Occurrence of iodinated x–ray contrast media in indirect potable reuse systems

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ABSTRACT

A lack of knowledge of the health and environmental risks associated with chemicals of concern (COCs) and also of their removal by advanced treatment processes, such as micro–filtration (MF) and reverse osmosis (RO), have been major barriers preventing establishment of large water recycling schemes. As part of a larger project monitoring over 300 COCs, iodinated x–ray contrast media compounds (ICM) were analysed in treated secondary wastewater intended for drinking purposes. ICM are the most widely administered intravascular pharmaceuticals and are known to persist in the aquatic environment. A direct injection liquid chromatography tandem mass spectrometry (DI–LC–MS/MS) method was used to monitor secondary treated wastewater from three major wastewater treatment plants in Perth, Western Australia. In addition, tertiary water

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treated with MF and RO was analysed from a pilot plant that has been built as a first step in trialling the aquifer recharge. Results collected during 2007 demonstrate that MF/RO treatment is capable of removing ICM to below the analytical limits of detection, with average RO rejection calculated to be greater than 92%. A screening health risk assessment indicated negligible human risk at the concentrations observed in wastewater.

Keywords: Iodinated x–ray contrast media, reverse osmosis, wastewater, water reuse, chemicals of concern, pharmaceuticals and personal care products.

INTRODUCTION

Iodinated x–ray contrast media (ICM) are the most widely administered intravascular pharmaceuticals, administered in very high doses (60–120 g) in radiographic procedures.[1] The ICM are considered safe and are widely used. Nevertheless, mild acute reactions such as nausea and pain in the area of injection have been reported in 15% of patients receiving ionic and 3% of the patients receiving non–ionic ICM. [2] Skin reactions after ICM administration, [3] kidney toxicity and thyroid toxicity in patients at risk have been also reported. [4] No studies have conducted on human health effects of ICM at chronic low exposure concentrations derived from food and water. However, environmental risk assessment at environmental concentrations in water (µg/L) indicates that the ratio between the predicted environmental concentration (PEC) and the predicted no–effect concentration (PNEC) is less than 0.0002. [5]

The ICM are designed to be highly soluble (through amide, carboxylic and hydroxyl terminal groups which also mask the toxicity of the aromatic ring) and have low biodegradability. They are metabolically stable, and are almost completely excreted from the body via urine or faeces within a day of administration. [6] While they are considered non–toxic to humans and wildlife, [1, 5, 7] the

persistence of ICM through conventional and activated sludge wastewater treatment plants (WWTP) is well documented. [7-10] In fact, conventional treatment plants are known to be "*transparent*" to compounds characterized by high solubility and the low biodegradability. Concentrations in the effluent from WWTP can be between 5–40 μg iodine/L, [8, 11, 12] particularly if the WWTP receive waste from hospitals or radiological clinics. The ICM also persist in the aquatic environment and may leach through the subsoil into groundwater aquifers. [11, 13] Studies have also reported μg/L level of ICM concentrations in both raw and treated drinking water. [14-16]

Tertiary wastewater treatment is also often unable to efficiently remove ICM. Removal through ozonation is slow and incomplete [11, 17, 18] and, while oxidation via UV/H_2O_2 is more efficient, the ICM that was tested (iopromide, 1-*N*,3-*N*-*bis*(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-1-*N*-methylbenzene-1,3-dicarboxamide) showed lower reactivity than any other pharmaceuticals. [19] Reverse osmosis (RO) alone appears to effectively remove adsorbable organic iodine (AOI) [11] and has also been demonstrated to efficiently remove five specific ICM compounds from secondary effluent. [20]

