Adaptation du DGT et fiabilisation du POCIS pour le suivi des pesticides et résidus de médicaments dans les eaux de surfaces

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« Pourquoi y a-t-il quelque chose plutôt que rien ? »

Leibniz

« L'éducation est l'arme la plus puissante qu'on puisse utiliser pour changer le monde. »

Nelson Mandela

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Droits d'auteurs

Table des matières

Table des illustrations

Table des tableaux

Introduction

De plus en plus rare dans certaines régions de la planète, l'eau est un constituant essentiel pour tous les organismes vivants. L'eau, menacée par son exploitation intensive et la pollution croissante de ses réserves, est devenue un bien extrêmement précieux à préserver, d'autant plus dans un contexte d'évolution climatique incertain. De par leur toxicité pour l'être humain et pour l'environnement, la pollution des eaux par les substances organiques de type pesticides ou résidus pharmaceutiques, issus des activités humaines, est un enjeu important. Les produits phytosanitaires ou pesticides sont utilisés depuis l'antiquité. Des traces d'utilisation de soufre et d'arsenic sont retrouvées dès 1000 ans avant J.-C. et au I^{er} siècle. C'est bien plus tard, au XIX^{ème} siècle, que l'utilisation des produits phytosanitaires s'est généralisée avec l'essor de la chimie minérale. Au siècle suivant, les avancées scientifiques, et surtout de la chimie organique, font apparaître les composés organiques de synthèses, ouvrant des possibilités importantes quant au nombre de molécules actives disponibles.

A ce jour, en France, un peu plus de 500 molécules organiques de synthèse sont utilisées comme produits phytosanitaires (BNVD 2013). Ces substances bénéficient d'une autorisation de mise sur le marché. Ainsi, certaines substances sont régulièrement interdites à l'usage ou voient leurs utilisations réduites, mais des substances nouvelles obtiennent l'autorisation de mise sur le marché. Au total, ce sont plus de 65 000 tonnes de pesticides vendus chaque année en France pour un chiffre d'affaire avoisinant les 2 milliards d'euros (BNVD 2015).

Les produits phytosanitaires sont utilisés pour protéger les cultures de dégradations par des organismes tiers (*e.g.* insectes, champignons) et pour lutter contre des plantes indésirables appelées « mauvaises herbes ». L'usage des pesticides en agricultures représente 90% du tonnage vendu, les 10% restants ont un usage non agricole (*e.g.* particuliers, collectivités ou gestionnaires de grandes infrastructures). Cependant, environ 65% de la contamination environnementale est issue des usages agricoles. Les pesticides et leurs métabolites (molécules issues de leur dégradation) sont susceptibles de se retrouver dans les différents compartiments de l'environnement (air, eau et sol). En effet, ces derniers se retrouvent, principalement après le lessivage des sols, dans le compartiment aquatique et contaminent les eaux de façon diffuse.

En France, un plan de réduction de l'utilisation des produits phytosanitaires (Plan Ecophyto – mesure proposée par le Grenelle de l'Environnement) a été mis en place avec pour objectif de réduire de moitié l'utilisation des pesticides d'ici 2018 (Plan Ecophyto I (2009)) mais cet objectif a été par la suite repoussé pour 2025 (Plan Ecophyto II (2015)). En effet, l'utilisation des pesticides, en France, a augmenté de 12% entre 2014 et 2016 (Ministère de l'Agriculture et de l'Alimentation) pour une surface agricole utilisée stable (27 millions d'hectares) (Statistique Développement Durable (Mars 2017)). Parallèlement à ces mesures essentiellement destinées à réduire les usages agricoles, les usages non-agricoles vont être fortement réduits par la limitation des ventes et des usages, issus de la loi Labbé.

Les médicaments issus de synthèses chimiques se sont également répandus au cours du XIX^{ème} siècle, grâce au progrès de la chimie, avec la synthèse de l'acide acétylsalicylique par Charles Frederich Gerhardt.

Actuellement, environ 3 000 substances pharmaceutiques sont disponibles sur le marché français (ANSM (2016)). Lors de l'injection de médicament, le corps (humain ou animal) n'utilise pas entièrement la molécule active et après excrétion, les résidus pharmaceutiques rejoignent les eaux usées. Les stations d'épuration des eaux résiduaires urbaines rejettent dans les eaux naturelles, utilisées comme exutoire, les résidus pharmaceutiques provenant du traitement des eaux résiduelles issues des particuliers mais aussi des d'hôpitaux ou de maison de retraite, lieux où la consommation de médicaments peut être élevée. En effet, la majorité des résidus de médicaments ne sont pas ou très peu éliminés par différents processus (*e.g.* dégradation, sorption, …) des eaux traitées dans les stations d'épuration (Miège et al. 2009) car ces dernières sont essentiellement conçues pour éliminer des substances nutritives comme le carbone, l'azote et le phosphore. La deuxième source d'entrée des résidus médicamenteux dans le compartiment aquatique est les rejets d'eaux usées traités des particuliers qui ne sont pas reliés aux réseaux d'eaux usées (« tout à l'égout ») : ce sont les assainissements non-collectifs. Le rejet se fait alors sur le terrain du particulier et peut, après infiltration, se retrouver dans le milieu aquatique. Ce type d'assainissement est très largement répandu en milieu rural. On ne peut pas exclure, comme source de résidus pharmaceutiques d'origine humaine, des rejets directs d'eaux usées non traitées à cause de surcharges de réseaux ou de tailles de stations non adaptées. La dernière source est une source de résidus médicamenteux pour les animaux (produits vétérinaires). Comme les humains, les animaux sont soignés ou traités préventivement (*e.g.* antiparasitaires) et relarguent par les urines ou les fèces, dans les champs ou les pâtures, les résidus pharmaceutiques. Un apport de ces substances au niveau des sols est aussi possible *via* l'épandage de fumier ou lisier issus des animaux présents dans divers types de bâtiments agricoles. Comme les pesticides, ces substances peuvent se retrouver dans les milieux aquatiques par lessivage ou infiltration.

Les premiers effets des résidus pharmaceutiques dans l'environnement ont été constatés à la fin du XX^{ème} siècle (Purdom et al. 1994, Yamamoto 1969). Depuis, un plan de réduction des rejets de substances préoccupantes pour l'environnement, dont des résidus médicamenteux, a été mis en place (Règlement (CE) n°1907/2006 du parlement européen et loi n°2009-967 – Article 37 relative à la mise en œuvre du Grenelle de l'Environnement) ainsi qu'un plan national sur les résidus médicamenteux dans les eaux (PNRM (2010-2015)). Ce dernier a pour principales mesures la réalisation d'états des lieux de la contamination des eaux par les résidus médicamenteux et le développement d'outils métrologiques.

Ces deux types de composés organiques (pesticides et résidus pharmaceutiques) se retrouvent donc dans le compartiment aquatique et contribuent à engendrer des effets néfastes sur l'environnement ou limiter les usages de l'eau pour l'Homme. Depuis la prise de conscience de cette problématique, l'Europe a mis en place des directives pour évaluer la qualité de l'eau. La Directive européenne Cadre sur l'Eau (DCE) fixe d'atteindre un bon état chimique et écologique des eaux pour 2015 (2000/60/EC 2000) avec des possibilités de report pour 2021 ou 2027. Dans le cadre de l'application de la DCE, des contrôles sont alors mis en place pour évaluer et surveiller la qualité des masses d'eau, qu'elles soient littorales, estuariennes, continentales de surface ou souterraines. Pour évaluer la présence de micropolluants, des échantillons d'eau sont prélevés (en général de 6 à 12 échantillons par an) et différents composés cibles ont été choisis (actuellement 45 molécules

ou groupes de molécules). C'est alors que se pose la question de la représentativité des grandeurs acquises, notamment en termes de représentativité temporelle. En effet, la concentration en composés organiques peut rapidement évoluer au cours de la journée, par exemple lors d'épisodes pluvieux. Lors de ces évènements, il peut y avoir un lessivage des sols et donc un pic de pollution ou au contraire lors de très grosses pluies, une forte dilution des substances cibles dans le milieu échantillonné due à l'augmentation du volume d'eau. De même, lors d'épisodes pluvieux importants, des rejets directs au niveau des réseaux de collecte des eaux usées ou stations d'épuration dus aux surcharges hydrauliques peuvent avoir lieu relarguant ainsi des eaux usées pas ou peu traitées dans le milieu récepteur. Même si ce mode de prélèvement est simple à mettre en œuvre et qu'il est souvent préconisé par les règlementations, il ne donne qu'une partie de l'information de l'état de contamination du milieu. L'échantillonnage ponctuel ne répond donc que partiellement à l'enjeu majeur de cette surveillance qui est d'estimer au mieux la pollution vis-à-vis des micropolluants organiques des milieux avec une contrainte financière. Le challenge actuel est donc, dans un budget contraint, d'avoir des dispositifs ou des stratégies qui permettent d'obtenir le maximum d'informations sur la qualité des milieux, de manière à répondre de façon plus robuste aux obligations règlementaires (*e.g.* DCE) ou de prendre des mesures correctives adaptées une fois les sources de perturbations identifiées (*e.g.* plan d'action à l'échelle d'un territoire).

L'échantillonnage passif semble pouvoir répondre à cette problématique d'amélioration de l'estimation de la pollution des milieux aquatiques. L'échantillonnage passif est une technique d'échantillonnage développée dans les années 1990. Elle consiste à placer un petit dispositif dans le milieu à échantillonner et de le laisser en place de quelques jours à plusieurs semaines. L'échantillonneur va accumuler les substances recherchées, pour lesquelles il a été construit, durant toute la période de déploiement. Les micropolluants seront accumulés de façon proportionnelle par rapport aux temps ; ainsi une concentration moyenne pourra être déterminée sur la durée d'exposition dans le milieu. Cette caractéristique permettra d'obtenir des données de la contamination du milieu durant la période échantillonnée et non pas sur la durée d'une fraction de seconde comme pour l'échantillonnage ponctuel. De même, du fait de l'accumulation des polluants dans l'échantillonneur, les limites de détection pourront être abaissées. Ainsi des substances transitant à de très faibles concentrations pourront être plus facilement détectées.

De nombreux échantillonneurs passifs ont depuis été développés pour les différentes classes de composés organiques. Ainsi, il existe des échantillonneurs pour les composés polaires jusqu'aux composés les plus hydrophobes : Polar Organic Chemical Integrative Sampler (POCIS) pour les composés avec $0 < \log Kow < 4$ (Alvarez et al. 2004), SemiPermeable Membrane Device (SPMD) pour les composés avec un $\log Kow > 4$ (Huckins et al. 1990), Low-Density PolyEthylene (LDPE) pour les composés avec un $\log Kow > 4$ (Booij et al. 1998) ou encore Chemcatcher® pour les composés avec un $1 < \log Kow < 7$ (Kingston et al. 2000). Les différents échantillonneurs passifs précédemment cités ont été déployés sur de nombreuses typologies de milieux aquatiques, mais surtout à des endroits où les enjeux autour des eaux étaient importants pour aider à qualifier la qualité des eaux. Ces lieux sont souvent l'aval des bassins versants qui aujourd'hui concentrent souvent les populations et où les eaux sont indispensables au développement des activités

économiques (*e.g.* tourisme, industries agricoles avec l'irrigation). A l'opposé, la partie très en amont des grands bassins versants, appelée « tête de bassin versant » est souvent peu documentée en termes de présence de micropolluants.

Les têtes de bassin versants ont longtemps été considérées comme des zones préservées par la pollution issue des activités humaines du fait du caractère très rural de ces zones et d'une activité économique centrée aujourd'hui sur l'agriculture d'élevage extensif, la sylviculture, l'hydroélectricité parfois et le tourisme vert. Ces zones, reconnues aujourd'hui comme essentielles à la biodiversité par la présence d'espèces patrimoniales et d'habitats d'espèces endémiques, doivent être surveillées pour, le cas échéant, prendre des mesures de préservation. Les nombreux petits cours d'eau et les zones humides sont des territoires caractéristiques de têtes de bassin de région de moyenne montagne comme par exemple sur le territoire de nord-est de la région Nouvelle-Aquitaine (*i.e.* ancienne région Limousin). Au-delà de leur intérêt pour la préservation d'espèces parfois menacées, ces zones sont essentielles au cycle de l'eau à l'échelle d'un grand territoire. Elles influencent directement la qualité et la quantité des eaux disponibles à l'aval des bassins, où les enjeux autour de l'eau sont aujourd'hui forts, d'autant plus dans un contexte d'évolution climatique.
Les têtes de bassin versant de moyenne montagne, comme on les trouve sur le nord-est de la région Nouvelle-Aquitaine, sont occupées par une agriculture de type poly-agriculture orientée sur l'élevage extensif d'ovins ou de bovins, avec parfois une diversification possible en fonction des conditions agro-climatiques comme par exemples les vergers de pommes. Pour des raisons économiques, les éleveurs se mettent à cultiver des céréales ou des prairies artificielles pour tendre vers l'autonomie alimentaire des exploitations. La modernisation récente des pratiques agricoles peut entraîner une dégradation de la qualité des eaux d'un point de vue chimique (nutriments, résidus pharmaceutiques, produits phytosanitaires) microbiologique et/ou hydromorphologique (piétinement des berges pour l'abreuvement du bétail). Depuis une décennie, de nombreux plans d'action se développent sur ces territoires avec pour objectifs de préserver ces milieux, mais aussi d'atteindre les objectifs de la DCE. A travers ces plans d'action, de nombreuses corrections de la dégradation des milieux aquatiques de tête de bassin versant ont été réalisées d'un point de vue hydromorphologique, car les dégradations sont facilement identifiables visuellement. A l'opposé, fautes de données et d'identification claire des problématiques, peu de travaux ont été initiés pour réduire l'apport de micropolluants dans les nombreux petits cours d'eau présents dans ces têtes de bassin versant. Malgré un gain significatif en 10 ans sur le volet hydromorphologique de la qualité des eaux, on constate aujourd'hui des difficultés de reconquête de certaines espèces de leurs territoires originels (*e.g.* truite fario, écrevisse à pied blanc, moule perlière). Se pose alors la question de l'effet de la qualité des eaux actuelles, mais sur le volet physico-chimique et notamment de micropolluants organiques issus de l'évolution des activités humaines (agriculture, forêt) ou de la consommation plus élevées de médicaments due aux populations âgées de ces territoires.

Les objectifs de ces travaux de thèse sont de contribuer à avoir une meilleure connaissance des données issues de l'échantillonnage. Cela passe par l'adaptation ou la fiabilisation d'échantillonneurs passifs afin de

les utiliser pour caractériser la présence en micropolluants organiques sur des têtes de bassin versant. Ainsi le manuscrit est organisé en 5 parties. La première partie (Chapitre I) est une synthèse bibliographique recentrée sur les Diffusive Gradient in Thin films (DGT) organiques (o-DGT), des échantillonneurs innovants adaptés du DGT utilisé depuis 1994 (Davison and Zhang 1994) pour échantillonner les métaux et métalloïdes. La seconde partie de ce travail de thèse (Chapitre II) présente le matériel utilisé et les méthodes ou protocoles mis en œuvre. Cela comprend la préparation d'échantillonnage, les stratégies d'échantillonnage, l'extraction des composés cibles mais aussi les méthodes analytiques développées et appliquées dans ces travaux. Enfin les dernières parties reprennent les principaux résultats et sont organisées en 3 parties :

- Le développement d'un échantillonneur innovant pour l'échantillonnage de composés ioniques de type pesticides grâce à l'adaptation de l'échantillonneur DGT est développé dans le chapitre III. Dans ce même chapitre, des tests d'évaluation et d'application ont été fait en laboratoire et en milieu naturel. Une comparaison entre deux échantillonneurs (o-DGT et POCIS) a également été réalisée en laboratoire à grande échelle et en milieu naturel.
- Une fiabilisation de l'outil POCIS a été conduite dans le chapitre IV. Cette fiabilisation passe par l'étude d'effets de matrice au niveau des détecteurs de spectrométrie de masse lors du dosage des substances cibles dans les extraits de POCIS. Par la suite, des préconisations sont données pour diminuer ou supprimer ces effets de matrice. De plus, afin de garantir une bonne quantification des substances organiques transitant dans un milieu aquatique, le POCIS doit être calibré. Pour cela, le taux d'échantillonnage de composés pharmaceutiques a été estimé en utilisant un pilote de taille importante mimant une rivière, de manière à se rapprocher le plus possible des conditions rencontrées en milieu naturel, notamment en termes d'écoulement.
- Une meilleure connaissance de l'état de contamination en pesticides et résidus pharmaceutiques de deux têtes de bassin versant a été obtenue dans le chapitre V grâce à l'application de deux types d'échantillonnage (ponctuel et passif avec l'échantillonneur POCIS).

Chapitre I. Bibliographie

Cette section est constituée d'un projet d'article d'état de l'art (« review ») qui sera soumis dans « Trends in Analytical Chemistry », où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

Adaptation of diffusive gradients in thin films (DGT) to sample organic pollutants in environment: an overview of o-DGT

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ABSTRACT

The adaptation of diffusive gradients in thin films (DGT) to sample organic pollutants in environment called o-DGT, which was really developed in 2012, can be adapted for various types of organic compounds (*e.g.* pesticides, pharmaceuticals, hormones, endocrine disrupting chemicals and household products and personal care products). To sample these different types of organic compounds, receiving phase, diffusive gel and membranes can be changed. The o-DGT is in development and has been studied in about 28 research articles. In total, 112 compounds have been tested to be sample by this new passive sampler for organic compounds. This review indicates the state-of-art of this passive sampler describing theory, calculation of water concentration with determination of diffusive coefficient, preparation of the device (choice of the receiving gel, diffusive layer and membranes), studied compounds, the robustness of o-DGT and field applications. A last part of this review is focus in perspectives of study of o-DGT with the feedback of DGT use to sample inorganic contaminants.

INTRODUCTION

By its low cost and simplicity, grab sampling is commonly performed to estimate concentration of micropollutants in waters (Allan et al. 2006). However, this technique has some limitations such as the large volume of water required to concentrate trace of pollutant or the lack of temporal representativeness (Allan et al. 2006). Complementarily to this method, passive sampling provides *in situ* pre-concentrated samples and allows access to time-weighted average concentration (TWAC), also called C_w (concentration in water). Passive samplers consisted basically in a binding phase able to concentrate targeted compounds deployed within various devices in the environment. Organic contaminants can be sampled by Polar Organic Chemical Integrative Sampler (POCIS) (Alvarez et al. 2004), Chemcatcher® (Kingston et al. 2000), Semi-Permeable Membrane Device (SPMD) (Huckins et al. 1990) or Membrane-Enclosed Sorptive Coating (MESCO) (Paschke et al. 2006). Some passive samplers (*e.g.* POCIS or SPMD) were shown, however, to be affected by environmental conditions (Fauvelle et al. 2017, Harman et al. 2012) such as temperature, biofouling or water flow velocity. Consequently, sampling rates (Rs) used for TWAC estimations can vary between the studied systems (Alvarez et al. 2004, Buzier et al. 2018 - submitted to Chemosphere, Li et al. 2010a, Togola and Budzinski 2007). Given that sampling rates calibration is expensive and time consuming, calibration are not optimized for each targeted system and inaccuracies in TWAC estimation may arise (Buzier et al. 2018 - submitted to Chemosphere). and induces to use these passive sampler in a semi-quantitative mode with an error on TWAC of a factor *c.a.* 2 for *e.g.* POCIS (Poulier et al. 2014).

Concerning the introduction of a diffuse layer in a passive sampler to organic compounds to limit the influence of environmental parameter, in 2011, Bondarenko et al. (2011) proposed the diffusive model like DGT passive sampler to sample organic compounds. DGT differs from the other passive samplers by the presence of a diffusive layer (hydrogel) that constrains pollutant mass transfer mostly to diffusion within this layer. TWAC derivation consequently requires only calibration of the diffusion coefficient of the compound within the hydrogel, allowing limiting the influence of environmental conditions. DGT was initially developed for inorganic compounds (Davison and Zhang 1994) and DGT device from DGT Research® was firstly use to sample organic compounds in water in 2012, with an adaptation called o-DGT (Chen et al. 2012). The adaptation of DGT to organic compounds mainly consist in changing the binding phase. Since this first adaptation, there is a growing interest for o-DGT (**Figure I.1**) and adaptation to various organic compounds have been proposed (pesticides, pharmaceuticals, hormones, endocrine disrupting chemicals and household and personal care products). Currently, 28 research articles and one review (on three passive sampler for organic compounds: POCIS, o-DGT and Chemcatcher®) have been published. 22/28 articles have been published on o-DGT or DGT-like development (tests on binding phases, elution, robustness or analyte conservation). Application of o-DGT on water or soil are the aim of 5 others articles (and use diffusive coefficient from other studies), a comparison before POCIS and o-DGT are performed by one article.

This review proposes an overview of o-DGT passive sampler since its first adaptation in 2011 to the present 2018 and discusses its current limitations and future development needed regarding the knowledge developed with inorganic compounds. Theory of DGT is presented in a first part, and then all preparation procedures and configurations of the sampler are detailed. Finally, the o-DGT robustness and its applications are presented in a last part.

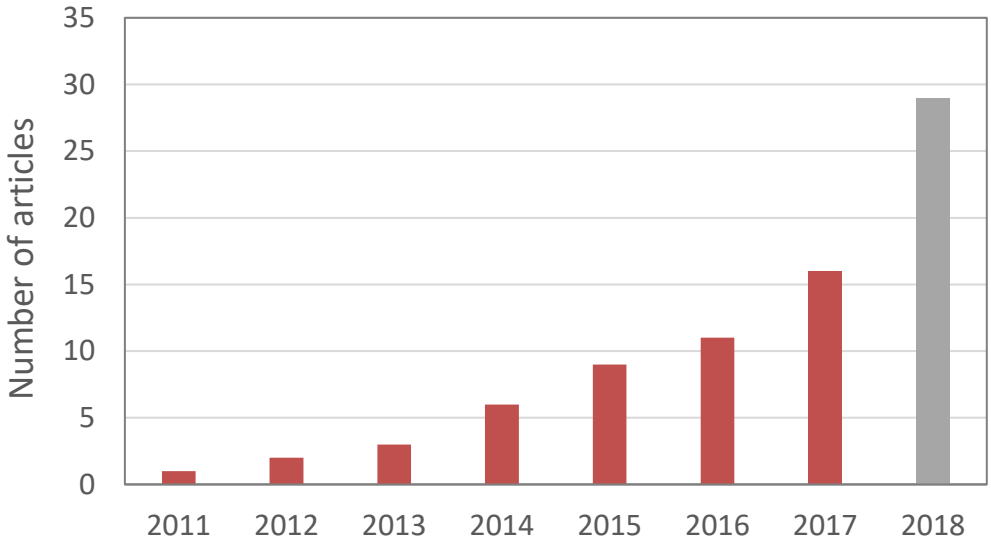

Figure I.1: Publication history for the adaptation and uses of the o-DGT.

THEORY AND MODELLING

Similarly to the initial DGT samplers, o-DGT are usually composed of two hydrogels: a diffusive gel covering a binding gel. A microporous membrane can be added to protect the diffusive gel against particles in the sampled medium. The binding gel is separated from the solution by the diffusive gel and by a diffusive boundary layer created at the water/sampler interface (**Figure I.2**). Mass transfer to the binding gel is constrained to diffusion only and quantification can be derived from Fick's first law. For simplicity, modelling of TWAC is commonly made under five assumptions: i) absence of interaction between analyte and diffusive gel, ii) concentration at the interface between the binding and diffusive gel is negligible, iii) time to reach steady-state is negligible, iv) diffusive boundary layer thickness is negligible and v) lateral diffusion is negligible. In these conditions, the flux density (φ) can be expressed by Davison and Zhang (1994):

$$\varphi = \frac{D \times C_w}{\Delta_g} \qquad \textbf{Equation I.1}$$

where D is the diffusion coefficient of the analyte in the diffusive gel (compound and temperature dependent) and C_w is the concentration of analyte in studied environment (water). Flux density can also be defined by the following equation:

$$\varphi = \frac{m}{\mathcal{A} \times t} \qquad \textbf{Equation I.2}$$

where m is the mass of the analyte in the binding gel, $\mathcal{A}$ is the exposure area and t is the exposure time. Combining equations (1) and (2), the concentration in the studied environment (water) can be quantified by:

$$C_w = \frac{m \times \Delta_g}{t \times D \times \mathcal{A}} \qquad \textbf{Equation I.3}$$

The exposure area, the exposure time and the diffusion layer thickness are known parameters. Diffusive coefficient must be previously calibrated (see next section), and the mass of the analyte can be determined after elution.

Such modelling should be convenient for most cases. Indeed, assumption i) and ii) are not environment dependent and are usually checked previously during the development of the sampler. Assumption iii), iv) and v) have never been validated for organic compounds but their behavior should be similar to inorganic compounds considering their diffusion rate are in the same order of magnitude (*i.e.* 10^{-6} cm^2 s^{-1} see part 4 and **Annexe 1**). For inorganic compounds, assumption iii) was shown to holds for deployments ≥ 24h (Davison and Zhang 2012). Warnken et al. (2006) shows that assumption iv) and v) are both invalid but the errors from each cancel each other out for standard devices as long as DBL (Diffusive Boundary Layer) thickness remains limited (*i.e.* valid for flow velocity > 2cm s^{-1}, (Gimpel et al. 2001)). Therefore, **Equation I.3** will fail only for a limited number of systems, mostly the ones displaying low flow conditions. Models have been developed to consider both DBL thickness and lateral diffusion in order to avoid making

assumption iv) and v) (Garmo et al. 2006, Santner et al. 2015). However, their use requires deployment of devices with various diffusive gel thickness and more sophisticated data treatment.

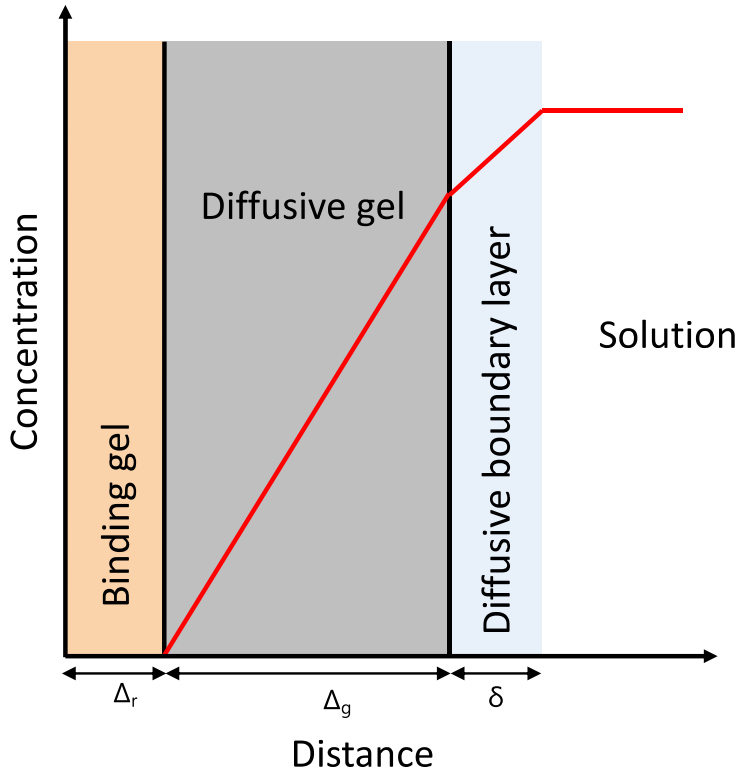

Figure I.2: Concentration gradient into o-DGT (Δ_r the thickness of the binding gel, Δ_g the thickness of the diffusive gel and δ the thickness of diffusive boundary layer).

DETERMINATION OF DIFFUSIVE COEFFICIENT

Determination of diffusion coefficients is performed using three method: i) the diffusion cell method, ii) by fitting **Equation I.3** following device deployment in controlled solution, iii) the stack of gels method. The first two methods have been used for long for inorganic compounds (Zhang and Davison 1999) whereas the last one is a method adapted from .

The diffusion cell method was the most use (**Table I.1**). A diffusion cell (see **Figure I.3**) is composed of two separated compartments connected with an opening where a diffusive gel is intercalated and allows mass transfer between the compartments by diffusion. One of the compartments ("source" compartment) is filled with a solution spiked with the analyte of interest whereas the other compartment ("receiving" compartment) is filled with the same solution not spiked with the analyte. The analyte diffusive through diffusive gel and a steady state is established after few minutes. Concentration in the receiving compartment is determined over time in order to determine the analyte flux through the diffusive gel and to derive the corresponding diffusion coefficient using Fick's first law (**Equation I.1**).

Figure I.3: Photo of diffusive cell.

The second method (ii), uses time series deployment of o-DGT samplers in known spiked solution. Accumulation of interest analyte into the binding gel *versus* time is determined allowing back calculation of the diffusion coefficient using **Equation I.3**. In contrast, to the first method, this one allows the use of lower concentrations (µg L^{-1} or less) that are more relevant compared to the targeted environmental applications.

