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# Platinum-based anticancer drugs in waste waters of a major UK hospital and predicted concentrations in recipient surface waters

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## HIGHLIGHTS

- Pt-based anticancer drugs have been measured in waste waters from a UK hospital.
- Concentrations of total aqueous Pt were highly variable.
- Median concentrations suggest that the majority of Pt is emitted from outpatients at home.
- Predicted concentrations in recipient waters are below EMEA guidelines.
- Nevertheless, the potential environmental effects of these drugs require investigation.

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## ABSTRACT

Concentrations of the cytotoxic platinum-based anticancer drugs, as total Pt, have been measured over a three week period in one of the main drains and in the effluent of the oncology ward of a major UK hospital (Derriford, Plymouth). Concentrations of Pt were highly variable in both discharges, and ranged from about 0.02 to 140 μg $L^{-1}$ in the oncology effluent and from about 0.03 to 100 μg $L^{-1}$ in the main drain. A comparison of drug administration figures over the study period with an estimate of the quantity of Pt discharged through the drains suggests that about 22% of total Pt is emitted to the environment from the hospital with the remainder being discharged by treated patients in the wider community. Administration figures for the three Pt-based drugs used in the hospital (cisplatin, carboplatin and oxaliplatin) coupled with published measurements on the removal of the drugs by conventional sewage treatment allowed the concentrations of Pt arising from each drug to be predicted in recipient surface waters as a function of water flow rate. For conditions representative of the region under study, concentrations of total Pt between a few tens and in excess of 100 pg $L^{-1}$ are predicted, with the principal form of the metal occurring as carboplatin and its metabolites. Although predicted concentrations are below EMEA guidelines warranting further risk assessment, the presence of substances in surface waters that are potentially carcinogenic, mutagenic and teratogenic and yet whose environmental effects are not understood is cause for concern.



## 1. Introduction

For many years, surgery and radiotherapy were the main means of managing cancer. Although these approaches are able to remove local tumours, they do not have a great impact on general prognosis because most deaths in patients are caused by metastatic spread of the disease. Presently, antineoplastic agents are employed, either alone or in combination with surgery or radiotherapy, to improve the outcome for cancer patients. Most anticancer drugs inhibit the proliferation of cancerous cells but are non-selective inasmuch as they are also toxic to non-cancerous cells. Consequently, a concern arising from the administration of antineoplastic agents is their potential effects on aquatic life once emitted to the environment.

Cytotoxic drugs are a group of antineoplastic agents that function by interacting with DNA and interfering with the process of cell division. Because of their non-selectivity, coupled with potentially genotoxic, mutagenic and carcinogenic properties, it has been hypothesised that all eukaryotic organisms may be at risk from exposure to these chemicals (Johnson et al., 2008) and that threshold values for lowest effect concentrations in the environment are inappropriate (Kosjek and Heath, 2011). Accordingly, there has been an increasing interest in the environmental distributions and behaviour of cytotoxic drugs and their metabolites over the past decade. Recent advances in analytical capabilities have allowed the concentrations and fluxes of many cytotoxic chemicals to

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be established in their principal environmental sources (hospital discharges and treated sewage effluents) and, for fewer cytotoxics, their concentrations in receptors (mainly rivers and tap water) (Kosjek and Heath, 2011). Where cytotoxics are not detectable or data are lacking, concentrations and fluxes have been predicted from information on drug usage and water consumption (Johnson et al., 2008; Rowney et al., 2009; Besse et al., 2012).

Platinum-based cytotoxics are coordination complexes of Pt which are used in 50–70% of cancer patients (Hannon, 2007). The environmental distributions and impacts of these drugs and their metabolites are, however, particularly poorly defined. The chemical and pharmacokinetic properties of the principal complexes in use, cisplatin (*cis*-dichlorodiammineplatinum(II)), carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)) and oxaliplatin ([1*R*,2*R*]-1,2-cyclohexanediamine-*N*,*N*′)oxalate(2-)-*O*,*O*′platinum(II)), are shown in Table 1. The drugs are mainly used in combination therapy for the treatment of solid tumours and, specifically, ovarian, oesophageal and bladder carcinoma, tumours of the head and neck, testicular tumours, small cell lung cancer and metastatic colorectal cancer (Michalke, 2010). The mechanism of action of cisplatin involves the formation of reactive, aquated complexes (*cis*-$PtCl(OH_2)(NH_3)_2^+$ = monoaquacisplatin; *cis*-$Pt(OH_2)_2(NH_3)_2^{2+}$ = diaquacisplatin) inside the cell through the replacement of the chloro ligands by water molecules:

$$cis - PtCl_2(NH_3)_2 + H_2O \leftrightarrow cis - PtCl(OH_2)(NH_3)_2^+ + Cl^- \quad (1)$$

$$cis - PtCl(OH_2)(NH_3)_2^+ + H_2O \leftrightarrow cis - Pt(OH_2)_2(NH_3)_2^{2+} + Cl^-. \quad (2)$$

The aquated complexes then bind directly with DNA to form intrastrand cross-links between bases, thereby inhibiting the cell division process (Berners-Price and Appleton, 2000; Lau and Ensing, 2010). The precise modes of action of carboplatin and oxaliplatin are less clear, but appear to involve aquation as a precursor to DNA binding (Desoize and Madoulet, 2002). Compared with cisplatin, carboplatin is considerably more stable and less reactive because of the relatively low lability of the bidentate dicarboxylate ligand in the *cis* position.