A key initiative of the Western Australian State Water Strategy is 30% wastewater reuse by 2030. Groundwater provides about 60% of Perth's drinking water and using highly treated wastewater water to recharge aquifers beneath the Swan Coastal Plain provides the potential to meet a major component of this goal. The Groundwater Replenishment Trial (GWRT) will inject 5 GL/year of recycled water treated by microfiltration (MF), reverse osmosis (RO) and UV into the Gnangara groundwater mound, with re–extraction for drinking water planned for the future. The GWRT will assess the feasibility of the treatment and reinjection technologies, as well as community acceptance of groundwater replenishment. Depending on the success of the trial, a full–scale scheme would provide 25–35 GL/y (GL=Gigalitre) of drinking water (10 % of Perth's water supply) by 2015. A further environmental benefit of aquifer recharge is prevention of the decline in groundwater levels

that might otherwise occur as a result of abstraction or decreased rainfall. In the lead up to the GWR Trial a three year project was conducted to undertake chemical and microbiological risk assessments, develop health based water quality guidelines, [21] and characterise the treated wastewater to be used in the trial. As part of the wastewater characterisation program, involving over 300 chemicals, a rapid method for ICM analysis using direct injection liquid chromatography tandem mass spectrometry (DI–LC–MS/MS) has been developed. [20] Results for eight ICM compounds (i.e. iohexol, iothalamic acid, ioxaglic acid, iomeprol, iopamidol, diatrizoic acid, iodipamide, and iopromide) in secondary wastewater from metropolitan WWTP in Perth, Western Australia are presented. In addition, samples were taken from the Beenyup Pilot Plant (BPP), a pilot tertiary treatment plant employing MF/RO that was built.

MATERIAL AND METHODS

Sampling

Samples were collected in two separate sampling events. The aim of the first event was to compare ICM concentrations in secondary treated wastewater collected from the three major Perth metropolitan WWTPs: Beenyup (120 ML/day, ML=Megalitre), Subiaco (60 ML/day) and Woodman Point (160 ML/day). While differences exist between the three WWTPs, the treatment process at each plant is comparable. First, large material such as rags and plastics is removed through screening and inorganic grit is removed by settling. Primary treatment removes the majority of solids through sedimentation, while advanced secondary treatment uses an activated sludge process that consumes organic material through microbial action. The secondary wastewater is discharged to the ocean after final clarification. Samples at Beenyup and Subiaco WWTPs were collected from the final discharge to ocean, while Woodman Point effluent was sampled within

Kwinana Water Reclamation Plant (KWRP), a full scale MF/RO plant that supply water (e.g. for cooling or to generate high pressure steam) to neighbouring industrial facilities.

Composite samples (24 h) were collected using a refrigerated automated sampling unit on three days at Woodman Point and two days at Beenyup and Subiaco WWTPs over a four week period (24/05/2007 – 19/06/2007). In addition, field and trip blanks were collected on each day of sampling. Samples were preserved with 100 mg/L sodium azide, added as a solid to the amber glass sample bottles before sampling, and stored at 4 °C until analysis.

In the second sampling event, samples were taken from Beenyup WWTP only on three consecutive days (25/09/07 – 27/09/07). Tertiary treated water samples were also taken after processing through the BPP. While this pilot plant provides water representative of that which will be produced by the GWR trial, it only receives about 140 kL/day of secondary effluent, and produces about 100 kL/day of MF/RO treated water. Sample compositing and preservation were identical to the first sampling event and field and trip blanks were also collected each day.

Standards and Chemicals

The eight ICM analysed in the study were iopromide (IOP) (1-*N*,3-*N*-*bis*(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-1-*N*-methylbenzene-1,3-dicarboxamide) (Bayer Schering Pharma AG, Berlin, Germany), iomeprol (IOM) (1-*N*,3-*N*-*bis*(2,3-dihydroxypropyl)-5-(2-hydroxy-*N*-methylacetamido)-2,4,6-triiodobenzene-1,3-dicarboxamide) (Bracco s.p.a., Milano, Italy), iohexol (IOX) (1-*N*,3-*N*-*bis*(2,3-dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodobenzene-1,3-dicarboxamide), iopamidol (IOD) (1-*N*,3-*N*-*bis*(1,3-dihydroxypropan-2-yl)-5-[(2*S*)-2-hydroxypropanamido]-2,4,6-triiodobenzene-1,3-dicarboxamide), iothalamic acid (ITA) (3-acetamido-2,4,6-triiodo-5-(methylcarbamoyl)benzoic acid), amidotrizoic acid (DTZ) (3,5-diacetamido-2,4,6-triiodobenzoic acid), ioxaglic acid (IXA) (3-[(2-hydroxyethyl)carbamoyl]-2,4,6-

triiodo-5-(2-{[2,4,6-triiodo-3-(methylcarbamoyl)-5-(N-

methylacetamido)phenyl]formamido}acetamido)benzoic acid) and iodipamide (IDP) (3-[[6-(3-

carboxy-2,4,6-triiodoanilino)-6-oxohexanoyl]amino]-2,4,6-triiodobenzoic acid) (United States

