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Limitation of flow effect on passive sampling accuracy using POCIS with the PRC approach or o-DGT: a pilot-scale evaluation for pharmaceutical compounds.

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Abstract

Flow velocity is known to alter passive sampling accuracy. We investigated the POCIS (Polar Organic Chemical Integrative Sampler) with PRC (Performance Reference Compounds) approach and Diffusive Gradients in Thin Films samplers (o-DGT) to limit the effect of flow on the quantification accuracy of ten model pharmaceuticals compounds ($0.16 \leq \log K_{OW} \leq 4.51$). POCIS and o-DGT samplers were exposed for seven days in controlled pilot-scale (hundreds of liters) experiments under quiescent or flowing ($2 < V < 18$ cm s^{-1}) conditions. Under flowing conditions, both POCIS-PRC and o-DGT efficiently limited the flow effect ~~for the other compounds~~ and led, in most cases, to biases within analytical uncertainty (20%). Under quiescent conditions, o-DGT performed accurately (bias < 30% for most compounds) whereas the PRC approach was unsuitable to improve upon the accuracy of POCIS (PRC was unable to desorb). Therefore, both approaches are helpful in limiting the effects of flow on accuracy, but only o-DGT is efficient in quiescent conditions. However, o-DGT currently suffers from poorer sensitivity compared to POCIS, but the future development of o-DGT devices with wider windows could overcome this limitation.

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Keywords

Polar Organic Chemical Integrative Sampler (POCIS)

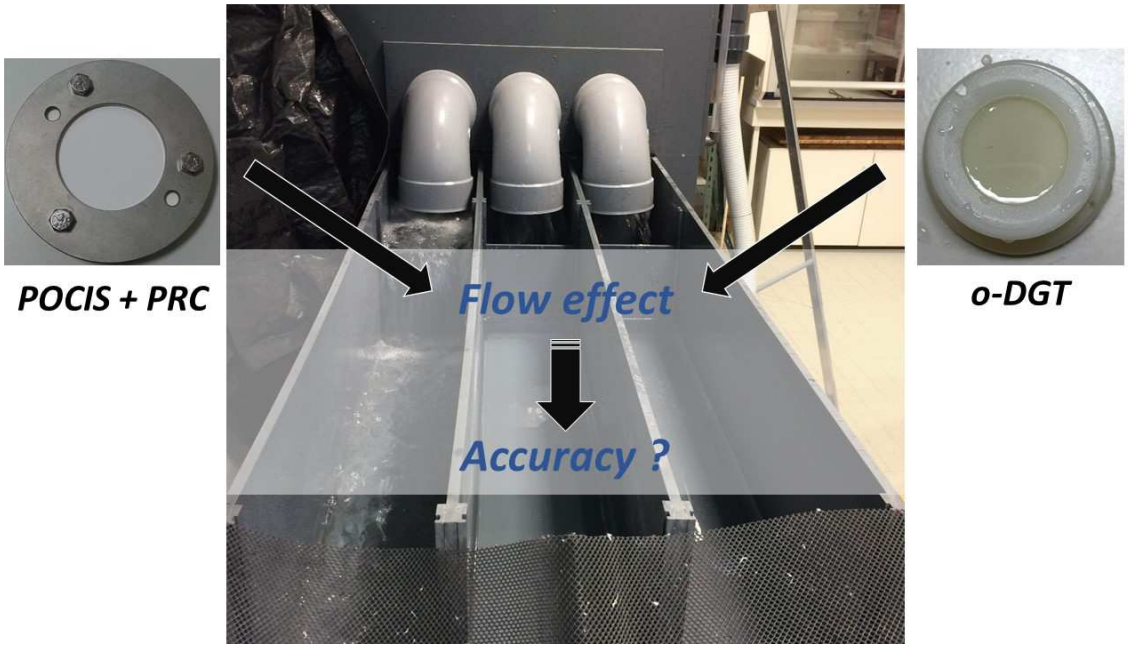
Diffusive Gradients in Thin Films (DGT)

Time-weighted average concentration

Flow velocity

Accuracy

Graphical abstract.



1. Introduction

Passive sampling has been used since 1999 for polar and semi-polar organic micropollutant monitoring in aquatic systems (Stuer-Lauridsen, 2005). Compared to conventional sampling (*i.e.,* grab sampling), passive sampling allows easier access to time-weighted average concentrations and increased sensitivity, thanks to its *in situ* concentration ability. However, passive sampling accuracy is known to be altered by several environmental factors (Gong et al., 2018; Harman et al., 2012; Li et

al., 2011). Among them, flow velocity is of particular concern, and conventional calibrations (*i.e.* determination of sampling rates) under laboratory controlled conditions can lead to more than 100% inaccuracy for field deployments (Poulier et al., 2014). Several strategies have been identified to correct flow effects (Fauvelle et al., 2017). The first one is to establish empirical relationships between sampling rate and flow velocity. This has been done for several polar organic compounds (Li et al., 2010), but these relationships do not allow sampling rate estimations at zero flow. Moreover, correcting for significant flow variations during the samplers' exposure could be tricky with such a strategy. In this context, *in situ* correction is preferable. Performance Reference Compounds (PRC) have been proposed as an *in situ* correction method for the effects of environmental factors, including flow velocity. Initially developed for hydrophobic compounds in Semipermeable Membrane Devices (Huckins et al., 2002), the PRC approach corrects the targeted compound sampling rate relative to the *in situ* desorption rate of a reference compound, assuming isotropic exchange. The PRC approach has been successfully developed for several polar pesticides (Mazzella et al., 2010), but it might not work for all compounds and all exposures (Booij and Chen, 2018; Harman et al., 2011). The last strategy identified is to increase the sampler's membrane resistance to limit the influence of its surrounding conditions. This strategy is implemented in the Diffusive Gradients in Thin Films (DGT) technique, which was initially developed for metals (Davison and Zhang, 1994), was recently adapted for organic compounds (Challis et al., 2016; Chen et al., 2012; Guibal et al., 2017) (o-DGT). Compared to other passive samplers, DGT devices include a diffusive gel (typically 0.8 mm thick) that constrains mass transfer mostly to the diffusion rate within the gel (Davison and Zhang, 2012). However, this tool is ~~however~~ not totally independent of flow velocity, as previously shown for metals (Gimpel et al., 2001). In fact, under low flow conditions, a significant diffusive boundary layer (DBL) is created in front of the sampler (Challis et al., 2016), altering the diffusion path to be considered. Although promising, all of these strategies have limitations. Their implementation is limited in the literature, and data on their efficiency are too scarce to provide guidance for choosing a relevant strategy to correct flow effects.