The last method (iii), adapted from Rusina et al. (2010), was only recently used by Amato et al. (2018) and Belles et al. (2017). Unspiked diffusive gels are stacked with one spiked with the targeted analytes. Analytes diffuse from spiked to unspiked gels and are quantified over time (analyze of unspiked diffusive gels). In contrast, to the two previous methods, the system used do not reach a steady state and Eq. 1 is not valid. Diffusion coefficients are therefore derived using known solutions to Fick's first law for the specific boundary conditions imposed with this method (*e.g.* analyte initially homogeneously distributed across a section of constant surface area, **Equation I.4**, Amato 2018).

$$C(x,t) = \frac{m}{A\sqrt{4\pi D}} e^{-\left(\frac{-x^2}{4Dt}\right)} \qquad \textbf{Equation I.4}$$

Diffusive coefficients are temperature dependent. The following equation (6) can be used to calculate diffusive coefficient at a desired temperature (Zhang and Davison 1995):

$$logD_{t_2} = \frac{1.37023\times(t_2-25)+8.36\times10^{-4}\times(t_2-25)^2}{109+t_2} + \log\frac{D_{25}\times(273-t_2)}{298} \qquad \textbf{Equation I.5}$$

Table I.1: Configuration of o-DGT (a: thickness of cast gel sheets, b: final thickness after hydration, c: thickness used for calculation, Diffusive coefficient calculated d: with membrane, e: without membrane, f: with diffusion cell, g: with o-DGT devices deploy).

Diffusive gel	Thickness of diffusive gel (mm)	Thickness of diffusive gel used for calculation of diffusive coefficient (mm)	Binding gel	Concentration (% mass:volume)	Interest analytes	Membranes	References
Agarose	0.5 to 1.75[c]	0.8[e,f]	Activated charcoal	5	Bisphenols	PTFE	Zheng et al. (2014)
Agarose	0.5 to 1.5[c]	1.0[c,e,f]	Oasis HLB	7	Pharmaceuticals, hormones and pesticides	No membrane	Challis et al. (2016)
Agarose	0.5 to 2.0[c]	0.8[c,e,f]	Oasis HLB	20	Household and personal care products	Nucleopore track-etch	Chen et al. (2017)
Agarose	0.75[c]	0.75[c,e,f,h]	Oasis HLB	10	Pharmaceuticals and pesticides	*n.i.*	Amato et al. (2018)
Agarose	1.0[c]	*n.c.*	Oasis HLB	7	Pharmaceuticals and pesticides	No membrane	Challis et al. (2018)
Agarose	0.35 to 2.0[c]	0.8[c,e,f]	Oasis HLB	20	Endocrine disrupting chemicals	Nucleopore track-etch	Chen et al. (2018)
Agarose	0.75[a]	0.9[b,e,f]	Oasis HLB	8	Pharmaceuticals, hormones and pesticides	No membrane	Stroski et al. (2018)
Agarose	0.16 to 0.84[b]	*n.c.*	Oasis HLB	7	Pharmaceuticals	No membrane	Buzier et al. (2018 - submitted to Chemosphere)
Agarose	0.5 to 1.4[c] - 0.8[b]	0.8[b,d,f]	PCM	1	Pharmaceuticals	PES	Ren et al. (2018)
Agarose	0.8[b]	0.8[b,e,f]	XAD-18	20	Sulfamethoxazole	PES	Chen et al. (2012)
Agarose	0.5 to 1.3[c] - 0.8[b]	0.8[b,e,f]	XAD-18	20	Pharmaceuticals	PES	Chen et al. (2013)
Agarose	0.8[b]	*n.c.*	XAD-18	20	Pharmaceuticals	PES	Chen et al. (2014)
Agarose	0.14 to 2.14[c] - 0.8[b]	*n.c.*	XAD-18	20	Pharmaceuticals	PES	Chen et al. (2015a)
Agarose	0.8[b]	*n.c.*	XAD-18	20	Pharmaceuticals	PES	Chen et al. (2015b)
Agarose	0.8[a] - 0.97[c]	0.97[c,f]	XAD-18	20	Pharmaceuticals	Nylon	D'Angelo and Starnes (2016)
Agarose	0.8[a,c]	0.8[a,c,e,f]	XAD-18	20	Illicit drug	PES	Guo et al. (2017a)
Agarose	0.25 to 1.25[a,c]	0.25 to 1.25[a,c,d,g]	XAD-18	20	Hormones	PVDF	Guo et al. (2017b)
Agarose	0.35 to 2.0 - 1.0[c]	1.0[c,e,f]	XAD-18	20	Endocrine disrupting chemicals	Nucleopore track-etch	Chen et al. (2018)

Agarose	0.8[a] - 0.97[c]	*n.c.*	XAD-18	20	Tetracycline	Nylon	D'Angelo and Martin (2018)
Agarose	0.8[a] - 0.89[c]	0.89[c,e,f]	XAD-18	*n.i.*	Pharmaceuticals	PES	Zhang (2018)
Agarose	0.8[a]	0.8[a,c,d,g]	XDA-1	10	Pharmaceuticals	PES	Xie et al. (2018a)
Agarose	0.8[c]	0.8[c,e,g]	XDA-1	10	Endocrine disrupting chemicals	No membrane	Xie et al. (2018b)
Agarose	1.2[c]	1.0[c,e,h]	Strata-X	10	Pesticides, endocrine disrupting chemicals and others	No membrane[i]	Belles et al. (2017)
Agarose	0.0 to 2.2[c]	*n.c.*	Strata-X	0.5 to 10	Pesticides, endocrine disrupting chemicals and others	No membrane[i]	Belles et al. (2018)
Nylon membrane	0.18[c]	0.18[c,e,f]	MIP	*n.c.*	4-chlorophenol	*n.i.*	Dong et al. (2014)
Polyacrylamide	0.5[a] - 0.77[b]	0.77[b,e,f,g]	Oasis HLB	3	Pesticides	No membrane	Guibal et al. (2017a)
Polyacrylamide	0.5[a] - 0.77[b]	0.77[b,e,f,g]	Oasis MAX	3	Pesticides	No membrane	Guibal et al. (2017a)
Polyacrylamide	0.75[a] - 0.9[b]	0.9[b,e,f]	Sepra ZT	7	Pharmaceuticals, hormones and pesticides	No membrane	Stroski et al. (2018)
Polyacrylamide	0.8[c]	0.8[c,d,f]	TiO_2	10	Herbicides	PES	Fauvelle et al. (2015)
Water	10.5	10.5	Activated charcoal	*n.i.*	Naphtalene	Glass microfiber	Bondarenko et al. (2011)
n.i.	*n.i.*	*n.i.*	*n.i.*	*n.i.*	Atrazine	*n.i.*	Lin et al. (2018)

SAMPLER CONFIGURATION

Diffusive layer.

The diffusive layer is commonly an hydrogel made of agarose or polyacrylamide. Nylon membranes were used as diffusive layer in only one study (Dong et al. 2014) to sample 4-chlorophenol. More than 80% of the studies used agarose diffusive gel whereas just over 10% used polyacrylamide diffusive gel (**Table I.1**). Both type of diffusive gels were tested in 6 studies (Chen et al. 2012, Chen et al. 2017, 2018, Fauvelle et al. 2015, Guibal et al. 2017a, Guo et al. 2017a). For these studies, the choice between agarose and polyacrylamide was based on three criteria: i) adsorption on the diffusive gel, ii) stability and reproducibility of the gel and iii) diffusion coefficient within the gel. Agarose was chosen by Chen et al. (2012) because significant adsorption of sulfamethoxazole was observed on polyacrylamide. The opposite result for agarose has been observed by Guibal et al. (2017a) with only 15% adsorption of some anionic pesticides on agarose diffusive gel, whereas only 5% of ionic pesticides was adsorbed on polyacrylamide gels Guibal et al. (2017a). On the other hand, no or poor adsorption in agarose and polyacrylamide was observed by Chen et al. (2017) for household and personal care products (methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, benzyparaben, heptylparaben, 4-hydroxybenzoic acid, butylated hydroxyanisole, butylated hydroxytoluene, ortho-phenylphenol, triclosan and triclocarban), Chen et al. (2018) for endocrine disruptive chemicals (bisphenol A, diethylstilbestrol estriol, estrone, nonylphenol, ortho-phenylphenol and β-estradiol) and Guo et al. (2017a) for illicit drug (ketamine, methamphetamine, amphetamine). Adsorption was also tested for other authors. Less than 5% adsorption on agarose was observed by many authors for bisphenols (Zheng et al. 2014), illicit drugs (Guo et al. 2017a), drugs (Zhang et al. 2018) and hormone (Guo et al. 2017b).

Secondly, agarose diffusive gel was chosen by Chen et al. (2017, 2018) because of agarose had better stability. However, Stroski et al. (2018) evaluated the resistance to degradation. Occasional degradation of agarose gel as diffusive gel was observed by Stroski et al. (2018) whereas polyacrylamide was fully intact.

At last, polyacrylamide diffusive gel was chosen by Fauvelle et al. (2015) because of higher diffusive coefficient was obtained (upper than a factor 1.5). Difference on diffusive coefficient between polyacrylamide and agarose gel was explained by the difference in pore size between the two types of gels. However, Zhang and Davison (1999) and Scally et al. (2006) showed that polyacrylamide contains smaller pore sizes compared to agarose gels which can reduce diffusive coefficient.

The protocols for the manufacture of agarose and polyacrylamide diffusive gels are the same for all authors and were adapted from Zhang and Davison (1999). Agarose diffusive gels are prepared from an agarose gel solution containing 1.5% agarose. This solution is prepared by dissolving agarose in preheated ultrapure water (about 80°C). The dissolution is completed when solution became transparent. The hot solution is then transferred between two pre-assembled and preheated casting glass plates. The assembly is left to cool to room temperature (below 36°C).

The second, polyacrylamide diffusive gel, is prepared by mixing 15% of monomer (acrylamide) and 0.3% of cross-linker (derivate of agarose) in ultrapure water. Polymerization is initiated by ammonium persulfate (10%, prepared daily) with TEMED (N,N,N',N'-Tetramethylethylenediamine) added as a catalyst. Volume

of ammonium persulfate and TEMED slightly vary between the authors, from 0.7 to 0.8% and from 0.04to 0.25% for ammonium persulfate and TEMED respectively. The solution is transferred between two pre-assembled casting glass plates. The assembly is maintained at about 45°C for 45 min.

Agarose and polyacrylamide gel are hydrated in ultrapure water bath for 24h. Ultrapure water baths are changed 3 times in order to remove excess of reagents. Gels are stored in $NaNO_3$ or NaCl solutions (from 10^{-2} to 10^{-1} M).

DGT device is known to be poorly sensitive to environmental conditions such as hydrodynamic flow for metals (Gimpel et al. 2001) thanks to the thickness of its diffusive layer. However, DBL (**Figure I.2**) may become significant in low flow conditions and alter DGT sampling by increasing the diffusion length (Davison and Zhang 2012). DBL thickness has been estimated by several authors for organic compounds. Values obtained are in the same order of magnitude in well stirred systems (average thicknesses from 0.22 to 0.25 mm) (Belles et al. 2018, Challis et al. 2016, Chen et al. 2013, Chen et al. 2017, 2018, Ren et al. 2018). Without taking into account this boundary layer, the estimate of the concentration should be 20% underestimated by **Equation I.3**. Some authors recommended the use of diffusive gel with a thickness at least 1.0 mm (Chen et al. 2013) to limit the significance of the DBL thickness. A ticker diffusive gel (1.2 mm) was chosen by Belles et al. (2017) to have a gel thickness several time higher than water boundary layer. Other authors propose to include $\delta \approx 0.20$ mm in calculation (Challis et al. 2016) to estimate concentration. It has been demonstrated for metals (Warnken et al. 2006) that, when using standard devices, the error made by neglecting DBL thickness is cancelled by the error made by neglecting lateral diffusion. This phenomenon is likely to concern also organic compounds and incorporating DBL thickness in concentration calculation for well stirred systems could alter its accuracy. In unstirred solutions, DBL thickness is found to increase up to 0.76 mm (average values, (Challis et al. 2016, Chen et al. 2012)). Such increase in the diffusion length will significantly alter sampling and concentration estimation has demonstrated by Buzier et al. (2018 - submitted to Chemosphere) for some pharmaceuticals. In unstirred solution, increasing diffusive gel thickness or incorporating DBL thickness in concentration calculation should improve accuracy. For some pharmaceuticals, Buzier et al. (2018 - submitted to Chemosphere) estimated that a 2.5 mm gel thickness should allow keeping <25% accuracies. It should be noted that such increase in the diffusion length will proportionally decrease the sampling rate and alter the sensitivity.

Binding gel.

A large types of binding phases were tested to sample organic micropollutants. A total of 17 binding phase have been identified (the list is available in **Table I.2**).

Four binding gels were tested by Zhang et al. (2018): Oasis® HLB, activated charcoal, MCX and XAD-18. The three first binding phases were not selected because of poor adsorptions were obtained for HLB phase, elutions were not efficient for some analytes (methcathinone and ephedrine) from activated charcoal or from MCX gels, therefore XAD-18 was chosen as binding gel. In the same way, 8 binding gels were tested by Xie et al. (2018a) to sample 20 pharmaceuticals. Selection was done by comparing adsorption capacity.

The best performance was obtained by XDA-1 gel and therefore this gel has been chosen. Three binding phases (HLB, XAD-18 and Strata-XL-A) were also tested by Chen et al. (2018). The uptake of endocrine disrupting chemicals by Strata-XL-A was more slowly than the two other phases. This result was also obtained by Chen et al. (2017) for household and personal care products. Therefore, in these two studies Chen et al. (2017, 2018), this binding phase was not selected. According to Chen et al. (2018), HLB and XAD-18 can be used to sample endocrine disrupting chemicals. For Chen et al. (2017), HLB was the best binding phase (compared to XAD-18 and Strata-XL-A) because of accumulate analytes linearly with deployment time and agreed with theoretical prediction. Guibal et al. (2017a) had tested two phases (Oasis® HLB and Oasis® MAX). Oasis® HLB phase was slightly better than Oasis® MAX when o-DGT were deployed in natural waters. Finally, 9 out of 17 were used, validated and are presented **Table I.1**.

The first proposed was XAD-18 to sample sulfamethoxazole (Chen et al. 2012) and was the binding gel the most used, 11/28 studies used it. Following these authors, XAD-18 allowed to sample pharmaceuticals (Chen et al. 2012, Chen et al. 2015a, Chen et al. 2014, Chen et al. 2013, Chen et al. 2015b, D'Angelo and Martin 2018, D'Angelo and Starnes 2016, Zhang et al. 2018), hormones (Chen et al. 2018, Guo et al. 2017b) and illicit drugs (Guo et al. 2017a). The second binding gel the most used was Oasis® HLB to sample pharmaceuticals (Amato et al. 2018, Buzier et al. 2018 - submitted to Chemosphere, Challis et al. 2016, 2018, Chen et al. 2018), hormones (Challis et al. 2016, Chen et al. 2018, Stroski et al. 2018), pesticides (Amato et al. 2018, Challis et al. 2016, 2018, Guibal et al. 2017a, Stroski et al. 2018) and personal care products (Chen et al. 2017). This receiving phase was the receiving phase in the most used in passive sampler as Polar Organic Chemical Integrative Sampler (POCIS) to sample organic compounds.

TiO_2 was also used for binding gel. This binding phase was already used to sample inorganic compound (phosphate) (Panther et al. 2010). TiO_2 was tested by Fauvelle et al. (2015) to sample glyphosate herbicide and AMPA (metabolite of glyphosate) because glyphosate or AMPA displays a phosphate moieties.

Concentration of binding phase into binding gel varied from 1 to 20% (wet mass:volume) with an average concentration of 13% (**Table I.1**). Protocols were adapted from Zhang 1995 and Chelex-100 binding gel where authors use 2g of resin Chelex-100 in 20 mL of gel solution. The less concentrated was Oasis® HLB receiving phase prepared by Guibal et al. (2017a). The effective binding capacity calculated with this concentration was sufficient for a long-term deployment (weeks to months).

Table I.2: List of binding gels tested by authors.

Binding phase tested	Authors
Activated charcoal	Zheng et al. (2014)
	Bodarenko et al. (2011)
CAD-40	Xie et al. (2018a)
D296	Xie et al. (2018a)
HLB	Zhang et al. (2018)
	Stroski et al. (2018)
	Challis et al. (2016)
	Chen et al. (2017)
	Guibal et al. (2017a)
	Amato et al. (2018)
	Challis et al. (2018)
	Chen et al. (2018)
	Buzier et al. (2018) – submitted to Chemosphere
LX-1180	Xie et al. (2018a)
LX-4027	Xie et al. (2018a)
MCX	Zhang et al. (2018)
NKA-9	Xie et al. (2018a)
Strata-X	Belles et al. (2017)
	Belles et al. (2018)
Strata-XL-A	Chen et al. (2017)
	Chen et al. (2018)
	Zhang et al. (2018)
	D'Angelo and Starnes (2016)
	Chen et al. (2012)
	Chen et al. (2013)
	Chen et al. (2014)
	Chen et al. (2015a)
	Chen et al. (2015b)
	Guo et al. (2017a)
	Guo et al. (2017b)
	Chen et al. (2018)
	D'Angelo (2018)
XAD-18	Xie et al. (2018a)
XDA-600	Chen et al. (2017)
PCM	Ren et al. (2018)
Sepra ZT	Stroski et al. (2018)
XDA-1	Xie et al. (2018b)
	Xie et al. (2018a)
TiO_2	Fauvelle et al. (2015)
MAX	Guibal et al. (2017a)
MIP	Dong et al. (2014)

Membranes.

Membranes play an optional role of protection of the diffusive gel against particles and degradation. Whatever the membranes used, pore size was 0.45 μm and the thickness was 0.14 mm (0.17 mm for nylon membrane used by D'Angelo and Starnes (2016).

The choice between different membranes was made by testing adsorption of targeted compounds on membranes or assuming the analyte should not interact with the selected membrane.

A total of 9 types of membranes were tested for o-DGT (list of membranes tested are available in **Table I.3**). Polyethersulfone (PES) membranes are the most popular for sampling polar organic compounds and were used in 10 studies. However, for four authors (Challis et al. 2016, Chen et al. 2017, Xie et al. 2018b, Zheng et al. 2014), interest compounds (2,4-D, acetochlor, atrazine, bisphenol A, bisphenol B, bisphenol F, carbamazepine, chlorpyrifos, clarithromycin, clothianidin, diazinon, diclofenac, enrofloxacin, erythromycin, estradiol, estriol, estrone, ethynylestradiol, fenoprofen, fluoxetine, gemfibrozil, ibuprofen, imidacloprid, ketoprofen, naproxen, paroxetine, propranolol, roxithromycin, sulfachlorpyridazine, sulfadimethoxane, sulfamethoxazole, sulfapyridine and sulfisoxazole) were significant adsorbed (from 10 to 100%) by this membrane.

Other authors choose to use naked o-DGT. This configuration was used by 7 articles and was the second most used strategy for o-DGT.

The other membranes used were PTFE (Zheng et al. 2014), nucleopore track-etch (Chen et al. 2017, 2018), PVDF (Guo et al. 2017b) and Nylon (D'Angelo and Martin 2018). Adsorption on membrane was tested by authors and, whatever membranes, no significant adsorption (<5%) was observed by these authors.

Table I.3: Membranes tested by authors.

Membranes tested	Authors
Cellulose nitrate	Chen et al. (2017)
Cyclopore track-etch	Chen et al. (2017)
Mixed cellulose ester (MCE)	Zhang et al. (2018)
	Zheng et al. (2014)
	Guo et al. (2017a)
Nucleopore polycarbonate	Chen et al. (2017)
Nucleopore track-etch	Chen et al. (2017))
	Chen et al. (2018)
Nylon	Zhang et al. (2018)
	Zheng et al. (2014)
	Guo et al. (2017a)
	D'Angelo et al. (2018)
PES	Xie et al. (2018b)
	Zheng et al. (2014)
	Challis et al. (2016)
	Chen et al. (2017)
	Ren et al. (2018)
	Xie et al. (2018a)
	Zhang et al. (2018)
	Chen et al. (2012)
	Chen et al. (2013)
	Chen et al. (2014)
	Chen et al. (2015a)
	Chen et al. (2015b)
	Fauvelle et al. (2015)
	Guo et al. (2017a)
PTFE	Zheng et al. (2014)
	Xie et al. (2018b)
	Zhang et al. (2018)
	Guo et al. (2017a)
PVDF	Guo et al. (2017b)
No membrane	Guibal et al. (2017a)
	Buzier et al. (2018) – submitted to Chemosphere
	Stroski et al. (2018)
	Xie et al. (2018b)
	Challis et al. (2016)
	Challis et al. (2018)

STUDIED COMPOUNDS

112 compounds have been tested from different action families: pharmaceuticals, hormones, illicit drugs, bisphenol, household products, personal care products, endocrine disrupting chemicals and pesticides. Pharmaceuticals were the most studied compounds. The list of compounds with their corresponding receiving phase is presented in **Annexe 1**. Compounds investigated displayed a wide range of hydrophobicity ($-3.43 < LogP < 7.51$). Glyphosate (tested in one article) and tetracycline (tested in one article) were the two most polar compounds whereas nonylphenol (tested in one article) and salinomycin (tested in two articles) were the two more hydrophobic compounds sampled by o-DGT.

The two most used binding phases are HLB and XAD-18 which have been tested for sampling 59 and 50 different compounds, respectively. The most studied compound was sulfamethoxazole (11 articles) and corresponds to the first compound tested on o-DGT (Chen et al. 2012). Sulfonamide was the pharmaceutical family the most deeply studied with 19 compounds. For this pharmaceutical family, four receiving phases were used: XAD-18, HLB, XDA-1 and PCM.

Each compound is characterized by a diffusion coefficient. These diffusion coefficients are detailed in **Annexe 1**. Diffusion coefficients are in the same order than diffusion coefficient of metals (*i.e.* 10^{-6} cm^2 s^{-1}). For a given compound, difference between diffusion coefficients determined by two different authors was lower than a factor 2, except for 4 compounds which diffusion coefficients varied for a factor slightly higher than 2 (factor 2.51, 2.37, 2.59 and 2.47 for chlorpyrifos, ciprofloxacin, clarithromycin and enrofloxacin, respectively). For these latter compounds, the larger difference is explained by the use of agarose or polyacrylamide diffusive gels (chlorpyrifos), the presence or not of a protective membrane (ciprofloxacin, clarithromycin and enrofloxacin), or the use of different methods of determination (clarithromycin and enrofloxacin). Diffusion coefficient obtained in polyacrylamide diffusive gel was lower than the one in agarose diffusive gel. This difference can be explained by the smaller pore size of polyacrylamide gels compared to agarose gels (Scally et al. 2006, Zhang and Davison 1999). The uncertainty of diffusive coefficient induces the more part of uncertainty in C_w (uncertainty in C_w is estimated in order of 23%) (Belles et al. 2018).

INFLUENCE OF ENVIRONMENTAL FACTORS: pH, IONIC STRENGTH, DOM AND DOC

The o-DGT robustness was tested by several authors with the study of pH and ionic strength. These parameters could influence o-DGT measurement by modifying the analyte speciation and/or the binding phase.

pH.

Depending on pH and its pKa, an organic compound can be neutral or ionic (cationic, anionic or zwitterionic). A wide range of pH had been tested by authors (from 3 to 11). The pH studies were performed using the ratio C_{DGT} / C_w (where C_{DGT} was the analyte concentration in solution estimated with o-DGT and C_w was the analyte concentration directly measured in solution). The ratio C_{DGT} / C_w have to be range

between 0.8 and 1.2 (20% of inaccuracy). Results show no influence of pH on uptake in o-DGT for sulfamethoxazole for pH ranged from 5 to 9 (Chen et al. 2012), for hormones for pH ranged from 3.5 to 9.5 (Chen et al. 2018), for household and personal care products for pH ranged from 3.5 to 9.5 (Chen et al. 2017), for 4-chlorophenol for pH ranged from 3 to 7 (Dong et al. 2014), for 17-β-estradiol for pH ranged from 5 to 8 (Guo et al. 2017b), for illicit drugs for pH ranged from 4 to 9 (Guo et al. 2017a), for antibiotics for pH ranged from 4.2 to 8.4 (Ren et al. 2018), for endocrine disruptive chemicals for pH ranged from 7 to 9 (Xie et al. 2018b), for methcathinone et ephedrine for pH ranged from 4 to 11 (Zhang et al. 2018) and for bisphenols for pH ranged from 4 to 8 (Zheng et al. 2014). However, some compounds were influenced by pH. It was the case of 4-chlorophenol at pH=8 with the inaccuracy was upper than 30% (Dong et al. 2014). The ratio C_{DGT} / C_w was calculated for aniobiotics by Xie et al. (2018a) for pH ranging from 4.8 to 8.9. For this author, a good accuracy was observed in most of case (>80%) but some compounds have influence when pH < 7.3 (norfloxacin, enrofloxacin and ofloxacin with a ration upper than 1.2 and for sulfadimethoxine with a ratio lower than 0.8). For Guibal et al. (2017a), ratio C_{DGT} / C_w was calculated for anionic pesticides. The ratio were not significantly different of 80% of accuracy excepted for chlorsulfuron with an inaccuracy <30%. This author have observed a decrease of ratio with increase of pH (Guibal et al. 2017a). Uptake difference between two receiving phases had been observed by two authors (Guibal et al. 2017a, Stroski et al. 2018). Similarly, the influence of pH on sampler uptake and diffusion was tested by Stroski et al. (2018) for 31 compounds (pharmaceuticals, hormones and pesticides). They hypothesized that sorption mechanism on the receiving phase changed with speciation of analyte, in other words there are a change of analyte-sorbent interaction due to speciation changing of analyte. The sorption mechanism changes resulted in decreased analyte uptake and sorption capacity. This author recommended future efforts involving the development and calibration considering pH as an important factor.

Ionic strength.

Ionic strength can affect sampling by the "salting-out" effect reducing the analyte solubility (Togola and Budzinski 2007, Xie et al. 1997, Zhang and Zhou 2005) and can reduces the electrostatic repulsions due to the screening effect of the surface charge (Fontecha-Camara et al. 2007, Joseph et al. 2011). Ionic strength effect was tested by 12 authors by varying ionic strength from 0.0001 to 1 M of NaCl. The effect was calculated with the ratio C_{DGT} / C_w and results showed sampling on o-DGT was independent on ionic strength from 0.001 to 0.5 M (Guo et al. 2017a, Guo et al. 2017b, Ren et al. 2018, Zhang et al. 2018, Zheng et al. 2014). The same results was observed for sulfamethoxazole by Chen et al. (2012) but with a higher effect at 0.5 M with a decrease of the ratio C_{DGT} / C_w but accuracy was higher than 70%. Chen et al. (2018) observed no effect on hormone uptake in o-DGT for ionic strength from 0.001 to 0.5 M except for estrone for ionic strength at 0.5 M with Strata-XL-A as binding phase with a ratio C_{DGT} / C_w ranging between 0.7 and 0.8. Chen et al. (2017) observed no effect on uptake of household and personal care products for ionic strength from 0.001 to 0.5 M except for butylated hydroxyanisole and triclosan for ionic strength at 0.5 M with a decrease of the ratio C_{DGT} / C_w but accuracy was higher than 70% and 50%, respectively. Xie et al.

(2018b) had tested ionic strength from 0.4 to 0.8 M and had observed no effect on endocrine disrupting chemicals sampling.

In contrast, ionic strength from 0.0001 to 0.1 M had no effect on 4-chlorophenol sampling but for higher ionic strength (0.7 M), the ratio C_{DGT} / C_w was upper than 1.2 (Dong et al. 2014).

Higher inaccuracy with relatively low ionic strength (0.01 to 0.3 M) was observed by only two authors (Guibal et al. 2017a, Xie et al. 2018a). For Guibal et al. (2017a), an effect of ionic strength was observed for chlorsulfuron with HLB as binding phase and for ioxynil with MAX as binding phase but ratios were always higher than 0.7. For Xie et al. (2018a), ionic strength had effect on the sampling of three macrolides (erythromycin, clarithromycin and azithromycin) for a low ionic strength (0. 001 M) with a ratio upper than 1.2. In this same study (Xie et al. 2018a), ratio was lower than 0.8 for 9 compounds (sulfapyridine, sulfadiazine, sulfamethoxazole, sulfathiazole, sulfachloropyridine, norfloxacin, ciprofloxacin, thiamphenicol and florfenicol). The difference between these pharmaceuticals and the three macrolides can be explained by their chemical form. At pH = 8, the 9 antibiotics with low ratio were charged negatively whereas the 3 macrolides were charged positively.

To conclude on ionic strength, o-DGT can be used to estimate contamination by organic compounds in freshwater (Chen et al. 2012, Chen et al. 2017, Guibal et al. 2017a, Guo et al. 2017a, Zhang et al. 2018, Zheng et al. 2014). This passive sampler can be also used to estimate contamination of some antibiotics with PCM as binding phase (Ren et al. 2018) or some endocrine disrupting chemicals with XDA-1 as binding phase (Xie et al. 2018b) in water with high ionic strength such as seawater.

Dissolved Organic Matter.