Pharmacopeia–USP, Maryland, USA). Methanol and acetonitrile (ChromAR HPLC grade) were

purchased from Mallinckrodt (New Jersey, USA); ammonium formate (purity 99.995%) was

purchased from Sigma–Aldrich (NSW, Australia); formic acid (purity 99%) was purchased from

Ajax FineChem (NSW, Australia). The MQ water used was purified using an IBIS Technology Ion

Exchange System followed by Elga Purelab Ultra System. Disposable syringe filters (Acrodisc®,

0.45μm pore size, 25 mm diameter) were purchased from PALL Life Sciences (NY, USA).

A working solution containing all eight ICM (0.1 μg/μL) was prepared freshly for each analytical

run, and calibration solutions were prepared by serial dilution of this working solution. Calibration

standards for post–RO water are prepared using MQ water, while calibration standards for

secondary wastewater samples are prepared in a representative secondary wastewater.

DI–LC–MS/MS Method

The DI–LC–MS/MS method avoided sample pre–concentration and the only sample preparation

required was filtering (Acrodisc® Syringe Filters 0.45μm) secondary treated wastewater samples

prior to injection in the LC–MS system. All DI–LC–MS/MS measurements were performed using

an Agilent 1100 HPLC system (Palo Alto, CA, USA) equipped with a solvent degasser unit, a

quaternary pump and a 100 well–plate autosampler, coupled to a Micromass Quattro Ultima Triple

Quadrupole instrument (Manchester, UK), fitted with an electrospray interface (ESI) that was

operated in positive ion mode. The method has previously been described in full, [20] including

validation data for both secondary treated wastewater and post–RO water. Quantitation of post–RO

samples was performed using an external calibration curves built in MQ water. To correct for possible matrix effects, quantitation of secondary wastewater samples was performed using standard addition.

Instrumental and/or laboratory contamination were also monitored by regular and methodical analysis of injector and procedural blanks, as well as field and trip blanks collected during sampling. About 33% of total samples analysed were blanks (i.e. trip blanks, procedural blanks and field blanks). The needle of the injector was also rinsed thoroughly before and after each injection to minimise potential carryover. On average after every 100 injections, the guard column was replaced, the analytical column back–flushed with acetonitrile for 60 min, and the mass spectrometer thoroughly cleaned to ensure consistent system performance.

Limits of detection (LODs), calculated from the concentration equivalent to a signal to noise ratio (S/N) of three, ranged between 0.10 (IXA) and 0.58 (ITA) µg/L in post–RO water and between 0.11 (IXA, IDP) and 0.97 µg/L (ITA) in secondary effluent. These LODs enabled easy detection of ICM in secondary wastewater and were suitable for studying the efficacy of MF/RO.

RESULTS

Comparison of ICM in Perth WWTPs

Comparison of ICM concentrations in secondary effluent from Perth's three major WWTPs is shown in Figure 1. The data is presented as average concentrations (µg/L) in samples collected on three days at Woodman Point and two days at Beenyup and Subiaco WWTPs over a four week period (24/05/2007 – 19/06/2007). Data from field and trip blanks are not included, as all results for

these samples were below LOQ.