This work focuses on the implementation of PRC with POCIS (Polar Organic Chemical Integrative Sampler) and o-DGT for correcting the effects of flow on the passive sampling of ten model pharmaceuticals compounds ($0.16 \leq \log K_{OW} \leq 4.51$). POCIS and o-DGT samplers were submitted to different flow velocities in controlled pilot-scale (hundreds of liters) experiments. The accuracy of the different strategies (POCIS without correction, POCIS with PRC and o-DGT) was evaluated for quiescent and flowing conditions.

2. Material and methods

2.1. Chemicals

A Gradient A10 Milli-Q system from Millipore produced ultra-pure water (UPW). Unless stated otherwise, all solvents were of LC–MS grade and reagents of analytical grade. The following pharmaceuticals were used and had a purity greater than 97%: atenolol (ATE), carbamazepine (CAR), diclofenac (DIC), fluoxetine (FLU), ketoprofen (KET), metoprolol (MET), paroxetine (PAR), propanolol (PRO), sulfamethoxazole (SUL) and trimethoprim (TRI). Stock pharmaceutical solutions (100 mg L^{-1}), working solutions (containing each pharmaceuticals at 1 mg L^{-1}) and internal standard solutions (10 mg L^{-1}, presented in Table 1) were prepared in methanol and stored at -18 C. Deuterated atrazine desisopropyl (DIA-d5) was used as PRC for POCIS samplers.

Table 1: Pharmaceuticals characteristics after HPLC separation and mass detection and internal standards used.

Pharmaceutical	Log K_{OW}	Retention time (min)	Mass (g mol-1)	Internal standard
Atenolol	0.16	2.32	266.1630	Salbutamol-d3
Carbamazepine	2.45	7.70	236.0950	Carbamazepine-d10
Diclofenac	4.51	9.07	295.0167	Diclofenac-d4
Fluoxetine	4.05	7.88	309.1341	Carbamazepine-d10
Ketoprofen	3.12	8.08	254.0943	Diclofenac-d4

Metoprolol	1.88	6.52	267.1834	Carbamazepine-d10
Paroxetine	1.23	6.69	329.1427	Carbamazepine-d10
Propanolol	3.48	7.30	259.1572	Propanolol-d3
Sulfamethoxazole	0.89	5.86	253.0521	Sulfamethoxazole-d4
Trimethoprim	0.91	4.75	290.1379	Trimethoprim-d3

2.2. Description of pilots

Control of experimental conditions is required to isolate the effects of flow. Pilot scale experiments offer the best method to mimic field conditions while maintaining experimental control. Two pilots were used to mimic the flow conditions a passive sampler is exposed to: an artificial river and a tank (Figure S1). The tank (200 L) was used to simulate a quiescent system (V_0 = 0 cm s^{-1}). The artificial river (500 L) was fed with a pump (flow rate = 13 m^3 h^{-1}) and divided into 3 channels (20.3 cm width and 152 cm length) with different flow velocities using a gate system. The mean velocities measured during exposures were V_1 = 2.5 ± 1.2 cm s^{-1}; V_2 = 6.3 ± 1.0 cm s^{-1} and V_3 = 17.5 ± 2.1 cm s^{-1} (n=8). Temperature was recorded every 10 min using a Tinytag temperature logger (TG-4100) and were 17±2°C and 15 ± 1°C during POCIS and o-DGT exposure, respectively.

All pilots were fed with tap water (composition shown in Table S1) spiked with the 10 pharmaceutical compounds at an initial concentration of 0.5 µg L^{-1} each. Continuous renewal of the water was performed at a rate of 15% volume per day. Water samples were taken four times during each experiment (at the beginning and after 3, 5 and 7 days) for pharmaceutical analysis (average concentrations are displayed in Table S2). A total of 100 mL of sample was filtered, adjusted to pH 7 and spiked with 10 µL of surrogates (simazine-d5, monuron-d6 and prometryn-d6) to identify any loss during the extraction step. Water samples were then transferred to SPE cartridges (Chromabond® HR-X; 60 mg, 3 mL 85 µm, preconditioned with 5 mL of methanol then 5 mL of UPW)

using a GX-241 automated system from Gilson. Water sample cartridges were finally dried and stored at -18°C before extraction.

2.3. Passive sampler preparation and exposure

POCIS were prepared by enclosing 200 mg of Oasis® HLB receiving phase within two polyethersulfone (PES) membranes, held by two stainless steel rings (20.5 cm^2 window). The Oasis® HLB was previously spiked with 4 µg g^{-1} of DIA-d5 (PRC) (Mazzella et al., 2010), and the PES membranes (90 mm diameter and 0.1 µm pore size from Pall Corporation) were previously washed according to Guibal et al. (2015). Duplicate POCIS were exposed parallel to the flow for 7 days at each flow velocity. Potential re-adsorption of PRC was checked using duplicate of POCIS blank (without PRC) exposed alongside the POCIS with PRC and was found to be insignificant (<1%). After exposure, POCIS were dismantled and the receiving phases were transferred to SPE cartridges for extraction. The exact mass of the receiving phase recovered for extraction was determined for estimation of compound concentration in water.

o-DGT samplers were prepared by enclosing a disc of binding gel and of diffusive gel in a piston type holder (3.14 cm^2 window, purchased from DGT Research). Gels were prepared according to Challis et al. (2016) and were composed of Oasis® HLB receiving phase embedded in 1.5% agarose gel (25 mg Oasis® HLB per disc, nominal) and 1.5% agarose gel only for the binding and diffusive gels, respectively. Diffusive gels were prepared with four different thicknesses: 0.16, 0.41, 0.61 and 0.84 mm (RSD $\leq$ 1.5%, n=4). Triplicate o-DGT samplers of each thickness were exposed parallel to the flow for 7 days at each flow velocity. After exposure, o-DGT samplers were dismantled and binding gel discs were recovered for extraction.

2.4. Pharmaceutical extraction and analysis

POCIS and water sample cartridges were eluted with 3 mL of methanol followed by 3 mL of a mixture of 75:25 *v:v* methanol:ethyl acetate. After elution, ten µL of a solution with internal standards were added to the water extracts. Extracts were then evaporated to dryness under

125 nitrogen flow and then reconstituted with 1 mL of methanol for POCIS extracts or 90:10
126 UPW:methanol for water extracts. POCIS extracts were diluted 10 times, and 10 µL of internal
127 standards solution was added.
128 o-DGT binding gel discs (containing Oasis® HLB receiving phase) were extracted with 3x3 mL of
129 methanol under sonication (210 W for 2 minutes). Extracts were spiked with 10 µL of internal
130 standards solution and evaporated to dryness under nitrogen flow. Extracts were finally
131 reconstituted with 1 mL of 90:10 UPW:methanol.
132 All samples were analyzed with an HPLC Infinity 1290 coupled with a Q-ToF 6540 equipped with
133 a Jet Stream electrospray ionization source (Agilent). The procedure is fully detailed in Guibal et al.
134 (2018). Briefly, chromatographic separation was performed with a RP18+ Nucleoshell column
135 (Macherey-Nagel), and UPW and methanol (with 5 mM ammonium formate and 0.1% acid formic for
136 both) were used as eluent during a 16 min analytical gradient. Autosampler and column
137 temperatures were kept at 4°C and 30°C, respectively. Mass acquisition was operated in the "all-
138 ions" positive mode (collision energies: 0, 10, 20 and 40 V). QA/QC was used to control any
139 deviations during analysis. Pharmaceutical characteristics after HPLC separation and mass detection
140 are displayed in Table 1 and analytical performances in Table S3.

