Platinum cytotoxic drugs in the municipal wastewater and drinking water, a validation method and health risk assessment

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ABSTRACT
Three cancerostatic platinum compounds (CPCs) including cisplatin, carboplatin and oxaliplatin are complexes of Pt and classified as probable carcinogenic compounds to humans. This study aimed to perform health risk assessment of platinum cytotoxic drugs for drinking water by developing a sensitive analytical method in the water resource of Qom Province in the central part of Iran. Concentrations of the platinum drugs were determined, including 0.2 ± 0.2 µg/L for cisplatin, 0.94 ± 0.36 µg/L for carboplatin and 0.27 ± 0.16 µg/L for oxaliplatin in influent samples, and 0.24 ± 0.07 µg/L for cisplatin, 0.28 ± 0.05 µg/L for carboplatin and 0.11 ± 0.01 µg/L for oxaliplatin in effluent samples. The results indicated that in all the well water samples related to the groundwater, the concentration of the platinum-based compounds was lower than the calculated limits of quantification (LOQ); the concentration of cisplatin, carboplatin and oxaliplatin across the samples in the station of drinking water distribution was also below the limits of detection (LOD). The resulting margin of exposure (MOE) is lower than one (MOE < 1) for the three groups including children, pregnant women and lactation women related to cisplatin and carboplatin was determined through exposure to raw and untreated drinking water. Further research is recommended to be conducted in this area, particularly environmental fate of metabolites and transformation products.

KEYWORDS
cisplatin; carboplatin; oxaliplatin; risk assessment; QOM; cytotoxic; drugs

Introduction
In recent years, much attention has been paid to the presence of pharmaceuticals in wastewater, surface water, and drinking water. Pharmaceuticals, along with their metabolites, are introduced into aquatic environments mainly through excreta, disposal of...
expired or unused medicine, aquaculture, and animal feeding (Boxall *et al.* 2012). Human excretion and improper disposal of pharmaceuticals including unused medicines from households and remained pharmaceuticals waste in oncology wards of hospitals are among factors, which can lead to high variable levels of such drugs in municipal waste waters; release of pharmaceuticals is detected in hospital effluents, effluent of wastewaters and water resources (Isidori *et al.* 2016). The World Health Organization (WHO) has reported that cancer is classified as the second cause of death (21%) (Ferrando-Climent *et al.* 2014). Platinum complexes as anticancer agents are chemotherapeutic agents used to treat cancer. They are coordination complexes of platinum. These drugs are used to treat almost 50% of cancer patients. In this form of chemotherapy, popular drugs include cisplatin, carboplatin and oxaliplatin. Platinum complexes the activity of such drugs through relying mostly on specific interactions with DNA, adjacent N-7 position of guanine, forming a 1,2 intra strand crosslink, leading to damage and ultimately to cell death (Fong 2016; Vyas *et al.* 2014). Cisplatin (cis-diaminedichloroplatinum (II)) and carboplatin (cis-diammine 1, 1-cyclobutanedicarboxylato-platinum (II)) are classified as probably carcinogenic to humans (group 2A) by the International Agency for Research on Cancer (IARC). Oxaliplatin ([(1R, 2R)-1, 2cyclohexanediamine-N, N0] oxalate (2-)-O, O0-platinum) as another platinum-complex may also be carcinogenic (Humans and Organization 1987; Rowney *et al.* 2009). High-performance LC (HPLC) coupled with triple quadruple (QqQ) mass spectrometry (MS) is the most extensively applied method for analyzing pharmaceutical residues in various environmental samples due to its versatility, specificity, and selectivity, as well as by enabling the detection of target compounds in the low nanogram per liter range (Negreira *et al.* 2013, 2014). Currently, there are over twenty anticancer drugs used in oncology wards of hospitals in Qom Province with specific physico-chemical properties; these complexes through hospital effluents as the main source of anticancer drugs to aquatic environments. The risks of anticancer drugs to humans are not very clear, mainly because of lack of toxicity testing in terms of approaches and tests used. Hence, residues of cytostatic compounds are the emerging pollutants in the environment, as many of these drugs are genotoxic and could cause adverse effects in aquatic ecosystems (Negreira *et al.* 2013). This study aims to conduct health risk assessment of platinum cytotoxic drugs for drinking water and develop of a simple, reliable, and sensitive analytical method based on off-line solid phase extraction (SPE) followed by LC–electrospray ionization (ESI)–MS/MS (QqQ) for platinum drugs in wastewater and drinking water resource of Qom Province in the central part of Iran.