Iothalamic acid, ioxaglic acid and iomeprol were always lower than the LOQ, while diatrizoic acid was detected only once above LOQ (Woodman point WWTP). Iopamidol, iohexol, iodipamide, and iopromide were always above LOQ, ranging between 0.2–10 μg/L. While Subiaco WWTP showed the highest average concentrations of ICM compared to Woodman Point or Beenyup WWTP, the results were influenced by the exceptionally high concentrations of iopamidol, iohexol and iopromide measured on one day (12/06/07). This may indicate that ICM concentrations can vary within WWTP, related to diurnal variations in discharge within the catchment (i.e. flow rate and quality of the WWTP influent). Additional sampling is required to determine the normal magnitude of variation. Radiological examinations in Perth are carried out at small metropolitan clinics that are evenly distributed over each of the three WWTP catchments, as well as at major hospitals, so it is not unexpected that ICM concentrations are similar at all three WWTP. The ICM showing the highest concentrations was iohexol, which averaged between 4–10 μg/L, confirming that the most commonly used ICM in Western Australia was probably Omnipaque 350, a commercial preparation of iohexol. Other commonly used iodinated contrast media include Ultravist 300 (iopromide) and Iopamiro 370 (iopamidol), [22] which were also simultaneously detected in all the samples analysed in this work. Despite being detected, concentrations measured in secondary treated wastewater were still two to three orders of magnitude lower than those ICM included Australian Guidelines for Water Recycling (Phase 2) [23] (iohexol, iopamidol and iopromide) and lower than ICM concentrations previously reported in European WWTP. [14-16]

Concentration of ICM at BPP

Results from pre–RO (post–MF) water from three consecutive days at BPP are presented in Figure

2. Three ICM were consistently above LOQ in the wastewater – iodipamide (0.7–0.9 µg/L), iohexol (2.3–7.4 µg/L), and iopromide (1.4–2.8 µg/L), while diatrizoic acid was measured above LOQ on two days (1.4–2.5 µg/L). Considering the detection of iopamidol in the first sampling event (Fig. 2), only iothalamic acid, iomeprol and ioxaglic acid were not measured above LOQ at Beenyup. Again, data from field and trip blanks were below LOQ and concentrations measured in the secondary effluent were still two to three orders of magnitude lower than the health guidelines values.

The concentration of ICM in post–RO water from the Beenyup Pilot Plant was always below LOQ and this is consistent with measurements previously presented for the KWRP [20], which also uses MF/RO to produce high quality process water for industrial use. The non–detection of any ICM in post–RO water samples is attributed to the high molecular weight of the ICM, promoting RO membrane rejection of the compounds. Together the results from BPP and KWRP confirm the efficacy of RO for removal of the ICM measured from secondary treated wastewater at these concentrations.

DISCUSSION

A literature survey to determine ICM concentrations reported globally has demonstrated that there are very few studies of ICM that have been published outside of Germany (Table 1). In this context, the results from our study are a valuable addition to the global knowledge base of ICM in secondary wastewater as well as in post–RO treated water. The ICM concentrations we found in secondary wastewater in this study are similar to those reported in other WWTPs, suggesting that dosage and ICMs prescribed are consistent and further confirming that conventional wastewater treatment plants do not effectively remove ICM from raw influent wastewater.

Removal efficiencies for RO can only be estimated from our data because all the compounds were

below detection in post–RO water. However, if we use an upper bound of half the post–RO water LOD, average RO removal efficiencies from the Beenyup Pilot Plant were (± relative standard deviation, usually n = 3): diatrizoic acid 92±3%; iodipamide 94±1%; iohexol 95±2%; iopromide 95±2%. We can compare this RO removal efficiencies calculated using data previously reported for Kwinana Water Reclamation Plant (KWRP), [20] where efficiencies were: diatrizoic acid 96±1%; iodipamide 92±3%; iohexol 95±1%; iopromide 97±1%; iopamidol 97±1%. Removal efficiency was not calculated for those ICMs present in wastewater at concentrations lower than the secondary wastewater LOQ or only slightly greater than the post–RO water LOQ (e.g. iopamidol at Beenyup WWTP and iothalamic acid, ioxaglic acids and iomeprol at both Beenyup and Woodman Point WWTPs). Spiking experiments would be necessary to estimate the actual removal efficiency of the RO treatment, similar to studies already carried out for nanofiltration and microfiltration. [24, 25]