141 ## 2.5. Exposure concentration estimation

142 Time-weighted average concentrations for the pilots (C_w) were estimated using both POCIS
143 and o-DGT. Two kinds of estimations were done: a "standard" and an "advanced" estimation (see
144 details below). The "standard" estimation aims to represent a routine estimation and was performed
145 with simple and widespread strategies (devices and data treatment) from literature. The "advanced"
146 determination was performed using more sophisticated strategies from the literature that are
147 believed to correct for flow effect.

2.5.1. Estimation based on POCIS

The "standard" estimation of C_W based on POCIS (n=2) was performed using Eq. 1 (Alvarez et al., 2004):

$$C_w = {}^{m}/_{R_S t} \quad (1)$$

where m is the accumulated mass of compound in the sampler, R_S is the sampling rate, and t is the deployment time. For routine purposes, dedicated calibrations are not conceivable, and R_S values must be taken from the literature. For a given compound, the most relevant value (*i.e.,* adequacy between calibration conditions and our study's conditions) was chosen from literature, among references using a similar POCIS configuration (200 mg Oasis® HLB) (Table S4). We considered R_S values only if linear velocity or quiescence was specified. Then, we kept the R_S determined with the closest flow velocity from our pilot study. When several values matched this criterion, we considered the relevance of water matrix or doping level.

The PRC approach was used as an "advanced" procedure to correct R_S values for flow effects. DIA-d5 was selected as PRC (Carpinteiro et al., 2016; Li et al., 2018a; Mazzella et al., 2010), and corrections were made using the procedure detailed in Mazzella et al. (2010). Briefly, the elimination rate constant of DIA-d5 (k_{ePRC}) was determined for each flow velocity, and a corrected sampling rate (R_S^{cor}) was calculated using Eq. (2):

$$R_S^{cor} = R_S^{ref} \times \left(\frac{k_{ePRC}}{k_{ePRC}^{ref}} \right) \quad (2)$$

where R_S^{ref} and k_{ePRC}^{ref} are the sampling rate and the PRC elimination rate constant, respectively, for the reference condition. The highest flow velocity (V_3 = 17.5 ± 2.1 cm s^{-1}) was taken as the reference condition and sampling rates determined in this condition (R_S^{ref}) are presented in Table S5. C_W was finally calculated using R_S^{cor} in Eq. 1.

2.5.2. Estimation based on o-DGT

The "Standard" estimation of C_W was based on o-DGT samplers equipped with 0.84 mm diffusive gels (n=3) and performed using Eq.3 (Zhang and Davison, 1995):

$$C_w = \frac{m\Delta_g}{A_g t \mathrm{D}} \qquad (3)$$

where m is the accumulated mass of compound in the sampler, Δg is the diffusive gel thickness, D is the diffusion coefficient in the diffusive gel, A_g is the geometric exposure area (3.14 cm^2), and t is the deployment time. D values were taken from Challis et al(Challis et al., 2016) and corrected for temperature (T) using the Stokes-Einstein equation (Eq.4) where η is the water viscosity (taken from Lemmon et al., NIST chemistry WebBook):

$$\frac{D_1 T_1}{\eta_1} = \frac{D_2 T_2}{\eta_2} \qquad (4)$$

The "advanced" estimation of C_W was made using a more sophisticated model (Eq.5, Santner et al., 2015) that considers the thickness of the DBL (δ) and lateral diffusion within the sampler:

$$C_w = \frac{m}{k_{ld} A_g t}\left(\frac{\Delta_g}{D} + \frac{\delta}{D_w}\right) \qquad (5)$$

where k_{ld} is the lateral diffusion flux increase coefficient (calculated according to Santner et al., 2015), and D_w is the diffusion coefficient in water (modeled using the Hayduk-Laudie equation described in Schwarzenbach et al., 1993). C_W was estimated alongside δ through direct adjustment of Eq.5 with Statistica software (version 6.1, Statsoft) on the full set of exposed o-DGT (*i.e.,* triplicate samplers equipped with 0.16; 0.41; 0.61 or 0.84 mm diffusive gels). δ values are displayed in Table S6.

2.5.3. Performance of passive samplers

To discuss the accuracy on time-weighted average concentrations in pilots estimated using passive samplers, the average measured concentration determined on grab samples was taken as the reference concentration. The performance of passive samplers is consequently discuss through the comparison of C_w values determined with a given passive sampling procedure (C_w^{PS}; *i.e.* POCIS or o-DGT and "standard" or "advanced") and the corresponding concentration determined with grab sampling (C_w^{GS}). Given that C_w^{GS} were not identical for POCIS and o-DGT exposure and for V_0 and $V_{1\text{-}3}$ flow velocities, the comparison between passive sampling procedures and flow velocities is made on the normalized value of C_w^{PS} to C_w^{GS} for clarity.

198 # 3. Results and discussion

199 ## 3.1. POCIS C_w estimation without PRC

200 Normalized water concentrations determined using POCIS sampling with R_s from literature
201 ("standard" procedure) are presented in Figure 1. Except for diclofenac, concentration differences
202 with grab sampling were lower than 140%, which agrees with the 138% uncertainty reported by
203 Poulier et al. (2014) during field deployment for pesticide monitoring. The important concentration
204 differences reported for diclofenac indicate that the R_s values chosen were not relevant for our
205 system. Considering that these values (Di Carro et al., 2014) were determined in conditions very close
206 to our study (flow velocities, doping level, water matrix and temperature), the R_s robustness for this
207 compound appears low. For the other compounds, concentration difference with grab sampling was
208 lower than 100% in non-quiescent conditions ($V_{1\text{-}3}$) with few exceptions (atenolol V_1 and V_2,
209 ketoprofen V_2). Moreover, most of concentration differences were between 50 and 75% (normalized
210 values between 0.25 and 0.5). These differences are higher than analytical uncertainty (typically 20%)
211 and probably arise from discrepancies between calibration conditions and our studied system,
212 although the R_s values were selected with the aim of limiting such discrepancies. Among them, flow
213 velocity could be of concern but other parameters should not be excluded. Positioning of the POCIS
214 (*i.e.,* parallel or perpendicular to flow) will affect hydrodynamics but is rarely indicated in the
215 literature. When considering quiescent conditions only (V_0), estimations were satisfactory
216 (concentration differences $\leq$ 57%, except sulfamethoxazole). Good performance for this condition
217 probably arose from the ease of choice for R_s, since calibrations in quiescent conditions were
218 available for each studied compound. This highlight the necessity, for the accurate use of POCIS, to
219 utilize calibrations performed in conditions very similar to the studied system.