Dissolved Organic Matter (DOM) can had two type of effects. First, DOM can cause competition over analyte for sorption to the binding phase and secondly, reactions between DOM and analytes can alter analyte diffusion (Davison et al. 2015, Guo et al. 2017b). These three effects can alter analyte uptake by o-DGT samplers. Indeed, a slight alteration (the ratio C_{DGT} / C_w was 0.6) of triclosan sampling was observed (Chen et al. 2017) for DOM concentration higher than 2 mgDOM L^{-1}. This hydrophobic compounds bind to DOM making diffusion trough diffusive gel more difficult. Dong et al. (2014) similarly observed alteration of 4-chlorophenol sampling for DOM concentration ranging from 9.8 to 36.5 mgC L^{-1}. Conversely, sampling of several compounds (hormones and household and personal care chemicals) was found unaltered with DOM concentrations ranging from 0 to 20 (Chen et al. 2017, 2018) or 31 mg L^{-1} (Guo et al. 2017b).

It is likely that sampling alteration caused by DOM is compound dependent but also DOM dependent. Until more work is done to investigate DOM effect, interpretation of o-DGT derived concentration should be made with caution when DOM is significantly present.

APPLICATION & FIELD DEPLOYMENT

Field deployments were tested in different environmental matrix. The first application was made in a river in United-Kingdom (Chen et al. 2012) to estimate contamination of sulfamethoxazole. Deployment of o-

DGT was performed during 14 days. Deployments in river were also performed by Zheng et al. (2014), Guo et al. (2017a), Zhang (2018), Guibal et al. (2017a) and Stroski et al. (2018) for 7 to days-duration. These authors concluded that o-DGT devices were suitable to detect organic pollution in freshwaters.

Three authors have tested deployment in coastal waters (Ren et al. 2018, Xie et al. 2018a, Xie et al. 2018b). After 3-day deployment of o-DGT (XDA-DGT) in coastal waters, no biofouling was observed on the diffusive gel (Xie et al. 2018b) and five endocrine disrupting chemicals were detected. For 3 compounds (estradiol, Bisphenol A and acetochlor), differences between concentration determined by o-DGT and concentrations determined by spot sampling was observed (Xie et al. 2018b). Differences were explained because spot sampling cannot provide TWAC (Xie et al. 2018a, Xie et al. 2018b).

Deployment of o-DGT was performed in WasteWater Treatment Plant (WWTP) influent and effluent from 6h to 28 day (Challis et al. 2016, Chen et al. 2013, Chen et al. 2015b, Chen et al. 2017, 2018, Dong et al. 2014, Guo et al. 2017a, Guo et al. 2017b, Ren et al. 2018). A 7-day deployment was recommended by Chen et al. (2013). This duration allows to stay in kinetic uptake regime and to avoid significant biofouling. Biofouling was also observed by Challis et al. (2016) with a long-term deployment (21 days) but accumulation was still linear and indicated that sampler capacity was sufficient to traditional deployment times (from 2 to 4 weeks) in impacted surface waters.

The last application of o-DGT was in soils system to estimate labile concentration of atrazine (Lin et al. 2018), sulfonamides and trimethoprim (Chen et al. 2015a, Chen et al. 2014). Deployment time was 1 day (Chen et al. 2015a, Lin et al. 2018) and from 5h to 481h (≈ 20 days) (Chen et al. 2014).

FUTURE NEEDS FOR O-DGT DEVELOPMENT

This review collected studies which demonstrated the potential of o-DGT. The o-DGT is of particular interest compared to other passive sampler since it have a better robustness over flow variation (Buzier et al. 2018 – submitted to Chemosphere) and allows deployments in soils (Chen et al. 2015a, Chen et al. 2014, Lin et al. 2018). However, a disadvantage of o-DGT compared to others passive samplers for organic contaminants is its lower sampling rates. These reduced sampling rates are mostly due reduced exposure area of o-DGT compared to other passive samplers (Buzier et al. 2018 - submitted to Chemosphere, Chen et al. 2013, Guibal et al. 2017a) . An increase of surface area should allow to increase sampling rates and consequently improve sensitivity. Buzier et al. (2018 - submitted to Chemosphere) estimated for pharmaceutical compounds that a 160 cm^2 sampling area (~7 cm radius) similar sampling rates compared to Polar Organic Chemical Integrative Sampler (POCIS). Such a theoretical o-DGT configuration must however be tested in the field, since physical constrains on these larger gels could be significant.

In many cases, where organic pollutants are present in very low concentration, long deployment times (*e.g.* several weeks) would be preferred to increase analyte concentration in the sampler. However, longer deployment in environmental systems will favor biofouling formation in front of the samplers as already observed by Challis et al. (2016), Chen et al. (2013). Although biofouling was not studied for organic compounds passive sampling, it is likely to alter analyte sampling as observed for inorganic compounds

(Feng et al. 2016, Pichette et al. 2009, Uher et al. 2017, Uher et al. 2012). It was shown by Devillers et al. (2017) that some metals were adsorbed onto biofouling resulting in decreasing compound concentration at the water/sampler interface and consequently in smaller diffusion rate into the sampler. Given that several organic compounds have a high affinity for organic matter (Chen et al. 2017), it is likely that these compounds will bind to biofouling and consequently their passive sampling should be altered. However, such behaviors still have to demonstrated for organic compounds.

A standardization of the calibration procedures (*i.e.* diffusion coefficient determination, see previous sections) should be done to homogenize results. Indeed, determination of diffusive coefficient can be performed by three different methods. Determination of diffusion coefficients with the time series deployments method allows using more environmentally relevant concentrations and could be considered as the most relevant method. However, it results from model fitting to not only diffusion process but also to compound binding within the sampler. Rather than a physical diffusion coefficient, it is a calibration parameter that should be called an "effective diffusion coefficient". Moreover, some authors did not take into account the entire diffusion path (diffusive gel and membrane). Considering that membranes were previously shown to alter diffusion coefficient of some metals (Buzier et al. 2014), it is possible that diffusion of some organic compounds is also altered. Until it is demonstrated that the membrane used has no influence on the diffusion of the targeted compounds, it is advisable to incorporate the membranes in the experiments of diffusion coefficient determination.

CONCLUSION

This review investigated the various available binding gel combined with diffusive gel and membranes used for o-DGT. This recent passive sampler shows great performance for the monitoring of organic compounds in environmental water bodies or in soil systems. A large type of organic compounds has been tested: ionic, polar and apolar compounds with logP ranged from -3.43 to 7.51. If we combine all the binding and diffusive gels available (two diffusive gels and nine binding gels), 18 configurations are possible. However, the two most commonly used configurations are agarose-XAD18 and agarose-HLB..

These two configurations allow to sample organic compounds in a large range of pH (4-9) and ionic strength (0.001 to 0.1 M). This robustness indicated that o-DGT can be used in most natural waters. However, each compound has a different comportment due to its chemical form. It is important to adapt the configuration of the sampler to the know properties of studied compounds.

Considering that, compared to other samplers o-DGT is less influenced by flow variations and allows deployment in several environmental compartments (*e.g.* water, soil and sediment), it seems to have a great potential for monitoring a large class of organic pollutants in environment with an uncertainty estimated in order of 20% (Belles et al. 2018, Buzier et al. 2018 - submitted to Chemosphere) .

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Chapitre II. Matériels et méthodes

II.1. Matériels et qualité des réactifs.

Les réactifs et le matériel utilisés dans les expérimentations de laboratoire ou sur le terrain sont présentés dans le **Tableau II.1** et **Tableau II.2**. Le matériel et l'appareillage employés spécifiquement pour l'analyse des pesticides et des résidus de médicaments sont détaillés dans le **Tableau II.3**.

Tableau II.1 : Réactifs et matériels utilisés.

Réactif / Matériel	Caractéristiques	Fournisseur	Chapitre(s)
Acétate d'éthyle	Qualité LC-MS Pureté ≥ 99,5 %	Sigma Aldrich Carlo Erba	Chap. III – IV – V
Acide formique	Qualité analytique 99-100 %	Normapur	Chap. III.B
Acrylamide	Pureté ≥ 98,0 %	Sigma-Aldrich	Chap. III.B
Agarose	Réactif biologique	Sigma-Aldrich	Chap. III
Agent réticulant « cross-linker »	Produit breveté Solution aqueuse à 2 %	DGT Research	Chap. III
Azote	Qualité 5.0	Linde Gas	Chap. III.B – IV.B – V.B
Cartouche SPE HR-X	Taille particule 85 µm 60 mg 3 mL	Macherey-Nagel	Chap. III – IV – V
Cartouche SPE vide	3 mL	Macherey-Nagel	Chap. III – IV – V
DGT (piston)	Produit commercial	DGT Research	Chap. III
Eau minérale	-	Evian	Chap. III – IV – V
Eau ultrapure (EUP)	Résistivité > 18,2 MΩ/cm	MilliQ - Millipore	Chap. III – IV – V
Filtre GF/F	Pores 0,7 µm Diamètre 47 mm	Whatman	Chap. III – IV – V
HCl	Qualité analytique Concentration ≥ 37,0 %	Prolabo Normapur	Chap. III.B – IV – V
H_3PO_4	Concentration ≥ 85,0 %	Sigma-Aldrich	Chap. III.B
Isopropanol	Qualité LCMS	J.T. Baker	Chap. III.B
K_2HPO_4	Pureté ≥ 99,0%	Prolabo	Chap. III.B
KH_2PO_4	Pureté ≥ 99,0%	Prolabo	Chap. III.B
Membranes PolyEstherSulfone (PES)	Pores 0,1 µm Diamètre 90 mm	Pall Supor®	Chap. III – IV – V
Méthanol (MeOH)	Qualité analytique	Carlo Erba J.T. Baker Scharlau	Chap. III – IV – V
Méthanol (MeOH)	Qualité LC-MS	Carlo Erba J.T. Baker Scharlau	Chap. III – IV – V
$NaNO_3$	Pureté ≥ 99,5 %	Prolabo	Chap. III.B
NaOH	Pureté ≥ 99,0 %	Merck	Chap. III.B – V

N,N,N',N'-tétraméthyléthylènediamine (TEMED)	Pureté ≥ 99,5 %	Sigma-Aldrich	Chap. III
Oasis® HLB	Taille particule 60 µm	Waters	Chap. III – IV – V
Oasis® MAX	Taille particule 30 µm	Waters	Chap. III.B
Persulfate d'ammonium	Pureté ≥ 98 %	Fisher Scientific	Chap. III
POCIS	Produit commercial ou réalisé "maison"	ExposMeter Atelier Faculté des Sciences Limoges	Chap. III – IV – V

Tableau II.2 : Matériels utilisés.

Matériel	Caractéristiques / Modèle	Fournisseur	Chapitre(s)
Agitateur magnétique	Hytrel HTR 8068	IKA Color Squid	Chap. III – IV – V
Bain à ultrason	210 W / TS 540	Bioblock Scientific	Chap. III – IV – V
Cellule de diffusion	-	Atelier Faculté des Sciences Limoges	Chap. III.B
Chromatographie ionique	930 Compact IC Flex	Metrohm	Chap. III – IV – V
COT-mètre	Multi N/C 2100S	Analytikjena	Chap. III – IV – V
Courantomètre	Flo-Mate 2000	Marsh McBirney	Chap. III – IV – V
Etuve	Ecocell	MMM group	Chap. III – IV – V
Evaporateur petits volumes	TurboVap® LV	Biotage	Chap. III.C – IV.C – V.C
Evaporateur rotatif	Labo-rota S-300	Resona Technics	Chap. III.C – IV – V
Générateur azote	N_2Pico	Claind	Chap. III.C – IV.C – V.C
Micromètre	0-25 mm	Iso Master®	Chap. III
Module extraction (SPE)	-	Visiprep	Chap. III.B – IV.B – V
Module extraction phase solide (SPE)	GX-241	Gilson	Chap. III.C – IV.C
Oxymètre	HQ30D flexi	Hach	Chap. III – IV – V
pH-mètre	Five Easy	Mettler Toledo	Chap. III – IV – V
Pompe péristaltique	Masterflex L/S 7519-10	Cole-Parmer Instrument Company	Chap. III.C – IV.C
Pousse seringue	-	Kd-Scientific	Chap. III.C – IV.C
Réservoir	200 L	Atelier Faculté des Sciences Limoges	Chap. III.C – IV.C
Rivière artificielle	500 L – 3 canaux	Atelier Faculté des Sciences Limoges	Chap. III.C – IV.C
Sonde multi-paramètres	Multi 3420 Set G	WTW	Chap. III – IV – V
Sonde pH	Sentix® 41-3 Sentix® 940-3 LE438	WTW WTW Mettler Toledo	Chap. III – IV – V
Sonde température	TG-4100	Tinytag	Chap. III – IV.C
Table agitation	KS 501 Digital	IKA-Werke	Chap. III – IV – V
Tampons pH	pH 4 & 7	Russell	Chap. III – IV – V
Titrateur automatique	Titrator TR 154	Schott Gerate	Chap. III – IV – V
"Vortex"	-	Heidolph	Chap. III – IV – V

Tableau II.3 : Matériels, réactifs et appareillages utilisés pour l'analyse des composés étudiés.

Matériel / Réactif / Appareillage	Caractéristiques / Modèle	Fournisseur	Chapitre(s)
Acide formique	Pureté > 99 %	Agilent Carlo Erba J.T. Baker	Chap. III – IV – V
Chromatographie liquide	1290 Infinity	Agilent	Chap. III – IV – V
Chromatographie liquide	Ultimate 3000	Dionex	Chap. V.B
Colonne C18	2,1 * 150 mm – 1,8 µm RRHD Zorbax Eclipse +	Agilent	Chap. III.C – IV.B – V.B
Colonne C18	2,0 * 100 mm – 2,7 µm RP18+ Nucleoshell	Macherey-Nagel	Chap. III – IV.C – V.C
Colonne C18	2,0 * 110 mm – 3,0 µm Gemini-NX	Phenomenex	Chap. V.B
Eau ultrapure	Résistivité > 18,2 MΩ/cm	MilliQ - Millipore	Chap. III – IV – V
Formate d'ammonium	LCMS Pureté > 99 %	Agilent Scharlau	Chap. III – IV – V
Générateur azote	Nigen LCMS 40-1	Claind Brezza	Chap. III – IV – V
Isopropanol	Qualité LC-MS	J.T. Baker	Chap. III – IV – V
Méthanol	Qualité LC-MS	Carlo Erba J.T.Baker Scharlau	Chap. III – IV – V
Spectromètre de masse à temps de vol	Accurate Mass 6540	Agilent	Chap. III – IV – V
Spectromètre de masse triple quadripôle	API2000	AB Sciex	Chap. V.B

II.2. Propriétés et caractéristiques des molécules étudiées.

Les molécules étudiées dans ces travaux ont été sélectionnées en tenant compte des molécules détectées dans les eaux de rivières d'après la litérature scientifiques internationales et nationales mais également des données de consommation à l'échelle locale.

II.2.1. Pesticides.

Les principales caractéristiques des pesticides neutres et ioniques étudiés sont présentées dans le **Tableau II.4** et **Tableau II.5**. Deux méthodes analytiques sont utilisées pour l'analyse des pesticides : la méthode analytique n°1 (MA1) est employée pour l'analyse des pesticides neutres et la méthode analytique n°2 (MA2) pour l'analyse des pesticides ioniques. Les standards deutérés utilisés sont présentés dans le **Table II.6**.

Tableau II.4 : Liste des pesticides neutres étudiés ([1]http://chemicalize.com).

Pesticide	Usage	N°CAS	Pureté (%)	Fournisseur	LogP[1]
3-hydroxy-carbofuran	Métabolite	16655-82-6	99,0	Dr. Ehrenstorfer GmbH	1,13
Acétochlore	Herbicide	34256-82-1	98,0	Dr. Ehrenstorfer GmbH	3,50
Alachlore	Herbicide	15972-60-8	99.5	Dr. Ehrenstorfer GmbH	3,59
Atrazine	Herbicide	1912-24-9	99,0	Dr. Ehrenstorfer GmbH	2,20
Azoxystrobine	Fongicide	131860-33-8	99,5	Dr. Ehrenstorfer GmbH	4,22
Bénoxacor	Herbicide	98730-04-2	99,5	Dr. Ehrenstorfer GmbH	2,44
Carbaryl	Insecticide	63-25-2	98,9	Dr. Ehrenstorfer GmbH	2,46
Carbendazime	Fongicide	10605-21-7	99,5	Dr. Ehrenstorfer GmbH	1,80
Carbofuran	Insecticide	1563-66-2	99,0	Dr. Ehrenstorfer GmbH	2,05
Chlorfenvinphos	Insecticide	470-90-6	99,0	Dr. Ehrenstorfer GmbH	4,30
Chlortoluron	Herbicide	15545-48-9	99,0	Dr. Ehrenstorfer GmbH	2,44
Cybutryne (Irgarol)	Fongicide	28159-98-0	99,0	Dr. Ehrenstorfer GmbH	2,99
Cyproconazole	Fongicide	94361-06-5	99,0	Dr. Ehrenstorfer GmbH	2,85
Dichlorophényl-méthyluréa (DCPMU)	Métabolite	3567-62-2	97,7	Dr. Ehrenstorfer GmbH	1,85
Dichlorophényl-uréa (DCPU)	Métabolite	2327-02-8	98,5	Dr. Ehrenstorfer GmbH	2,04
Atrazine-déséthyl (DEA)	Métabolite	6190-65-4	99,0	Dr. Ehrenstorfer GmbH	1,54
Terbuthylazine-déséthyl (DET)	Métabolite	30125-63-4	99,5	Dr. Ehrenstorfer GmbH	1,82
Atrazine-déisopropyl (DIA)	Métabolite	1007-28-9	98,7	Dr. Ehrenstorfer GmbH	1,12
Diméthachlore	Herbicide	50563-36-5	98,0	Dr. Ehrenstorfer GmbH	2,59
Diméthénamide	Herbicide	87674-68-8	99,0	Dr. Ehrenstorfer GmbH	2,92
Diméthoate	Insecticide	60-51-5	98,0	Dr. Ehrenstorfer GmbH	0,34
Diméthomorphe	Fongicide	110488-70-5	99,0	Dr. Ehrenstorfer GmbH	3,28
Diuron	Herbicide	330-54-1	98,0	Dr. Ehrenstorfer GmbH	2,53
Epoxiconazole	Fongicide	133855-98-8	98,5	Dr. Ehrenstorfer GmbH	3,74
Flurochloridone	Herbicide	61213-25-0	99,0	Dr. Ehrenstorfer GmbH	3,25
Flurtamone	Herbicide	96525-23-4	98,3	Dr. Ehrenstorfer GmbH	4,64
Flusilazole	Fongicide	85509-19-9	96,5	Dr. Ehrenstorfer GmbH	4,68
Hexazinone	Herbicide	51235-04-2	96,0	Dr. Ehrenstorfer GmbH	1,37
Imidaclopride	Insecticide	138261-41-3	98,0	Dr. Ehrenstorfer GmbH	0,87
Isopropylphényl-méthyluréa (IPPMU)	Métabolite	34123-57-4	99,5	Dr. Ehrenstorfer GmbH	1,58

Isopropylphényl-uréa (IPPU)	Métabolite	56046-17-4	99,0	Dr. Ehrenstorfer GmbH	1,87
Isoproturon	Herbicide	34123-59-6	99,0	Dr. Ehrenstorfer GmbH	2,57
Linuron	Herbicide	330-55-2	99,5	Dr. Ehrenstorfer GmbH	2,68
Métazachlore	Herbicide	67129-08-2	98,5	Dr. Ehrenstorfer GmbH	2,98
Méthomyl	Insecticide	16752-77-5	99,5	Dr. Ehrenstorfer GmbH	0,72
Métolachlore	Herbicide	51218-45-2	98,0	Dr. Ehrenstorfer GmbH	3,45
Métoxuron	Herbicide	19937-59-8	99,5	Dr. Ehrenstorfer GmbH	1,77
Norflurazon	Herbicide	27314-13-2	94,0	Dr. Ehrenstorfer GmbH	2,42
Norflurazon-desméthyl	Métabolite	23576-24-1	99,0	Dr. Ehrenstorfer GmbH	1,98
Pirimicarbe	Insecticide	23103-98-2	98,7	Dr. Ehrenstorfer GmbH	1,80
Simazine	Herbicide	122-34-9	98,0	Dr. Ehrenstorfer GmbH	1,78
Tébuconazole	Fongicide	107534-96-3	98,5	Dr. Ehrenstorfer GmbH	3,69
Terbuthylazine	Herbicide	5915-41-3	98,5	Dr. Ehrenstorfer GmbH	2,48
Thiodicarbe	Insecticide	59669-26-0	99,0	Dr. Ehrenstorfer GmbH	2,03

Tableau II.5 : Liste des pesticides ioniques étudiés ([1]Pesticide Properties DataBase : http://sitem.herts.ac.uk/aeru/ppdb).

Pesticide	Usage	N°CAS	Pureté (%)	Fournisseur	LogP[1]	pKa[1]
Bentazone	Herbicide	25057-89-0	99,0	Dr. Ehrenstorfer GmbH	-0,46	3,51
Chlorsulfuron	Herbicide	64902-72-3	97,0	Dr. Ehrenstorfer GmbH	-0,99	3,40
Ioxynil	Herbicide	1689-83-4	99,0	Dr. Ehrenstorfer GmbH	2,20	4,10
Mécoprop	Herbicide	7085-19-0	98,7	Dr. Ehrenstorfer GmbH	-0,19	3,11

Tableau II.6 : Liste des standards deutérés utilisés et leurs caractéristiques (*Etalon interne MA1 et MA2 : étalon interne utilisé respectivement pour la méthode analytique n°1 et n°2 ; Etalon de recouvrement : étalon utilisé pour l'extraction des échantillons ponctuels).

Pesticide deutéré	Usage*	N°CAS	Pureté (%)	Fournisseur
Atrazine-d5	Etalon interne MA1	163165-75-1	99,0 98,5 99,6	Dr. Ehrenstorfer GmbH Dr. Ehrenstorfer GmbH HPC Standards GmbH
Bentazone-d6	Etalon interne MA2	25057-89-0	98,5	Dr. Ehrenstorfer GmbH
Carbaryl-d3	Etalon interne MA1	1433961-56-8	98,5 97,5	Dr. Ehrenstorfer GmbH
Carbofuran-d3	Etalon interne MA1	1007459-98-4	98,0 99,9	Dr. Ehrenstorfer GmbH HPC Standards GmbH
Chlorpyrifos-d10	Etalon interne MA1	285138-81-0	97,0 99,5	Dr. Ehrenstorfer GmbH HPC Standards GmbH
DEA-d6	Etalon interne MA1	1216649-31-8	98,0 99,0	Dr. Ehrenstorfer GmbH
DIA-d5	Composé de performance et de référence (PRC)	1189961-78-1	98,0 99,7	Dr. Ehrenstorfer GmbH Analytical Standard Solutions
Diméthoate-d6	Etalon interne MA1	12119794-81-6	99,6	HPC Standards GmbH
Diuron-d6	Etalon interne MA1	1007536-67-5	98,0 99,9	Dr. Ehrenstorfer GmbH HPC Standards GmbH
MCPA-d3	Etalon interne MA2	352431-14-2	95,0 98,5	Dr. Ehrenstorfer GmbH HPC Standards GmbH
Méthomyl-d3	Etalon interne MA1	1398109-07-3	99,9	HPC Standards GmbH
Métolachlore-d6	Etalon interne MA1	1219803-97-0	97,7 98,0	Dr. Ehrenstorfer GmbH
Metsulfuron-méthyl-d3	Etalon interne MA2		96,0	Dr. Ehrenstorfer GmbH
Monuron-d6	Etalon de recouvrement	217488-65-8	98,0 98,2	Dr. Ehrenstorfer GmbH HPC Standards GmbH
Pirimicarbe-d6	Etalon interne MA1	1015854-66-6	97,5 99,8	Dr. Ehrenstorfer GmbH HPC Standards GmbH
Prometryne-d6	Etalon de recouvrement	1705649-52-0	99,9 97,0	Dr. Ehrenstorfer GmbH
Simazine-d5	Etalon de recouvrement	220621-41-0	99,0 97,0	Dr. Ehrenstorfer GmbH
Tébuconazole-d6	Etalon interne MA1	-	95,0 97,0	Dr. Ehrenstorfer GmbH
Tébuconazole-d9	Etalon interne MA1	1246818-83-6	99,1	HPC Standards GmbH

II.2.2. Résidus pharmaceutiques et traceurs humains.

Les composés pharmaceutiques avec leur pureté, leur famille et leur fournisseur sont présentés dans le **Tableau II.7**. Les étalons internes utilisés pour l'analyse des composés pharmaceutiques (méthode analytiques MA3) sont listés dans le **Tableau II.8**.

Tableau II.7 : Liste des composés pharmaceutiques étudiés et leurs caractéristiques ([1]http://chemicalize.com).

Composé pharmaceutique	Classe d'action	N°CAS	Pureté (%)	Fournisseur	LogP[1]
Acétaminophène	Anti-inflammatoire	103-90-2	99,9	HPC Standards GmbH	0,91
Aténolol	β-bloquant	29122-68-7	99,3	HPC Standards GmbH	0,43
Bézafibrate	Anti-cholestérol	41859-67-0	99,6	HPC Standards GmbH	3,99
Bisoprolol	β-bloquant	66722-44-9	98,1	Santa Cruz	2,20
Caféine	Traceur Humain	58-08-2	98,5	Dr. Ehrenstorfer	-0,55
Carbamazépine	Antibiotique	298-46-4	99,5	Dr. Ehrenstorfer	2,77
Clarithromycine	Antibiotique	81103-11-9	99,4	HPC Standards GmbH	3,24
Dexaméthasone	Anti-inflammatoire	50-02-2	98,0 99,2	Sigma-Aldrich HPC Standards GmbH	1,68
Diazépam	Psychotrope	439-14-5	99,9	Neochema GmbH	3,08
Diclofénac	Anti-inflammatoire	15307-86-5	99,5 99,9	Dr. Ehrenstorfer HPC Standards GmbH	4,26
Econazole	Anti-fongique	27220-47-9	98,0	Dr. Ehrenstorfer	5,35
Erythromycine	Antibiotique	114-07-8	97,0	HPC Standards GmbH	2,60
Fenbendazole	Anti-parasitaire	43210-67-9	99,5	Sigma-Aldrich	3,41
Fénofibrate	Anti-cholestérol	49562-28-9	99,9		5,28
Flunixine	Anti-inflammatoire	38677-85-9	99,9 99,8	Sigma-Aldrich HPC Standards GmbH	3,69
Fluoxétine	Psychotrope	54910-89-3	99,8	HPC Standards GmbH	4,17
Gemfibrozil	Anti-cholestérol	25812-30-0	99,0	Dr. Ehrenstorfer	4,39
Griséofulvine	Anti-fongique	126-07-8	97,4	Sigma-Aldrich	2,17
Indométacine	Anti-inflammatoire	53-86-1	99,9	HPC Standards GmbH	3,53
Kétoprofène	Anti-inflammatoire	22071-15-4	99,1	HPC Standards GmbH	3,61
Lincomycine	Antibiotique	154-21-2	99,0 99,9	Santa Cruz HPC Standards GmbH	-0,32
Metformine	Antidiabétique	1115-70-4	98,2		-0,92
Métoprolol	β-bloquant	51384-51-1	99,8	HPC Standards GmbH	1,76
Métronidazole	Antibiotique	443-48-1	99,3	HPC Standards GmbH	-0,46
Monensine	Antibiotique	17090-79-8	98,8	HPC Standards GmbH	4,82
Nadolol	β-bloquant	42200-33-9	99,1	Dr. Ehrenstorfer	0,87
Oméprazole	Inhibiteur pompe à	73590-58-6	99,9	HPC Standards GmbH	2,43
Paraxanthine	Métabolite caféine	611-59-6	99,0	Santa Cruz	0,24
Paroxétine	Psychotrope	61869-08-7	98,3 99,8	Santa Cruz HPC Standards GmbH	3,15
Périndopril	β-bloquant	107133-36-8	97,0	Santa Cruz	0,63
Praziquantel	Antiparasitaire	55268-74-1	99,7	Sigma-Aldrich	2,30
Prednisolone	Anti-inflammatoire	50-24-8	99,4	HPC Standards GmbH	1,27
Propanolol	β-bloquant	525-66-6	99,9	HPC Standards GmbH	2,58
Pyrantel	Antiparasitaire	15686-83-6	95,1	Sigma-Aldrich	1,96
Roxithromycine	Antibiotique	80214-83-1	91,7	HPC Standards GmbH	3,00
Salbutamol	Anti-asthme	18559-94-9	99,5	Dr. Ehrenstorfer	0,34
Sotalol	β-bloquant	3930-20-9	98,5	Dr. Ehrenstorfer	-0,40
Sucralose	Traceur Humain	56038-13-2	99,0	Dr. Ehrenstorfer	-0,47
Sulfadiazine	Antibiotique	68-35-9	99,3 99,4	Sigma-Aldrich HPC Standards GmbH	0,39

Sulfamérazine	Antibiotique	127-79-7	99,8	HPC Standards GmbH	0,52
Sulfaméthoxazole	Antibiotique	723-46-6	99,9	Sigma-Aldrich	0,79
Sulfaméthoxypyridazine	Antibiotique	80-35-3	99,0	Dr. Ehrenstorfer	0,47
Terbutaline	Anti-asthme	23031-25-6	99,0	Dr. Ehrenstorfer	0,44
Thioridazine	Psychotrope	50-52-2	98,0	European Directorate for the Quality of Medicines & healthCare	5,47
Triclabendazole	Anti-parasitaire	68786-66-3	99,8	Sigma-Aldrich	5,88
Triméthoprime	Antibiotique	738-70-5	99,5	Sigma-Aldrich	1,28

Tableau II.8 : Liste des étalons internes utilisés pour l'analyse des composés pharmaceutiques et de leurs caractéristiques (*Etalon interne MA3 : étalon interne utilisé pour la méthode analytique n°3).