**Methods and materials**

**The study area**

This study was performed in Qom, Iran, in 2016, with approximately a million inhabitants and warm and dry climates. The municipal wastewater treatment plant (WWTP) considered in this study receives urban and hospital wastewater serving a population of 100,000–150,000 and has primary and secondary biological treatment processes ($Q = 0.5 \text{ m}^3 \text{ s}^{-1}$). Drinking water is supplied from groundwater, treated by reverse osmosis (RO) and distributed by water distribution stations ($Q = 60 \text{ lps}$).
Chemicals and reagents

All solvents were of HPLC grade and all chemicals were of analytical reagent grade. Formic acid (98–100%), ammonium hydroxide (25%), methanol, and HPLC-water were purchased from Merck (Darmstadt, Germany). Analytical standards of the cytotoxic compounds Cis-pt, Car-Pt, and Oxa-pt were supplied by Sigma-Aldrich at the highest available purity (>99%). The selected platinum compounds, according to their mode of action and chemical structure, are shown in Table 1. Individual solutions of each compound including Cis-pt (1500 µg/mL), Car-pt (4000 µg/mL), and Oxa-pt (2200 µg/mL) were prepared and stored in darkness at −20°C.

Sample collection, pretreatment and solid phase extraction (SPE)

The sampling process was performed from September 2016 to January 2016, where three types of sample were collected, including municipal wastewater (influent and effluent), drinking water samples from distribution stations and groundwater samples from wells of water supply. The coding and sample details are presented in Tables 4 and 5. The wastewater samples were collected in 1.5-L plastic bottles and then transferred directly to the laboratory. Twenty-four-hour flow-proportional composite samples of sewage influents and secondary effluents were collected during ten consecutive days in September 2016. Then, the samples were filtered on glass fiber filters and stored in a freezer (−20°C). All the samples were vacuum-filtered through 0.7 m pore size fiber glass filters followed by 0.45 m pore size cellulose ester membranes (Millipore, Billerica, MA) to remove suspended particles. Next, the samples were analyzed within 1 week after their sampling.

In this study, SPE was carried according to the EPA method. We used ENV+ SPE cartridges for recovery (%) conditioned with 5 mL methanol and 5 mL water at a flow rate of 5 mL/min. After conditioning, 5 mL of the spiked sample was passed through the cartridges. The sample flasks were then rinsed with 50 mL water, and the rinsate was also loaded onto the cartridges. The samples were eluted off the cartridges with 0.5 mL methanol and acetonitril (50:50 v/v) and transferred to the HPLC sample vials for analysis.

LC-MS/MS analysis

The liquid chromatography/autosampler system consisted of an Agilent Technologies separation module, ZORBAX, SB, C18 column (250 mm, 3.5 μm) with a 5-mm particle size, where the mobile phase was A = Water +0.1% formic acid, B = methanol +0.1%

### Table 1. Characteristics and physicochemical properties of platinum cytotoxic drugs.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular mass</th>
<th>Log(_{kw})</th>
<th>Solubility</th>
<th>(p_{ka})</th>
<th>Boiling point</th>
<th>Vapor pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>300</td>
<td>−2.19</td>
<td>14</td>
<td>7.2</td>
<td>575</td>
<td>1.16e-0.19</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>378</td>
<td>−1.78</td>
<td>11.7</td>
<td>6.6</td>
<td>772</td>
<td>4.59e-0.19</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>397</td>
<td>−1.65</td>
<td>7.9</td>
<td>6.1</td>
<td>780</td>
<td>4.8e-0.19</td>
</tr>
</tbody>
</table>
formic acid, (A / B) = 20:80 (V/V) flow rate: 0.3 ml/min, injection volumes: 5 μL. For the mass spectrometry, Agilent G6410 Triple Quadrapole Mass spectrometer equipped with a commercial ESI source was employed. For ESI-MS experiments, nitrogen was used as sheath gas (100 psi) at a drying gas flow of ml/min. The electrospray voltage was 4.5 kV and capillary temperature was 350°C. Multiple reaction monitoring (MRM) was used for the detection. For the platinum complex, [M+H]+ ions were monitored at m/z as the product ion, with the results shown in Table 2 and Figures 1–3 (Negreira et al. 2013; Nussbaumer et al. 2011).