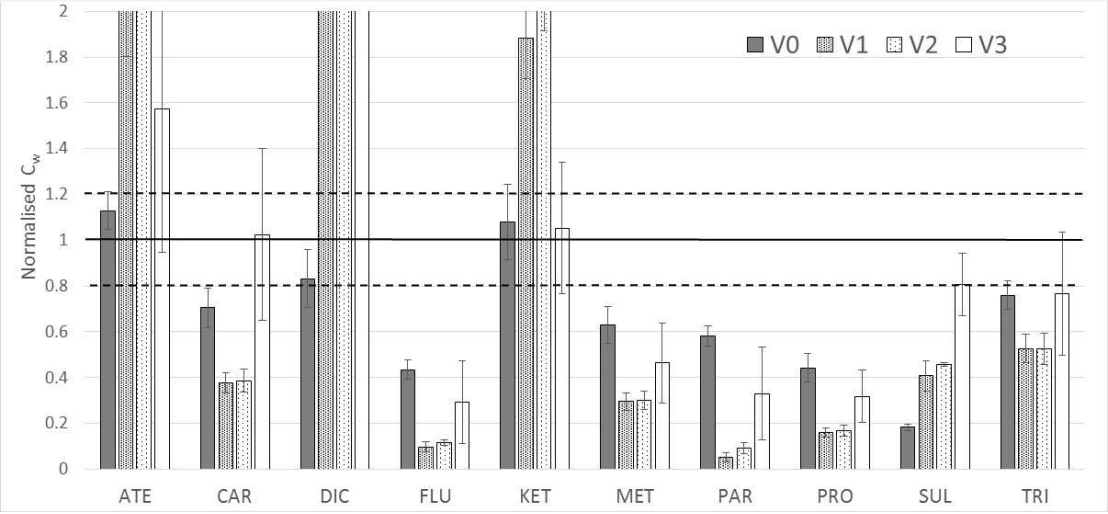


Figure 1: Mean C_w concentration (± SD) determined with POCIS and the "standard" procedure normalized to concentration determined with grab sampling. Flow velocities V_0, V_1, V_2 and V_3 were 0, 2.5, 6.3 and 17.5 cm s^{-1}, respectively. Dashed lines indicate typical analytical uncertainty (i.e. 20%). Values reach 2.2 and 2.4 for ATE at V_1 and V_2, respectively; 2.5, 3.4 and 4.5 for DIC at V_1, V_2 and V_3, respectively; 2.1 for KET at V_2.

3.2. PRC approach for POCIS

DIA-d5, proposed as a PRC for POCIS samplers (Mazzella et al., 2010), was investigated to correct C_w estimations for flow variations. For quiescent conditions (V_0), no PRC desorption from POCIS could be quantified (k_e~0). ~~This approach is therefore not suitable for quiescent systems.~~ For non-quiescent conditions, k_e values were 0.024, 0.031 and 0.046 d^{-1} for V_1, V_2 and V_3, respectively. These values are in the same range with values found in the literature: 0.034 d^{-1} (Carpinteiro et al., 2016), 0.044 d^{-1} (Belles et al., 2014), 0.046 d^{-1} (Li et al., 2018a) and 0.057 d^{-1} (Mazzella et al., 2010). However, the value of Mazzella et al. (2010) is twice the magnitude as the value we determined at the same flow velocity (V_1; 2-3 cm s^{-1}). This discrepancy possibly arose from the different exposure duration used to determine each value (*i.e.* 7 days in this study *versus* 28 days in Mazzella *et al.* study).

Normalized water concentrations determined using POCIS sampling with the PRC approach are displayed in Figure 2. For the reference condition (V_3) concentration differences with grab sampling were ≤ 31% except for sulfamethoxazole (51%). Values are consistent with target analytical accuracy (typically 20%) and highlight the adequacy of the reference sampling rate (R_s^{ref}) for the studied

system. This not surprising given that R_S^{ref} were determined using the same pilot and identical conditions as this study.

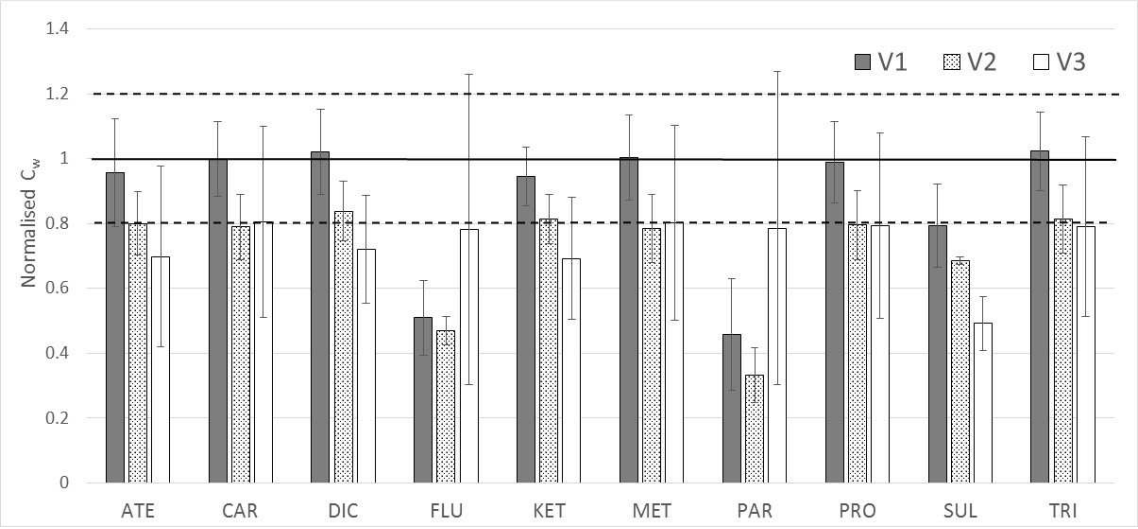


Figure 2: Mean C_w concentration (± SD) determined using POCIS with PRC normalized to concentration determined with grab sampling. Dashed lines indicate typical analytical uncertainty (i.e. 20%). No value could be calculated for quiescent condition (V_0) because there was no PRC desorption.