Composé pharmaceutique deutéré	Usage*	N°CAS	Pureté (%)	Fournisseur
Caféine-c3	Etalon interne M3	78072-66-9	98,0	Cambridge Isotope Laboratoires
Carbamazépine-d10	Etalon interne M3	132183-78-9	99,0	HPC Standards GmbH
Diclofénac-d4	Etalon interne M3	153466-65-0	98,0 99,0	Dr. Ehrenstorfer GmbH HPC Standards GmbH
Flunixine-d3	Etalon interne M3	1015856-60-6	99,2 99,7	Dr. Ehrenstorfer GmbH
Propanolol-d7	Etalon interne M3	1613439-56-7	99,9	HPC Standards GmbH
Salbutamol-d3	Etalon interne M3	1219798-60-3	98,0 97,6	Dr. Ehrenstorfer GmbH
Salbutamol-d9	Etalon interne M3	1781417-68-2	99,1	HPC Standards GmbH
Sulfaméthoxazole-d4	Etalon interne M3	1020719-86-1	98,5 97,9	Dr. Ehrenstorfer GmbH
Triclabendazole-d3	Etalon interne M3	1353867-93-2	99,3	HPC Standards GmbH
Triméthoprime-d3	Etalon interne M3	1189923-38-3	98,5	Dr. Ehrenstorfer GmbH

II.3. Protocoles expérimentaux.

II.3.1. Préparation des solutions mères et solutions « mix ».

Les solutions des standards de pesticides et de composés pharmaceutiques, appelées « solutions mères », ont été préparées dans les mêmes conditions. Le protocole est décrit **Figure II.1**. A partir des solutions mères, une solution « mix » est préparée (**Figure II.2**). Ces solutions ont été utilisées pour les expériences et pour l'analyse. Les solutions mères et les solutions appelées « mix » sont conservées au congélateur (-18°C) pendant 6 mois au maximum.

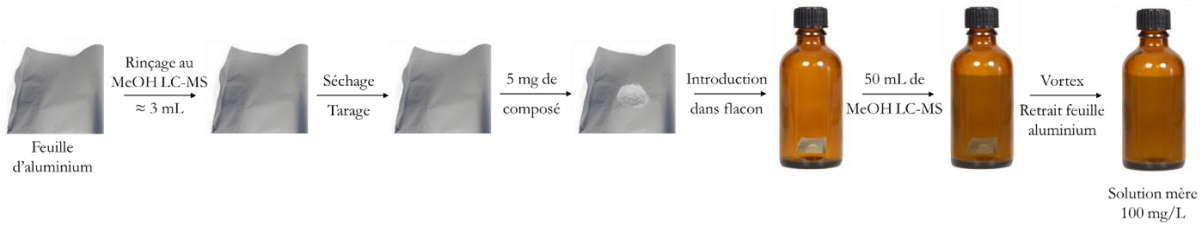

Figure II.1 : Protocole de préparation des solutions mères.

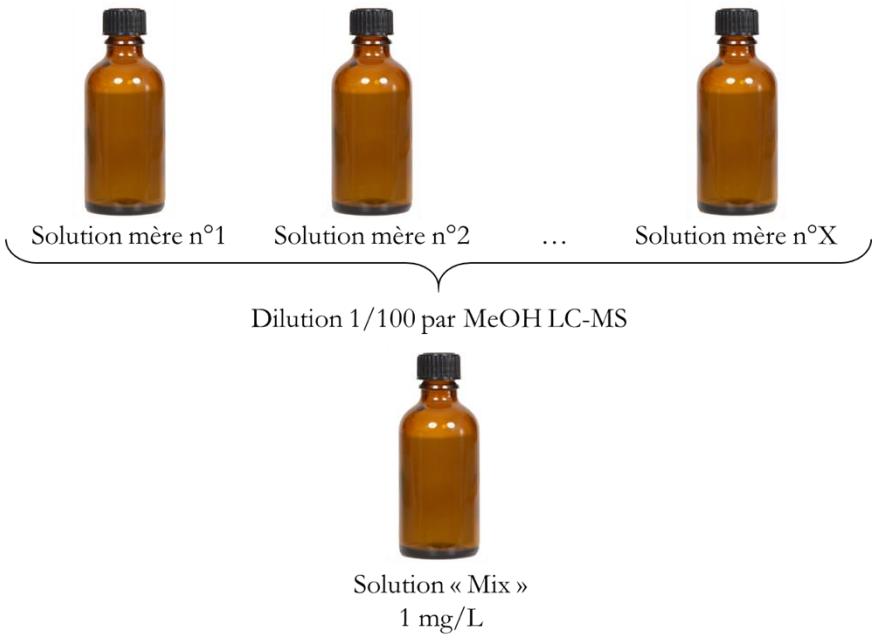

Figure II.2 : Protocole de préparation des solutions "mix".

II.3.2. Protocole POCIS & échantillons ponctuels.

Dopage de la phase réceptrice.

Avant montage de l'échantillonneur POCIS, la phase réceptrice (Oasis® HLB) est préalablement dopée avec un PRC (Performance Reference Compound) : la DIA-d5 (Mazzella et al. 2010). Le protocole de dopage est montré **Figure II.3** La phase est conservée au réfrigérateur à 4°C pour une durée maximale de 3 mois.

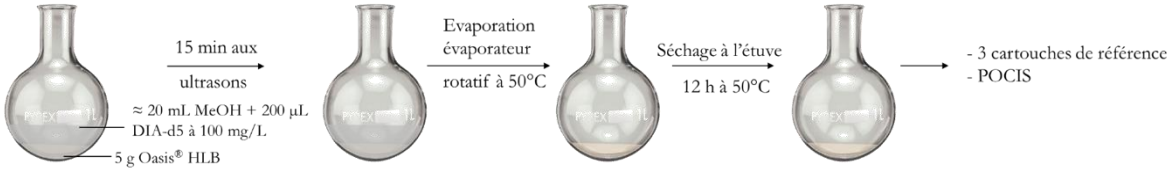

Figure II.3 : Dopage de la phase réceptrice (Oasis® HLB).

Nettoyage des membranes PES.

Les membranes en polyéthersulfone (PES) utilisées dans le POCIS sont préalablement lavées comme montré sur la **Figure II.4**. Ce protocole a été développé dans le chapitre IV.B. et a été appliqué à tous les chapitres (III, IV, et V).

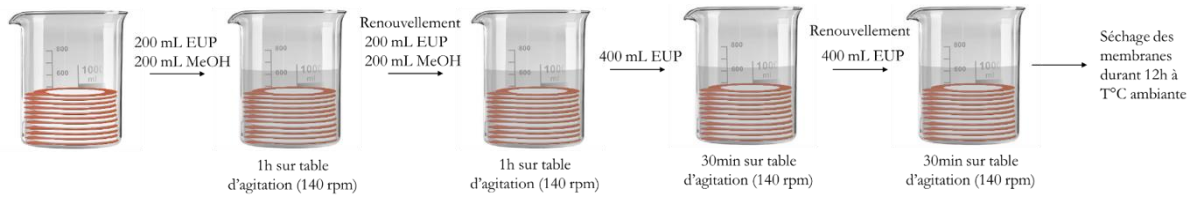

Figure II.4 : Protocole de lavage des membranes PES espacées par un séparateur en caoutchouc.

Montage d'un échantillonneur de type POCIS.

Le montage d'un POCIS, après le dopage de la phase réceptrice, est montré **Figure II.5**. Les membranes en PES lavées ont un côté brillant et un côté mat. Le côté brillant est placé vers l'extérieur, il limite l'attache du biofilm en milieu naturel. Le tout est maintenu par 3 boulons.

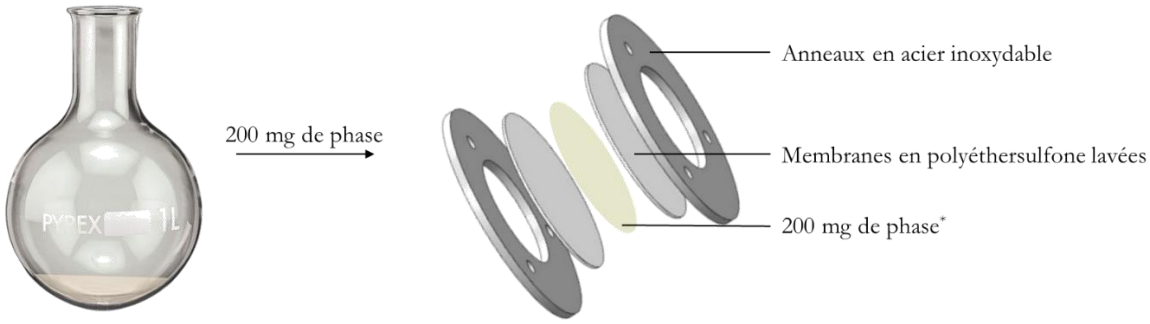

Figure II.5 : Montage d'un échantillonneur passif de type POCIS (*200 mg de phase Oasis® HLB dopée à la DIA-d5 ou Oasis® MAX).

Démontage d'un échantillonneur de type POCIS.

Une fois exposé, le POCIS est rincé et conservé au réfrigérateur (à environ 4°C) jusqu'à son traitement en vue de l'analyse. Le protocole est décrit **Figure II.6**. Ce protocole a été réalisé pour tous les POCIS employés dans ce travail de thèse.

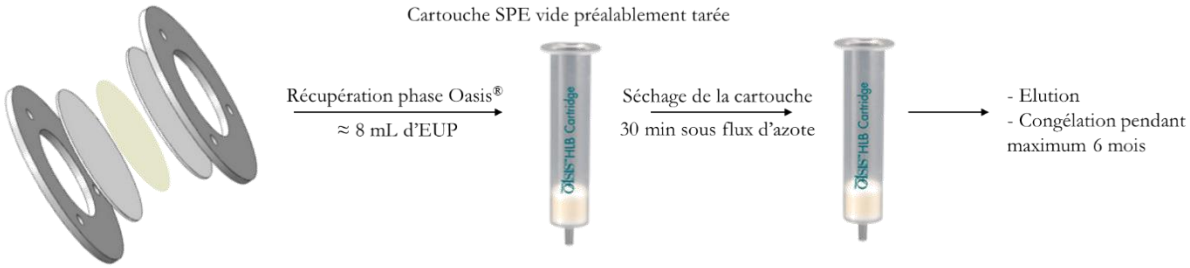

Figure II.6 : Démontage d'un échantillonneur passif de type POCIS.

Prélèvement ponctuel.

Des prélèvements ponctuels ont été effectués en milieu naturel (chapitres III.B et V.B) ou en laboratoire (chapitres III.C et IV.C). Le prélèvement est conservé dans une bouteille ambrée au réfrigérateur jusqu'à extraction (maximum 24h après le prélèvement), ensuite le protocole est détaillé **Figure II.7**.

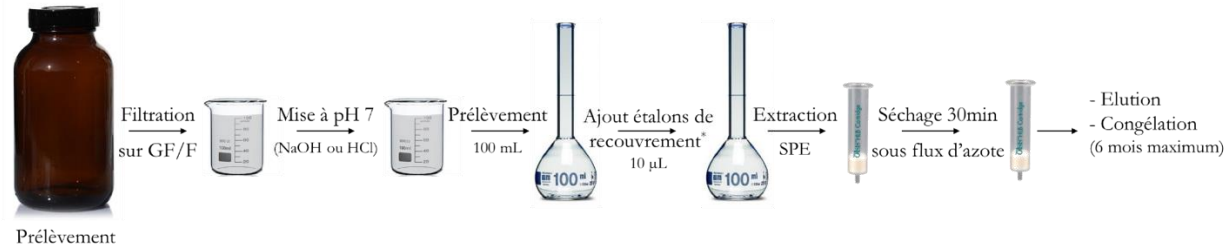

Figure II.7 : Protocole d'extraction des pesticides et des composés pharmaceutiques à partir d'un prélèvement ponctuel (*étalons de recouvrement : simazine-d5, monuron-d6 et prométryne-d6. Concentration dans le mix d'étalons de recouvrement : 5 mg/L pour la simazine-d5 et le monuron-d6 et 2,5 mg/L pour la prométryne-d6).

Élution des composés organiques.

Cette étape est identique pour les échantillonneurs passifs de type POCIS HLB, pour les prélèvements ponctuels et pour les cartouches de référence. Un tube en verre (permettant de récupérer l'éluât) est placé sur le module d'extraction Visiprep (chapitres III.B, IV.B et V) ou sur le module d'extraction automatisé Gilson (chapitres III.C et IV.C). Le protocole est détaillé sur la **Figure II.8** pour les composés polaires et moyennement polaires (pesticides neutres et composés pharmaceutiques) et sur la **Figure II.9** pour les pesticides ioniques. Les solvants utilisés sont des solvants de qualité LC-MS.

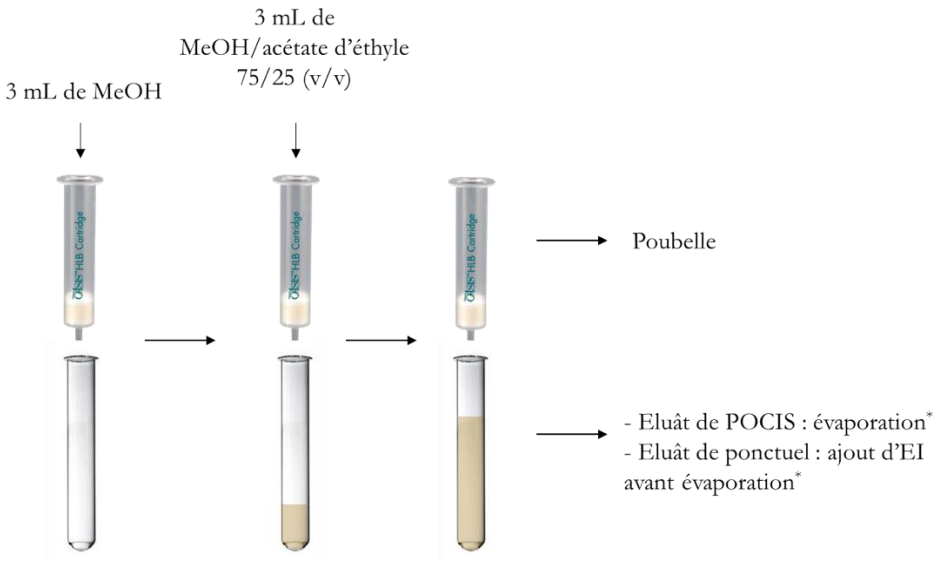

Figure II.8 : Élution des composés organiques polaires (*l'évaporation se fait à 35°C pendant 40 min).

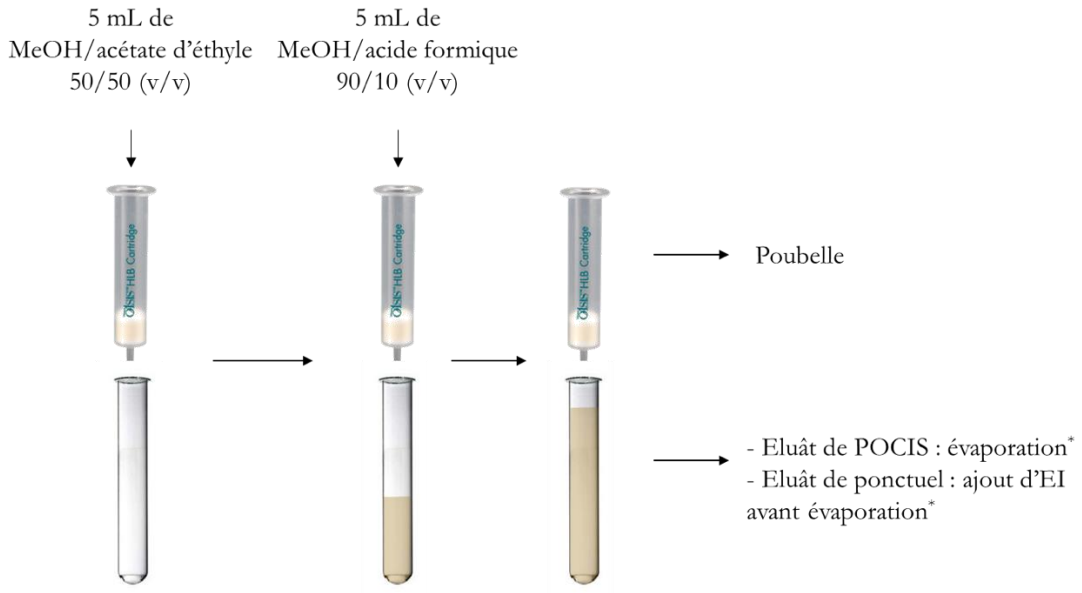

Figure II.9 : Élution des composés organiques ioniques à partir des POCIS MAX (*l'évaporation se fait à 35°C pendant 60 min).

Après élution, les extraits sont évaporés puis repris selon le protocole montré sur la **Figure II.10**. Les échantillons sont ensuite analysés (l'analyse est décrite dans la partie II.D).

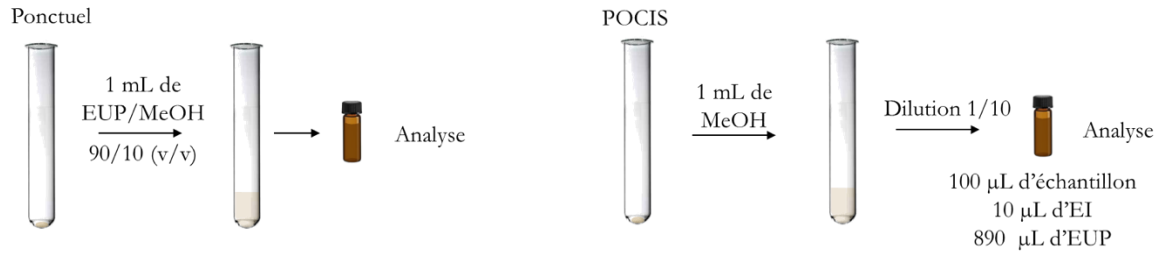

Figure II.10 : Traitement des éluâts après évaporation (les solvants sont de qualité LC-MS)**.**

II.3.3. Protocole o-DGT.

Préparation des gels diffusifs et des phases réceptrices.

Deux types d'hydrogel ont été utilisés comme gel diffusif et récepteur pour construire les o-DGT : soit en polyacrylamide soit en agarose. Pour les gels à base de polyacrylamide, une solution stock est préparée selon la **Figure II.11**. A partir de cette solution, sont préparés les gels diffusifs (**Figure II.12**) et les gels récepteurs (**Figure II.13**). Le coulage des gels se fait entre 2 plaques de verres séparées par un écarteur en téflon d'une épaisseur de 0,5 et 0,25 mm respectivement pour les gels diffusifs et les gels récepteurs. Lors du coulage des gels récepteurs, les plaques sont maintenues horizontalement à température ambiante (20°C) pendant 10 min pour avoir une décantation des particules d'Oasis® HLB ou d'Oasis® MAX.

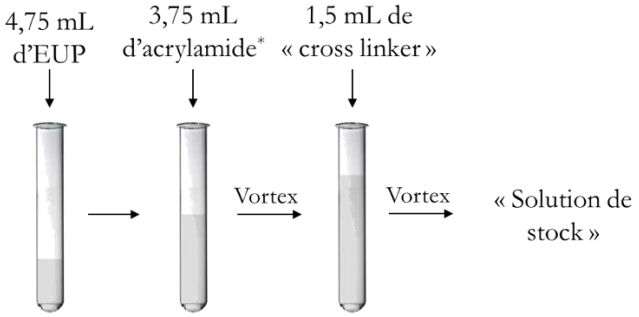

Figure II.11 : Préparation de la solution stock (* l'acrylamide est une solution à 40% (m:v) préparée préalablement).

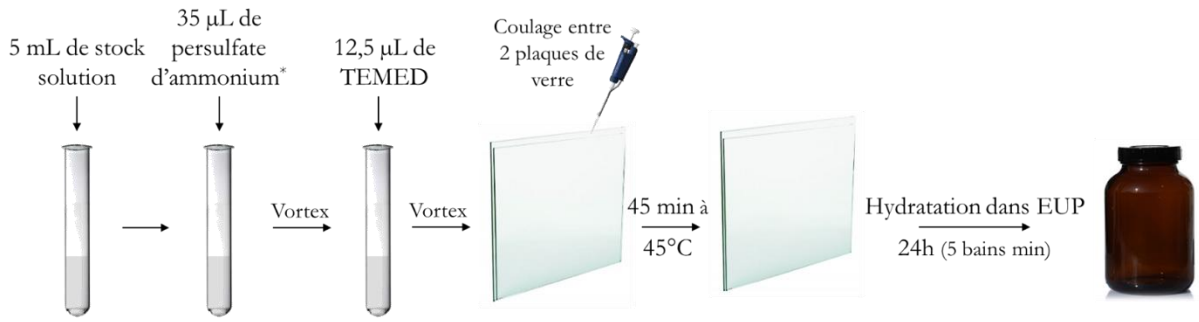

Figure II.12 : Protocole de fabrication de gels diffusifs en polyacrylamide (*le persulfate d'ammonium est une solution à 10% (m:v) préparée le jour même).

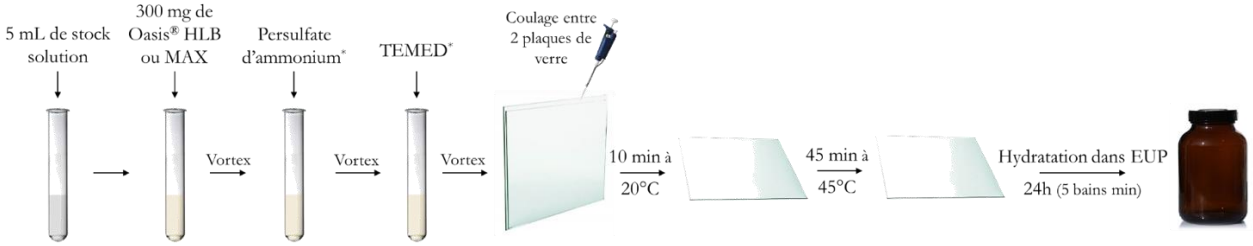

Figure II.13 : Protocole de fabrication de gels récepteurs à base de polyacrylamide (*30 et 65 µL de persulfate d'ammonium et 7,5 et 25 µL de TEMED respectivement pour le gel en Oasis® HLB ou Oasis® MAX).

Le protocole de fabrication des gels diffusifs et des gels récepteurs à base d'agarose sont respectivement présentés dans les **Figure II.14** et **Figure II.15**. Les gels diffusifs ont été coulés dans des plaques avec des écarteurs de 0,25; 0,50; 0,75 et 1,00 mm (chapitre III.C) et les gels récepteurs ont été coulés dans des plaques avec des écarteurs de 0,50 mm. Lors du coulage de ces derniers, les plaques sont maintenues horizontalement pour avoir une décantation des particules d'Oasis® HLB.

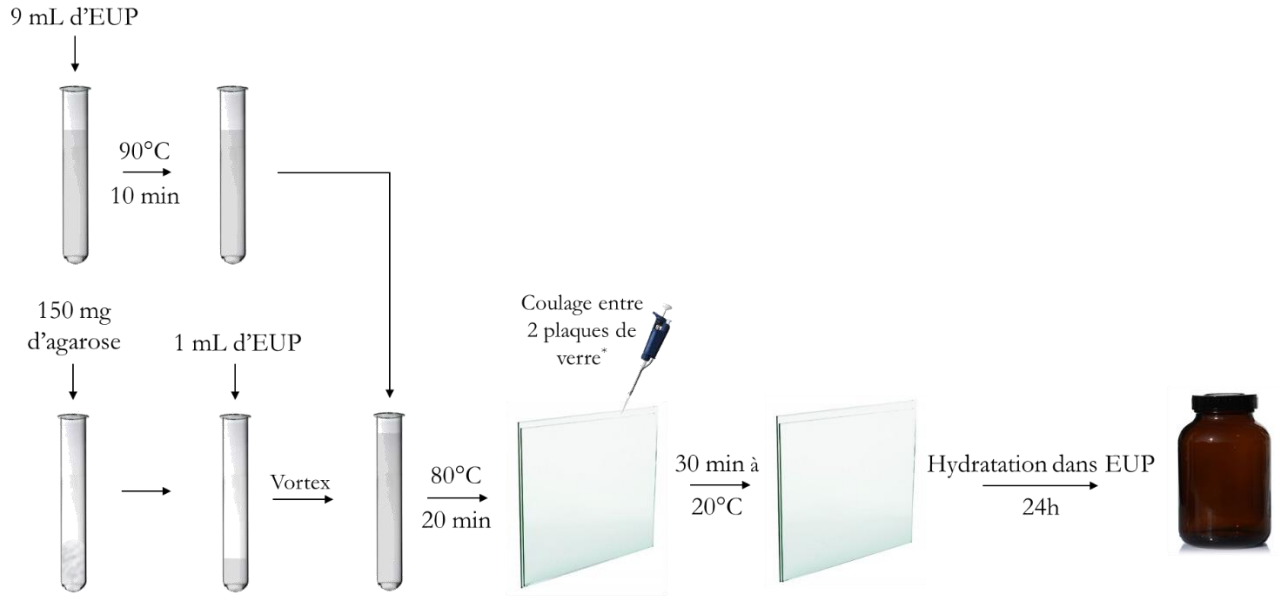

Figure II.14 : Protocole de fabrication de gels diffusifs à base d'agarose (*les plaques en verres sont préalablement chauffées à 80°C durant 15 min).

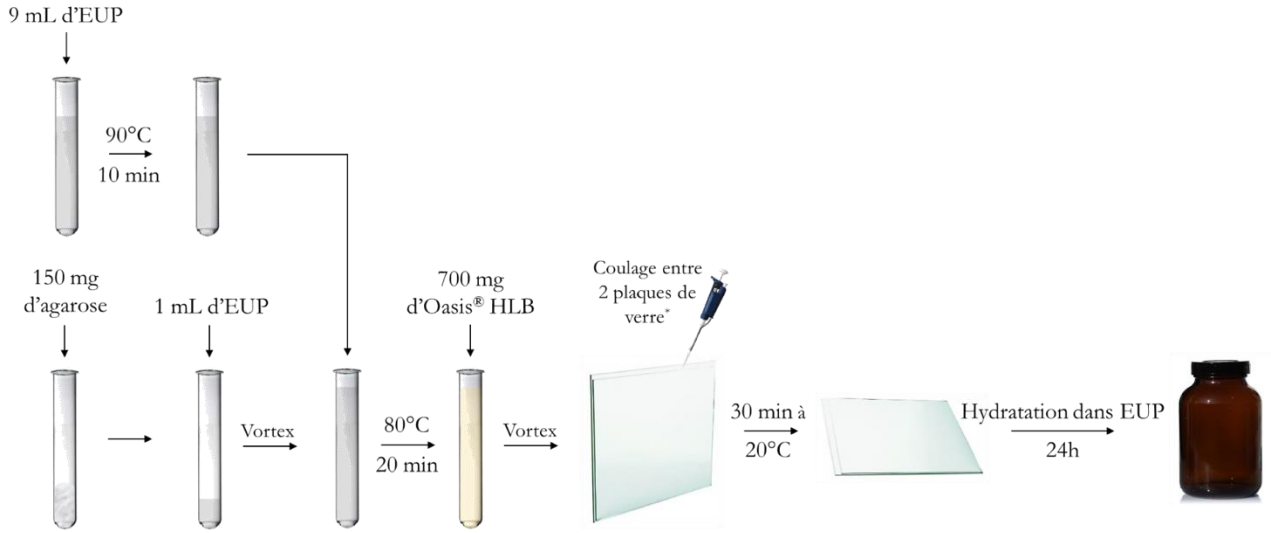

Figure II.15 : Protocole de fabrication de gels récepteurs à base d'agarose (*les plaques en verres sont préalablement chauffées à 80°C durant 15 min).

Découpe des disques.

Après hydratation des différents gels, des disques de 2 cm de diamètre sont découpées à l'aide d'un emporte-pièce. Les disques sont ensuite conservés jusqu'à utilisation dans une solution de nitrate de sodium à 0,01M à 4°C.

Montage d'un échantillonneur de type o-DGT.

Le montage d'un dispositif o-DGT se fait par superposition d'une phase réceptrice (Oasis® HLB ou MAX) en polyacrylamide (chapitre III.B) ou en agarose (chapitre III.C) puis d'une phase diffusive en polyacrylamide (chapitre III.B) ou en agarose (chapitre III.C) (**Figure II.16**). La phase réceptrice est positionnée de telle sorte que la poudre Oasis® soit en contact avec la phase diffusive (côté de la décantation). Les échantillonneurs sont conservés sous atmosphère humide dans des sacs zippés à 4°C pendant 24h maximum.

