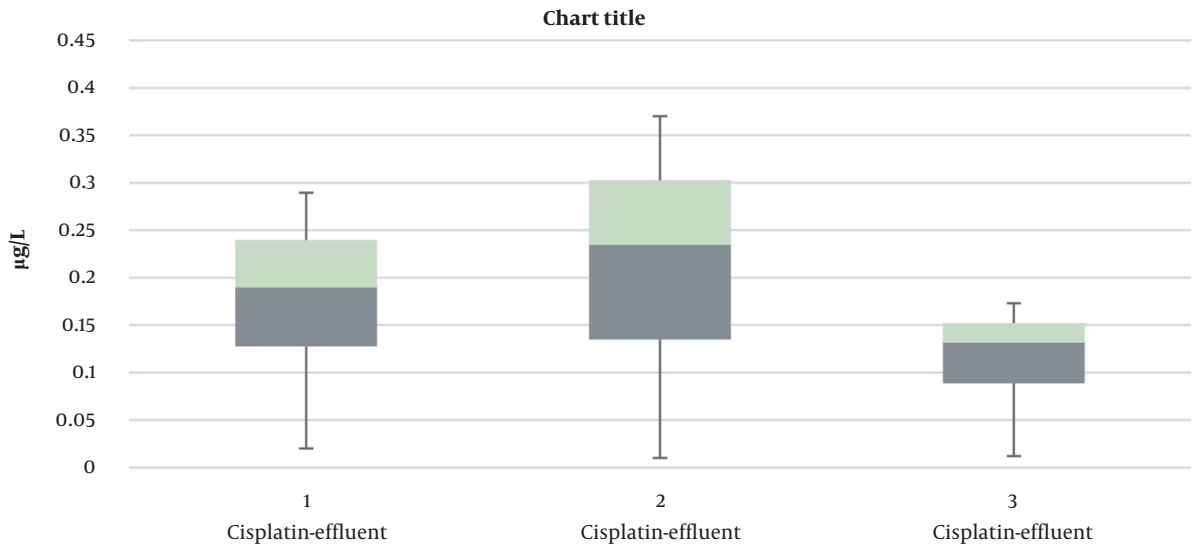


Figure 5. Box plot of cisplatin, carboplatin, and oxaliplatin in effluent samples

tween Indian wastewater and the wastewater in Qom City in the present study is due to the use of higher doses of platinum complex drugs in Qom City. By examining the characteristics and environmental behavior of platinum pharmaceutical compounds according to Figure 2, it is inferred that these compounds have low biodegradability (18, 19). In the study by Tripathi et al. on the environmental remediation of antineoplastic drugs, the degradation or deactivation of antineoplastic drugs in the wastewater and environment was highly influenced by the individual physicochemical behavior of antineoplastic drugs and their transformation products, which confirms the findings of the present study (20). By comparing the study findings of Ghafuri et al. on the toxicity characterization and environmental risk assessment of platinum cytotoxic drugs in hospital effluents with the results of the present study, it can be concluded that high concentrations of platinum complex drug residues were removed in the municipal wastewater system and treatment plant by adsorption to sludge and other particles (14). In a study on removing platinum compounds in the biological wastewater treatment process, Lenz et al. showed that cisplatin and carboplatin could be removed by 51% and 63% via adsorption, respectively (21). In a study on the removal of platinum complex drugs in a pilot-scale membrane bioreactor (MBR) system, the removal of these drugs due to adsorption onto sewage sludge was determined to be 60% on average (22). Based on the findings presented in Table 3 concerning the ecological risk of exposure to platinum complex drugs, the obtained RQ shows that the risk of environmental exposure is negligible for all three Pt compounds.

In a study by Rowney et al. on the prediction of cytostatic drugs in wastewater effluents, the concentration of the carboplatin drug compound, with a probability of 90%, was determined to be less than 1 ng/L (23). The study by Franquet-Griell et al. on predicting the concentrations of cytostatic drugs in sewage effluents and surface waters of Catalonia reported that the concentration of compounds of common drugs used in the effluent from the municipal wastewater treatment system was in the range of 2.7 - 0.06 μg/L (24). It seems that the differences in the results of the above study and those of the present study in terms of the determined concentrations are related to the physicochemical properties of drug compounds and their behavior in the aqueous medium, their dose and excretion rate, and the sampling process (23, 24). In the study by Daouk et al. on drug compounds in the wastewater of a university hospital in Switzerland and the prediction of platinum-based anticancer drugs, PEC values were calculated, confirming the results of the present study (25). Cunningham et al. investigated the environmental exposure to drug compounds, including anticancer drugs, and calculated the tolerable daily intake values to estimate the amount without observable health effects through drinking water and fish consumption. These values showed low exposure risk compared with ambient PEC concentrations and were similar to the present study's finding (26). In a study by Besse et al., which predicted anticancer levels in surface waters using the PEC model and assessed exposure risk, the PEC value for cisplatin, oxaliplatin, and carbo-

platin was 0.52 ng/L (27).