Compared to C_w estimation without correction of R_S^{ref}, C_w estimations with PRC correction was closer from estimation with grab sampling of approximately 25-30% at V_2 and of approximately 40-50% for V_1 (Figure S2). The use of the PRC approach to correct sampling rate for flow discrepancy allows therefore improving water concentration estimation. Compared to the reference condition (V_3), the PRC approach allowed similar accuracy for V_2 and improved accuracy for V_1 except for fluoxetine and paroxetine (Figure 2). The PRC approach appears to be a useful technique to handle flow discrepancies between POCIS calibration and field application for several compounds, consistent with the findings of the Mazzella et al. (2010) study. However, PRC correction was less efficient for fluoxetine and paroxetine. This in agreement with Booij and Chen (2018) or Harman et al. (2011) who stressed that the PRC approach has some limitations and might not work for all compounds.

It has been suggested that the use of DIA-d5 as a PRC might be limited to deployment times shorter than 15 days (Booij and Chen, 2018). Given that our results were obtained following 7 days deployment times, the efficiency of the PRC approach was further investigated for 15 and 21 days deployment times (Figure S3). Considering non-quiescent conditions only (V_{1-3}), no differences were

found for carbamazepine, diclofenac, ketoprofen, metoprolol, propanolol and trimethoprim between C_w estimated with 7, 15 and 21 days of deployment. For atenolol, fluoxetine, paroxetine and sulfamethoxazole, some differences were observed between C_w estimated with the different exposure times. However, given that part of these differences were almost the same between the reference condition (V_3, no PRC correction possibility) and the other conditions (V_{1-2}, PRC correction applied), these differences can be only partly a consequence a potential time-related limitation of the PRC correction. PRC correction efficiency appears therefore only little affected by the deployment time and the above conclusion for 7 days deployments might hold for more typical deployments (*i.e.* 2-3 weeks). Considering quiescent conditions, significant desorption of DIA-d5 was observed for 15 and 21 days deployments, enabling PRC correction. Although efficiency of the PRC correction increased with deployment time, C_w estimation with POCIS was never found to match C_w estimation with grab sampling. Discrepancies between POCIS and grab sampling estimations were about 50-80% and 40-70% for 15 and 21 days deployments, respectively. Therefore, in quiescent conclusion, efficiency of the PRC correction will depend on the deployment time but will never allow full correction of flow effect for typical field deployments (*i.e.* 2-3 weeks).

3.3. C_w estimation with o-DGT

Figure 3 presents normalized water concentrations determined using o-DGT sampling with the "standard" procedure, ~~except for clarithromycin, erythromycin, gemfibrozil and roxithromycin (discussed at the end of the section)~~. When the system was not quiescent (*i.e.,* $2 \leq V_{1-3} \leq 18$ cm s^{-1}), concentration difference with grab sampling was <50% for any compound. Given that most differences were in the same range of the analytical accuracy (typically 20%), o-DGT accuracy appears little affected by flow conditions between 2-18 cm s^{-1}. These results are in accord with previous studies on metals (Davison and Zhang, 2012; Gimpel et al., 2001). When the system was quiescent (V_0= 0 cm s^{-1}), the concentration difference with grab sampling was increased for all compounds and reached between 28% (ketoprofen) and 70% (paroxetine). This altered accuracy has

previously been described for metals (Davison and Zhang, 2012) and is attributed to the formation of a significant diffusive boundary layer in front of the sampler that increases the diffusion path of compounds. Inaccuracies consequently arise from the simplicity of Eq. 3, which does not account for this diffusion path increase.

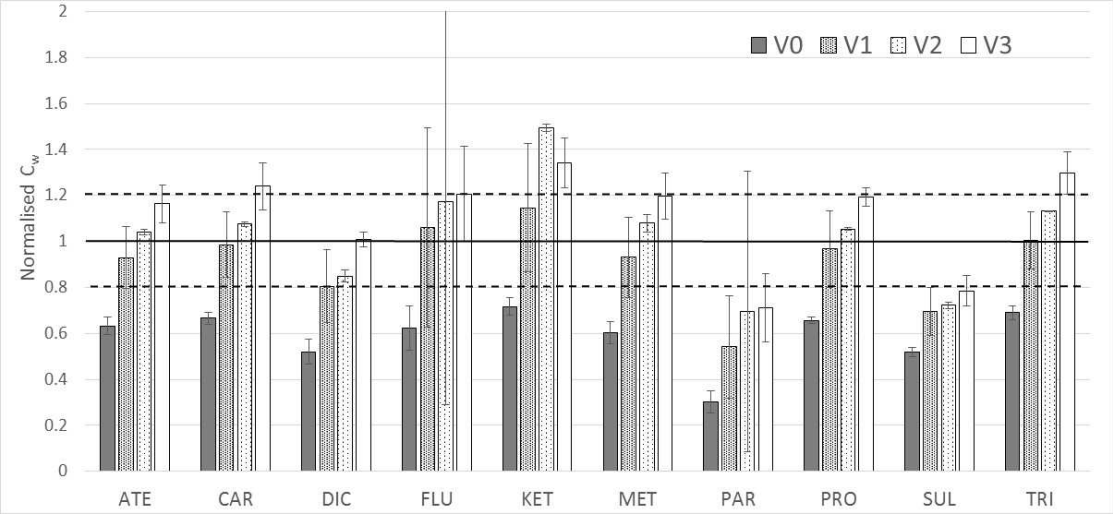


Figure 3: Mean C_w concentration (± SD) determined with o-DGT and the "standard" procedure normalized to concentration determined with grab sampling. Dashed lines indicate typical analytical uncertainty (i.e. 20%).

Similar to what is done for metals (Garmo et al., 2006), such inaccuracy could be limited by use of the "advanced" procedure based on the deployment of samplers with various diffusive gel thicknesses and data treatment with a model that considers DBL formation (Eq. 5). Normalized water concentrations determined with this procedure are displayed in Figure S4. Surprisingly, when the system was not quiescent ($V_{1\text{-}3}$), in most cases the "advanced" procedure produced higher concentration differences between C_w estimations based on grab and o-DGT sampling compared to the "standard" procedure (the example of V_2 is displayed in Figure 4). This indicates a limitation of the model that might arise from the inaccuracy of its input parameters. Indeed, the lateral diffusion flux increase coefficient (k_{ld}) was initially established for phosphates (Santner et al., 2015) that have a greater ability to diffuse (*i.e.,* higher diffusion coefficients) compared to the studied pharmaceuticals. D_w might also be questioned since values were estimated with an empirical model (Schwarzenbach et al., 1993). Conversely, for a quiescent system (V_0), the "advanced" procedure led to better C_w estimations except for fluoxetine, ketoprofen and paroxetine, which have similar levels of accuracy

when calculated with the "standard" procedure (Figure 4). The "advanced" procedure allows estimations within analytical uncertainty (<20%) except for diclofenac (29%), fluoxetine (47%), ketoprofen (29%) and paroxetine (73%). Therefore, the "advanced" procedure appears to be promising for producing accurate estimations in quiescent systems.