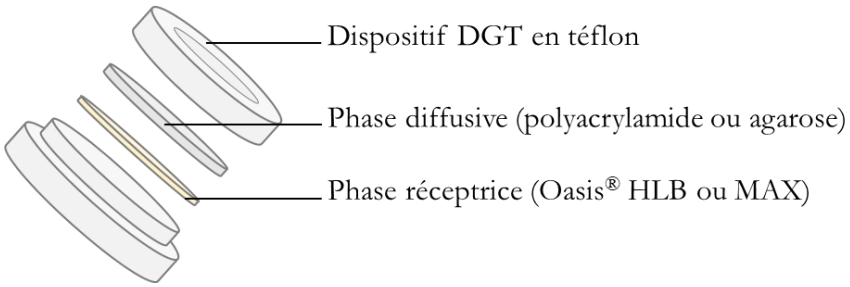

Figure II.16 : Montage d'un échantillonneur de type o-DGT.

Démontage d'un échantillonneur de type o-DGT.

Une fois exposé, le o-DGT est rincé à l'EUP afin d'arrêter l'accumulation de composés et est conservé au réfrigérateur (à environ 4°C) jusqu'à son démontage. Le protocole est décrit **Figure II.17**. Ce protocole a été utilisé pour tous les o-DGT utilisés dans ce travail de thèse (chapitre III).

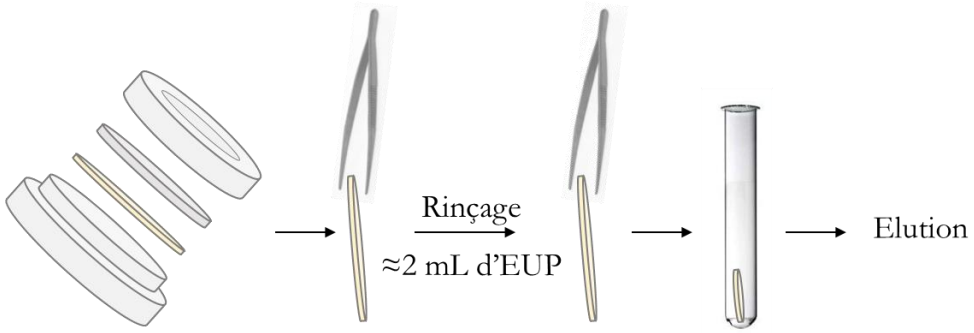

Figure II.17 : Protocole de démontage d'un échantillonneur passif de type o-DGT.

Élutions des phases réceptrices issues d'échantillonneur de type o-DGT.

Dans ces travaux, plusieurs types d'élutions ont été utilisées : les deux premiers ont été développés dans cette thèse et utilisés dans le chapitre III.B (**Figure II.18**) et un troisième a été adapté à partir de la littérature ((Challis et al. 2016)) et a été utilisé dans le chapitre III.C (**Figure II.19**).

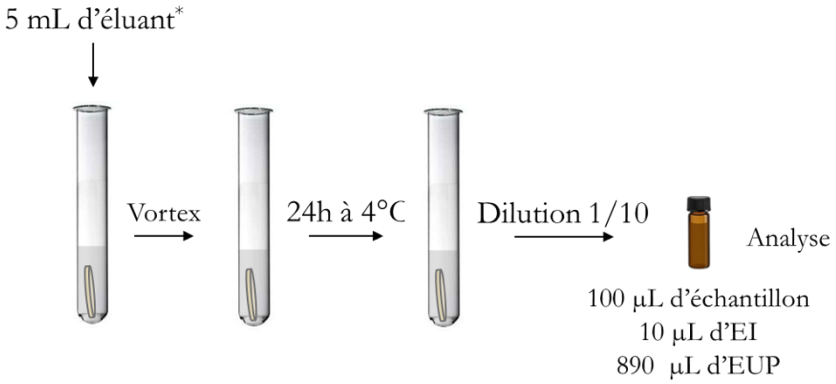

Figure II.18 : Protocole d'élution des phases réceptrices en polyacrylamide développé dans le laboratoire (*éluant : mélange MeOH LC-MS:acétate d'éthyle LC-MS (50:50 – v:v) pour Oasis® HLB et mélange MeOH LC-MS:acide formique 1M (90:10 – v:v) pour Oasis® MAX).

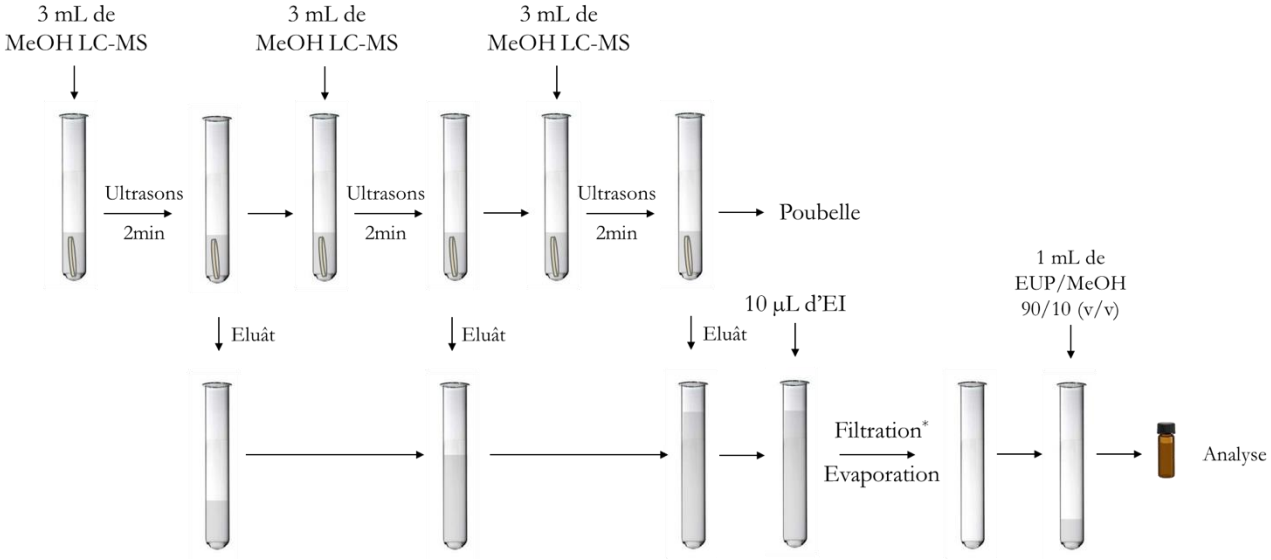

Figure II.19 : Protocole d'élution des phases réceptrices en agarose développée par Challis et al. (2016), et appliqué chapitre III.C (*filtration sur filtre PTFE 0,2 µm).

II.4. Méthodes analytiques.

L'analyse des contaminants organiques dans l'environnement nécessite des méthodes analytiques performantes et fiables. Ces méthodes utilisent la chromatographie liquide couplée à la spectrométrie de masse. Dans un premier temps, la chromatographie permet de séparer les composés présents dans un même échantillon. Le choix de la chromatographie dépend des molécules étudiées. Dans ces travaux, les composés organiques étudiés (pesticides et composés pharmaceutiques) sont majoritairement polaires ou moyennement polaires (-0,92 < LogP < 4) et quelques composés présentent des propriétés hydrophobes modérées (4 < LogP < 5,88), c'est pourquoi la séparation par chromatographie liquide a été choisie. Dans ces travaux, 3 méthodes ont été développées : méthode analytique n°1 pour l'analyse des pesticides neutres, méthode analytique n°2 pour l'analyse des pesticides ioniques et méthode analytique n°3 pour l'analyse des composés pharmaceutiques.

Dans un second temps, après séparation des composés, un spectromètre de masse à temps de vol (Q-ToF) ou triple quadripôle (QqQ) est utilisé comme détecteur. Après la séparation chromatographique, les molécules sont ionisées par une source électrospray (ESI) et séparées par le rapport masse/charge (m/z). Lors de l'utilisation du Q-ToF, l'acquisition s'est faite en mode "Allions". Dans ce mode d'acquisition, les ions ne sont pas filtrés par le quadripôle et les ions sont transférés dans une cellule de collision. Lors de l'utilisation du QqQ, l'acquisition se fait en mode SRM (Selected Reaction Monitoring) où des précurseurs sont sélectionnés puis fragmentés dans une cellule de collision. Pour le Q-ToF et le QqQ, la cellule de collision permet de fragmenter les molécules afin d'obtenir des ions fils et avoir un spectre de fragmentation. L'identification des molécules se fait par le temps de rétention, la masse exacte et le spectre de masse de la fragmentation de la molécule avec, au moins, un ion fils pour le Q-ToF et par le temps de rétention et la présence de deux ions fils pour le QqQ.

La première partie du développement des méthodes analytiques a été d'optimiser la séparation chromatographique des analytes et dans un second temps d'optimiser les paramètres de la spectrométrie de masse.

II.4.1. Caractéristiques des méthodes d'analyse.

Les composés ont été analysés avec différentes méthodes analytiques. Pour l'analyse des pesticides neutres, deux méthodes ont été utilisées (méthodes analytiques n°1 et 1'), pour l'analyse des pesticides ioniques et l'analyse des composés pharmaceutiques, les méthodes analytiques n°2 et 3 ont, respectivement, été utilisées. Les caractéristiques des méthodes analytiques (appareillage, débit, température de colonne et du passeur d'échantillon) et des paramètres de masse (paramètres sources, énergies de collision) sont présentés dans le **Tableau II.9**. Les gradients et les éluants de chaque méthode sont présentés dans le **Tableau II.10**. De même, pour assurer une bonne quantification, une correction par étalon interne a été utilisée. Le choix des étalons internes s'est fait en tenant compte de la famille chimique des molécules à corriger et de leur temps de rétention.

Tableau II.9 : Caractéristiques chromatographiques et spectrométriques pour l'analyse des composés organiques étudiés (*paramètres de la spectrométrie de masse optimisés).

Composé cible	**Pesticides neutres**		**Pesticides ioniques**	**Composés pharmaceutiques**
Méthode analytique	**Méthode analytique n°1**	**Méthode analytique n°1'**	**Méthode analytique n°2**	**Méthode analytique n°3**
Chapitres concernés	III.C, IV.B et V.B	V.B	III.B	III.C, IV.C et V.C
Caractéristiques chromatographiques				
Colonne utilisée	RRHD Zorbax Eclipse +	Gemini-NX	RP18+ Nucleoshell	RP18+ Nucleoshell
Appareillage	1290 Infinity	Ultimate 3000	1290 Infinity	1290 Infinity
Température colonne (°C)	30	40	30	30
Température passeur (°C)	5	10	4	4
Volume injecté (µL)	5	10	5	5
Débit (µL.min^{-1})	400	400	400	400
Caractéristiques spectrométrie de masse				
Analyseur	6540 Accurate Mass (Q-ToF)	API2000 (QqQ)	6540 Accurate Mass (Q-ToF)	6540 Accurate Mass (Q-ToF)
Température du gaz enveloppant (°C)	375*	-	400*	300*
Débit du gaz enveloppant (L.min^{-1})	12	-	12*	12*
Température du gaz séchant (°C)	130*	450	130*	100*
Débit du gaz séchant (L.min^{-1})	13*	-	13*	7*
Voltage du fragmenteur (V)	120*	-	130*	130*
Pression du nébuliseur (psi)	35*	45	20*	35*
Voltage du capillaire (V)	3500	5500	3500	3500
Voltage du skimmer (V)	65	-	65*	65*
Gamme de masse (m/z)	100 – 1500	59 – 1545	100 – 1500	100 – 1500
Masses de référence (m/z)	922,0098	-	112,9855 et 1033,9881	922,0098
Octopôle 1 RF (V)	750	-	750*	750*
Voltage nozzle (V)	300	-	300*	300*
Energies de collision (V)	0, 10, 20 et 40	-	0, 10, 20 et 40	0, 10, 20 et 40

Tableau II.10 : Gradients utilisés pour les différentes méthodes analytiques.

Gradient méthode analytique n°1		
Temps (min)	**EUP (%)**	**MeOH + 5mM formiate d'ammonium + 0,1% d'acide formique (%)**
0	90	10
0,5	90	10
3,5	50	50
14	30	70
17	10	90
20	10	90

Gradient méthode analytique n°1'		
Temps (min)	**EUP + 5mM acétate d'ammonium (%)**	**ACN (%)**
0	90	10
1	90	10
4	70	30
8	60	40
9,5	20	80
10,5	20	80
11	90	10
15	90	10

Gradient méthode analytique n°2		
Temps (min)	**EUP + 5mM acétate d'ammonium (%)**	**MeOH + 5mM acétate d'ammonium (%)**
0	90	10
0,5	90	10
2	50	50
5	45	55
7	10	90
10	10	90

Gradient méthode analytique n°3		
Temps (min)	**EUP + 5mM formiate d'ammonium + 0,1% d'acide formique (%)**	**MeOH + 5mM formiate d'ammonium + 0,1% d'acide formique (%)**
0	90	10
1	90	10
5	75	25
7	30	70
13	10	90
16	10	90

II.4.2. Validation des méthodes d'analyses.

Pour évaluer les méthodes d'analyses chromatographiques développées, une validation selon la norme NF T90-210 (AFNOR 2009) a été faite. Cette norme définit un protocole d'évaluation initiale d'une méthode d'analyse quantitative. Cette évaluation se fait sur les 4 paramètres suivants : fonction d'étalonnage, limite de quantification, interférences et exactitude.

Vocabulaire.

Conditions de fidélité intermédiaire : "Conditions où les résultats d'essai sont obtenus par la même méthode sur des individus d'essais identiques dans le même laboratoire avec des changements de conditions parmi lesquelles : personne, étalonnage, équipements, environnement, temps écoulé entre les mesures".

Conditions de répétabilité : "Conditions où les résultats d'essai indépendants sont obtenus par la même méthode sur des individus d'essai identiques dans le même laboratoire, par le même opérateur, utilisant le même équipement et pendant un court intervalle de temps".

Fonction d'étalonnage - linéarité.

Pour évaluer la linéarité de la méthode analytique, 5 gammes d'étalonnage sont préparées dans des conditions de fidélité intermédiaire avec au moins 5 niveaux de concentration (de 1 à 100 $\mu g.L^{-1}$). Pour les gammes d'étalonnage, des solutions "mix" ont été préparées (**Figure II.2**) par les différents opérateurs à partir des solutions mères. Les paramètres d'organisation des essais sont regroupés **Tableau II.11**. L'étude de l'étalonnage se fait par approche statistique (cas n°2) avec la loi de Fisher ($\alpha = 0,01$).

Tableau II.11 : Organisation des essais pour l'étude de la linéarité des méthodes analytiques.

	Gammes	Niveaux	Opérateurs	Jours d'analyse
Méthode analytique n°1	6	5	3	5
Méthode analytique n°2	5	7	5	5
Méthode analytique n°3	5	5	5	5

Limite de quantification.

La limite de quantification instrumentale ($LQ_{instrumentale}$) correspond à la plus faible concentration pouvant être quantifiée. L'étude de la limite de quantification se fait avec la préparation et l'analyse de 10 échantillons minimum dans des conditions de répétabilité (utilisation de la même solution "mix" par le même opérateur). Les paramètres d'organisation des essais sont regroupés **Tableau II.12**. L'exactitude sur les essais est calculée. La limite de quantification est validée si l'exactitude des essais a un écart maximal de 60% en vérifiant les deux équations suivantes :

$$LQ_p - 0,6 \times LQ_p < LQ_m - 2 \times \sigma \qquad \text{Équation II.1}$$

$$LQ_p + 0,6 \times LQ_p > LQ_m + 2 \times \sigma \qquad \text{Équation II.2}$$

Avec LQ_P : la limite de quantification présupposée (concentration correspondant au dopage de la solution), LQ_m : la moyenne des concentrations obtenue lors de l'analyse des essais et σ : l'écart-type obtenu lors de l'analyse des essais (n = 10).

Tableau II.12 : Organisation des essais pour l'étude des limites de quantification des méthodes analytiques.

	Séries	Répétitions	Opérateurs	Jours d'analyse
Méthode analytique n°1	5	2	1	1
Méthode analytique n°2	5	2	1	1
Méthode analytique n°3	5	2	1	1

Interférences.

Les échantillons analysés dans ce travail sont des échantillons exposés dans de l'eau, soit naturelle, soit du robinet, soit distillée. Les interférences sont généralement plus importantes dans de l'eau naturelle, c'est pourquoi les interférences ont été testées sur une matrice environnementale. Pour cela, des POCIS ont été exposés en rivière. Les extraits de ces POCIS sont collectés et rassemblés en un extrait pour l'étude des interférences. L'extrait reconstitué est alors analysé sans dilution (pour déterminer la concentration initiale) et avec dilution (d10 et d20) puis cet extrait est dopé avec le mix de molécules à 5 niveaux différents (10, 20, 30, 50 et 100 $\mu g.L^{-1}$). Deux répétitions sont préparées par niveau. Au total, ce sont 10 essais qui sont préparés dans des conditions de répétabilité. Les paramètres d'organisation des essais pour l'étude des interférences sont présentés **Tableau II.13**. La validation se fait lorsque la courbe : "concentration retrouvée - concentration initiale *vs.* concentration dopée" a:

- une pente ≈ 1
- pour ordonnée à l'origine ≈ 0

La validation est faite grâce à un test de Student avec α = 0,01.

Tableau II.13 : Organisation des essais pour l'étude des interférences des méthodes analytiques.

	Niveaux	Répétitions	Opérateurs	Jours d'analyse
Méthode analytique n°1	5	2	1	1
Méthode analytique n°2	5	2	1	1
Méthode analytique n°3	5	2	1	1

Exactitude.

L'étude de l'exactitude est réalisée sur deux niveaux (dopage à 25 et 100 $\mu g.L^{-1}$). Pour chaque niveau, cinq essais sont préparés. Ces 5 essais sont préparés et analysés dans des conditions de fidélité intermédiaire. Pour chaque essai, deux réplicats sont préparés et analysés dans des conditions de répétabilité. Les

paramètres d'organisation des essais pour l'étude de l'exactitude sont présentés **Tableau II.14**. L'exactitude est validée en vérifiant les deux équations suivantes :

$$C_r - x \times C_r < C_a - 2 \times \sigma \qquad \textbf{Équation II.3}$$
$$C_r + x \times C_r > C_a + 2 \times \sigma \qquad \textbf{Équation II.4}$$

Avec C_r : la concentration après dopage (25 ou 100 µg.L^{-1}), x : le pourcentage admissible, C_a : la concentration trouvée et σ : l'écart-type obtenu lors de l'analyse des essais (n = 10). Préalablement un test de Cochran puis un test d'ANOVA sont réalisés. Le premier permet de s'assurer que les variances entre les différents essais sont comparables (α = 0,01) et le second pour s'assurer que les moyennes des réplicats sont égales (α = 0,01).

Tableau II.14 : Organisation des essais pour l'étude de l'exactitude des méthodes analytiques.

	Niveaux	Séries	Répétitions	Opérateurs	Jours d'analyse
Méthode analytique n°1	2	5	2	5	5
Méthode analytique n°2	2	5	2	5	5
Méthode analytique n°3	2	5	2	5	5

Résultats de la validation des méthodes analytiques

La validation de méthode par rapport à la norme NF T90-210 a été faite pour les trois méthodes analytiques. Les résultats de la validation sont présentés dans le **Tableau II.15**, **Tableau II.16** et **Tableau II.17** pour, respectivement, les méthodes n°1, 2 et 3. Les transitions utilisées et les paramètres pour la quantification sur le spectromètre de masse triple quadripôle sont présentées **Tableau II.18**.

Tableau II.15 : Résultats de la validation de méthode pour la méthode analytique n°1 ([1]$LQ_{instrumentale}$ obtenues avec le couplage UHPLC-(Q)-ToF, [2]$LQ_{instrumentale}$ obtenues avec le couplage HPLC-QqQ utilisé uniquement pour le chapitre V.B, n.d. : non déterminé, ✓ : condition vérifiée).

Pesticide	Temps de rétention (min)	$[M-H]^+$ ($g.mol^{-1}$)	Linéarité		Vérification de l'exactitude	$LQ_{instrumentale}$[1] ($\mu g.L^{-1}$)	$LQ_{instrumentale}$[2] ($\mu g.L^{-1}$)	Absence d'interférences	Etalon interne
			Equation	r^2					
3-hydroxy-carbofuran	4,68	238,1071	y=0,0163	0,995	✓	2,0	2,0	✓	Méthomyl-d3
Acétochlore	13,59	270,1245	y=0,0112	0,991	✓	5,0	1,0	✓	Métolachlore-d6
Alachlore	13,65	270,1245	y=0,0076	0,987	✓	1,0	2,0	✓	Métolachlore-d6
Atrazine	8,54	216,1003	y=0,0102	0,997	✓	0,5	1,0	✓	Atrazine-d5
Azoxystrobine	11,30	404,1228	y=0,0074	0,986	✓	0,1	1,0	✓	Atrazine-d5
Bénoxacor	9,96	260,024	y=0,0026	0,988	✓	0,5	*n.d.*	✓	Diuron-d6
Carbaryl	7,33	202,0863	y=0,0286	0,986	✓	0,5	5,0	✓	Carbaryl-d3
Carbendazime	3,89	192,0768	y=0,0081	0,969	✓	0,5	1,0	✓	Méthomyl-d3
Carbofuran	6,73	222,1125	y=0,0874	0,977	✓	0,5	1,0	✓	Carbofuran-d3
Chlorfenvinphos	16,06 et 16,50	358,9752	y=0,0104	0,929	✓	0,1	1,0	✓	Chlorpyrifos-d5
Chlortoluron	8,30	213,0789	y=0,0153	0,991	✓	0,1	2,0	✓	Diuron-d6
Cybutryne (Irgarol)	12,15	254,1435	y=0,0148	0,988	✓	0,1	1,0	✓	Atrazine-d5
Cyproconazole	12,40	292,1199	y=0,0039	0,994	✓	0,5	*n.d.*	✓	Tébuconazole-d6
Dichlorophényl-méthyluréa (DCPMU)	8,95	219,0086	y=0,0037	0,990	✓	0,5	2,0	✓	Diuron-d6
Dichlorophényl-uréa (DCPU)	7,95	204,9930	y=0,0009	0,990	✓	1,0	5,0	✓	Diuron-d6
Atrazine-déséthyl (DEA)	5,12	188,0697	y=0,0113	0,995	✓	0,5	1,0	✓	DEA-d6
Terbuthylazine-déséthyl (DET)	7,26	202,0855	y=0,0062	0,973	✓	0,5	1,0	✓	Atrazine-d5
Atrazine-désisopropyl (DIA)	4,22	174,0541	y=0,0093	0,994	✓	0,5	1,0	✓	DEA-d6
Diméthachlore	9,53	256,1091	y=0,0086	0,996	✓	0,5	*n.d.*	✓	Diuron-d6

Diméthénamide	11,17	276,0805	y=0,0083	0,984	✓	0,1	*n.d.*	✓	Métolachlore-d6
Diméthoate	4,76	230,0062	y=0,0372	0,989	✓	0,1	1,0	✓	Méthomyl-d3
Diméthomorphe	11,57 et 12,41	388,1301	y=0,0067	0,928	✓	0,5	1,0	✓	Métolachlore-d6
Diuron	9,30	233,0239	y=0,0089	0,988	✓	0,1	1,0	✓	Diuron-d6
Epoxiconazole	14,18	330,0806	y=0,0133	0,992	✓	0,5	*n.d.*	✓	Tébuconazole-d6
Flurochloridone	12,82	312,0165	y=0,0025	0,978	✓	0,5	*n.d.*	✓	Métolachlore-d6
Flurtamone	11,30	334,1038	y=0,0298	0,989	✓	0,1	*n.d.*	✓	Diuron-d6
Flusilazole	14,84	316,1061	y=0,0233	0,991	✓	0,5	*n.d.*	✓	Tébuconazole-d6
Hexazinone	6,67	253,1659	y=0,0105	0,986	✓	0,1	1,0	✓	Atrazine-d5
Imidaclopride	4,42	256,0596	y=0,0161	0,993	✓	0,1	*n.d.*	✓	Carbofuran-d3
Isopropylphényl-méthyluréa (IPPMU)	8,54	193,1335	y=0,0159	0,997	✓	0,5	1,0	✓	Diuron-d6
Isopropylphényl-uréa (IPPU)	7,65	179,1179	y=0,0064	0,994	✓	0,5	1,0	✓	Diuron-d6
Isoproturon	8,95	207,1492	y=0,0250	0,987	✓	0,1	1,0	✓	Diuron-d6
Linuron	10,86	249,0184	y=0,0054	0,985	✓	0,1	1,0	✓	Diuron-d6
Métazachlore	8,74	278,1046	y=0,0066	0,995	✓	0,1	1,0	✓	Métolachlore-d6
Méthomyl	3,70	163,0536	y=0,0096	0,994	✓	1,0	1,0	✓	Méthomyl-d3
Métolachlore	13,95	284,1407	y=0,0104	0,990	✓	0,5	2,0	✓	Métolachlore-d6
Métoxuron	5,73	229,0738	y=0,0152	0,997	✓	0,1	1,0	✓	Diuron-d6
Norflurazon	9,53	304,0458	y=0,0233	0,991	✓	0,1	*n.d.*	✓	Diuron-d6
Norflurazon-desméthyl	8,30	290,0288	y=0,0142	0,992	✓	0,1	*n.d.*	✓	Diuron-d6
Pirimicarbe	8,97	239,1503	y=0,0101	0,993	✓	0,5	1,0	✓	Pirimicarbe-d6
Simazine	6,70	202,0854	y=0,0094	0,985	✓	0,1	1,0	✓	Atrazine-d5
Tébuconazole	15,73	308,1524	y=0,0126	0,990	✓	0,5	*n.d.*	✓	Tébuconazole-d6
Terbuthylazine	11,30	230,1155	y=0,0083	0,989	✓	0,1	1,0	✓	Atrazine-d5
Thiodicarbe	8,12	355,0551	y=0,0018	0,993	✓	0,1	1,0	✓	Pirimicarbe-d6

Tableau II.16 : Résultats de la validation de méthode pour la méthode analytique n°2 (✓ : condition vérifiée).

Pesticide	Temps de rétention (min)	$[M-H]^+$ ($g.mol^{-1}$)	Linéarité		Vérification de l'exactitude	$LQ_{instrumentale}$ ($\mu g.L^{-1}$)	Absence d'interférences	Etalon interne
			Equation	r^2				
Bentazone	2,34	239,0489	y=0,9959	0,999	✓	0,5	✓	Bentazone-d6
Chlorsulfuron	2,67	356,0230	y=0,9950	0,999	✓	0,5	✓	Metsulfuron-d3
Ioxynil	3,17	369,8231	y=0,9920	0,998	✓	0,5	✓	MCPA-d3
Mécoprop	3,64	213,0325	y=1,0027	0,995	✓	2,0	✓	MCPA-d3

Tableau II.17 : Résultats de la validation de méthode pour la méthode analytique n°3 (✓ : condition vérifiée).