Despite differences in plant size and water use, removal efficiencies for the BPP and KWRP were very similar. Literature concerning removal of ICM by RO plants is very scarce, by our estimated removal efficiencies also compare very well to the estimated removal efficiency of > 90% for iopromide in virgin RO membranes by Snyder and others, [24, 26] and 97% removal efficiency of AOI. [11] To the best of our knowledge, no other studies reporting removal of ICMs by RO plants have been published to date. The high rejection efficiencies observed at the advanced treatment plants were expected on the basis of the high MW of the compounds (600–1300 Da) compared the nominal molecular weight cut–off of the membranes (100–150 Da). [27, 28] Other parameters that play an important role in the rejection mechanisms include compound–specific physico–chemical properties, such as solubility, diffusivity, polarity, hydrophobicity, pKa, and specific membrane properties (e.g., permeability, pore size, hydrophobicity, and charge), as well as membrane operating conditions (e.g., flux, transmembrane pressure, and regeneration). However, studies of iopromide rejection by microfiltration and nanofiltration have significantly lower removal

efficiencies, of <25% and 58% respectively, [25] which indicates size exclusion is the major factor influencing removal.

Because not all the ICM measured in this study are in the AGWR, [23] health values were also calculated using the lowest therapeutic dose from the pharmacopeia (Table 2). The lowest therapeutic dose [23] of each ICM was multiplied by the proportion of the contaminant in water compared to other exposure pathways, assumed to be 90%. A safety factor of 1000 was used to derive the health value (10 for intra–species variability; 10 for using the lowest therapeutic dose instead of the non–observed effect concentration; and 10 for protection of sensitive population subgroups including children and infants). Risk Quotients (RQ) were calculated as the ratio between the maximum reported concentration of each ICM in secondary wastewater and the corresponding health based value (Table 2). For those ICM not detected, the RQ reported was calculated using the average LOQ achieved for the analyte. In secondary effluent, all RQs were 1 to 3 orders of magnitude below 1, even when the maximum concentration was used to calculate the ratio. These results indicate that a very low human risk is anticipated at the concentrations of ICM observed in secondary effluent. Furthermore, in our study ICMs in post–RO water were always lower than LOQ (<0.1–0.58 μg/L) thus 2 to 4 orders of magnitude lower than the health based values. These risk estimates agree with the I_{70} (lifetime intake based on 2L/day water consumption over 70 years) calculated from drinking water intake for a range of ICM used in Germany (i.e. iopamidol, iopromide, ioxaglic acid iothalamic acid and diatrizoic acid). [30] For these compounds I_{70} was between 5×10^2 and 4×10^3 μg, which is 4 to 5 orders of magnitude lower than a single therapeutic dose (approximately 2×10^7 μg).

CONCLUSION

Comparison of ICM in different WWTP showed that average ICM concentration ranged between 1 and 10 μg/L. Iohexol showed the highest average concentrations, up to 10.8 μg/L, while concentrations of the other ICM ranged between 0.1 and 5 μg/L. Iothalamic acid, ioxaglic acid and iomeprol were always lower than the LOQ. Following on from our initial study, [20] the results presented here further confirm that RO is an effective treatment to remove iopamidol, diatrizoic acid, iodipamide, iohexol, and iopromide to below LOQ. The non–detection of any ICM in post–RO treated water samples was attributed to the high molecular weight of the ICM, promoting RO membrane rejection of the compounds, with rejection consistently greater than 92%. While several ICM were measured in secondary treated wastewater, all concentrations were one to three orders of magnitude lower than health based values. Concentrations of ICM in post–RO water were always lower than LOQ (<0.1–0.58 μg/L) thus 2 to 4 orders of magnitude lower than the health based values and therefore represent a very low risk in potable reuse of this water.

ACKNOWLEDGEMENTS

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FIGURE CAPTIONS

Figure 1. ICM concentrations in wastewater samples collected from three Perth metropolitan WWTPs: Subiaco, Woodman Point, and Beenyup WWTP. LOQs for secondary wastewater are also reported for comparison. All data from field and trip blanks were below LOQs and therefore not included.