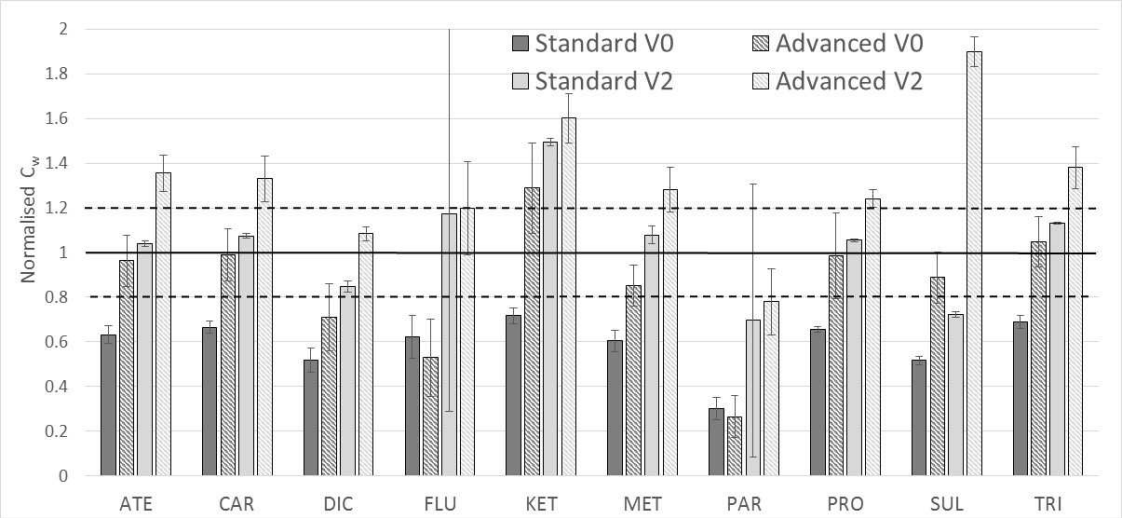
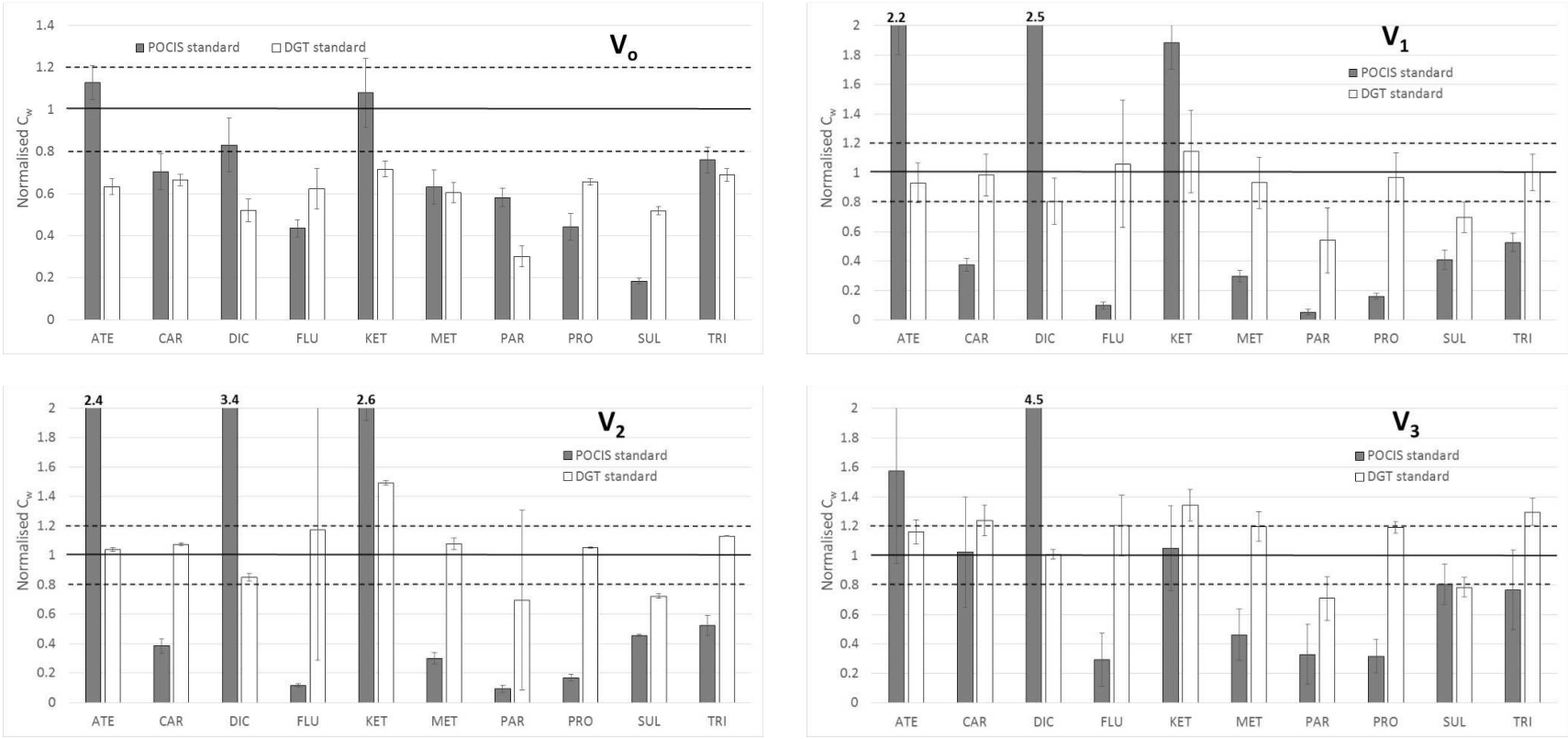


Figure 4 : Mean C_w concentration (± SD) determined for V_0 and V_2 flow velocities using o-DGT with "standard" or "advanced" procedure normalized to concentration determined with grab sampling. Dashed lines indicate typical analytical uncertainty (i.e. 20%).