The study focused on the platinum complex compounds in hospital wastewater that cause ecotoxicity of wastewater. This study showed that high-performance liquid chromatography-mass spectrometry (HPLC-MS)/MS could be an important tool in identifying these compounds.

In order to reduce the environmental toxicity of hospital wastewater, appropriate methods of cytotoxic waste management and raising awareness among the related staff should be considered. According to the additional findings from the study of environmental effects and health consequences of platinum complex drugs, these compounds can cause toxicity in aquatic environments, including hospital effluents, sewage, and groundwater.

5.1. Conclusions

Cytotoxic platinum drugs are life-saving for cancer patients. Unfortunately, recent studies have demonstrated that these drugs are not completely removed from the wastewater system. Complementary studies should be implemented, including the assessment of genotoxicity and toxicity effects of cytotoxic platinum drugs and the removal methods of residual platinum compounds. This study indicated that managing cytotoxic wastes from hospital oncology wards is vital for environmental pollution control. Considering the low efficiency of conventional wastewater treatment systems in removing platinum cytotoxic pharmaceutical compounds, using other methods to remove these compounds, such as advanced oxidation processes and membrane systems, is inevitable.

Acknowledgments

This project was supported by the Qom University of Medical Sciences and Health Services.

Footnotes

Authors' Contribution: Ahmad Reza Yari: Data collection; Mohammad Reza Khaksar: Analysis and interpretation of results; Yadollah Ghafuri: Study concept and design.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: This study was approved by the Biomedical Research Ethics Committee of Qom University of Medical Sciences (IR.MUQ.REC.1396.83).

Funding/Support: This study was supported by the Qom University of Medical Sciences and Health Services.

References

1. World Health Organization. *Pharmaceuticals in Drinking-water*. World Health Organization; 2011.
2. Ghafuri G, Nabizadeh R. Composition and quantity of cytotoxic waste from oncology wards: A survey of environmental characterization and source management of medical cytotoxic waste. *Biosci Biotechnol Res Commun*. 2017;**10**(3):438–44. https://doi.org/10.21786/bbrc/10.3/17.
3. Alimohammadi M, Asadi-Ghalhari M, Ghafuri Y. Development of an analytical method for determination of carboplatin and oxaliplatin in resource water, prediction and environmental risk assessment. *J Environ Treat Tech*. 2020;**8**:1168–75.
4. Yu W, Chen Y, Dubrulle J, Stossi F, Putluri V, Sreekumar A, et al. Cisplatin generates oxidative stress which is accompanied by rapid shifts in central carbon metabolism. *Sci Rep*. 2018;**8**(1):4306. [PubMed ID: 29523854]. [PubMed Central ID: PMC5844883]. https://doi.org/10.1038/s41598-018-22640-y.
5. Radonjic K, Stojic I, Zivkovic V, Srejovic I, Jeremic N, Jakovljevic V, et al. The Platinum(II) Complexes Induced Oxidative Stress of Isolated Rat Heart. *Ser J Exp Clin Res*. 2017;**18**(2):111–7. https://doi.org/10.1515/sjecr-2016-0059.
6. Lewandowski M, Gwozdzinski K. Nitroxides as Antioxidants and Anticancer Drugs. *Int J Mol Sci*. 2017;**18**(11):2490–516. [PubMed ID: 29165366]. [PubMed Central ID: PMC5713456]. https://doi.org/10.3390/ijms18112490.
7. Roque-Diaz Y, Sanadar M, Han D, López-Mesas M, Valiente M, Tolazzi M, et al. The Dark Side of Platinum Based Cytostatic Drugs: From Detection to Removal. *Processes*. 2021;**9**(11):1873. https://doi.org/10.3390/pr9111873.
8. Zhang J, Chang VW, Giannis A, Wang JY. Removal of cytostatic drugs from aquatic environment: a review. *Sci Total Environ*. 2013;**445-446**:281–98. [PubMed ID: 23337605]. https://doi.org/10.1016/j.scitotenv.2012.12.061.
9. Nassour C, Nabhani-Gebara S, Barton SJ, Barker J. Aquatic ecotoxicology of anticancer drugs: A systematic review. *Sci Total Environ*. 2021;**800**:149598. [PubMed ID: 34426323]. https://doi.org/10.1016/j.scitotenv.2021.149598.
10. Dehghanpour S, Pourzamani HR, Amin MM, Ebrahimpour K. Evaluation of toxic effects of platinum-based antineoplastic drugs (cisplatin, carboplatin and oxaliplatin) on green alga Chlorella vulgaris. *Aquat Toxicol*. 2020;**223**:105495. [PubMed ID: 32371336]. https://doi.org/10.1016/j.aquatox.2020.105495.
11. EPA. *Exposure assessment tools and models*. EPI Suite v4, 1; 2013. 2013 p.
12. Santana-Viera S, Montesdeoca-Esponda S, Sosa-Ferrera Z, Santana-Rodríguez JJ. Cytostatic drugs in environmental samples: An update on the extraction and determination procedures. *TrAC Trends Anal Chem*. 2016;**80**:373–86. https://doi.org/10.1016/j.trac.2015.08.016.
13. Aurelien Bde H, Sylvie B, Alain D, Jerome G, Yves P. Ecotoxicological risk assessment linked to the discharge by hospitals of bioaccumulative pharmaceuticals into aquatic media: The case of mitotane. *Chemosphere*. 2013;**93**(10):2365–72. [PubMed ID: 24063751]. https://doi.org/10.1016/j.chemosphere.2013.08.034.
14. Ghafuri Y, Yunesian M, Nabizadeh R, Mesdaghinia A, Dehghani MH, Alimohammadi M. Correction to: Environmental risk assessment of platinum cytotoxic drugs: a focus on toxicity characterization of hospital effluents. *Int J Environ Sci Technol*. 2017;**14**(12):2783. https://doi.org/10.1007/s13762-017-1586-6.
15. Burns EE, Csiszar SA, Roush KS, Davies IA. National scale down-the-drain environmental risk assessment of oxybenzone in the United States. *Integr Environ Assess Manag*. 2021;**17**(5):951–60. [PubMed ID: 33913597]. [PubMed Central ID: PMC8453704]. https://doi.org/10.1002/ieam.4430.