The present study is the first to report concentrations of Pt-based cytotoxic drugs, as total Pt, in the waste waters from a UK hospital. We use data on the administration of the drugs in the outpatient oncology ward encompassing the sampling period to evaluate the relative magnitude of environmental sources of the cytotoxic substances from the hospital and from treated patients in the wider community. Published information on the removal of the drugs by conventional sewage treatment is also used to predict concentrations of clinically-derived Pt in recipient surface waters of varying flow rates and the significance of these concentrations relative to those arising from other environmental sources of Pt.

## 2. Materials and methods

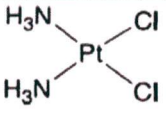
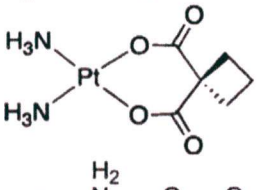
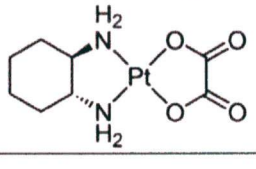
### 2.1. Study site

Derriford Hospital, Plymouth, is a large university hospital serving about 450,000 people in southwest England. The hospital includes a major cancer care centre and an aseptic facility for manufacturing and dispensing chemotherapy drugs. Solid and liquid wastes arising from the pharmaceutical facility are treated as hazardous and disposed of by incineration. Waste water from the outpatient oncology ward, where drugs are administered intravenously, is carried by an underground, open, semi-circular concrete drain of about 15 cm in diameter (drain 1). After about 10 m, this drain discharges into one of the main drains that receives general waste from about 50 % of the hospital (drain 2). No flow data are available for drain 1, but about 100,000 $m^3$ of water is annually discharged through drain 2 (~3.2 L $s^{-1}$).

### 2.2. Sampling and sample preparation

Samples were collected on week days during June and July 2012 over a 21 day period, thereby encompassing a three week chemotherapy cycle. Drains were accessed through a series of manholes with the assistance of the hospital estates personnel between 12 noon and 1 pm, or midway through the working day (8.30 am to 5 pm) and a few hours after the administration of the first round of infusions. Drain 1 was sampled immediately outside the oncology ward and at a distance of about 5 m from its discharge into drain 2, and drain 2 was sampled a few metres downstream of the input from drain 1. Samples were collected manually by placing a 1 L high density polyethylene bucket into the waste stream with the aid of a 4 m length of nylon string. Once sufficient waste water had been collected, the bucket was carefully raised and a screw-capped 60 mL polyethylene centrifuge tube filled to the mark. The bucket was then rinsed successively with 0.1 M $HNO_3$, hypochlorite disinfectant solution and distilled water before being stored in a plastic zip-lock bag until required for the next sampling. In the laboratory, 50 mL of sample was vacuum filtered through a Whatman 542 hardened ashless filter paper (pore size = 2.7 μm) using a Pyrex filtration unit.

**Table 1**
Chemical and pharmacokinetic properties of the three Pt-based anticancer drugs (Lenz et al., 2005; Rowney et al., 2009; National Toxicology Program, 2011 and references therein).

| Drug | Formula | Structure | Molecular weight | Water solubility[a], g $L^{-1}$ | Log $K_{ow}$[a] | Plasma elimination half-life, h |
|---|---|---|---|---|---|---|
| Cisplatin | *cis*-$PtCl_2(NH_3)_2$ |  | 300.05 | 2.5 | −2.19 | 130 ± 24 to 327 ± 91 |
| Carboplatin | *cis*-[$Pt(NH_3)_2$(CBDCA-*O*,*O*′)], (CBDCA = 1,1-cyclobutanedicarboxylate) |  | 371.25 | 11.7 | −0.46 | 139 ± 38 |
| Oxaliplatin | Pt(dach)ox (dach = cyclohexanediamine; ox = oxalate) |  | 397.29 | 7.9 | −0.05 (±1.32) | 273 ± 19 |

[a] At 25 °C.

Filters were stored in polypropylene centrifuge tubes at −22 °C pending digestion (see below). Filtrates were transferred to centrifuge tubes where the pH and conductivity were measured using an Acorn pH 6 meter and YSI 85 handheld dissolved oxygen/conductivity meter, respectively. Filtrates were then acidified with 1 mL of concentrated HCl (Fisher Scientific, TraceMetal Grade) and stored at room temperature and in the dark before being analysed (within two weeks of processing).

### 2.3. Filter digestion

Defrosted and dried filters were digested in boiling aqua regia. Thus, each filter was placed into an acid-cleaned 50 mL Pyrex beaker before 12 mL of a solution of three parts concentrated HCl and 1 part concentrated $HNO_3$ (both TraceMetal Grade) was added. The contents were heated to 85 °C on a hot plate and in a fume cupboard for about 60 min. The cooled digests were diluted to 20 mL in individual polypropylene centrifuge tubes with 0.1 M $HNO_3$ and stored at room temperature and in the dark pending analysis. For quality assurance purposes, triplicate 250 mg portions of certified auto catalyst pellets (National Institute of Standards and Technology 2556) were digested likewise, and control digests were performed in quadruplicate in the absence of solid material.