### Table 2. Specific MRM conditions for determination of platinum cytotoxic drugs.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time</th>
<th>Segment</th>
<th>ESI</th>
<th>Product ion</th>
<th>MS/MS transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>5.3</td>
<td>2</td>
<td>ESI+</td>
<td>[M + H]+</td>
<td>300 &gt; 248</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>5.3</td>
<td>1</td>
<td>ESI+</td>
<td>[M + H]+</td>
<td>372 &gt; 355.0</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>5.3</td>
<td>1</td>
<td>ESI+</td>
<td>[M + H]+</td>
<td>398 &gt; 96.0</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)

**Figure 1.** LS-MS/MS chromatogram in MRM mode of carboplatin at 1 ng/mL.

![Figure 2](image2.png)

**Figure 2.** LS-MS/MS chromatogram in MRM mode of Oxaliplatin at 1 ng/mL.
Preparation of calibration standards and method validation

The analytical curves were prepared using concentrations of 1, 5, 10, 25, and 50 ng/mL for cisplatin, carboplatin and oxaliplatin. The correlation coefficients of 0.9998, 0.9987, and 0.999 were obtained for cisplatin, carboplatin and oxaliplatin, respectively. Determination of the analytical rate of the platinum compounds was carried through analysis 5 blank were spiked with five concentrations (1.5, 10.25, and 50.00 ng/mL). The relative standard deviations in percentage (RSD%) of the platinum cytotoxic compounds (n = 5) were below 15% across all the cases. A recovery of more than 50% was considered adequate to obtain the required sensitivity.

The limits of detection (LOD) and limits of quantification (LOQ) were calculated using the following equations:

\[ \text{LOD} = 3 : 3\sigma / S \]
\[ \text{LOQ} = 10\sigma / S \]

where \( \sigma \) is the standard error of the intercept and \( S \) is the slope of the standard additions calibration curve. The final results are presented in Table 3 (Meeravali et al. 2014).

Development of health risk assessment for platinum cytotoxic drugs

The assessment of the health risk related to the presence of the platinum cytotoxic drugs in drinking water approach included health exposure risk assessment from drinking water based on the threshold of toxicological concern (TTC) and margin of exposure (MOE) (Benford et al. 2010). TTC is a method for deriving limits for compounds with limited or no toxicity data. The recommended threshold in this study was set at 0.15 mg/person/d, based on an excess of risk of \( 10^{-6} \) for carcinogenic and genotoxic compounds (Stanard et al. 2015).

**Table 3.** Quality control and method validation parameters of platinum cytotoxic drugs.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Linearity ((R^2))</th>
<th>LOD ((\mu g/L))</th>
<th>LOQ ((\mu g/L))</th>
<th>Recovery %</th>
<th>1 ng/mL</th>
<th>5 ng/mL</th>
<th>10 ng/mL</th>
<th>10 ng/mL</th>
<th>50 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>0.999</td>
<td>0.017</td>
<td>0.056</td>
<td>0.70</td>
<td>6.5</td>
<td>8.2</td>
<td>5.8</td>
<td>5.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>0.999</td>
<td>0.013</td>
<td>0.043</td>
<td>0.78</td>
<td>6.0</td>
<td>6.4</td>
<td>7.8</td>
<td>6.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>0.999</td>
<td>0.009</td>
<td>0.036</td>
<td>0.74</td>
<td>7.5</td>
<td>7.7</td>
<td>9.9</td>
<td>8.8</td>
<td>7.9</td>
</tr>
</tbody>
</table>