Figure 2. ICM concentration in pre–RO samples collected from the BPP, Perth WA. LOQs for both wastewater and RO water are also plotted. All data from field and trip blanks and post–RO samples were all below LOQs and therefore not plotted.
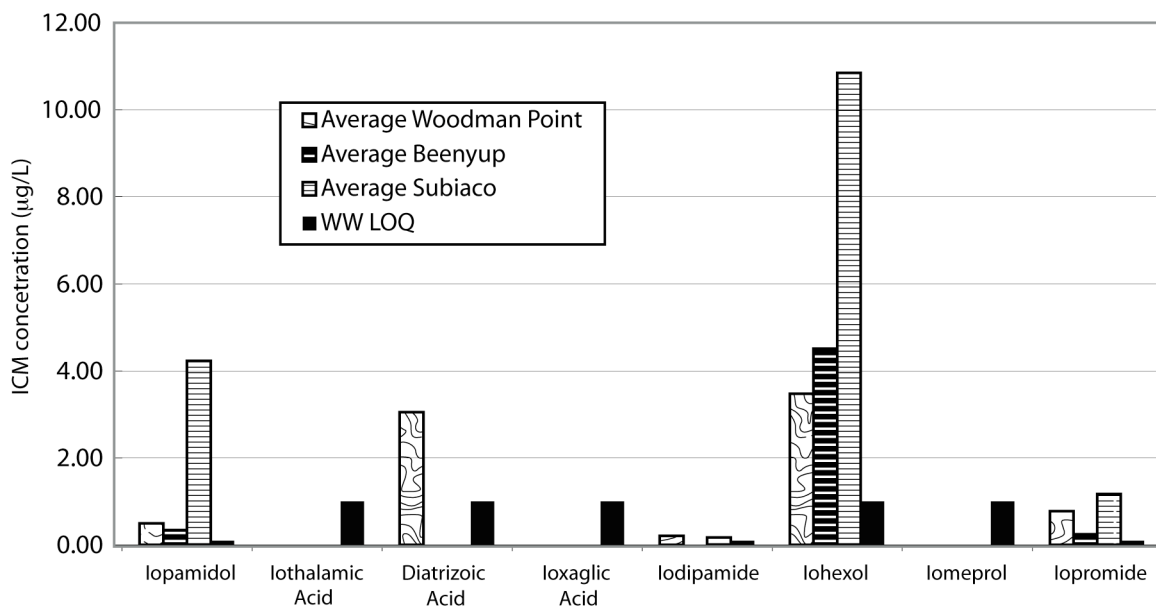
Fig.1
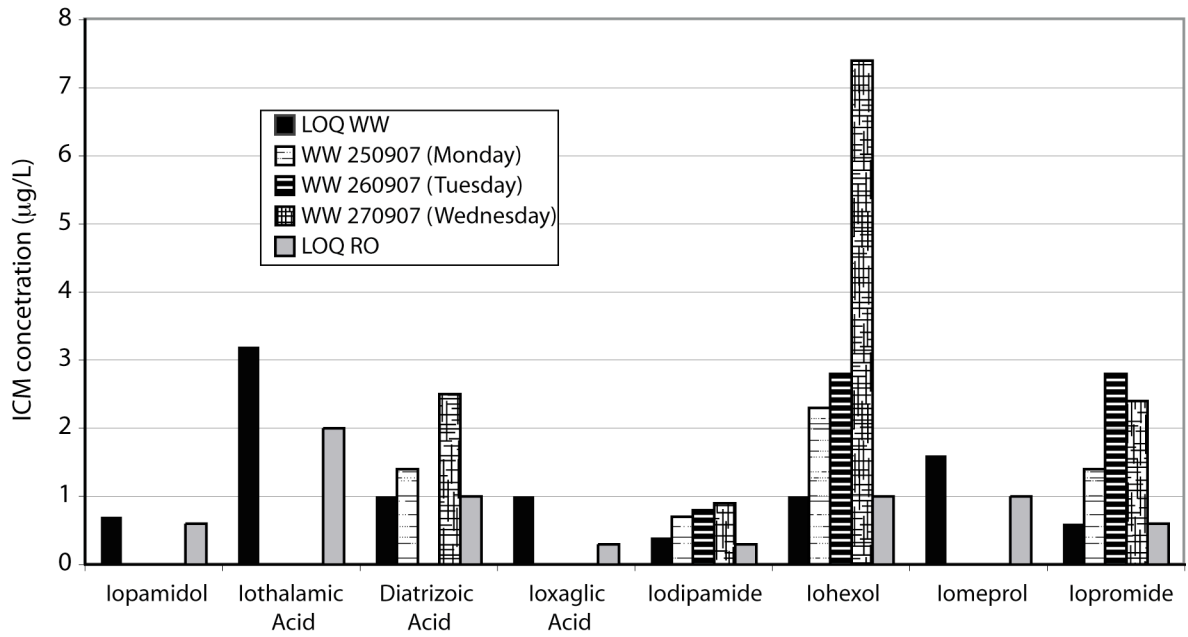
Fig.2