### 2.4. Platinum analysis

Filtrates, digests and quadruplicate samples of Plymouth tap water were analysed for total Pt (as $^{195}Pt$) using a Thermo Scientific X Series II bench top quadrupole inductively coupled plasma-mass spectrometer (ICP-MS) with a collision cell. Samples were introduced to the plasma via a concentric glass nebuliser and conical impact bead spray chamber. Forward power was 1.4 kW, plasma, auxiliary and nebuliser gas flows were set at 15 L $min^{-1}$, 0.7 L $min^{-1}$ and 0.8 L $min^{-1}$, respectively, and dwell time per reading was 10 ms with 50 sweeps and three replicates. The instrument was calibrated externally using a blank and five standards (up to 50 μg $L^{-1}$) prepared by serial dilution of a 1 mg $mL^{-1}$ Pt plasma emission standard in 0.1 M HCl, and internally by the addition of 50 μg $L^{-1}$ of $^{193}Ir$ to all samples and standards. A standard was analysed as a check after every ten samples and the five samples of either side of any check that deviated by more than 10% of its true value were reanalysed.

The relative standard deviation of replicate measurements of Pt in all samples was generally less than 10% and the limit of detection, calculated from 5 σ of multiple measurements of the lowest standard, was about 15 ng $L^{-1}$. Since no suitable reference material exists for Pt in medical waste water, we made a combined, semi-quantitative assessment of analytical accuracy and digestion efficacy by determining Pt in digests of NIST 2556. The measured Pt concentration of 602 ± 9.5 μg $g^{-1}$ was about 86% of the certified concentration (697.4 ± 2.3 μg $g^{-1}$), presumably reflecting the incomplete digestion of refractory catalytic particles (residual solids were evident in solutions after aqua regia digestion).

## 3. Results

### 3.1. Pt-based drug usage

The quantities of Pt-based anticancer drugs administered in the outpatient oncology ward of Derriford Hospital during each day of the study period are shown in Table 2. Also shown are the equivalent quantities of Pt administered as cisplatin, $Pt_{cis}$, carboplatin, $Pt_{car}$, and oxaliplatin, $Pt_{oxa}$, and as derived from the relative contributions of Pt to the total molecular mass of each compound; the total quantity of Pt administered, $Pt_{tot}$, was obtained from the sum of Pt arising from each drug. Both the quantities and distributions of drugs administered vary over the study period. For example, on days 7 and 12 all three drugs were used, while on days 5 and 11 no drugs were administered. Overall, the total quantity of Pt administered in the ward was 4.16 g, and Pt was distributed with a ratio of $Pt_{cis}$:$Pt_{car}$:$Pt_{oxa}$ = 1.00:5.09:3.34.

**Table 2**
Quantities of Pt-based drugs and equivalent quantities of Pt administered at Derriford Hospital during the study period.

| Day | cisplatin ($Pt_{cis}$), mg | Carboplatin ($Pt_{car}$), mg | Oxaliplatin ($Pt_{oxa}$), mg | $Pt_{tot}$, mg |
|---|---|---|---|---|
| 1 | 45 (29.3) | 530 (278.6) | 0 | 307.9 |
| 2 | 0 | 0 | 440 (216.1) | 216.1 |
| 3 | 0 | 0 | 380 (186.6) | 186.7 |
| 4 | 149 (96.9) | 250 (131.4) | 0 | 228.3 |
| 5 | 0 | 0 | 0 | 0 |
| 6 | 45 (29.3) | 470 (247.0) | 0 | 276.3 |
| 7 | 105 (68.3) | 500 (262.8) | 200 (98.2) | 429.2 |
| 8 | 0 | 0 | 560 (275.0) | 275.0 |
| 9 | 75 (48.8) | 128 (67.3) | 0 | 116.0 |
| 10 | 105 (68.3) | 0 | 200 (98.2) | 166.5 |
| 11 | 0 | 0 | 0 | 0 |
| 12 | 110 (71.5) | 950 (499.2) | 260 (127.7) | 698.5 |
| 13 | 44 (28.6) | 250 (131.5) | 0 | 160.0 |
| 14 | 0 | 750 (394.1) | 620 (304.5) | 698.6 |
| 15 | 0 | 440 (231.2) | 340 (167.0) | 398.2 |
| Sum | 678 (440.9) | 4268 (2242.9) | 3000 (1473.2) | 4157.0 |

### 3.2. Characteristics and Pt concentrations of drain water samples

The chemical characteristics and Pt contents of the samples collected from drains 1 and 2 are shown in Table 3. Conductivity and pH vary considerably in both drains, presumably reflecting the heterogeneous input of a variety of wastes (but principally urine) to the ward and the hospital. The w/v concentrations of both aqueous and particulate total Pt ($[Pt_{tot}]_{aq}$ and $[Pt_{tot}]_p$, respectively) are also highly variable in both drains. For example, aqueous concentrations span four orders of magnitude in drain 1, with a maximum concentration of about 140 μg $L^{-1}$, and, where detected, over three orders of magnitude in drain 2, with a maximum concentration of 95 μg $L^{-1}$; particulate Pt was not detected in all samples but measured values spanned about two orders of magnitude.