**Figure 3.** LS-MS/MS chromatogram in MRM mode of cisplatin at 1 ng/mL.
Dearfield and Moore (2005). In this study, the amount of drinking water needs was considered based on age, sex and health status. Regarding the EPA standard exposure factors and dietary reference intake by EFSA and using a questionnaire-based survey about water consumption for water needs by QoM Province water supply management, drinking water consumption was determined as 2.5 L/d for adults (60 kg), 1 L/d for children (16.7 kg and 2–6 years), 2.8 L/d for pregnant women and 3.1 L/d for lactation women (Zizza et al. 2009; Gandy 2015).

The drinking water equivalent concentration (DWEL) represents the concentration of a pharmaceutical per liter of water, which does not result in significant risk to the health of consumers over a lifetime of 70 years. It was estimated according to the US EPA methodology for deriving ambient water quality criteria for the protection of human health, the resulting MOE (DWEL/C\text{platinum complex}) was higher than one (MOE > 1), suggesting that there was no appreciable risk of human exposure (Barlow et al. 2006; Houeto et al. 2012).

### Results and discussion

**Occurrence of platinum cytotoxic drugs in wastewater and drinking water**

The important aim of this study was to gather information and monitor the occurrence of platinum cytotoxic drugs in municipal wastewaters (influent and effluent) and drinking water in Qom. The results of eliminating platinum cytotoxic drugs in WWTPs and water treatment by reverse osmosis system are shown in the following tables.

**Concentrations of platinum cytotoxic drugs measured in influents and effluents in wastewater treatment plant (WWTP) in QoM**

The analysis of the wastewater samples showed the presence of cisplatin, carboplatin, and oxaliplatin in the influent and effluent of municipal wastewater, as shown in Table 6.
Concentrations of the platinum drugs included 0.52 ± 0.2 μg/L for cisplatin, 0.94 ± 0.36 μg/L for carboplatin and 0.30 ± 0.17 μg/L for oxaliplatin in the influent samples, as well as 0.24 ± 0.07 μg/L for cisplatin, 0.38 ± 0.05 μg/L for carboplatin and 0.11 ± 0.01 μg/L for oxaliplatin in the effluent samples (Table 1). Considering the results of the concentration of the platinum-based compounds in the influent and effluent samples, we noticed that amounts of the compounds measured in the wastewater influents were in general higher, as compared to the effluents (Figures 4 and 5). The elimination efficiency of the platinum-based compounds of cisplatin, carboplatin, and oxaliplatin was 52%, 59%, and 60%, respectively. Considering the characteristics and physicochemical properties of the platinum complex as poorly biodegradable during conventional biological treatment, we can conclude that sorption process has an important role in elimination of these compounds. The study of Lenz et al. on platinum compounds in biological wastewater treatment, removal efficiencies of cisplatin and carboplatin were obtained to be 51% and 63%, respectively (Lenz et al. 2005). Their results also revealed that the elimination of platinum-based compounds by wastewater treatment was due to both removal of suspended solids of wastewater and adsorption of platinum compounds onto activated sludge. Moreover, pt from chemotherapeutic drugs was also detected in influents (1 ng/L to 250 μg/L) and effluents (2 μg/L to 145 μg/L) of sewage treatment plants, which are in line with the results of this study (Rowney et al. 2009). In the study by Isidory et al. on anticancer drugs in hospital and municipal wastewater from Slovenia and Spain, concentration of platinum drugs (cisplatin and all metabolites) measured as total –pt in wastewater influent samples was 27 ± 3 and 23 ± 1 ng/l, respectively, whereas in the effluent samples, it was <LOQ (Isidori et al. 2016).

Figure 4. Concentration of various platinum cytotoxic compounds measured in each of sampling sites.