Composé pharmaceutique	Temps de rétention (min)	$[M-H]^+$ ($g.mol^{-1}$)	Linéarité		Vérification de l'exactitude	$LQ_{instrumentale}$ ($\mu g.L^{-1}$)	Absence d'interférences	Etalon interne
			Equation	r^2				
Acétaminophène	2,04	152,0706	y=0,0197	0,988	✓	0,1	✓	Salbutamol-d3
Aténolol	2,32	267,1703	y=0,0304	0,974	✓	0,1	✓	Salbutamol-d3
Bézafibrate	8,33	362,1154	y=0,0002	0,982	✓	0,5	✓	Flunixine-d3
Bisoprolol	7,15	326,2326	y=0,0122	0,994	✓	0,1	✓	Propanolol-d3
Caféine	5,05	195,0877	y=0,0102	0,997	✓	0,2	✓	Caféine-c3
Carbamazépine	7,70	237,1022	y=0,0102	0,991	✓	0,2	✓	Carbamazépine-d10
Clarithromycine	8,15	748,4842	y=0,0031	0,952	✓	0,1	✓	Flunixine-d3
Dexaméthasone	8,05	415,1891	y=0,0016	0,908	✓	0,2	✓	Carbamazépine-d10
Diazépam	8,33	285,0789	y=0,0070	0,989	✓	0,1	✓	Flunixine-d3
Diclofénac	9,07	296,0240	y=0,0100	0,993	✓	2,0	✓	Diclofénac-d4
Econazole	8,57	381,0323	y=0,0029	0,993	✓	0,1	✓	Triclabendazole-d3
Erythromycine	7,81	734,4685	y=0,0043	0,942	✓	0,2	✓	Carbamazépine-d10
Fenbendazole	8,54	268,0539	y=0,0095	0,983	✓	0,1	✓	Triclabendazole-d3
Fénofibrate	10,88	361,1201	y=0,0113	0,950	✓	0,1	✓	Triclabendazole-d3
Flunixine	8,71	297,0845	y=0,0080	0,977	✓	0,1	✓	Flunixine-d3

Fluoxétine	7,88	310,1413	y=0,0056	0,985	✓	0,2	✓	Carbamazépine-d10
Gemfibrozil	10,20	251,1642	y=1,0052	0,987	✓	5,0	✓	Triclabendazole-d3
Griséofulvine	7,84	353,0786	y=0,0049	0,987	✓	0,1	✓	Carbamazépine-d10
Indométacine	9,20	358,0841	y=0,0123	0,967	✓	2,0	✓	Diclofénac-d4
Kétoprofène	8,08	255,1016	y=0,0648	0,990	✓	0,5	✓	Diclofénac-d4
Lincomycine	4,30	407,2210	y=0,0030	0,996	✓	0,1	✓	Triméthoprime-d3
Metformine	0,60	130,1087	y=0,0204	0,949	✓	0,5	✓	Salbutamol-d3
Métoprolol	6,52	268,1907	y=0,3050	0,779	✓	0,1	✓	Carbamazépine-d10
Métronidazole	2,25	172,0717	y=0,0045	0,932	✓	0,2	✓	Triclabendazole-d3
Monensine	13,71	688,4630	y=0,0112	0,904	✓	1,0	✓	Triclabendazole-d3
Nadolol	5,62	310,2013	y=0,0695	0,997	✓	0,2	✓	Sulfaméthoxazole-d4
Oméprazole	7,51	346,1220	y=0,0029	0,924	✓	0,1	✓	Carbamazépine-d10
Paraxanthine	3,48	181,0720	y=0,0040	0,970	✓	0,5	✓	Caféine-c3
Paroxétine	6,69	330,1500	y=0,0102	0,978	✓	0,1	✓	Carbamazépine-d10
Périndopril	7,60	369,2384	y=0,0057	0,979	✓	0,1	✓	Carbamazépine-d10
Praziquantel	8,35	313,1911	y=0,0023	0,949	✓	0,1	✓	Flunixine-d3
Prednisolone	7,81	383,1829	y=0,0014	0,917	✓	1,0	✓	Carbamazépine-d10
Propanolol	7,30	260,1645	y=0,0118	0,977	✓	0,5	✓	Propanolol-d3
Pyrantel	4,51	207,0950	y=0,0045	0,971	✓	0,08	✓	Triméthoprime-d3
Roxithromycine	8,22	837,5318	y=0,0009	0,963	✓	0,5	✓	Flunixine-d3
Salbutamol	2,16	240,1594	y=0,0118	0,994	✓	0,2	✓	Salbutamol-d3
Sotalol	1,68	273,1267	y=0,0123	0,996	✓	0,2	✓	Salbutamol-d3
Sucralose	5,72	419,0038	y=0,0012	0,828	✓	1,0	✓	Caféine-c3
Sulfadiazine	2,39	251,0597	y=0,0128	0,984	✓	0,1	✓	Sulfaméthoxazole-d4
Sulfamérazine	3,60	265,0754	y=0,0175	0,988	✓	0,1	✓	Sulfaméthoxazole-d4
Sulfaméthoxazole	5,86	254,0594	y=0,0127	0,993	✓	0,2	✓	Sulfaméthoxazole-d4
Sulfaméthoxypyridazine	5,24	281,0703	y=0,0183	0,991	✓	0,2	✓	Sulfaméthoxazole-d4
Terbutaline	2,13	226,1438	y=0,0126	0,988	✓	0,1	✓	Salbutamol-d3
Thioridazine	8,24	371,1610	y=0,0058	0,979	✓	0,1	✓	Flunixine-d3
Triclabendazole	10,05	360,9545	y=0,0124	0,969	✓	0,2	✓	Triclabendazole-d3
Triméthoprime	4,75	291,1452	y=0,0106	0,987	✓	0,2	✓	Triméthoprime-d3

Tableau II.18 : Transitions MRM et paramètres de la spectrométrie de masse QqQ utilisés avec la méthode analytique n°1' ([1]potentiel de déclustering ; [2]potentiel de sortie de cellule).

Pesticide	Temps de rétention (min)	1ère transition (quantification) (m/z)	DP[1] (V)	Énergie de collision (V)	CXP[2] (V)	2ème transition (quantification) (m/z)	DP[1] (V)	Energie de collision (V)	CXP[2] (V)
Acétochlore	10,77	270/224	25	20	5	270/148	25	20	5
Alachlore	10,75	270/238	25	30	10	270/162	25	30	10
Atrazine	7,90	216/174	25	25	4	216/104	25	25	4
Azoxystrobine	10,43	404/372	46	21	14	404/329	46	41	10
Carbaryl	7,70	202/145	41	15	6	202/127	41	39	6
Carbendazime	4,42	192/160	26	27	4	192/105	26	53	6
Carbofuran	7,22	222/123	41	31	6	222/165	41	17	6
Chlortoluron	7,52	213/72	30	35	4	213/46	30	35	4
Cyproconazole	10,11	292/70	36	33	4	292/125	36	39	8
Atrazine-déséthyl (DEA)	4,52	188/146	30	25	3	188/104	30	25	3
Terbuthylazine-déséthyl (DET)	6,55	202/146	30	25	4	202/104	30	25	4
Atrazine-désisopropyl (DIA)	2,54	174/104	30	35	3	174/132	30	35	3
Diuron	8,23	233/72	30	40	3	233/46	30	40	3
Diméthomorphe	9,92	388/301	26	41	6	388/165	26	29	10
Epoxiconazole	10,42	330/121	51	25	6	330/101	51	65	4
Flurtamone	10,25	334/247	88	37	6	334/178	88	53	6
Flusilazol	10,62	316/247	86	25	8	316/165	86	35	10
Hexazinone	5,87	253/171	21	21	6	253/71	21	49	4
Imidaclopride	4,45	256/175	56	31	6	256/209	56	21	16
Isoproturon	8,21	207/72	30	35	4	207/165	30	35	4
Linuron	10,12	249/160	30	30	4	249/182	30	30	4
Métazachlore	9,13	278/134	30	30	4	278/210	30	30	4
Méthomyl	2,47	163/88	21	13	4	163/106	21	13	4

Métolachlore	10,73	284/252	20	30	4	270/176	20	30	4
Norflurazon	8,83	304/284	111	31	22	304/160	111	41	22
Norflurazon-desméthyl	7,55	290/270	76	35	8	290/160	76	41	4
Pirimicarbe	7,56	239/72	21	35	4	239/182	21	21	6
Simazine	6,24	202/132	30	30	4	202/124	30	30	4
Tébuconazole	10,55	308/70	91	41	4	308/125	91	47	4
Terbuthylazine	10,04	230/174	30	25	4	230/146	30	25	4

II.4.3. Assurance qualité et contrôle qualité (QA/QC).

Pour mesurer et assurer la qualité des résultats des contrôles d'assurance qualité ont été mis en place tout au long des expériences ou lors des analyses. Pour cela 3 types de QA/QC ont été utilisés : des blancs expériences, des blancs terrains et des contrôles de qualité analytique.

Chaque expérience a été accompagnée de "blanc expérience". Ces blancs sont très variés selon les expériences :

- lors de l'extraction d'échantillon ponctuel (naturel ou de laboratoire), une prise d'essai sur de l'eau d'Evian est faite en parallèle (chapitres III.C, IV.C et V) ;
- lors des tests d'adsorption des pesticides ioniques sur les phases diffusives, des tubes avec de l'eau dopée mais sans phase réceptrice et des tubes avec de l'eau non dopée mais avec une phase réceptrice ont été utilisés comme blancs expériences (chapitre III.C),
- des échantillonneurs ont été déployés dans de l'eau non dopée (expérience de calibration et de fiabilisation du o-DGT - chapitre III.C),
- l'élution des o-DGT a été réalisée sur des phases réceptrices "vierges" (chapitre III),
- la quantification des éléments majeurs sur des échantillons ponctuels a été faite sur de l'eau ultrapure (chapitre III.B, IV.B et V).

En ce qui concerne les déploiements, des blancs ont été utilisés. En effet, lors de la fabrication des échantillonneurs (POCIS ou o-DGT), des "blancs terrains" ont été fabriqués pour s'assurer qu'il n'y ait pas de contamination en laboratoire ou lors des manipulations sur le terrain. Ces échantillonneurs sont, lors de chaque déploiement terrain, emmenés sur le terrain, ils sont déballés et remballés puis conservés au réfrigérateur durant toute la période d'exposition. Ils sont ensuite démontés, repris, élués et analysés en même temps et dans les mêmes conditions que les autres échantillonneurs.

Durant chaque analyse, des contrôles qualités ont été effectués. Tous les 10 échantillons analysés, deux niveaux de standards ainsi qu'un blanc (EUP) sont analysés afin de prévenir toute dérive de l'instrument analytique.

II.5. Théorie des échantillonneurs passifs utilisés.

Un échantillonneur passif est déployé pendant une certaine durée d'exposition (*e.g.* 15 jours pour des mesure sur le terrain) dans le milieu à analyser. Durant cette période, ils accumulent les analytes et de retour au laboratoire, les analytes cibles sont extraits des échantillonneurs. L'accumulation se fait en deux temps. Le premier est un régime cinétique (phase linéaire) où il y a une proportionnalité entre la concentration échantillonnée et le temps d'exposition dans le milieu. Le second temps est un régime d'équilibre où la concentration dans l'échantillonneur sera stable. Quel que soit l'échantillonneur passif utilisé, pour calculer une concentration moyennée dans le temps d'un composé cible dans le milieu de déploiement, l'échantillonnage doit se faire durant la phase linéaire d'accumulation.

Théorie de l'échantillonneur passif de type POCIS.

Le POCIS est la technique d'échantillonnage passif basée sur la diffusion des analytes à travers une membrane (généralement en PES) jusqu'à la phase réceptrice sur laquelle les composés se fixent. Une vue éclatée de cet échantillonneur est présentée **Figure II.5**. La concentration dans le milieu échantillonné est calculée avec l'équation II.5 :

$$C_W = \frac{C_{POCIS}}{k_u \times t} \qquad \textbf{Équation II.5}$$

Où C_w est la concentration du milieu ($ng.L^{-1}$), C_{POCIS} est la concentration retrouvée dans la phase réceptrice après élution ($ng.g^{-1}$), k_u est le taux d'adsorption ($L.g^{-1}.j^{-1}$) et t est le temps d'exposition (j). Le taux d'adsorption est relié au taux d'échantillonnage (R_s) par l'équation II.6 :

$$k_u = \frac{R_S}{m_{phase}} \qquad \textbf{Équation II.6}$$

Où R_s est le taux d'échantillonnage ($L.j^{-1}$) et m_{phase} est la masse de phase réceptrice dans le POCIS (≈ 0,200 g).
Le taux d'échantillonnage est spécifique à chaque molécule et doit être calibré préalablement en laboratoire ou *in-situ*.

Expérience de calibration POCIS : détermination des taux d'échantillonnage.

Dans ces travaux, le taux d'échantillonnage des composés pharmaceutiques a été déterminé. La calibration a été faite grâce à une rivière artificielle à échelle de laboratoire pour des conditions dynamiques (**Figure II.20**) et grâce à un réservoir de 200 L pour des conditions statiques. La rivière artificielle est constituée d'un réservoir de 500 L qui, à l'aide d'une pompe (13 m^3/h) et de trappes, alimente trois canaux mimant un écoulement en rivière. A la sortie des trois canaux, l'eau dopée retombe dans le réservoir. L'ensemble est construit en polychlorure de vinyle (PVC). Avant le déploiement des POCIS, l'eau du robinet est dopée à 0,5 $\mu g.L^{-1}$ de chaque composé pharmaceutique et un temps d'équilibrage de 48h est réalisé. Le montage des POCIS se fait le même jour à partir de la même phase Oasis® HLB. Les membranes PES sont préalablement lavées comme indiqué sur la **Figure II.4**. Pour ne pas changer l'hydrodynamique, des "faux" POCIS (c'est-à-dire sans phase réceptrice) sont placés dans les canaux. Les POCIS ayant

accumulés les composés cibles sont démontés le lendemain de leur retrait selon le protocole décrit sur la **Figure II.6**. Les cartouches sont alors congelées et éluées toutes en même temps en suivant le protocole de la **Figure II.8**.

Les POCIS vont accumuler les composés pharmaceutiques dans leur phase réceptrice. Afin d'obtenir la courbe d'accumulation, les échantillonneurs sont retirés après différentes durées d'exposition. Il y a une proportionnalité entre le temps d'exposition et la masse accumulée dans l'échantillonneur. Pour connaître la concentration exacte de l'eau dopée et ainsi déterminer la concentration moyenne de l'eau lors du déploiement de chaque échantillonneur, un prélèvement ponctuel est réalisé tous les 2 ou 3 jours maximum (dans les deux pilotes). Les caractéristiques de l'expérience sont détaillées dans le **Tableau II.19**.

Après un certain temps d'exposition, les courbes d'accumulation deviennent curvilinéaires, la concentration en analyte dans la phase réceptrice peut alors s'écrire :

$$\frac{C_{POCIS}}{C_w} = K_{HLB} \times (1 - e^{-k_e \times t}) \qquad \textbf{Équation II.7}$$

$$y = pr1 \times (1 - e^{-pr2 \times t}) \qquad \textbf{Équation II.8}$$

Où K_{HLB} est le coefficient de partage entre la phase réceptrice et l'eau, k_e est le taux de désorption ($L.g^{-1}.j^{-1}$). La régression curvilinéaire permet de déterminer les deux paramètres K_{HLB} et k_e. Le taux d'échantillonnage est alors déterminé grâce à l'équation suivante :

$$R_s = K_{HLB} \times k_e \times m_{phase} \qquad \textbf{Équation II.9}$$

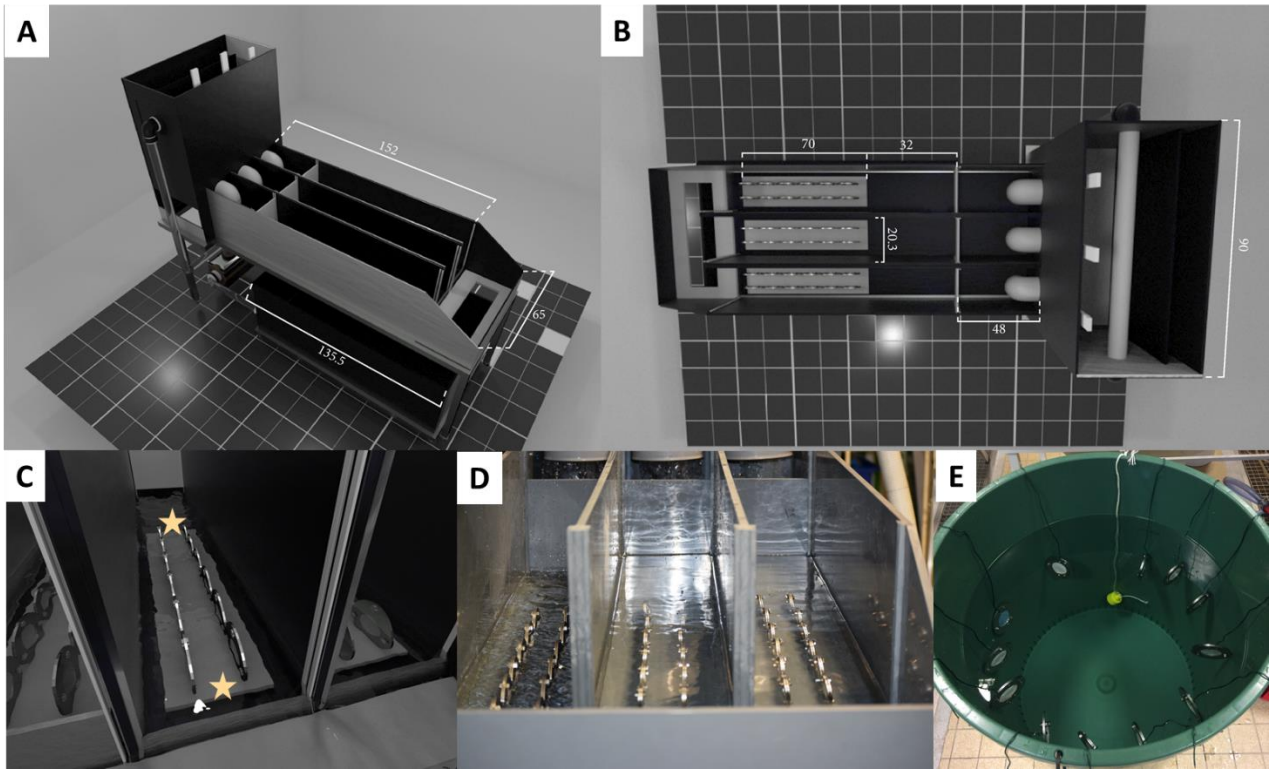

Figure II.20 : Les deux pilotes utilisés pour la détermination des taux d'échantillonnage (Rs) des composés pharmaceutiques (A, B, C : images de synthèse de la rivière artificielle avec A : vue au 3/4, B : vue du dessus et C : vue des canaux avec l'emplacement où les mesures de courant ont été faites, D : photo des canaux durant l'exposition et E : photo du réservoir pour la vitesse nulle).

Tableau II.19 : Paramètres de calibration pour la détermination des taux d'échantillonnage des composés pharmaceutiques.

Paramètre	Valeur
Durée d'exposition	1, 3, 5, 7, 10, 15 et 21 jours
Phase réceptrice	Oasis® HLB
Réplicat	Duplicat par date
Positionnement	Parallèle au courant
Vitesses de courant	0, 2-3, 6-7 et 20 $cm.s^{-1}$
Concentration	≈ 0,5 $\mu g.L^{-1}$
Température	16,0 ± 1,5 °C
Matrice	Eau du robinet
Volume rivière	500 L
Volume tank (vitesse nulle)	200 L
Echantillonnage ponctuel	Chaque 2-3 jours
Mesure vitesse de courant	Chaque 2-3 jours
Mesure de la température	Chaque 15 min
Renouvellement	15% du volume/jour
Débit	13 $m^3.h^{-1}$

Théorie de l'échantillonneur passif de type o-DGT.

La technique DGT (ou o-DGT) est une technique d'échantillonnage passif basée sur la diffusion des analytes à travers un gel diffusif jusqu'à la phase réceptrice sur laquelle les composés se fixent. Une vue éclatée de cet échantillonneur est présentée **Figure II.16**. La concentration dans le milieu échantillonné est calculée avec l'équation suivante :

$$C_W = \frac{m_{DGT} \times \Delta_g}{D \times \mathcal{A} \times t} \qquad \textbf{Équation II.10}$$

Où C_w est la concentration du milieu (µg.L^{-1}), m est la masse retrouvée sur la phase réceptrice après élution (ng), Δ_g est l'épaisseur de la phase diffusive (cm), D est le coefficient de diffusion (cm^2.s^{-1}), $\mathcal{A}$ est la surface d'exposition (cm^2) et t est le temps d'exposition (s).

Le coefficient de diffusion est spécifique à chaque molécule est doit être déterminé préalablement en laboratoire.

Expérience de calibration o-DGT : détermination des coefficients de diffusion.

Deux méthodes ont été utilisées pour déterminer les coefficients de diffusion des pesticides ioniques.

La première méthode utilise une cellule de diffusion (**Figure II.21**). Deux compartiments (compartiment "source" et compartiment "récepteur") sont connectés par un gel diffusif. La fenêtre d'exposition est de 1,77 cm^2. Le compartiment source est rempli avec une solution de $NaNO_3$ à 10^{-2} M dopée avec un pesticide ionique à 1 mg.L^{-1}. Le compartiment récepteur est rempli avec une solution de $NaNO_3$ à 10^{-2} M. Chaque compartiment est agité de façon continue avec un agitateur à hélices. Un prélèvement dans le compartiment récepteur toutes les 20 ou 30 min pendant 3h.

La deuxième méthode consiste à exposer des o-DGT dans une solution de concentration connue avec des temps d'exposition différent. Un cristallisoir de 3 L est rempli avec une solution de $NaNO_3$ à 10^{-2} M dopée avec un mix des pesticides ioniques à 1 mg.L^{-1}. Les o-DGT sont prélevées toutes les 2h pendant 40h. Ils sont ensuite démontés comme décrit dans la **Figure II.17** et élués comme décrit dans la **Figure II.18**.

Les caractéristiques de deux méthodes sont détaillées dans le **Tableau II.20**. Quelle que soit la méthode, une relation linéaire est tracée :

$$m_{Cr} = a \times t + b \qquad \textbf{Équation II.11}$$

Où m_{Cr} est la masse dans le compartiment récepteur (µg) et t le temps (s). La pente de la droite peut s'écrire :

$$a = \frac{D \times \mathcal{A} \times C_{Cs}}{\Delta_g} \qquad \textbf{Équation II.12}$$

Où D est le coefficient de diffusion (cm^2.s^{-1}), $\mathcal{A}$ est la surface d'exposition (1,77 cm^2), C_{Cs} est la concentration du compartiment source (1 mg.L^{-1}) et Δ_g est l'épaisseur de la phase diffusive (cm). Le coefficient de diffusion est déterminé par l'équation suivante :

$$D = \frac{a \times \Delta_g}{\mathcal{A} \times C_{Cs}} \qquad \textbf{Équation II.13}$$

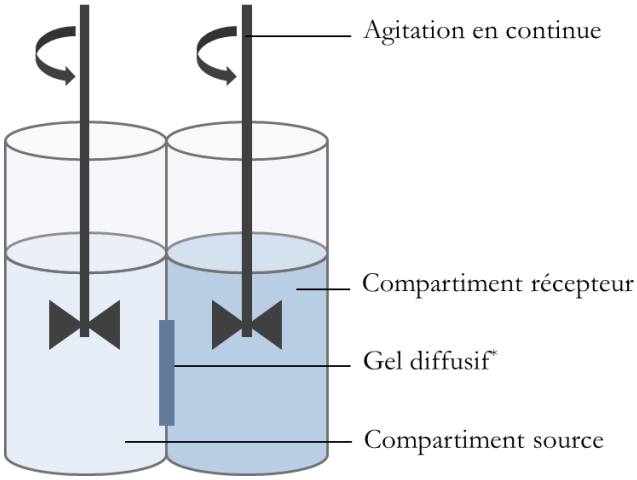

Figure II.21 : Cellule de diffusion (*Dans ces travaux, seuls des coefficients de diffusion à travers des gels en polyacrylamide ont été déterminé par cellule de diffusion).

Tableau II.20 : Paramètres de l'expérience pour la détermination des coefficients de diffusion des pesticides ioniques.

Paramètre	Valeur	
	Méthode 1	**Méthode 2**
Temps / Durée d'exposition	Toutes les 20-30 min pendant 3h	Toutes les 2h pendant 60h
Phase diffusive	Polyacrylamide	
Réplicat	Quadriplicat	Triplicat pour 5 durées
Concentration	1 $mg.L^{-1}$	
Température	20°C	5°C
Matrice	$NaNO_3$ à 10^{-2} M	
Volume	70 mL	3L
Agitation	Agitateur à hélices	Agitateur magnétique

Données utilisées.

Dans cette section, les taux d'échantillonnage et les coefficients de diffusion spécifiques à chaque molécule qui ont été utilisés dans ces travaux sont présentés dans le **Tableau II.21** pour les pesticides neutres, dans le **Tableau II.22** pour les pesticides ioniques et dans le **Tableau II.23** pour les composés pharmaceutiques. Les limites de quantification avec le couplage chromatographie liquide - spectrométrie de masse et échantillonnage passif (POCIS ou o-DGT) sont également présentées pour chaque molécule concernée pour 14 jours d'exposition.

Tableau II.21 : Valeurs des LQ_{POCIS} calculées pour les deux méthodes analytiques ([1]méthode analytique n°1 et [2]méthode analytique n°1') **à partir des taux d'échantillonnage** ([3]données issues de Lissalde et al. (2011) et Poulier et al. (2014)).

Pesticide	LQ_{POCIS}^{1} (ng.L^{-1})	LQ_{POCIS}^{2} (ng.L^{-1})	Taux d'échantillonnage[3] (mL.j^{-1})
3-hydroxy-carbofuran	7,3	7,3	197
Acétochlore	10,8	2,2	333
Alachlore	2,1	4,2	345
Atrazine	1,3	2,6	283
Azoxystrobine	0,3	2,2	336
Bénoxacor	-	-	-
Carbaryl	2,2	21,2	169
Carbendazime	1,2	2,4	304
Carbofuran	0,9	1,7	425
Chlorfenvinphos	0,3	2,6	278
Chlortoluron	0,3	4,2	341
Cybutryne (Irgarol)	0,3	3,0	238
Cyproconazole	1,2	-	316
Dichlorophényl-méthyluréa (DCPMU)	1,0	4,1	356
Dichlorophényl-uréa (DCPU)	1,7	8,3	431
Atrazine-désethyl (DEA)	1,2	2,4	305
Terbuthylazine-désethyl (DET)	1,3	2,5	290
Atrazine-déisopropyl (DIA)	2,4	4,8	149
Diméthachlore	1,3	-	292
Diméthénamide	0,2	-	462
Diméthoate	0,5	4,4	163
Diméthomorphe	0,9	1,9	395
Diuron	0,4	3,1	234
Epoxiconazole	0,9	-	404
Flurochloridone	-	-	-
Flurtamone	0,2	-	360
Flusilazole	0,9	-	437
Hexazinone	0,3	2,5	288
Imidaclopride	0,3	-	290
Isopropylphényl-méthyluréa (IPPMU)	1,1	2,1	349
Isopropylphényl-uréa (IPPU)	1,0	2,0	362
Isoproturon	0,3	2,3	316
Linuron	0,3	2,4	306
Métazachlore	0,3	2,5	289
Méthomyl	2,4	2,4	306
Métolachlore	1,1	4,3	338

Métoxuron	0,3	2,7	274
Norflurazon	0,3	-	285
Norflurazon-desméthyl	0,3	-	284
Pirimicarbe	1,3	2,6	285
Simazine	0,3	2,6	281
Tébuconazole	1,1	-	351
Terbuthylazine	0,2	1,5	488
Thiodicarbe	0,5	4,3	168

Tableau II.22 : Valeurs des LQ_{POCIS} et $LQ_{o\text{-}DGT}$ calculées à partir des taux d'échantillonnage ([1]données issues de Fauvelle et al. (2012)) **et des coefficients de diffusion** ([2]données déterminées dans ces travaux - chapitre III.B).

Pesticide	LQ_{POCIS} (ng.L^{-1})		$LQ_{o\text{-}DGT}$ (ng.L^{-1})		Taux d'échantillonnage[1] (mL.j^{-1})		Coefficient de diffusion[2] (10^{-6} cm².s^{-1})	
	HLB	MAX	HLB	MAX	HLB	MAX	HLB	MAX
Bentazone	1,8	2,1	2,9	3,2	205	171	3,6	4,3
Chlorsulfuron	2,6	3,8	4,0	4,1	140	94	2,7	3,1
Ioxynil	0,9	1,4	2,4	3,7	424	266	4,6	6,0
Mécoprop	19,4	11,9	2,9	3,1	74	120	3,8	3,9

Tableau II.23 : Valeurs des LQ_{POCIS} et $LQ_{o\text{-}DGT}$ calculées à partir des taux d'échantillonnage ([1]données déterminées dans ces travaux - chapitre IV.C) **et des coefficients de diffusion** ([2]données issues de Challis et al. (2016)).

Composé pharmaceutique	LQ_{POCIS}[1] (ng.L^{-1})	$LQ_{o\text{-}DGT}$ (ng.L^{-1})	Taux d'échantillonnage[1] (mL.j^{-1})	Coefficient de diffusion[2] (10^{6} cm².s^{-1})
Acétaminophène	0,7	-	111	-
Aténolol	0,4	1,2	228	2,13
Bézafibrate	1,3	-	276	-
Bisoprolol	0,3	-	278	-
Caféine	0,6	-	263	-
Carbamazépine	0,4	1,7	443	2,93
Clarithromycine	0,2	1,7	351	1,45
Dexaméthasone	0,4	-	388	-
Diazépam	0,5	-	160	-
Diclofénac	4,3	15,4	334	3,07
Econazole	-	-	0	-
Erythromycine	0,4	3,4	379	1,42
Fenbendazole	-	-	0	-
Fénofibrate	-	-	0	-

Flunixine	0,2	-	450	-
Fluoxétine	0,3	2,0	514	2,36
Gemfibrozil	9,5	52,6	377	2,24
Griséofulvine	0,3	-	347	-
Indométacine	4,0	-	365	-
Kétoprofène	1,2	4,7	313	2,53
Lincomycine	0,3	-	307	-
Metformine	-	-	0	-
Métoprolol	0,3	1,1	346	2,18
Métronidazole	0,4	-	462	-
Monensine	7,1	-	101	-
Nadolol	0,5	-	313	-
Oméprazole	1,0	-	75	-
Paraxanthine	1,5	-	246	-
Paroxétine	0,2	1,1	371	2,28
Périndopril	0,3	-	273	-
Praziquantel	0,9	-	422	-
Prednisolone	1,9	-	383	-
Propanolol	1,0	4,9	392	2,44
Pyrantel	0,2	-	539	-
Roxithromycine	0,9	9,2	404	1,28
Salbutamol	1,0	-	157	-
Sotalol	0,7	-	231	-
Sucralose	3,3	-	220	-
Sulfadiazine	0,4	-	202	-
Sulfamérazine	0,5	-	175	-
Sulfaméthoxazole	1,0	1,8	154	2,70
Sulfaméthoxypyridazine	0,7	-	207	-
Terbutaline	0,7	-	103	-
Thioridazine	-	-	0	-
Triclabendazole	-	-	0	-
Triméthoprime	0,5	1,9	350	2,56

II.6. Les sites naturels d'étude

Les déploiements terrain ont été faits sur cinq rivières et parfois certains affluents avec des bassins versants différents. Trois rivières ont été utilisées pour des expositions uniques (la Pude, les Eaux Claires et la Seugne). Sur l'Auvézère et l'Aixette, les deux autres rivières, un suivi semi-continu de, respectivement, 3 ans et 1 an a été fait avec l'exposition de POCIS.