Also given in Table 3 is the particulate–water partitioning of $Pt_{tot}$, shown in terms of the percentage of $Pt_{tot}$ present in each sample in aqueous form and as calculated as follows:

$$\text{aqueous } Pt_{tot}, \% = \frac{[Pt_{tot}]_{aq}}{[Pt_{tot}]_{aq} + [Pt_{tot}]_p} \cdot 100\%. \quad (1)$$

Note that where $Pt_{tot}$ was not detected in the particulate phase, an aqueous percentage of 100 has been assumed. In most cases, the majority of $Pt_{tot}$ was measured in the aqueous phase, and in only two cases in drain 1 and one case in drain 2 was there a greater proportion of $Pt_{tot}$ in the particulate phase. Presumably, association with particulate matter results from the rapid adsorption of the drugs and their metabolites to solid material in the waste water.

Neither the concentration of $Pt_{tot}$ in either phase nor the partitioning of $Pt_{tot}$ was correlated with the reaction-controlling variables measured (i.e. conductivity or pH). Moreover, $[Pt_{tot}]_{aq}$ was not related to $[Pt_{tot}]_p$ in either drain, and any measure of $Pt_{tot}$ in drain 1 was unrelated to an equivalent or different measure of $Pt_{tot}$ in drain 2. Furthermore, relationships were not evident between concentrations of $Pt_{tot}$ and daily total quantities of Pt in drugs used in the oncology ward (Table 2); significantly, Pt was observed in the drain waters on days when no Pt-based drugs were administered.

## 4. Discussion

### 4.1. Nature of the hospital source of Pt

Platinum has a number of sources to the environment, with the principal anthropogenic one being the emission of fine, Pt-bearing particles from the catalytic converter of motor vehicles (Zereini et al., 2007).

**Table 3**
Chemical characteristics and Pt concentrations in drains 1 and 2 of Derriford Hospital (nd = not detected).

| Drain 1 | | | | | | Drain 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Day | pH | Conductivity, μS $cm^{-1}$ | $[Pt_{tot}]_{aq}$, μg $L^{-1}$ | $[Pt_{tot}]_p$, μg $L^{-1}$ | Aqueous $Pt_{tot}$, % | pH | Conductivity, μS $cm^{-1}$ | $[Pt_{tot}]_{aq}$, μg $L^{-1}$ | $[Pt_{tot}]_p$, μg $L^{-1}$ | Aqueous $Pt_{tot}$, % |
| 1 | 3.00 | 601 | 1.37 | 0.06 | 96.03 | 8.30 | 392 | 1.48 | 0.02 | 98.46 |
| 2 | 6.80 | 282 | 0.48 | nd | 100 | 7.24 | 214 | 0.26 | 0.06 | 82.18 |
| 3 | 6.80 | 630 | 39.06 | 2.14 | 94.82 | 8.40 | 472 | 2.72 | nd | 100 |
| 4 | 7.02 | 143 | 0.24 | 0.18 | 57.93 | 6.32 | 417 | 0.55 | 0.08 | 87.42 |
| 5 | 7.70 | 275 | 5.17 | nd | 100 | 8.80 | 438 | 0.39 | 9.54 | 3.89 |
| 6 | 6.56 | 225 | 0.29 | nd | 100 | 8.40 | 446 | 0.19 | nd | 100 |
| 7 | 7.10 | 280 | 137.83 | 2.52 | 98.21 | 6.95 | 365 | 80.63 | 3.96 | 95.32 |
| 8 | 6.80 | 357 | 6.94 | 0.07 | 98.96 | 6.70 | 234 | 1.70 | nd | 100 |
| 9 | 6.91 | 278 | 1.42 | 0.37 | 79.27 | 7.06 | 494 | 1.61 | nd | 100 |
| 10 | 6.40 | 216 | 4.17 | 0.05 | 98.71 | 6.86 | 352 | 95.07 | 0.49 | 99.49 |
| 11 | 6.48 | 175 | 0.30 | nd | 100 | 6.58 | 538 | 0.06 | nd | 100 |
| 12 | 2.88 | 621 | 0.02 | nd | 100 | 6.52 | 453 | nd | nd | nd |
| 13 | 5.98 | 175 | 0.14 | nd | 100 | 5.15 | 164 | 0.19 | nd | 100 |
| 14 | 7.07 | 272 | 0.11 | 0.10 | 51.22 | 6.26 | 335 | 0.06 | nd | 100 |
| 15 | 6.38 | 235 | 0.89 | nd | 100 | 6.20 | 794 | 0.03 | nd | 100 |
| Min | 2.88 | 143 | 0.02 | 0.05 | 51.22 | 5.15 | 164 | 0.03 | 0.02 | 3.89 |
| Max | 7.70 | 630 | 137.83 | 2.52 | 100 | 8.80 | 794 | 95.07 | 9.54 | 100 |
| Median | 6.80 | 275 | 0.89 | 0.14 | 98.96 | 6.86 | 417 | 0.47 | 0.28 | 100 |

Since Pt was not detected in Plymouth tap water, it is reasonable to assume that all measured Pt in the present study is derived from the administration and subsequent excretion of Pt-based anticancer drugs. (Note that intravenous infusions are prepared in the hospital pharmacy and that excess or spilled drugs and contaminated equipment and clothing are treated as hazardous waste and incinerated.)