Figure 5. Platinum cytotoxic compounds in the influents and effluent wastewater treatment plant during monitoring period of study.
Concentrations of platinum cytotoxic drugs measured in groundwater and drinking water

The results of the concentration of the platinum-based compounds are shown in Table 5. In all the well water samples related to the groundwater, concentration of the platinum-based compounds was lower than the calculated LOQ, and the concentration of cisplatin, carboplatin and oxaliplatin across the samples in the station of drinking water distribution was <LOD. Based on these results, it is reasonable to conclude that reverse osmosis treatment system has a significant effect on the removal of platinum-based compounds in drinking water ($p_{value} < 0.001$). Study on quantitative determination of platinum complex in drinking water is very limited. Among such studies is the one by Rowny on cytotoxic drugs in raw drinking water of Thames catchment, where the concentration of 0–145 ng/L was predicted for alkylating agent group (cisplatin, carboplatin, and oxaliplatin) (Rowny et al. 2009). The results of this study are comparable with those obtained in our study. According to the WHO report, platinum complex levels in drinking water have been estimated as 100 pg/L, with a similar value in glacier ice. However, the very high level reported for platinum complex in tap water from Liverpool, at 60 000 pg/L, requires further investigation (Rowney et al. 2009). In the study of cytotoxic drug concentrations in European rivers by Johnson, it was found that with 90 percentile (worst case) prediction, carboplatin concentration was determined below 1 ng/L (Johnson et al. 2013).

Table 5. Concentrations of the platinum cytotoxic drugs measured in the ground water and drinking water.

<table>
<thead>
<tr>
<th>Sample code</th>
<th>Cisplatin</th>
<th>Carboplatin</th>
<th>Oxaliplatin</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well water-1</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.10</td>
</tr>
<tr>
<td>Well water-2</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.14</td>
</tr>
<tr>
<td>Well water-3</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.3</td>
</tr>
<tr>
<td>Well water-4</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.12</td>
</tr>
<tr>
<td>Well water-5</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.09</td>
</tr>
<tr>
<td>Well water-6</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.08</td>
</tr>
<tr>
<td>Well water-7</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>7.01</td>
</tr>
<tr>
<td>Drinking water-station-1</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.00</td>
</tr>
<tr>
<td>Drinking water-station-2</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.14</td>
</tr>
<tr>
<td>Drinking water-station-3</td>
<td>&lt;LOQ</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.21</td>
</tr>
<tr>
<td>Drinking water-station-4</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.13</td>
</tr>
<tr>
<td>Drinking water-station-5</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.02</td>
</tr>
<tr>
<td>Drinking water-station-6</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.12</td>
</tr>
<tr>
<td>Drinking water-station-7</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>7.09</td>
</tr>
</tbody>
</table>

Concentrations of platinum cytotoxic drugs measured in groundwater and drinking water

The results of the concentration of the platinum-based compounds are shown in Table 5. In all the well water samples related to the groundwater, concentration of the platinum-based compounds was lower than the calculated LOQ, and the concentration of cisplatin, carboplatin and oxaliplatin across the samples in the station of drinking water distribution was <LOD. Based on these results, it is reasonable to conclude that reverse osmosis treatment system has a significant effect on the removal of platinum-based compounds in drinking water ($p_{value} < 0.001$). Study on quantitative determination of platinum complex in drinking water is very limited. Among such studies is the one by Rowny on cytotoxic drugs in raw drinking water of Thames catchment, where the concentration of 0–145 ng/L was predicted for alkylating agent group (cisplatin, carboplatin, and oxaliplatin) (Rowny et al. 2009). The results of this study are comparable with those obtained in our study. According to the WHO report, platinum complex levels in drinking water have been estimated as 100 pg/L, with a similar value in glacier ice. However, the very high level reported for platinum complex in tap water from Liverpool, at 60 000 pg/L, requires further investigation (Rowney et al. 2009). In the study of cytotoxic drug concentrations in European rivers by Johnson, it was found that with 90 percentile (worst case) prediction, carboplatin concentration was determined below 1 ng/L (Johnson et al. 2013).