II.6.1. Bassin versant des Eaux Claires, la Seugne et la Pude

Les Eaux Claires.

Les Eaux Claires est un cours d'eau situé dans le département de la Charente (16). Il prend sa source à la Prévalerie et se jette dans la Charente. Il mesure 13,7 km et draine les eaux d'un bassin versant de 39 km². En termes d'occupation du sol, 43% du bassin est occupé par des terres agricoles, 40% par des forêts et milieux semi-naturels et 17% par des territoires artificialisés. Le site de prélèvement se situe sur la commune de Torsac à 1,2 km de la source (**Figure II.22**). Ce point est un point du Réseau de Contrôle et de Surveillance (RCS) de la DCE (2000/60/EC 2000). Ce site d'étude a été utilisé pour l'exposition d'échantillonneurs de type o-DGT et POCIS lors du développement du o-DGT (chapitre III.B).

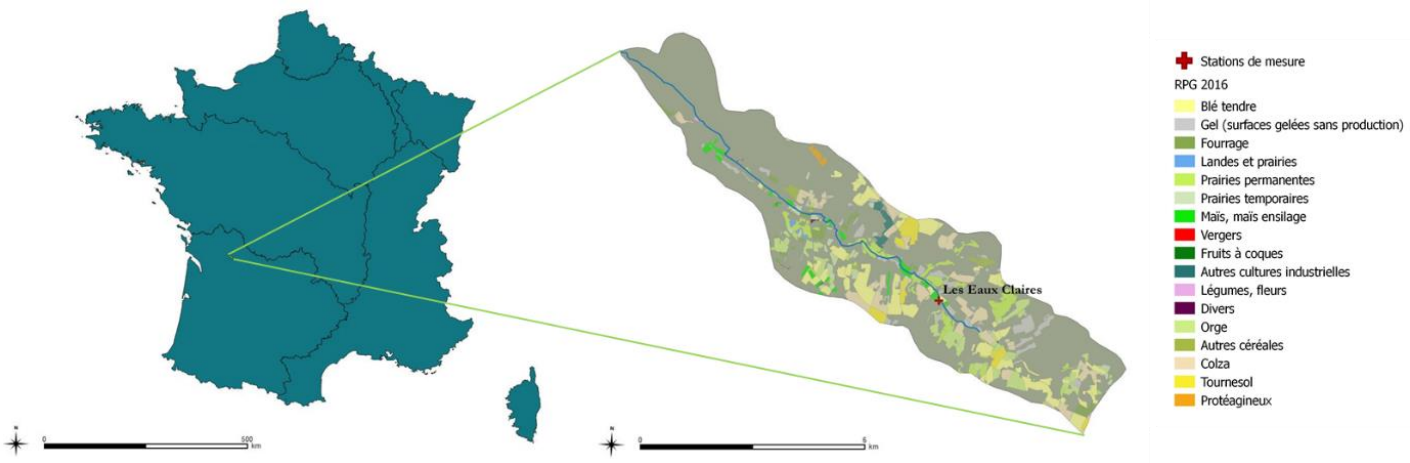

Figure II.22 : Bassin versant des Eaux Claires et son occupation du sol (RPG 2016).

La Seugne.

La Seugne est un cours d'eau situé dans le département de la Charente-Maritime (17). Il prend sa source au lieu-dit Chez Bourdeau dans la commune de Montlieu-la-Garde et se jette dans la Charente. Il mesure 82,3 km et draine les eaux d'un bassin versant de 7428 km². En termes d'occupation du sol, 76% du bassin est occupé par des terres agricoles (**Figure II.23**). Caractéristique particulière, la haute vallée de la Seugne est classée en zone Natura 2000. Le site de prélèvement se situe sur la commune de Saint-Germain-de-Lusignan à 39,5 km de la source. Ce point est un point du Réseau de

Contrôle et de Surveillance (RCS). Ce site d'étude a été utilisé pour l'exposition d'échantillonneurs de type o-DGT et POCIS lors du développement du o-DGT (chapitre III.B).

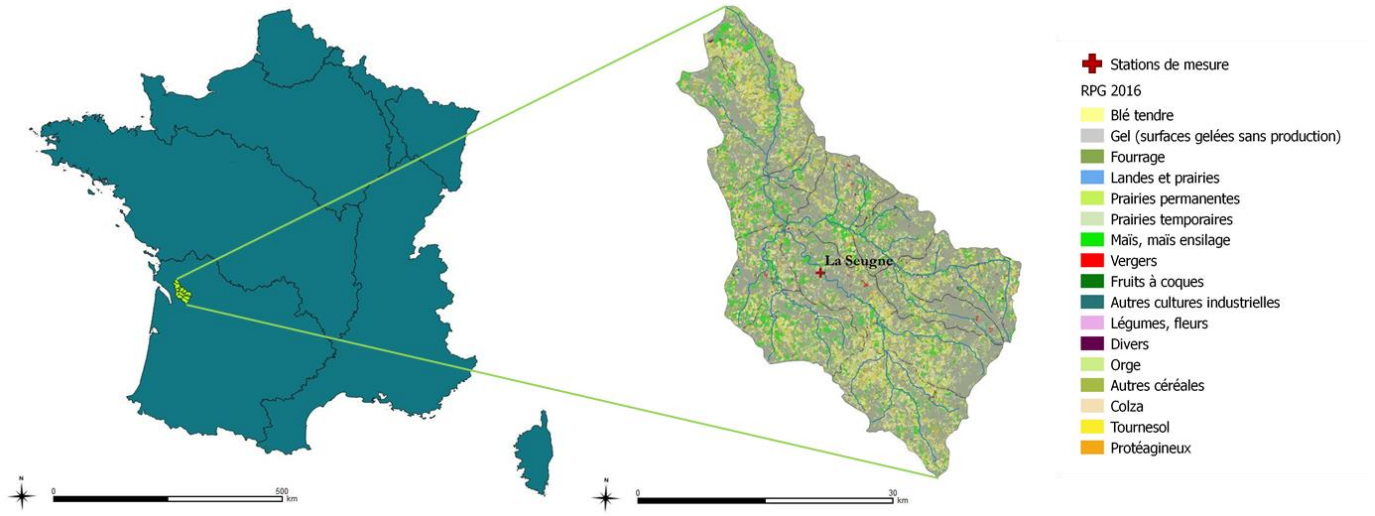

Figure II.23 : Bassin versant de la Seugne et son occupation du sol (RPG 2016).

La Pude.

La Pude est un cours d'eau situé dans le département de la Dordogne (24). Il prend sa source à Gout-Rossignol (nord-ouest de la Dordogne) et se jette dans la Lizonne (un sous-affluent de la Dordogne). Il mesure 19,7 km et draine les eaux d'un bassin versant de 73 km². En termes d'occupation du sol, 91% du bassin est occupé par des terres agricoles et 8,5% par des forêts. Le site de prélèvement se situe sur la commune de Nanteuil-Auriac-de-Bourzac à 18,2 km de la source (**Figure II.24**). Ce site d'étude a été utilisé pour l'exposition de POCIS lors du développement du lavage des membranes PES (chapitre IV.B).

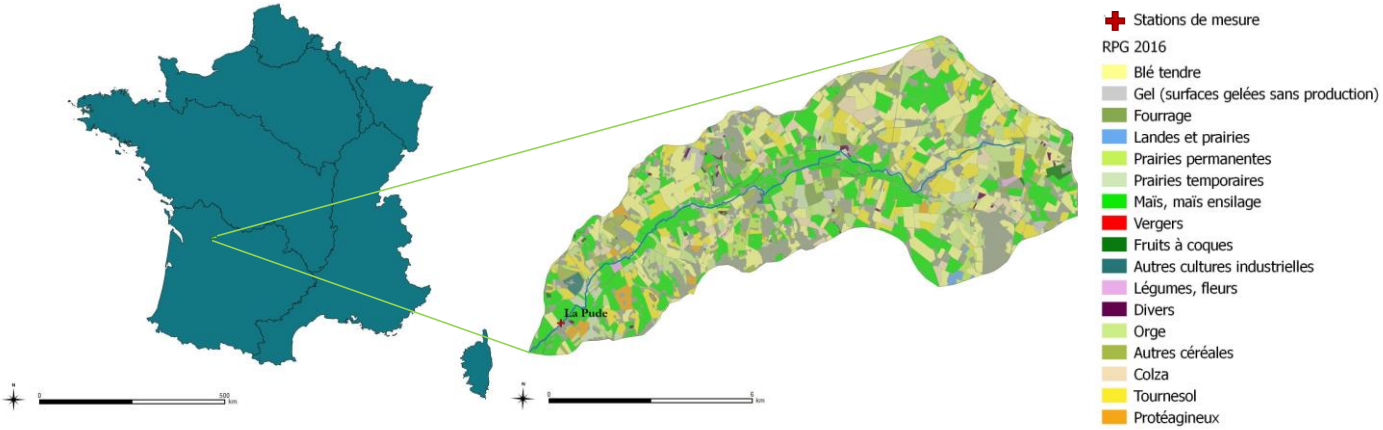

Figure II.24 : Bassin versant de la Pude et son occupation du sol (RPG 2016).

II.6.2. Bassins versants de l'Auvézère et de l'Aixette.

L'Auvézère amont et l'Aixette ont été choisis comme bassins versants représentatifs des têtes de bassin versant. En effet, leur rang de Strahler est de 3 et ils se situent dans l'ancienne région Limousin (aujourd'hui Nouvelle-Aquitaine), source de nombreux cours d'eau. Ces deux bassins versants sont ruraux avec, principalement, de l'élevage extensif de bovins et d'ovins avec des prairies permanentes ou temporaires pour nourrir le bétail. Les nombreux pâturages sont petit à petit remplacés par des cultures de céréales pour nourrir le bétail. Ces changements de pratiques récents destinés à assurer une meilleure rentabilité des exploitations provoquent un potentiel accroissement de la pression en produits phytosanitaires sur les cours d'eau.

Deux tributaires sont considérés dans ces travaux : le Rau d'Arnac et l'Arthonnet pour, respectivement le bassin de l'Auvézère et le bassin de l'Aixette. Ces deux tributaires ont un nombre Strahler de 2.

Bassin versant de l'Auvézère amont.

L'Auvézère est un cours d'eau situé dans le sud-ouest de la France en région Nouvelle-Aquitaine. Il prend sa source au lieu-dit Camp de César dans la commune de Saint-Germain-les-Belles située dans le département de la Haute-Vienne (87) et se jette dans l'Isle (un sous-affluent de la Dordogne). Il mesure 112,2 km et draine les eaux d'un bassin versant de 900 km². En termes d'occupation du sol, 62% du bassin est occupé par des terres agricoles (dont des prairies, des cultures céréalières pour l'alimentation du bétail, de la pomiculture ou la culture de petits fruits rouges), 36% par de forêts et milieux semi-naturels et un peu moins de 2% par des territoires artificialisés. L'occupation du sol est détaillée sur la **Figure II.25**. Sur cette même figure, sont représentés les 3 sites de prélèvements. Deux sites de prélèvement sont situés sur un affluent de l'Auvézère, sur le Rau d'Arnac, le dernier est situé sur le cours d'eau principal : l'Auvézère à l'amont à 22km de la source.

Figure II.25 : Bassin versant de l'Auvézère et son occupation du sol (RPG 2016).

Bassin versant de l'Aixette.

L'Aixette est un cours d'eau situé dans le département de la Haute-Vienne (87). Il prend sa source à Bussière-Galant et se jette dans la Vienne. Il mesure 27,1 km et draine les eaux d'un bassin versant de 152 km². En termes d'occupation du sol, 53% du bassin est occupé par des zones agricoles (dont des prairies, des cultures céréalières), 43% par des forêts et des milieux semi-naturels et un peu moins de 4% par des territoires artificialisés. L'occupation du sol est détaillée sur la **Figure II.26**. Sur cette même Figure, sont représentés les 3 sites de prélèvements. Deux sites sont situés sur le cours d'eau principal (l'Aixette) et un dernier est situé sur un affluent de l'Aixette : l'Arthonnet. Ces points de prélèvement sont répartis sur la surface du bassin versant de l'Aixette et permettent de réaliser un bilan de la contamination. Un contrat territorial appelé « Vienne médiane et ses affluents » a été mis en place pour caractériser les eaux de ce territoire afin de définir ultérieurement des actions pour atteindre les objectifs de bonne qualité écologique et chimique des eaux.

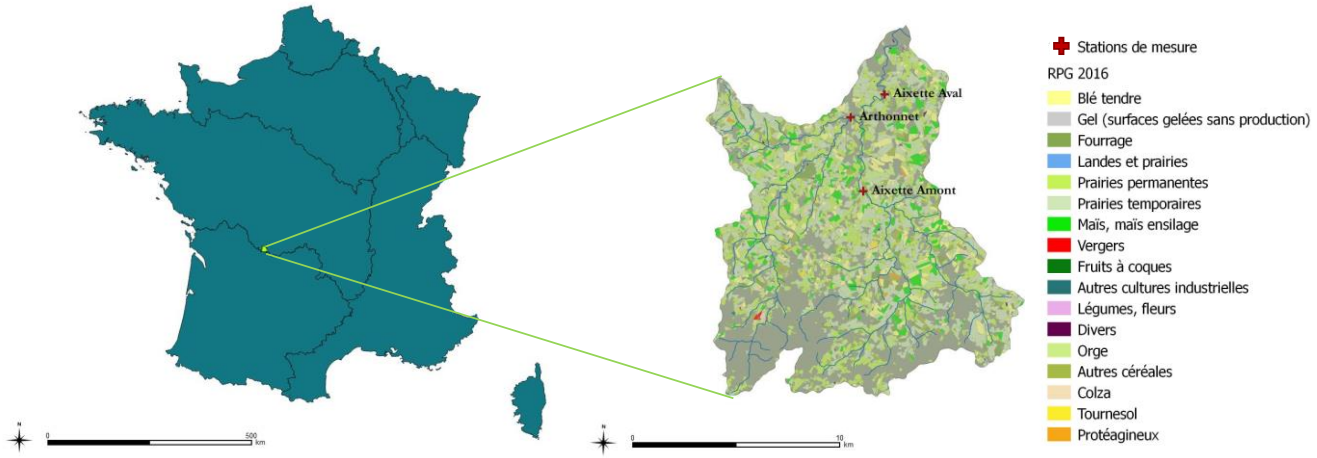

Figure II.26 : Bassin versant de l'Aixette et son occupation du sol (RPG 2016).

II.7. Mode de déploiement des échantillonneurs passifs

Les dispositifs sont déployés dans les cours d'eau selon trois techniques : installation « en drapeau », en cagette ou à plat. Lorsque la lame d'eau est assez grande et susceptible d'être constante durant la période d'exposition, l'installation « en drapeau » est privilégiée. Les échantillonneurs sont placés droits et parallèles au courant grâce à un poteau métallique planté dans le lit de la rivière. Les échantillonneurs sont maintenus avec un filet. Un exemple de déploiement « en drapeau » est présenté **Figure II.27**. En revanche, lorsque la lame d'eau n'est pas assez importante, notamment au niveau de ruisseaux, l'installation est faite à plat sur une dalle ou sur des plots en béton. Le tout est accroché à la rive grâce à une chaîne. De même, certains sites ont un socle rocheux (granitique) et ce type de sol rend, parfois, difficile ou impossible l'implantation de piquet. Dans ce cas, l'installation se fera également à plat. Un exemple de ce type de déploiement est présenté **Figure II.28**. Lorsque la lame d'eau est importante, un déploiement en cagette peut être réalisé. Les échantillonneurs sont positionnés dans une cagette ouverte et cette dernière est accrochée de part et d'autre

de la rive grâce à des cordes. Les échantillonneurs se retrouvent face au courant (positionnés en perpendiculaire) (**Figure II.29**),

Pour évaluer l'influence du positionnement sur l'accumulation des composés cibles, des tests sur le positionnement des échantillonneurs de type POCIS ont été réalisés sur trois sites d'études (La Pude, Arnac Aval et l'Aixette). Sur chaque site d'étude, des quadriplicats de POCIS ont été exposés à deux endroits du cours d'eau : un premier où le courant est fort (de 25 à 45 $cm.s^{-1}$) et un deuxième endroit où le courant est moins fort (de 1 à 10 $cm.s^{-1}$). Les trois positionnements (parallèle, perpendiculaire et couché) ont été testés sur chaque site et pour les 2 gammes de vitesse de courant. Au total, 72 POCIS ont été exposés. Les POCIS exposés perpendiculairement sont soumis à de plus forts risques d'endommagement par des débris (branches) se trouvant dans l'eau. En moyenne, une différence de 35% a été observée entre les différents positionnements. L'effet du positionnement est alors négligeable par rapport à la mesure semi-quantitative obtenue lors de l'échantillonnage par POCIS ((Poulier et al. 2014)).

Figure II.27 : Échantillonneurs passifs (POCIS et o-DGT) installés « en drapeau » sur un piquet.

Figure II.28 : Échantillonneurs passifs (POCIS et o-DGT) installés à plat sur une dalle.

Figure II.29 : Échantillonneurs passifs (POCIS et o-DGT) installés dans une cagette.

Chapitre III. Développement d'un échantillonneur passif innovant

III.1. Introduction intermédiaire

Les composés organiques présents dans l'environnement sont nombreux et ont diverses origines. Ils peuvent être classés selon leur polarité (traduit généralement par le LogP ou LogKow). Chaque échantillonneur passif est associé à une classe : le Chemcatcher® et le Semi-Perméable Membrane Device (SPMD) pour les composés apolaires et le POCIS pour les composés moyennement polaires et polaires. En revanche, pour les composés très polaires ou ioniques, aucun dispositif n'est développé.

De récentes études ont montré le potentiel de l'utilisation de dispositifs DGT pour l'échantillonnage de molécules organiques. C'est le cas avec l'étude de Chen et al. (2012), pour échantillonner le sulfaméthoxazole ou encore l'étude de Fauvelle et al. (2015) pour échantillonner le glyphosate et l'un de ses métabolites (l'AMPA). Le dispositif DGT est un échantillonneur utilisé depuis le début des années 90 pour l'échantillonnage des métaux (Davison and Zhang 1994). Cet échantillonneur est composé d'un gel diffusif qui permet de contrôler le transfert des molécules du milieu échantillonné vers la phase réceptrice. Ce dispositif sera donc moins influencé par les vitesses de courant par rapport au POCIS.

Ce chapitre relate le développement d'un échantillonneur innovant en utilisant les avantages de deux dispositifs : le DGT « classique » et le POCIS. Ce dispositif fait partie de la famille des DGT et est adapté aux composés organiques. Il est appelé o-DGT par de nombreux auteurs comme dans l'article de Chen et al. (2012) qui fut le premier à le nommer ainsi. Le dispositif innovant o-DGT utilisera donc le gel diffusif du DGT (gel en polyacrylamide ou en agarose) et la phase réceptrice du POCIS (Oasis® HLB ou MAX). La phase réceptrice ne sera pas sous forme de poudre « libre » comme dans le POCIS mais la poudre sera incorporée à un hydrogel (du même matériau que le gel diffusif). Les caractéristiques de cet échantillonneur innovant seront alors testées avec, dans un premier temps, la détermination des coefficients de diffusion des molécules étudiées. Cette étape est très importante pour déterminer la concentration des micropolluants dans l'eau. Dans un deuxième temps, l'élution des phases réceptrices sera également testée et un facteur d'élution sera alors déterminé. L'objectif de l'élution est d'avoir le meilleur rendement possible dans un temps relativement acceptable. Afin que l'échantillonneur puisse être utilisé en milieu naturel, il faudra évaluer sa capacité et sa robustesse. Le premier paramètre permettra de connaître le temps de déploiement maximum avant la saturation de la phase réceptrice ainsi que la partie linéaire d'accumulation. Le second permettra de savoir sur quelle gamme de pH ou de force ionique (correspondant à des conditions environnementales) ce dispositif innovant estimera correctement la concentration des composés organiques du milieu échantillonné. La dernière étape sera de valider cet échantillonneur avec une exposition en laboratoire dans des eaux naturelles dopées.

Après cette validation, deux échantillonneurs (o-DGT et POCIS) seront donc opérationnels pour étudier la pression en pesticides et résidus pharmaceutiques polaires et moyennement polaires en milieu naturel. Il faudra alors répondre à la problématique suivante : Quel est l'échantillonneur le plus adapté à notre étude entre POCIS et o-DGT sur la contamination des têtes de bassin versant ? Pour y répondre, une expérience avec une rivière artificielle à l'échelle de laboratoire permettra de simuler des conditions proches des conditions environnementales. Les deux échantillonneurs

seront, avant d'être exposés en milieux naturels, exposés à plusieurs vitesses de courant dans de l'eau de robinet (matrice intermédiaire entre de l'eau distillée et de l'eau naturelle). Ces expériences de laboratoire apporteront les premières réponses pour le choix de l'échantillonneur passif.

L'objectif de ce chapitre consiste à :

- Développer un échantillonneur innovant mélangeant les avantages du DGT et du POCIS pour les pesticides ioniques.
- Déterminer les caractéristiques du o-DGT pour les pesticides ioniques : coefficient de diffusion, capacité et élution.
- Tester la robustesse du o-DGT pour les pesticides ioniques : exposition à différent pH et force ionique en laboratoire et dans deux eaux naturelles.
- Comparaison des performances du o-DGT et du POCIS : en laboratoire et en milieu naturel.

III.2. Publication "Passive sampling of anionic pesticides using the Diffusive Gradients in Thin films technique (DGT)".

Cette section est constituée d'une version adaptée d'un article publié dans la revue « Analytical Chemica Acta », où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

Guibal, R., Buzier, R., Charriau, A., Lissalde, S. and Guibaud, G. (2017a) Passive sampling of anionic pesticides using the Diffusive Gradients in Thin films technique (DGT). Analytica Chimica Acta 966, 1-10.

Passive sampling of anionic pesticides using the Diffusive Gradients in Thin films technique (DGT).

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ABSTRACT

DGT passive samplers using Oasis® HLB or Oasis® MAX sorbent were developed for anionic pesticides sampling. They were tested using four model compounds (*i.e.* bentazon, chlorsulfuron, ioxynil and mecoprop). Polyacrylamide diffusive gel was found to be more suitable than agarose gel for most anionic pesticides sampling. An elution procedure was optimized and diffusion coefficients were determined for quantitative use of the samplers. Depending on the DGT configuration used (HLB or MAX), accuracies better than 30% were demonstrated in laboratory for pH from 3 to 8 and ionic strengths from 10^{-2} to 1 M. Combined with the effective binding capacities of samplers (≥ 9 µg for each pesticide) and limits of quantification of the method (≤ 13 ng L^{-1} using Q-TOF detector) monitoring of numerous aquatic systems can be expected. Except for ioxynil, accurate quantifications were demonstrated in laboratory using a spiked natural water for HLB-DGT whereas MAX-DGT did not give satisfactory results. A further in situ validation was performed in two rivers and showed identical detection fre-quency between HLB-DGT and POCIS of anionic pesticides (bentazon and mesotrione) whereas calculated concentrations, although within the same order of magnitude, could differ (<70%). HLB-DGT could therefore constitute an interesting alter-native to other passive samplers for the monitoring of several anionic pesticides in aquatic systems but more work is re-quired for quantification of molecules from hydroxybenzonitrile chemical group (ioxynil).

Keywords: anionic pesticides, herbicides, passive sampling, Diffusive Gradients in Thin films, water analysis

INTRODUCTION

Passive sampling is gaining interest for monitoring water quality and its use as a complement to spot sampling was recently proposed in the framework of regulatory monitoring programs (2000/60/EC 2000, 2013/39/EC 2013, Poulier et al. 2014). The main advantage of passive sampling lies in the determination of time-weighted average concentrations of chemicals (TWAC), allowing complementary knowledge on system contamination combined with spot concentrations. In addition, the potential gain in quantification limits can improve detection for some trace pollutants. Among the various passive samplers, POCIS (Polar Organic Chemical Integrative Sampler) with Oasis® HLB sorbent is the most commonly used for the study of polar pesticides (Ahrens et al. 2015, Harman et al. 2012, Morin et al. 2012). Environmental parameters (mainly water flow rate) may, however, increase uncertainty of pesticide quantification (Miège et al. 2015, Mills et al. 2014). Indeed, the calculation of TWAC requires the use of sampling rates that were shown to be flow dependant (Alvarez et al. 2007, Li et al. 2010b, Lissalde et al. 2014). TWAC estimation under different field conditions can therefore be biased by the use of laboratory-derived sampling rates. The PRC (Performance and Reference Compound) approach was developed to overcome this limitation by an *in-situ* correction of sampling rates, but it is not validated for ionic pesticides due to anisotropic behaviour (Miège et al. 2015). Currently, quantification accuracy using POCIS under environmental conditions is assumed to lie between -50% and + 100% (Poulier et al. 2014).

The DGT (Diffusive Gradients in Thin films) passive sampler has been used for more than 20 years for sampling inorganic compounds such as trace metals, metalloids or phosphorus (Bennett et al. 2010, Garmo et al. 2003, Turner et al. 2012, Zhang et al. 1995). This sampler differs from other passive samplers by the incorporation of a diffusive gel layer able to control analyte transfer in the sampler. TWAC estimation using DGT device requires, therefore, only the diffusional characteristics of compounds (*i.e.* diffusion length and diffusion coefficient). The influence of water flow rate on quantification is relatively well documented compared to passive samplers currently used for pesticides (*e.g.* POCIS) (Garmo et al. 2006, Uher et al. 2013, Warnken et al. 2006). Diffusion length in the DGT system is composed of the diffusive gel length and water boundary layer length. Flow rate decrease induce increase in water boundary layer length and subsequent modification of diffusion length. This phenomenon has been shown to alter TWAC estimation only for low flow rates conditions (*i.e* < 10 $cm.s^{-1}$) (Buzier et al. 2014, Gimpel et al. 2001, Turner et al. 2014). In a context where the development of new passive samplers for ionic organic compounds is recommended (Miège et al. 2015), DGT appears to be potentially an interesting tool. Recent developments have adapted DGT to organic compounds by using various binding phases, but currently apply to only a few substances. The first attempt to develop an organic version of DGT was for antibiotics in river (Chen et al. 2012) and wastewater (Chen et al. 2013) using an XAD-18 binding layer. Other DGT developments allowed sampling of bisphenols (activated charcoal) (Zheng et al. 2014) and 4-chlorophenol (molecularly imprinted polymer) (Dong et al. 2014). Sampling of anionic pesticide using only poorly addressed. Few years ago, an attempt to sample an anionic pesticide (glyphosate) and its metabolite (aminomethyl phosphonic acid) using titanium dioxide DGT was not robust in synthetic freshwater (Fauvelle et al. 2015). Only very recently, DGT based on Oasis® HLB sorbent (Challis et al. 2016) used in POCIS and Strata-X sorbent (Belles et al.

2017) were proposed to sample polar organic compounds such as pesticides, pharmaceuticals and personal care products. Challis et al. (2016) demonstrated the potential of this technique for an anionic pesticide (2,4-D) but this method was not optimized for such compounds and no field validation was demonstrated for anionic pesticides.

This work aimed at optimising a DGT device for monitoring anionic pesticides. Four anionic herbicides from different chemical groups were chosen as model compounds: bentazon (pKa 3.3; benzothiazinone), chlorsulfuron (pKa 3.4; sulfonylurea), ioxynil (pKa 4.1; hydroxybenzonitrile) and mecoprop (pKa 3.1; aryloxyalkanoïc acids). Oasis® HLB (hydrophilic-lipophilic balanced polymer) and Oasis® MAX (polymer with additional quaternary ammonium functional groups), frequently used for pesticide extraction (Carpinteiro et al. 2010, Fauvelle et al. 2012, Li et al. 2011, Petrie et al. 2016), were selected as binding materials. In the present work binding on both sorbents and diffusive gel was studied and an elution procedure was optimized (solvent composition and elution duration). Effective binding capacities and diffusion coefficients were determined for TWAC estimations. The effect of pH and ionic strength was evaluated and a further application of the DGT to spiked natural waters was performed in laboratory. Finally, the developed DGT were validated on field and compared to POCIS passive sampler following *in situ* deployment in two rivers.

MATERIALS AND METHODS

Reagents and general procedures.

Ultrapure water (UPW) was produced by a Gradient A10 Milli-Q system from Millipore. Reagents used for HPLC-MS analysis were of HPLC-MS grade (methanol from J.T. Baker, formic acid from Agilent and ammonium formate from Scharlau). Pesticides (bentazone, chlorsulfuron, ioxynil and mecoprop) (>97 %) and internal standards (bentazone-d6, MCPA-d3 and metsulfuron-methyl-d3) (>95%) were obtained from Dr. Ehrenstorfer GmbH. Pesticide properties are presented in **Table III.1**. All other reagents were of analytical grade. Oasis® HLB or Oasis® MAX sorbent were purchased from Waters. Laboratory experiments (except analysis) were run at 20±1°C or, if experiment duration exceeded 24h, at 5±1°C to avoid pesticides degradation.