Clearly, the lack of relationships observed in our data and the high degree of variation in $Pt_{tot}$ measured in the drains reflect the randomness of the excreted source of $Pt_{tot}$, variability in the short-term consumption of water, and the nature of the sampling protocol. Thus, measured concentrations of $Pt_{tot}$ will depend on the amount of Pt-based drugs that patients have excreted in the oncology ward, the degree of dilution of excreted drugs by both ward and hospital waste waters, and the time lag between excretion events and sample collection. Sampling once per day over the 15 day period will only provide a snapshot of $Pt_{tot}$ at that particular time, and any time lag may explain why concentrations of $Pt_{tot}$ are sometimes lower in drain 1 than in drain 2, where waste water from the oncology ward is diluted with waste from other parts of the hospital.

The discrepancies between administered quantities of Pt and measured drain concentrations of $Pt_{tot}$ may also be attributed to pharmacokinetic constraints on the excretion of the drugs and their applications in combination therapy. Platinum-based anticancer drugs are generally used in conjunction with other chemotherapeutic agents and the proportions (or presence) of the different drugs may vary over the treatment cycle (Zarogoulidis et al., 2009; Tang et al., 2013). Thus, Pt-based drugs may be administered at the beginning or middle of the regime, with or without other chemotherapy drugs, but not used later on in the cycle. Since the elimination of cisplatin and its metabolites can take up to several weeks (Monjanel-Mouterde et al., 2003) and the half-life for the elimination of carboplatin and its metabolites is several days (Elferink et al., 1987), Pt may enter the sewers of the hospital at any time (Monday to Friday, 8.30 am to 5 pm) both on the day that the Pt-based anticancer drugs were administered or on a subsequent visit to the outpatient unit.

Despite these discrepancies and the constraints on our sampling protocol, the results of the present study are both qualitatively and quantitatively comparable with the limited data on Pt concentrations in clinical wastes that have been reported in the literature. Kümmerer et al. (1999) collected samples every 2 h over a 24-h period from the main drains (but not effluent from the oncology wards) of several European hospitals and found $Pt_{tot}$ concentrations in unfiltered, acidified aliquots of up to about 3.5 μg $L^{-1}$. Lenz et al. (2005) modified the wastewater collection facility of the oncology in-patient ward of Vienna University Hospital in order to allow the collection of 24-h composite samples over a period of 28 days. Concentrations in both filtered and digested particulate aliquots were highly variable, and combined, total concentrations ranged from 4.7 to 145 μg $L^{-1}$ with the majority of Pt occurring in the aqueous phase; as in our study, measurements of $Pt_{tot}$ did not correlate with the daily quantities of Pt administered. In a subsequent publication, Lenz et al. (2007) report total Pt concentrations in samples collected at the same facility ranging from 3 to 250 μg $L^{-1}$. The remarkable similarity of our results to those reported by Lenz et al. (2005), in terms of both the concentration range and partitioning of Pt, reflect similar demographics and types and incidences of cancer within the European Union, coupled with common chemotherapeutic practice and usage of Pt-based drugs in the UK and Austria (Johnson et al., 2013).

### 4.2. Predicted fluxes and species of Pt in hospital waste waters

Ultimately, all Pt administered to patients will be discharged into the aquatic environment. Using the measured $Pt_{tot}$ concentrations and administered doses, however, we can estimate the quantities and percentages of Pt that are discharged directly from the hospital and, from mass balance, therefore, those that are discharged through the wider community. Thus, using data for drain 2, where the flow rate is more constant and is reasonably well defined (about 3.2 L $s^{-1}$), we estimate a flux of $Pt_{tot}$ of 2.02 μg $s^{-1}$ based on a median concentration ($[Pt_{tot}]_{aq} + [Pt_{tot}]_p$) of 0.63 μg $L^{-1}$. For the 15-day period of study, and for a window of 8.5 h per day when the outpatient oncology ward is open, we estimate that the total quantity of Pt discharged from the hospital is 925 mg, or about 22% of the total quantity of Pt administered.

Our estimate of discharged to administered $Pt_{tot}$ is very similar to that derived by Lenz et al. (2005) for the inpatient oncology ward of Vienna University Hospital (27 ± 12%) and suggests that the majority of Pt used in chemotherapy is excreted in the home environment and that hospital effluents do not represent the principal source of the drugs to municipal waste waters. Less certain in both studies, however, are the relative contributions of $Pt_{cis}$, $Pt_{car}$ and $Pt_{oxa}$ to the total quantities of metal discharged, and the precise chemical species of Pt in the waste water. In theory, the relative contributions from each drug may be determined from their administered quantities and pharmacokinetic profiles. However, there are uncertainties associated with the latter because elimination is multiphasic and dependent on the dose administered and the health and condition of individual patients (Bues-Charbit et al., 1987; Kintzel and Dorr, 1995); moreover, estimated rates appear to depend on the assay method employed and the timeframe over which observations were made (Desoize and Madoulet, 2002; see also the range in estimated elimination half-lives for cisplatin in Table 1). Accounting for the

elimination rates in Table 1, the order of abundance in hospital waste water sampled in the present study is assumed to be: $Pt_{car} > Pt_{oxa} \gg Pt_{cis}$.