3.4. Comparison of POCIS and o-DGT



316 *Figure 5: Mean C_w concentration (± SD) determined using POCIS or o-DGT (both with "standard" procedure) normalized to concentration determined with grab sampling. Dashed lines indicate*
317 *typical analytical uncertainty (i.e. 20%).*

318

For routine water surveys, simple procedures are required, and “standard” procedures are likely to be used. In this context, o-DGT shows better accuracy (Figure 5) in non-quiescent conditions (V_{1-3}) with some exceptions for V_3 where accuracy is similar (carbamazepine, ketoprofen, sulfamethoxazole and trimethoprim). Quiescent conditions (V_0) led to more varied results (Figure 5). POCIS was more accurate for atenolol, diclofenac, ketoprofen and paroxetine whereas o-DGT was more accurate for fluoxetine, propranolol, and sulfamethoxazole. Both tools performed similarly for carbamazepine, metoprolol and trimethoprim. For routine purposes, this study currently supports the use of o-DGT to limit the effect of flow in non-quiescent conditions, whereas in quiescent conditions, the choice depends on the target compounds.

In cases where the use of more sophisticated procedure is conceivable, estimations can be improved with the “advanced” procedure using PRCs. For non-quiescent conditions, o-DGT performance was already close to the analytical accuracy (typically 20%) and no improvement over the “standard” procedure was required. For POCIS, the use of DIA-d5 as a PRC was required to obtain similar accuracies for most of the studied compounds. However, this approach was less efficient for fluoxetine and paroxetine. In quiescent conditions, o-DGT estimations were improved with the “advanced” procedure for most compounds (Figure 4). Given that in quiescent conditions PRC was unable to desorb for 7 days deployment time, o-DGT estimations with the “advanced” procedure were compared to POCIS with the “advanced” procedure (PRC approach) using 21 days deployment time (Figure 6). For atenolol, carbamazepine, metoprolol, propranolol, sulfamethoxazole and trimethoprim, C_w estimations based on o-DGT were closer from estimation based on grab sampling, compared to estimation based on POCIS. O-DGT and grab sampling estimation were even identical when considering analytical uncertainty. For diclofenac, fluoxetine, ketoprofen and paroxetine, o-DGT and POCIS showed similar performances with the advanced procedure in C_w estimation.

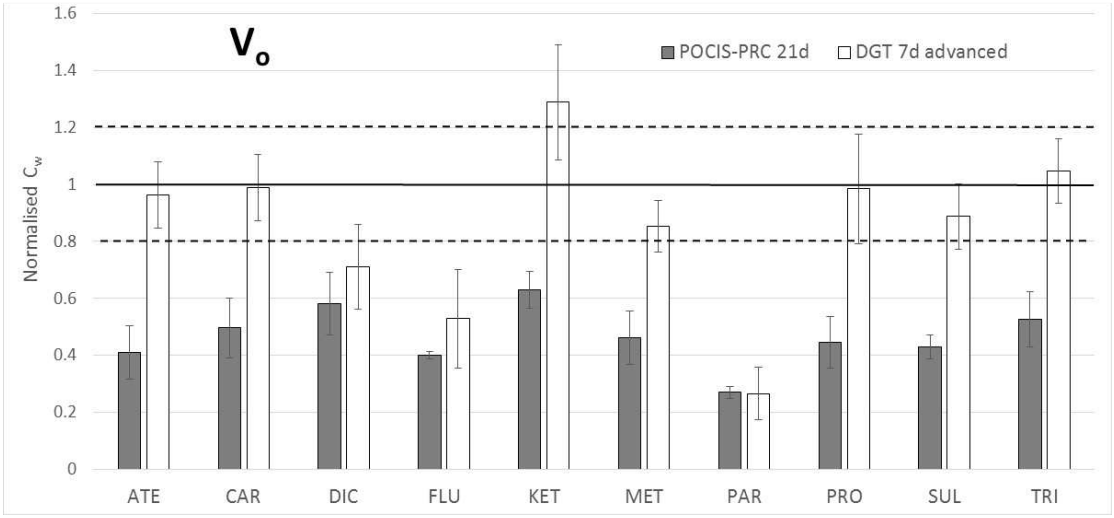


Figure 6: Mean C_w concentration (± SD) determined for V_0 using POCIS (21 days deployment with PRC) and o-DGT (7 days deployment with "advanced" procedure) normalized to concentration determined with grab sampling. Dashed lines indicate typical analytical uncertainty (i.e. 20%).

Overall, if implementation of the PRC approach is conceivable for POCIS, flow effects will be limited for both POCIS and o-DGT and each will perform with accuracies within acceptable analytical error (<20%) for most of the studied compounds. However, only o-DGT currently achieves such accuracy in quiescent conditions. Nevertheless, an important advantage of POCIS compared to o-DGT is its higher sampling rates, especially at high flow velocities (Table S7), resulting in a greater POCIS sensitivity. Although a recent comparison of POCIS and o-DGT showed similar detection frequencies in four freshwater systems (Challis et al., 2018), lower sensitivity of o-DGT (up to 67 times for fluoxetine) may be an issue for some compounds depending on the targeted system contamination. POCIS use may be therefore preferred in such context. The choice of strategy to limit flow effects will be driven by the study constrains in terms of sensitivity, accuracy and flow conditions. If sensitivity is favored (*e.g.,* low-contaminant systems), then POCIS with PRC should be chosen. Conversely, if sensitivity is not a limiting constraint (*e.g.,* contaminated systems), both POCIS with PRC or o-DGT can be chosen. However, if quiescent (or nearly quiescent) conditions are expected, then o-DGT should be chosen to achieve better accuracy. Anyway, it must be stressed, that flow velocity is not the only condition that affects passive sampling in aquatic systems (*e.g.,* pH, temperature, biofouling), and the above recommendations may be reconsidered in the future.

3.5. Future improvements

For a given sampler, different behaviors were observed among the studied compounds and some failures were identified whatever the sampler used. For POCIS, correction with DIA-d5 as PRC was not fully satisfactory for fluoxetine and paroxetine. Therefore, more suitable PRCs still have to be identified for these two compounds. Indeed, Li et al. (2018b) identified very recently Antipyrine-d3 as a promising PRC for pharmaceuticals compounds. Furthermore, when many compounds are targeted, simultaneous implementation of several PRCs will probably be required for extensive flow effect correction.