Table 6. MOE calculated for platinum cytotoxic drugs concentration and DWEL found in the raw drinking water from ground water.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration in ground water (ng/L)</th>
<th>TTC (μg/d)</th>
<th>Pregnancy women</th>
<th>Lactation women</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>children adult</td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnancy women</td>
<td>Lactation women</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>children adult</td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>56$^a$</td>
<td>0.15</td>
<td>0.74</td>
<td>1.2</td>
<td>0.94</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>43$^a$</td>
<td>0.15</td>
<td>41.7</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>37$^a$</td>
<td>0.15</td>
<td>1.11</td>
<td>1.6</td>
<td>1.43</td>
</tr>
</tbody>
</table>

$^a$LOQ of cisplatin. $^b$LOQ of carboplatin. $^c$LOQ of oxaliplatin.
Health risk assessment for platinum cytotoxic drugs

The results of risk assessment of the platinum cytotoxic drugs according to the previously mentioned method are shown in Table 6. Due to the results of the concentration of the platinum-based compounds in groundwater and drinking water, health risk was assessed only for raw drinking water related to groundwater. Accordingly, valid LOQ exists and as specified in Recommendation 2013/647/EU, concentrations below the LOQ were replaced by LOQ/2 (middle-bound scenario), and each of cisplatin, carboplatin and oxaliplatin as concentration of these compounds was determined (Cunningham et al. 2009). In this study, considering toxicological threshold concern of 0.0025 μg/kg/d (which corresponds to 0.15 μg/person/d divided by 60 kg) with an excess risk set at 10^-6, the corresponding DWEL was determined.

Figure 6. MOE results for estimation health risk of children by cisplatin.

Figure 7. MOE results for estimation health risk of pregnancy woman.
for groups including adults (60 ng/L), children (41.7 ng/L), pregnancy women (53 ng/L), and lactation women (48 ng/L).

The results of MOE calculated for the concentration of the platinum cytotoxic drugs and DWEL found in raw drinking water related to groundwater are shown in Table 6. The resulting MOE was determined as lower than one (MOE < 1) for the groups including children, pregnant women and lactation women related to cisplatin and carboplatin. The relationship between MOE and human cancer risk is uncertain and requires further clarification on the dose–response relationship. Based on point estimation of MOE < 1 for the groups, using the software package @Risk for Excel Version 5.5.0 with 10,000 iterations data confidence level of 90%, as demonstrated in Figures 6–9. The MOE results for the health risk estimation of pt-based anti-cancer drugs from groundwater confirm the previous results regarding the observed risk
estimate about such drug complexes. The study of Fonseca et al. on ecotoxicological assessment of the anticancer drug cisplatin showed that the mode of action of cisplatin may pose a risk to aquatic environment at the range of ng/L (Fonseca et al. 2017). In prioritizing anticancer drugs for environmental monitoring and risk assessment purposes, carboplatin is considered a priority contaminant with respect to its occurrence in wider environments (Booker et al. 2014). Children in the present study were found to be more prone to risk of carboplatin. The results were consistent with the EMEA guideline about the threshold value that refers to the predicted environmental concentration (PEC) of 10 ng/L for cytotoxic drugs for environmental risk assessment. Moreover, due to amounts of the platinum complex in groundwater, risk of exposure was predictable (EMEA 2006; Besse et al. 2012).

**Conclusion**

The results of this study exhibited no risk levels from exposure to platinum cytotoxic complex from drinking water; however, appreciable risk for children and lactation women exposed to raw drinking water without any treatment. It should be noted that genotoxic agents are considered not to have a threshold, but induce DNA damage linearly, which is dose dependent. It is also theoretically assumed that even a single molecule of a genotoxic carcinogen may cause a mutation and thus, results in an increased cancer incidence, although the increased risk may be infinite estimably small. One of the important aims of this study was to make decision on emerging pollutants and individual cytotoxic drugs in drinking water resources and develop advanced water treatment plans. Definitely, limitations of our study should not be overlooked. One of the substantial points was that the platinum-based compounds were found in 10% of the samples in groundwater, and metabolites of these compounds were not quantified. However, we recommend that further work be conducted in this area, particularly on environmental fate of metabolites and transformation products. Our results require confirmation by other methodologies for assessing the risk to human health through exposure, especially bioassay test. Finding represent a preliminary work for platinum residual in aquatic environment and a strategic plan for release, monitoring and treatment of cytotoxic drug residue in the sewage of hospitals must be considered.

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