Although some information exists on the precise metabolites of Pt drugs in urine (at least with regard to $Pt_{cis}$; Hann et al., 2003), more significant regarding Pt speciation in recipient waste water are the precise composition of the aqueous medium, and in particular [$Cl^-$], and the chemical equilibria and kinetic constraints governing the formation of different species. In hospital and municipal waste waters, it is predicted that there will be a progressive, time-dependent increase in the relative proportions of both monoaquacisplatin and diaquacisplatin through aquation (Eqs. (1) and (2)) to an extent that is inversely related to the concentration of $Cl^-$ in the medium (tap water in the Plymouth region is characterised by a chloride content between about 20 and 40 mg $L^{-1}$; Law and Turner, 2011). Although less is known about the modes of action of carboplatin and oxaliplatin and the speciation of excreted metabolites, it is reasonable to surmise, from their chemical similarities with cisplatin, that progressive, kinetically-controlled aquation also takes place.

Given the greater reactivities of the aquated products towards natural surfaces and polyelectrolytes than those of the corresponding parent drugs (Curtis et al., 2010; Turner and Mascorda, accepted for publication), it is assumed that they will represent the principal forms of Pt to interact with suspended solids and ligands in waste water. The highly variable partitioning of $Pt_{tot}$ observed in our samples suggests that these interactions are heterogeneous, likely being dependent on the quantity and nature of particulate matter as well as the reactivities and formation kinetics of aquated metabolites.

### 4.3. Predicted environmental concentrations of Pt

Critical from both a budgetary and environmental effects perspective is the extent of removal of reactive species of Pt discharged in clinical waste and from treated patients in the wider community during waste water treatment. Lenz et al. (2005) studied the adsorption of the three Pt-based drugs to activated sludge particles suspended in various waste waters at concentrations of about 4 g $L^{-1}$ and at pH 6–7. In order to allow for realistic speciation (i.e. aquation), the drugs underwent ageing in NaCl solution ([$Cl^-$] = 61 mg $L^{-1}$) for at least 48 h before being spiked into the suspensions. The results revealed average removals of 92%, 72% and 78% for cisplatin, carboplatin and oxaliplatin, respectively, presumably through the adsorption of reactive, aquated products to suspended sludge particulates.

Applying these percentage removals to our Pt administration figures (or to Pt released both from the hospital and the wider community) allows us to estimate a range of possible concentrations of Pt arising from each drug in non-tidal, surface aquatic waters receiving treated waste. Taking cisplatin as an example, 92% removal during waste treatment indicates that 35.3 mg of the administered drug is emitted to the aqueous environment over a three week period. This is equivalent to a flux of about 19.5 ng $s^{-1}$, or 1.95 pg $L^{-1}$ for dispersion into water flowing at 10 $m^3$ $s^{-1}$ (that includes water derived from the effluent itself). An implicit assumption of this approach is that all Pt compounds are delivered to the treatment process continuously and in the aqueous phase. It is also important to appreciate that computed concentrations in receiving waters encompass all chemical and physical forms of each drug (i.e., the parent molecule and various metabolites in the dissolved, colloidal and adsorbed states). Fig. 1 shows the predicted concentrations of $Pt_{cis}$, $Pt_{car}$ and $Pt_{oxa}$, as well as $Pt_{tot}$, as a function of the flow rate of the receiving waters, modelled between 1 and 100 $m^3$ $s^{-1}$. Clearly, concentrations increase with decreasing dilution or flow rate of receiving waters, and at the lowest flow rate modelled the predicted concentration of $Pt_{tot}$ is about 540 pg $L^{-1}$. The dominant form of Pt is $Pt_{car}$ and at the lowest flow rate considered its predicted concentration is about 350 pg $L^{-1}$, or about 650 pg $L^{-1}$ of the parent drug. This value is very similar to a predicted environmental concentration of 670 pg $L^{-1}$ reported by Besse et al. (2012) based on French consumption data and a ten-fold dilution factor of treated waste water. It is, however, considerably lower than the 10 ng $L^{-1}$ predicted environmental concentration for an individual drug that acts as a trigger for further environmental risk investigation (EMEA, 2006). With respect to the location under study, wastes from Derriford Hospital and about 20% of the population of the city of Plymouth (or 11% of the population that the hospital serves) are processed at a sewage treatment plant that continuously discharges at a mean rate of 0.2 $m^3$ $s^{-1}$ into a tidal river (River Plym). Given that the mean annual flow of the river is 2.60 $m^3$ $s^{-1}$ but that mean monthly flow is regularly less than 1 $m^3$ $s^{-1}$, $Pt_{tot}$ concentrations in excess of 100 pg $L^{-1}$ could occur for periods around low water.

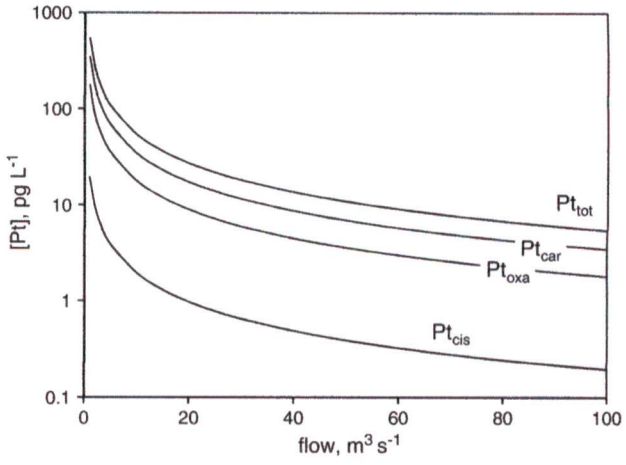



**Fig. 1.** Predicted concentrations of Pt in waste-receiving surface water as a function of flow rate, based on administration figures for Derriford Hospital over the three week study period.