Table 1: Concentration of X–ray contrast media in secondary effluent and post–RO samples from various water treatment facilities. RO rejection is also reported.

Compound	Secondary effluent (µg/L)	Post–RO (µg/L)	RO rejection (%)	Country	Reference
Diatrizoic acid	4.1	n.a.	n.a.	Germany	[9]
	1.1	n.a.	n.a.	Germany	[29]
	15	n.a.	n.a.	Germany	[12]
	5.7	n.a.	n.a.	Germany	[18]
	0.9–4.90	< 0.4	> 96±1	Australia	[20]
	<1–2.5	< 0.3	> 92±3	Australia	*This study*
Iothalamic acid	0.14	n.a.	n.a.	Germany	[9]
	0.09	n.a.	n.a.	Germany	[29]
	< 0.7	< 0.6	n.a.	Australia	[20]
	< 0.9	< 0.3	n.a.	Australia	*This study*
Iopamidol	4.7	n/a	n.a.	Germany	[9]
	0.59	n/a	n.a.	Germany	[29]
	1.1	n/a	n.a.	Germany	[18]
	0.4–0.62	< 0.2	> 97±1	Australia	[20]
	< 0.2	< 0.2	n.a.	Australia	*This study*
Iopromide	9.3	n.a.	n.a.	Spain	[8]
	8.1	n.a.	n.a.	Germany	[9]
	3.1	n.a.	n.a.	Germany	[29]
	21	n.a.	n.a.	Germany	[12]
	5.2	n.a.	n.a.	Germany	[18]
	0.165	< 0.025	> 92*	USA	[24]

	0.125	0.072	> 42**	USA	[24]
	0.43–1.35	< 0.2	> 97±1	Australia	[20]
	1.4–2.8	< 0.2	96±2	Australia	*This study*
Iomeprol	1.3	n.a.	n.a.	Germany	[9]
	2.06	n.a.	n.a.	Germany	[29]
	2.3	n.a.	n.a.	Germany	[18]
	< 0.7	< 0.2	n.a.	Australia	[20]
	< 0.8	< 0.2	n.a.	Australia	*This study*
Iohexol	7	n.a.	n.a.	Germany	[12]
	2.80–4.76	< 0.2	95±1	Australia	[20]
	< 0.5	< 0. 3	n.a.	Australia	*This study*
Iodipamide	0.14–0.23	< 0.1	92±3	Australia	[20]
	0.7–0.9	< 0.1	94±1	Australia	*This study*
Ioxaglic acid	< 0.3	< 0.1	n.a.	Australia	[20]
	< 0.3	< 0.1	n.a.	Australia	*This study*

*RO rejection using virgin membranes; ** RO rejection using fouled membranes

Table 2: ICM guideline limits and Risk Quotients calculated using the maximum reported concentration of each ICM in secondary wastewater.

Compound	Health based value (µg/L)	Risk Quotient
Diatrizoic acid	360	0.04
Iothalamic acid	350	0.0004
Iopamidol	360	0.01
Iopromide	680	0.03
Iomeprol	810	0.003
Iohexol	650	0.01
Iodipamide	540	0.002
Ioxaglic acid	350	0.009