For any study, it may be of interest to limit the number of tools required and the complexity of procedures used. However, given that each sampler has limitations, improvements are required to generalize the use of one sampler. A current limitation of POCIS is accuracy in quiescent conditions because of limitation of the PRC approach. Improving POCIS accuracy in quiescent systems will require the development of a PRC able to desorb in this condition or the development of a new strategy. Therefore, further improvements on POCIS are currently speculative. Conversely, several improvements can be proposed for o-DGT. First, decreasing biases in quiescent systems to allow accurate use of the "standard" procedure could be achieved with an increase in diffusive gel thickness. Using thicker gel will result in limiting the impact of DBL formation on the diffusion path and therefore limit the inaccuracy of Eq. 3. It was estimated (Table S8) that using 2.5-mm-thick diffusive gels and the "standard" procedure would allow achieving accuracies better than 25% in quiescent systems. However, such gel thickness increase will also alter o-DGT method sensitivity by a 2.8 factor because of the length increase of the diffusion path. Second, the lack of sensitivity of o-DGT compared to POCIS could be overcome. Sensitivity differences are a consequence of sampling rate differences (Table S7). This difference was previously demonstrated for several antibiotics (Chen et al., 2013) and anionic pesticides (Guibal et al., 2017) to be largely due to sampling area difference. Therefore, increasing the sampling area of o-DGT should result in increased sampling rates (Eq. S1 and S2) and higher sensitivity. It can be calculated (Table S9) that a 160 cm^2 sampling area (~7 cm

radius) should allow sampling rates not lower than conventional POCIS ones (except for fluoxetine and ketoprofen), even if gel thickness is increased for quiescent systems. This design would result in similar sensitivity compared with POCIS. Such a theoretical o-DGT configuration must be tested in the field, since physical constrains on these larger gels could be significant.

4. Conclusions

Both POCIS with PRC approach and o-DGT were shown to limit flow effect on passive sampling accuracy. However, none of these approaches is currently universal and each one have some drawbacks. Therefore, before choosing an approach, preliminary validation on the targeted compounds and deployment conditions is advisable. Limitation of flow effect using both approaches was not fully satisfactory for all compounds. To overcome these limitations, it will require improvement of calibrations for both samplers and development of new PRCs for POCIS. Therefore, future improvements are probably more speculative for POCIS than for o-DGT samplers. The o-DGT approach has probably a better potential to allow in the future limitation of flow effect on a wide range of compounds. Conversely, POCIS samplers already propose better sensitivity compared to o-DGT samplers. Therefore, unless new designs allowing better sensitivity of o-DGT samplers are proposed and validated, POCIS samplers could still be preferred for micropollutants monitoring in natural systems.

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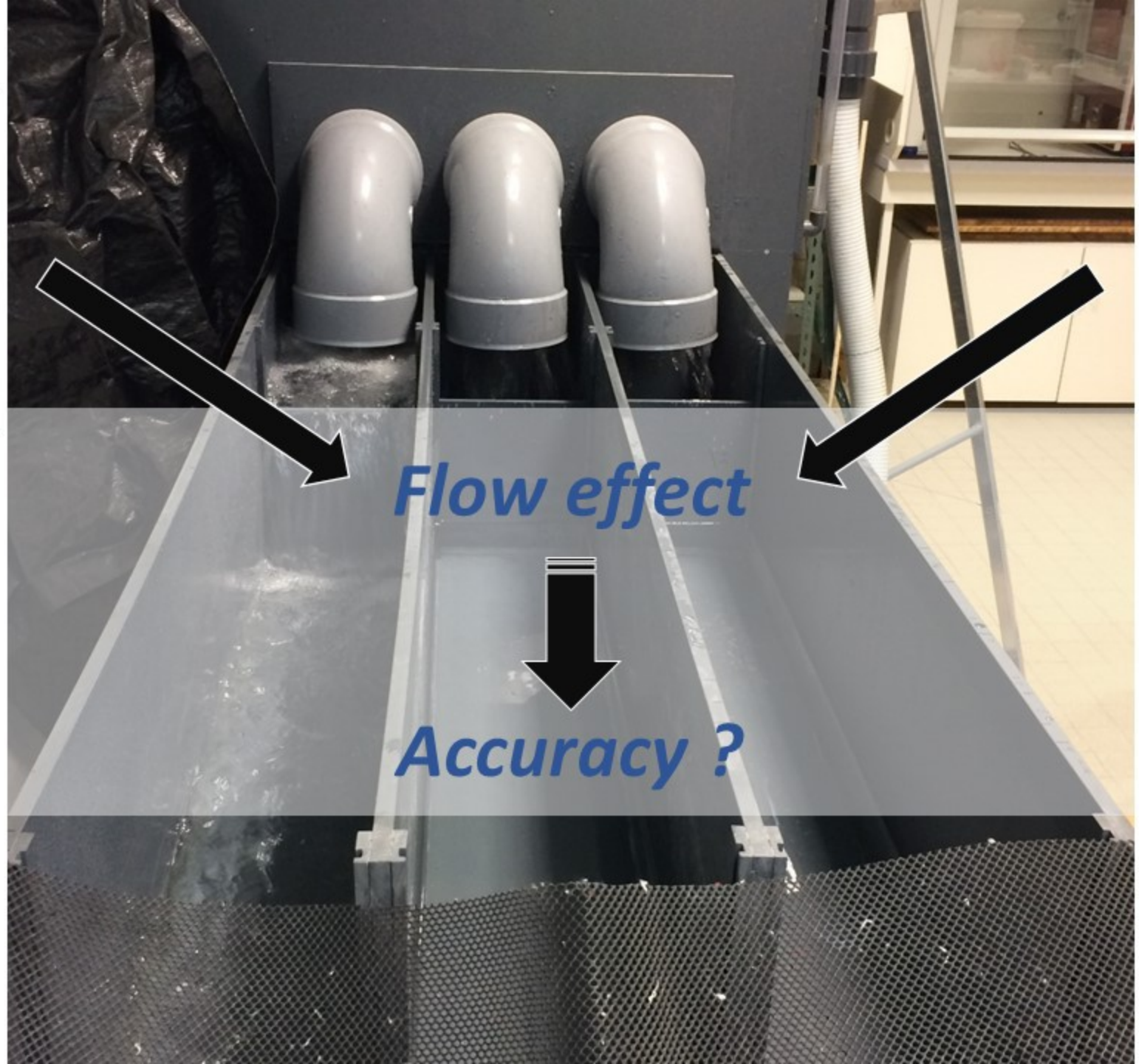
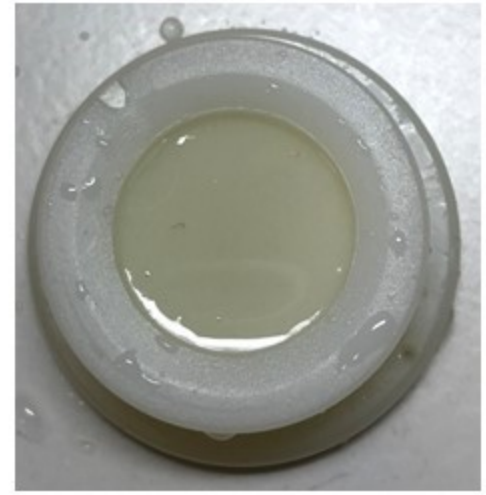
POCIS + PRC





o-DGT