For comparison, Table 4 shows the measured concentrations of total dissolved Pt (i.e. from all environmental sources) in various rivers and estuaries. In surface waters draining heavily urbanised catchments, Pt concentrations in excess of 1000 pg $L^{-1}$ are reported, largely because of inputs derived from vehicular emissions. In pristine rivers–estuaries or those not directly impacted by urbanisation, concentrations of less than 100 pg $L^{-1}$ are more typical, with a minimum reported concentration of 8 pg $L^{-1}$. Our estimates shown in Fig. 1 suggest that Pt concentrations in surface waters arising from the excretion of Pt-based anticancer drugs could exceed concentrations resulting from natural inputs. However, it is unlikely that the degree of contamination resulting from these drugs could be ascertained from measurements of total Pt because inputs from this source coexist with, typically much larger, inputs from vehicle emissions in the urban setting (Lenz et al., 2007).

**Table 4**
Published concentrations of dissolved Pt in river and estuarine waters.

| Environment | Salinity | [$Pt_{tot}$], pg $L^{-1}$ | Reference |
|---|---|---|---|
| Tama River, Tokyo | 0.2 | 6100 | Obata et al. (2006) |
| Tama Estuary, Tokyo | 3.2 | 6860 | |
| | 23.8 | 940 | |
| Ara Estuary, Tokyo | 5.1 | 2030 | |
| | 16.0 | 2650 | |
| Lérez River, NW Spain | <0.1 | 41 | Cobelo-García et al. (2013) |
| | 0.5 | 8 | |
| Lérez Estuary, NW Spain | 3.0 | 12 | |
| | 6.7 | 35 | |
| | 27.4 | 96 | |
| Duman River, E Russia[a] | – | 35 | Soyol-Erdene and Huh (2012) |
| Lena River, NE Russia[a] | – | 70 | |
| River Indigirka, NE Russia[a] | – | 99 | |
| Huang He, N China[a] | – | 123 | |

[a] Salinities not specified; median concentrations reported for multiple samples.

### 4.4. Environmental impacts of Pt-based drugs in surface waters

Critical to the likely behaviour and impacts of the Pt-based drugs in the surface water environment is the salinity (or, strictly, chlorinity) of the recipient waters. Thus, where waste is discharged to fresh water a relatively high proportion of each drug is predicted to remain aquated and, therefore, reactive, with a propensity to interact with biotic and abiotic surfaces and, potentially, accumulate in biota. With increasing salinity of recipient water, the proportion of reactive species is predicted to decline as aquated metabolites are converted back to their relatively unreactive, chlorinated parents, although kinetic constraints on chlorination may ensure that this is a slow process (Curtis et al., 2010).

In a recent study, Turner and Mascorda (accepted for publication) compared the adsorption of the three Pt-based drugs to estuarine sediment suspended in river water (salinity < 0.1; $[Cl^-] = 17.6\ mg\ L^{-1}$) and estuarine water (salinity = 3.20; $[Cl^-] = 1800\ mg\ L^{-1}$) after a 24-h period of incubation of the drugs in river water. The sediment–water distribution coefficients for cisplatin and carboplatin were about 770 mL $g^{-1}$ and 550 mL $g^{-1}$, respectively, in river water, and about 170 mL $g^{-1}$ and 90 mL $g^{-1}$, respectively in estuarine water; coefficients for oxaliplatin were similar (about 70 mL $g^{-1}$) in both media. The interaction of cisplatin has been studied with both the freshwater vascular plant, *Lemna minor* (Supalkova et al., 2008), and the estuarine–coastal macroalga, *Ulva lactuca* (Easton et al., 2011). Although Pt was measurably accumulated in both studies, no phytotoxicity (efficiency of photochemical energy conversion) was observed in *U. lactuca* up to a $Pt_{cis}$ concentration of 30 μg $L^{-1}$ and the concentration for growth inhibition of *L. minor* (96 h EC50 $Pt_{cis}$) was as high as 1.4 mg $L^{-1}$.

Despite these observations, and the inability to analytically detect and discriminate Pt-based drugs and metabolites at environmental concentrations, the presence of cytotoxic substances in surface waters should be cause for concern. In order to better understand the environmental risks posed by these and other cytotoxic drugs, more information is required on their toxicities, both individually and in combination, to a wider range of organisms and over a greater variety of end-points, and in particular, longer-term end-points that include more than one generation.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.scitotenv.2014.05.127. These data include Google maps of the most important areas described in this article.

## References

Berners-Price SJ, Appleton TG. The chemistry of cisplatin in aqueous solution. In: Kelland LR, Farrell N, editors. Platinum-based drugs in cancer therapy. Totowa, NJ: Humana Press; 2000. p. 3–35.

Besse J-P, Latour J-F, 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;39:73–86.

Bues-Charbit M, Gentet J-C, Bernard J-L, Breant V, Cano J-P, Raybaud C. Continuous infusion of high-dose cisplatin in children: pharmacokinetics of free and total platinum. Eur J Cancer Clin Oncol 1987;23:1649–52.

Cobelo-García A, Lopez-Sanchez DE, Almecija C, Santos-Echeandia J. Behavior of platinum during estuarine mixing (Pontevedra Ria, NW Iberian Peninsula). Mar Chem 2013; 150:11–8.