16. Pereira A, Silva LJG, Lino CM, Meisel LM, Pena A. A critical evaluation of different parameters for estimating pharmaceutical exposure seeking an improved environmental risk assessment. *Sci Total Environ*. 2017;**603-604**:226–36. [PubMed ID: 28628814]. https://doi.org/10.1016/j.scitotenv.2017.06.022.
17. Sengar A, Vijayanandan A. Human health and ecological risk assessment of 98 pharmaceuticals and personal care products (PPCPs) detected in Indian surface and wastewaters. *Sci Total Environ*. 2022;**807**(Pt 1):150677. [PubMed ID: 34599960]. https://doi.org/10.1016/j.scitotenv.2021.150677.
18. Ashfaq M, Nawaz Khan K, Saif Ur Rehman M, Mustafa G, Faizan Nazar M, Sun Q, et al. Ecological risk assessment of pharmaceuticals in the receiving environment of pharmaceutical wastewater in Pakistan. *Ecotoxicol Environ Saf*. 2017;**136**:31–9. [PubMed ID: 27810578]. https://doi.org/10.1016/j.ecoenv.2016.10.029.
19. Souza DM, Reichert JF, Martins AF. A simultaneous determination of anti-cancer drugs in hospital effluent by DLLME HPLC-FLD, together with a risk assessment. *Chemosphere*. 2018;**201**:178–88. [PubMed ID: 29524818]. https://doi.org/10.1016/j.chemosphere.2018.02.164.
20. Tripathi AK, David A, Govil T, Rauniyar S, Rathinam NK, Goh KM, et al. Environmental Remediation of Antineoplastic Drugs: Present Status, Challenges, and Future Directions. *Processes*. 2020;**8**(7):747. https://doi.org/10.3390/pr8070747.
21. Lenz K, Koellensperger G, Hann S, Weissenbacher N, Mahnik SN, Fuerhacker M. Fate of cancerostatic platinum compounds in biological wastewater treatment of hospital effluents. *Chemosphere*. 2007;**69**(11):1765–74. [PubMed ID: 17624406]. https://doi.org/10.1016/j.chemosphere.2007.05.062.
22. Lenz K, Mahnik SN, Weissenbacher N, Mader RM, Krenn P, Hann S, et al. Monitoring, removal and risk assessment of cytostatic drugs in hospital wastewater. *Water Sci Technol*. 2007;**56**(12):141–9. [PubMed ID: 18075190]. https://doi.org/10.2166/wst.2007.828.
23. Rowney NC, Johnson AC, Williams RJ. Cytotoxic drugs in drinking water: a prediction and risk assessment exercise for the Thames catchment in the United Kingdom. *Environ Toxicol Chem*. 2009;**28**(12):2733–43. https://doi.org/10.1897/09-067.1.
24. Franquet-Griell H, Gomez-Canela C, Ventura F, Lacorte S. Predicting concentrations of cytostatic drugs in sewage effluents and surface waters of Catalonia (NE Spain). *Environ Res*. 2015;**138**:161–72. [PubMed ID: 25721243]. https://doi.org/10.1016/j.envres.2015.02.015.
25. Daouk S, Chevre N, Vernaz N, Widmer C, Daali Y, Fleury-Souverain S. Dynamics of active pharmaceutical ingredients loads in a Swiss university hospital wastewaters and prediction of the related environmental risk for the aquatic ecosystems. *Sci Total Environ*. 2016;**547**:244–53. [PubMed ID: 26789362]. https://doi.org/10.1016/j.scitotenv.2015.12.117.
26. Cunningham VL, Binks SP, Olson MJ. Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. *Regul Toxicol Pharmacol*. 2009;**53**(1):39–45. [PubMed ID: 19013494]. https://doi.org/10.1016/j.yrtph.2008.10.006.
27. Besse JP, Latour JF, Garric J. Anticancer drugs in surface waters: what can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? *Environ Int*. 2012;**39**(1):73–86. [PubMed ID: 22208745]. https://doi.org/10.1016/j.envint.2011.10.002.