Curtis L, Turner A, Vyas N, Sewell G. Speciation and reactivity of cisplatin in river water and seawater. Environ Sci Technol 2010;44:3345–50.

Desoize B, Madoulet C. Particular aspects of platinum compounds used at present in cancer treatment. Crit Rev Oncol Hematol 2002;42:317–25.

Easton C, Turner A, Sewell G. An evaluation of the toxicity and bioaccumulation of cisplatin in the marine environment using the macroalga, *Ulva lactuca*. Environ Pollut 2011; 159:3504–8.

Elferink F, van der Vijgh WJ, Klein I, Vermorken JB, Gall HE, Pinedo HM. Pharmokinetics of carboplatin after iv administration. Cancer Treat Rep 1987;71:1231–7.

EMEA. Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00. London: European Medicines Agency; 2006.

Hann S, Koellensperger G, Stefanka Zs, Stingeder G, Fürhacker M, Buchberger W, et al. Application of HPLC–ICP-MS to speciation of cisplatin and its degradation products in water containing different chloride concentrations and in human urine. J Anal Atom Spectrom 2003;18:1391–5.

Hannon MJ. Metal-based anticancer drugs: from a past anchored in platinum chemistry to a post-genomic future of diverse chemistry and biology. Pure Appl Chem 2007;79: 2243–61.

Johnson AC, Jürgens MD, Williams RJ, Kümmerer K, Kortenkamp A, Sumpter JP. Do cytotoxic chemotherapy drugs discharged into rivers pose a risk to the environment and human health? An overview and UK case study. J Hydrol 2008;348:167–75.

Johnson AC, Oldenkamp R, Dumont E, Sumpter JP. Predicting concentrations of the cytostatic drugs cyclophosphamide, carboplatin, 5-fluorouracil, and capecitabine throughout the sewage effluents and surface waters of Europe. Environ Toxicol Chem 2013;32:1954–61.

Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. Cancer Treat Rev 1995;21:33–64.

Kosjek T, Heath E. Occurrence, fate and determination of cytostatic pharmaceuticals in the environment. Trends Anal Chem 2011;30:1065–87.

Kümmerer K, Helmers E, Hubner P, Mascart G, Milandri M, Reinthaler F, et al. European hospitals as a source of platinum in the environment in comparison with other sources. Sci Total Environ 1999;225:155–65.

Lau JK-C, Ensing B. Hydrolysis of cisplatin — a first-principles metadynamics study. Phys Chem Chem Phys 2010;12:10348–55.

Law S, Turner A. Thallium in the hydrosphere of southwest England. Environ Pollut 2011; 159:3484–9.

Lenz K, Hann S, Koellensperger G, Stefanka Z, Stingedeer G, Weiseenbacher N, et al. Presence of cancerostatic platinum compounds in hospital wastewater and possible elimination by adsorption to activated sludge. Sci Total Environ 2005;345:141–52.

Lenz K, Koellensperger G, Hann S, Weiseenbacher N, Mahnik SN, Fuerhacker M. Fate of cancerostatic platinum compounds in biological wastewater treatment of hospital effluents. Chemosphere 2007;69:1765–74.

Michalke B. Platinum speciation used for elucidating activation or inhibition of Pt-containing anti-cancer drugs. J Trace Elem Med Biol 2010;24:69–77.

Monjanel-Mouterde S, Ciccolini J, Bagarry D, Zonta-David M, Duffaud F, Favre R, et al. Population pharmacokinetics of cisplatin after 120-h infusion: application to routine adaptive control with feedback. J Clin Pharm Ther 2003;28:109–16.

National Toxicology Program. 12th report on carcinogens. http://ntp.niehs.nih.gov/go/roc12, 2011. [accessed July 2013].

Obata H, Yoshida T, Ogawa H. Determination of picomolar levels of platinum in estuarine waters: a comparison of cathodic stripping voltammetry and isotope dilution-inductively coupled plasma mass spectrometry. Anal Chim Acta 2006;580:32–8.

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;28:2733–43.

Soyol-Erdene TO, Huh Y. Dissolved platinum in major rivers of East Asia: implications for the oceanic budget. Geochem Geophys Geosyst 2012;13:Q06009.

Supalkova V, Beklova B, Baloun J, Singer C, Sures B, Adam V, et al. Affecting of aquatic vascular plant *Lemna minor* by cisplatin revealed by voltammetry. Bioelectrochemistry 2008;72:59–65.

Tang Y, Wang Y, Teng XZ. Sequence-dependent effect of gemcitabine and cisplatin on A549 non-small-cell lung cancer cells. Mol Med Rep 2013;8:221–6.

Turner A, Mascorda L. Particle–water interactions of platinum-based anticancer drugs in river water and estuarine water. Chemosphere 2014. [accepted for publication].

Zarogoulidis K, Mylonaki E, Kakavelas P, Zarogoulidis P, Tsiouda T, Rapti E, et al. Topotecan–carboplatin–etoposide combination as 1st line treatment in patients with small cell lung cancer. Lung Cancer 2009;66:226–30.

Zereini F, Wiseman C, Püttmann W. Changes in palladium, platinum, and rhodium concentrations, and their spatial distribution in soil along a major highway in Germany from 1994 to 2004. Environ Sci Technol 2007;41:451–6.