Table III.1: Main physicochemical characteristics of the studied pesticides (Pesticides Properties DataBase: http://sitem.herts.ac.uk/aeru/ppdb/en).

Pesticide	N°CAS	pKa	Solubility in water (mg/L)	log P
Bentazon	25057-89-0	3.3	570	-0.46
Chlorsulfuron	64902-72-3	3.4	12500	-0.99
Ioxynil	1689-83-4	4.1	3034	2.20
Mecoprop	93-65-2	3.1	250000	-0.19

DGT preparation.

Polyacrylamide and agarose diffusive gels were tested. Polyacrylamide (15% acrylamide, 0.3% DGT Research patented cross-linker) and agarose (1,5% agarose) diffusive gels were prepared according to the procedure of Zhang and Davison (1999). Binding gels were prepared with polyacrylamide only. 300 mg of sorbent material (Oasis® HLB or Oasis® MAX) were mixed with 10 mL of a solution containing 15% acrylamide and 0.3% DGT Research patented cross-linker. Then, for HLB and MAX binding gels, respectively 60 or 130 µL of 10 % ammonium persulfate solution and 15 or 50 µL of TEMED catalyst were added. Binding gels were immediately cast between two glass plates separated by Teflon® spacers (0.5 mm thickness), placed at 4°C for 30 min to allow settling of sorbent particles then at 45 °C for about 45 min to complete polymerization. All gels were hydrated in UPW for 24 h with at least five bath renewals and then stored in 10^{-2} M $NaNO_3$ solution at 4°C before use. After hydration, the average thicknesses of the polyacrylamide diffusive gel and of the HLB and MAX binding gels were 0.77 (±0.05, n=19), 0.69 (±0.01, n=4) and 0.67 mm (±0.01, n=4), respectively. The DGT system assembly was performed by enclosing a binding gel disc and a polyacrylamide diffusive gel disc inside a piston type molding (DGT Research Ltd.). HLB-DGT and MAX-DGT will refer to DGT equipped with HLB or MAX binding gels, respectively.

Uptake and desorption of pesticides by diffusive and binding gels.

Sorption of anionic pesticides by diffusive gels was investigated to evaluate their suitability for the DGT technique. For this purpose, polyacrylamide or agarose diffusive gels were immersed (n=3) for 4h in solution containing 10 µg L^{-1} of each pesticide. A control experiment was performed without diffusive gel. Sorption was estimated according to the difference between initial concentration and concentration measured after 4h in solution.

To evaluate uptake by binding gels, 24 binding gels (HLB or MAX) were immersed for 12 h at 20°C in 10 mL of solutions containing a mixture of the four pesticides (50, 100 and 250 µg L^{-1} each in 10^{-2} M $NaNO_3$). Desorption was tested by soaking binding gels previously loaded with 2.5 µg of pesticides (by immersion for 12 hours in a solution containing 250 µg L^{-1} of each pesticide). Soaking was performed in triplicate on HLB and MAX binding gels for 48 h in 5 mL of 10^{-2} M $NaNO_3$ solutions at pH 6 and 8 at 5°C.

Elution procedure.

For both binding gels, three eluents (v/v) were tested: a methanol / ethyl acetate mixture (50:50) (E1) previously used for HLB (Guibal et al. 2015b, Lissalde et al. 2011); a methanol / 1 M formic acid mixture (90:10) (E2) previously used for MAX (Fauvelle et al. 2012) and a methanol / 1 M NaOH mixture (70:30) (E3) previously used for 4-chlorophenol DGT sampler (Zheng et al. 2014). The elution yields were determined following immersion of pre-loaded binding gels (n=6) in 5 mL of either E1, E2 or E3 at 5°C. Binding gels were pre-loaded with 2.5 µg of each pesticide by immersion for 12 hours in a solution containing 250 µg L^{-1} of each pesticide. 100 µL of each eluents were sampled for analysis after a contact time of 1, 6, 10, 24 and 48h. Elution yields were determined as the ratio between eluted pesticide mass

and initially loaded pesticide mass. For further experiments, E1 and E2 were used for the elution of HLB and MAX, respectively, with a contact time of 24h.

Effective binding capacity.

To allow accurate TWAC calculation, accumulation in the DGT sampler must reflect exactly the mass transferred within the diffusive gel by diffusion. In such conditions, a plot of accumulated mass versus time behaves linearly (see Eq. 3). The boundary of the linear domain where TWAC calculation is valid represents the effective binding capacity of the binding gel. Effective binding capacities of HLB- and MAX-DGT were tested in 3 L solutions prepared with a mixture of 900 µg L^{-1} of each pesticide and 10^{-2} M $NaNO_3$. DGT systems were deployed at 5°C between 2 and 40 h (in triplicate for 6, 10, 18, 24 and 30 h). Binding gels were then retrieved for elution and analysis. Pesticide monitoring in exposure solutions showed that concentrations were nearly constant (RSD<10%) during the experiment (see example in **Figure III.1**and **Figure III.2**).

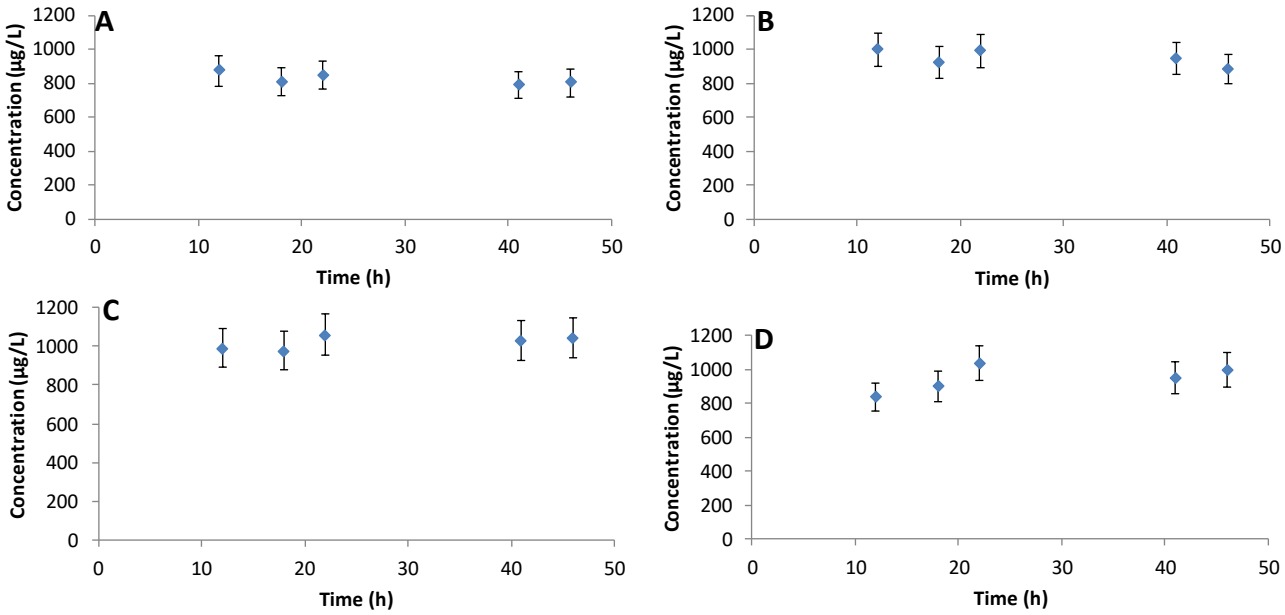

Figure III.1: Pesticides concentrations (A: bentazon, B: chlorsulfuron, C: ioxynil and D: mecoprop) in synthetic exposure solution at 5°C during 48h (binding capacity experiment for HLB-DGT).

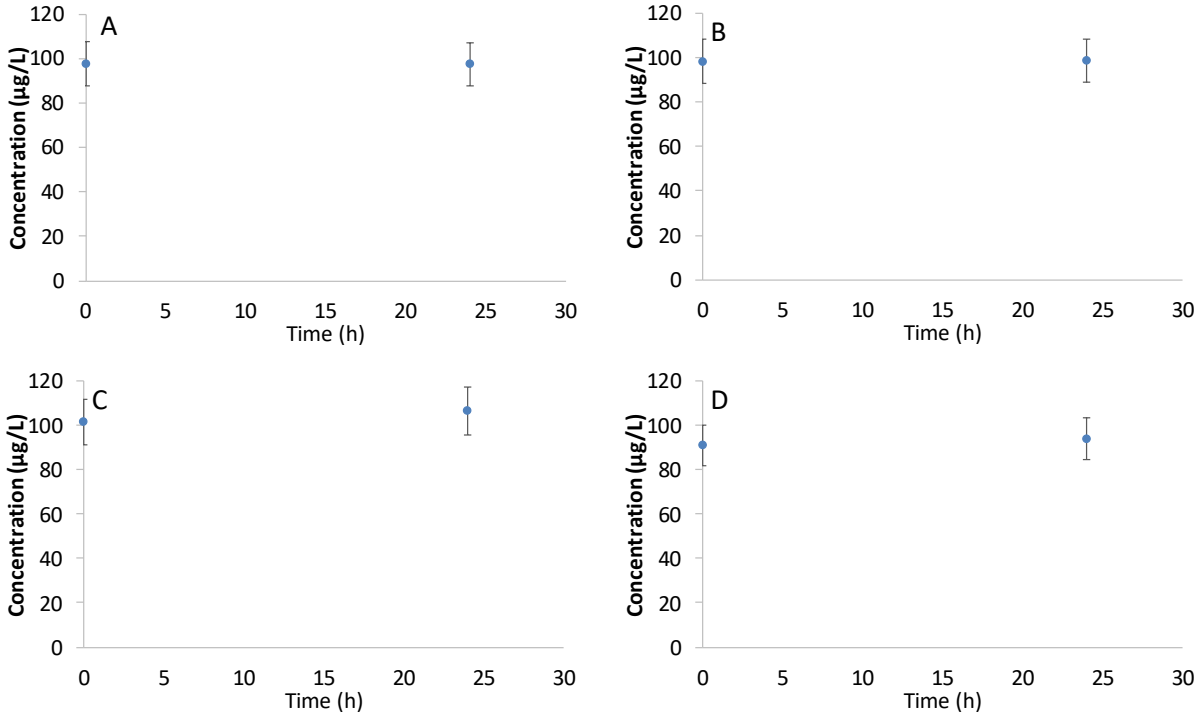

Figure III.2: Pesticides concentrations (A: bentazon, B: chlorsulfuron, C: ioxynil and D: mecoprop) in synthetic exposure solution at 20°C during 24h (10^{-2} M ionic strength experiment, MAX-DGT).

Diffusion coefficients.

Diffusion coefficients of pesticides within the diffusive gel are necessary for TWAC estimation (see next section). In this study, two kinds of diffusion coefficients were determined. The first one is a diffusion coefficient representing the "physical" diffusion coefficient of a molecule in the diffusive gel (D_{cell}). The second one is an effective diffusion coefficient (D_{eff}) representing a calibration coefficient with the same dimensions as the diffusion coefficient. Both coefficients were estimated using **Equation III.1**:

$$D = \frac{q_m \Delta_g}{C_s A} \qquad \text{Equation III.1}$$

where D is the diffusion coefficient, q_m the pesticide flux, Δg the diffusive gel thickness (0.77 mm), C_s the pesticide concentration in solution (1 mg L^{-1} each) and A the exposure area.

D_{cell} were determined using a diffusion cell as described in Devillers et al. (2016). Briefly, experiments were run in triplicate (20°C; pH 5) using 10^{-2} M $NaNO_3$ carrier solutions. The mass transferred from the source to the receptor compartment was followed for 3 or 4 hours. D_{cell} was calculated according to **Equation III.1** using 1.77 cm^2 as the exposure area of the diffusion cell (A). q_m was determined as the slope of the linear regression of the pesticide mass transferred by diffusion vs. the exposure time (**Figure III.3**).

D_{eff} were derived from the effective binding capacity experiments. **Equation III.1** was used with 3.14 cm^2 as the exposure area of the DGT molding (A). q_m was determined as the slope of the linear regression of the pesticide mass

uptake vs. time during the uptake capacity experiment. RSD on D_{eff} was calculated using **Equation III.2**. RSD on the linear regression slope of the uptake capacity (q_m) was calculated for each molecule whereas RSD was estimated at 3% for the diffusion gel thickness (Δ_g) (n=61, unpublished results), set at 10% for the pesticide concentration in bulk solution (C_s) and set at 1% for the DGT exposure area (A).

$$RSD_{D_{eff}} = \sqrt{RSD_{q_m}^2 + RSD_{\Delta_g}^2 + RSD_{C_s}^2 + RSD_A^2} \qquad \textbf{Equation III.2}$$

D_{cell} and D_{eff} values were corrected for temperature (T) using the Stokes-Einstein equation (**Equation III.3)**. Water's viscosity values (η) were taken from NIST chemistry WebBook (Lemmon et al. 2010).

$$\frac{D_1 T_1}{\eta_1} = \frac{D_2 T_2}{\eta_2} \qquad \textbf{Equation III.3}$$

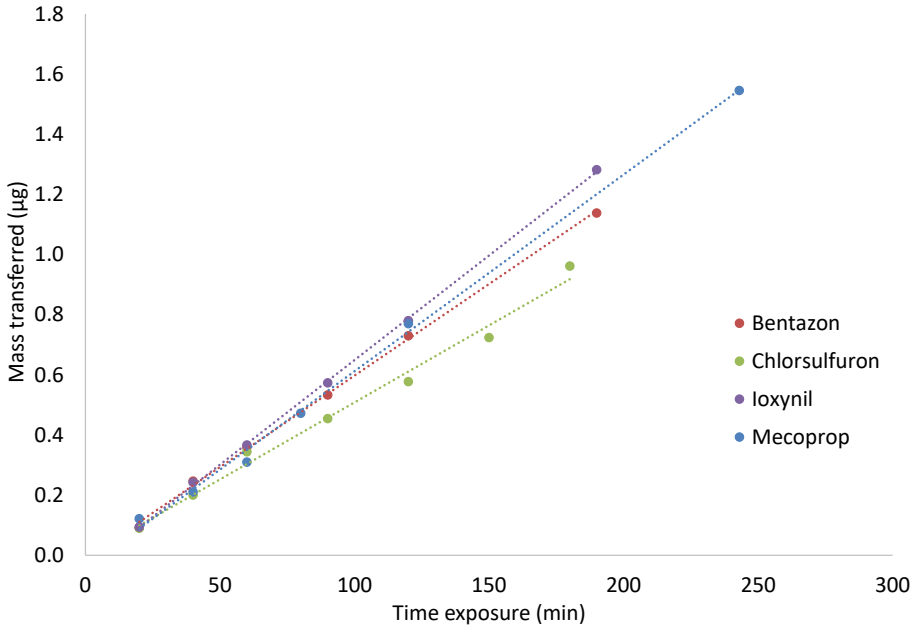

Figure III.3: Example of linear regression of the pesticide mass transferred by diffusion versus the exposure time (exposure area 1.77 cm²).

DGT calculations.

The concentration of pesticide in solution (C_{DGT}) was determined following the analysis of binding gel eluates using **Equation III.4** derived from Fick's first law (Zhang and Davison 1995):

$$C_{DGT} = \frac{m\Delta_g}{tD_{eff}A_g} \qquad \textbf{Equation III.4}$$

where m is the accumulated pesticide mass on the binding gel, A_g is the geometric exposure area (3.14 cm²) and t is the deployment duration.

m was calculated using **Equation III.5** from the eluate concentration (C_e), eluate volume (V_e = 5 mL) and elution yield (f_e) previously determined.

$$m = \frac{C_e V_e}{f_e} \qquad \textbf{Equation III.5}$$

Effect of pH, ionic strength and stir rate.

pH effect on DGT performance was investigated at 20°C in 1 L solutions containing a mixture of the four pesticides (100 µg L^{-1} each in 10^{-2} M $NaNO_3$). pH was adjusted to 3, 5, 7 or 8 using phosphate buffer (≈10^{-3} M). Triplicate DGT systems were immersed for 24 h and retrieved for binding gel elution and analysis. The influence of ionic strength was evaluated in a similar way in solutions containing 10^{-2}, 10^{-1} or 1 M $NaNO_3$ (pH≈5). Stir rate influence was similarly investigated by immersion of duplicate DGT systems in solutions (10^{-2} M $NaNO_3$; pH≈5) unstirred or stirred at 60 and 140 rpm. An example of pesticide concentration stability in exposure solutions during the experiments is provided in **Figure III.2**.

Validation and applications to natural waters.

DGTs accuracy was first tested under controlled laboratory conditions in spiked natural water: Evian® mineral spring water. Evian® water is neutral and highly mineralized, and its composition is displayed in **Table III.2**. Water was spiked with 0.1 µg L^{-1} of each pesticide. 12 devices of each DGT (HLB or MAX) were immersed in 3 L of stirred spiked solution at 5°C. 6 devices were retrieved after 7-days exposure and 6 others after 14 days for binding gel elution and analysis.

Table III.2: Major element composition of the natural waters (χ stands for electrical conductivity (corrected to 20°C), DOC for Dissolved Organic Carbon and ND for "not determined").

	pH	χ µS/cm	DOC mgC/L	HCO_3^- mg/L	Cl^- mg/L	NO_3^- mg/L	SO_4^{2-} mg/L	Na^+ mg/L	K^+ mg/L	Ca^{2+} mg/L	Mg^{2+} mg/L
Runoff	5.0	29.5	0.5	3.0	2.7	4.4	1.0	2.4	0.4	1.3	0.4
Evian®	7.2	500	<0.3	360	6.8	3.7	12.6	6.5	1.0	80	26
R1 River (deployment/ retrieval)	7.9/7.8	800/ 1278	7.7/ND	ND	74/191	27/22	52/125	46/133	4.7/9.1	104/ 138	4.6/9.3
R2 River (deployment/ retrieval)	7.8/7.7	624/ 630	15.9/ ND	ND	13/13	25/27	9.5/8.6	5.8/7.3	1.4/1.4	116/98	1.6/1.6

DGT were finally validated under field condition and compared to POCIS samplers following an *in situ* deployment in two French rivers. The first river labelled R1 is 80 km long and its 7500 km² watershed is mostly composed of agricultural lands (76%). The second river labelled R2 is 14 km long and its 39 km² watershed is significantly composed of agricultural lands (43%). Triplicate DGT (HLB and MAX) and duplicate POCIS (HLB and MAX) were deployed simultaneously in both rivers during 14 days in June 2016. HLB- and MAX-POCIS were prepared by enclosing 200 mg of sorbent powder between two PES membranes sealed by two stainless rings. According to Guibal et al. (2015a) recommendation, PES membranes were previously washed with two successive 1h baths in 50:50 MeOH:UPW followed by two 30 min baths in UPW. Spot samples were taken upon samplers' deployment and retrieval to determine waters composition (**Table III.2**) except temperature which was recorded every 10 min using a Tinytag temperature logger (TG-4100) (average temperatures were 17 and 14°C at R1 and R2 rivers, respectively) to allow correction diffusion coefficient (**Equation III.3**). Flow velocities at samplers' deployment were found to be 0.07 and 0.25 m s^{-1} at R1 and R2 rivers, respectively. Flow velocities at samplers' retrieval were slightly lower (0.04 and 0.20 m s^{-1} at the R1 and R2 rivers, respectively). After retrieval, POCIS samplers were handled and extracted as detailed in Guibal et al. (2015b) and TWAC of anionic pesticides were calculated as detailed in Fauvelle et al.(2012). DGT samplers were treated as detailed in the previous sections and TWAC of anionic pesticides were calculated **Equation III.4** (for other molecules than the four studied in this paper, TWAC were estimated using the mean D_{eff} value of the four studied molecules).

Pesticide analysis.

Exposure solutions or POCIS and DGT extracts were analysed by HPLC-TOF. When a higher sensitivity was required (*e.g.* application to natural waters), DGT eluates were pre-concentrated (evaporation from 5 mL to dryness and reconstitution into 1 mL of a 90:10 (v:v) UPW/methanol mixture) and analysed without dilution.

Chromatographic separation was performed with an HPLC 1290 Infinity apparatus from Agilent. The detector was a high resolution, accurate mass quadrupole - time of flight mass spectrometer (Agilent 6540 Q-TOF) and equipped with an Agilent Jet Stream electrospray ionization source (ESI). Chromatographic separation was performed with a HPLC 1290 Infinity apparatus from Agilent (**Figure III.4**). An analytical gradient of 10 min was used with UPW and methanol with 5 mM ammonium formate (**Table III.3**). Chromatographic separation was performed with a Nucleoshell® RP18 plus column (50 mm length, 3 mm internal diameter) from Macherey-Nagel. Column and autosampler temperatures were maintained at 30 °C and 4 °C, respectively. Deuterated pesticides were used as internal standards (bentazone-d6, MCPA-d3 and metsulfuron-methyl-d3). Optimized HPLC conditions and retention times are shown **Table III.4**. Because peak shape is altered in purely organic samples, DGT eluates were systematically diluted 10-fold in UPW prior to analysis. The detector was a quadrupole combined with a time-of-flight mass spectrometer (Accurate Mass LC/MS 6540 Agilent) and equipped with an Agilent Jet Stream electrospray ionization source (ESI) operating in the negative ionization mode. Mass acquisition was performed in the "All-ions" mode and collision cell energies were: 0, 10, 20 and 40V. Optimized source parameters and other TOF-MS parameters are shown in **Table III.5**.

Instrumental limits of quantification (LOQ_i) were evaluated according to a previous study (Guibal et al. 2015b) by injecting ten times standards with concentration ranging from 0.1 to 2 µg L^{-1}. LOQ_i were established at 0.5, 0.5, 0.5 and 2 µg L^{-1} for bentazon, chlorsulfuron, ioxynil and mecoprop, respectively.

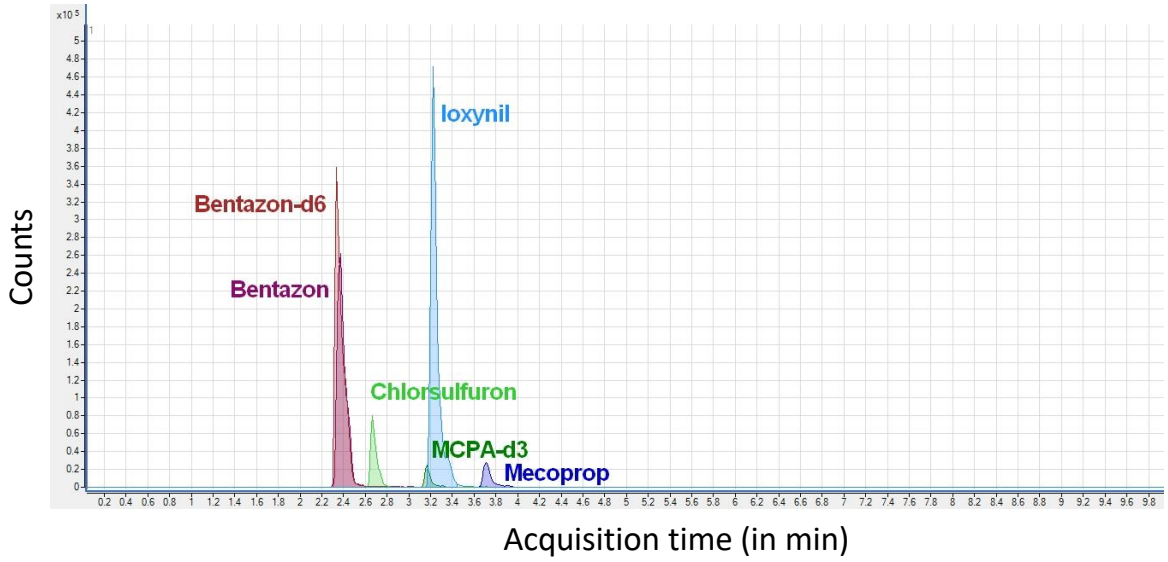

Figure III.4: Extracted ion chromatograms corresponding to the analysis of pesticides in a spiked sample by HPLC-(Q)-TOF in All-ions mode.

Table III.3: Gradient used for the chromatographic separation.

Time	UPW with 5 mM ammonium formate	Methanol with 5 mM ammonium formate
0	90	10
0.5	90	10
2	50	50
5	45	55
7	10	90
10	10	90

Table III.4: HPLC and mass detection characteristics for each pesticide. LOQ_i stands for instrumental limit of quantification.

Pesticide	Retention time (min)	Mass (Da)	Accurate mass $[M-H]^-$	LOQ_i (µg/L)	Internal standard
Bentazon	2.34	240.0569	239.0489	0.5	Bentazon-d6
Chlorsulfuron	2.67	357.0299	356.0230	0.5	Metsulfuron-d3
Ioxynil	3.17	370.8304	369.8231	0.5	MCPA-d3
Mecoprop	3.64	214.0397	213.0325	2	MCPA-d3

Table III.5: HPLC-TOF-MS operational parameters in negative ESI ion mode (*optimized source parameters).

Parameter	Value
Sheath gas temperature*	400°C
Sheath gas flow*	12 L/min
Drying gas temperature*	130°C
Drying gas flow*	13 L/min
Fragmentor voltage*	130 V
Nebulizer pressure*	20 psi
Capillary voltage	3500 V
Mass range	100 – 1500 m/z
Reference masses	112.9855 and 1033.9881 m/z
Octopole 1 RF*	750 V
Nozzle voltage*	300 V
Skimmer voltage*	65 V

RESULTS AND DISCUSSION

Uptake and desorption on diffusive and binding gels.

Table III.6 shows pesticide sorption for polyacrylamide and agarose diffusive gels. Slight sorption of the four pesticide was estimated for polyacrylamide (~5%) and agarose (~15%) diffusive gels. For bentazon, chlorsulfuron and ioxynil, sorption on polyacrylamide gels was not significant compared to control whereas sorption on agarose gels was significantly higher (<0.01). Sorption of mecoprop is more ambiguous given the high SD of replicates. Challis et al.(2016) observed no sorption of another anionic pesticide (2,4-D) on agarose gel. Sorption of anionic pesticides on agarose gel might therefore differ between molecules. Significant sorption on diffusive gel could limit diffusion in the sampler and alter TWAC calculation (Davison and Zhang 2012). Therefore, polyacrylamide diffusive gel could be more suitable than agarose gel for sampling of most anionic pesticides and was further used in this study.

Table III.6: Percentage of sorbed pesticide (± SD) in absence (control) or in presence of a polyacrylamide or agarose diffusive gel (n=3).

	Bentazon	Chlorsulfuron	Ioxynil	Mecoprop
control	6 %	2 %	2 %	5 %
polyacrylamide	4 % ± 7	5 % ± 3	5 % ± 11	7 % ± 17
agarose	17 % ± 2	15 % ± 6	15 % ± 5	13 % ± 18

Uptake of each pesticide on HLB or MAX binding gels was similar at all tested concentrations: it was nearly complete (≥94%), except for bentazon and mecoprop on HLB which showed slightly lower uptakes (>80%) (**Table III.7**). The additional ammonium functional groups of the MAX sorbent (positively charged at any pH) probably strengthened interactions with bentazon and mecoprop (Bauerlein et al. 2012). No desorption of pesticides from either binding gel was observed for 48h in 10^{-2} M $NaNO_3$ solution at pH 6 or 8. Pesticides therefore remain bound in slightly acidic or alkaline media of moderate ionic strength. Irreversibility of sorption for the four pesticides under usual environmental conditions, which is mandatory for the validity of Eq. 3, was therefore demonstrated and both binding gels should be suitable for the DGT technique.

Table III.7: Mean uptake of pesticides on HLB and MAX binding gels (SD in parentheses, n = 24).

	HLB	**MAX**
Bentazon	81% (3)	96 % (2)
Chlorsulfuron	94% (4)	94 % (2)
Ioxynil	98% (1)	99 % (1)
Mecoprop	88% (4)	94 % (2)

Elution procedure.

The best elution yields were obtained with E1 eluent (50:50 methanol / ethyl acetate mixture) after 24h and E2 eluent (90:10 methanol / 1 M formic acid mixture) after 48 h for HLB and MAX binding gels, respectively (**Figure III.5**). E3 eluent (70:30 methanol / 1 M NaOH mixture) gave lower elution yields and was not further considered in this study. Given these results, elution of the binding gels is suitable for pesticide recovery but eluent composition needs to be adapted for each binding phase. Regarding elution kinetic, increasing elution time from 24 to 48h improved slightly elution yields for MAX binding gels (14%, 9%, 25% and 6% increase for bentazon, chlorsulfuron, ioxynil and mecoprop, respectively) but not for HLB binding gels. For convenience, a 24h elution time was further used for both binding gels. Elution yields for the rest of this study are displayed in **Table III.8**.

Elution of HLB binding gels was nearly complete (≥95%) for all pesticides whereas elution on MAX binding gels was partial for ioxynil (46%) and >70% for the three other compounds. Elution repeatability for bentazon and ioxynil was found to be better with MAX compared to HLB binding gels.

Table III.8: Elution yields (fe) for HLB (with methanol:ethyl acetate (50:50)) and MAX (with methanol:1 M formic acid (90:10)) binding gels used in this study (SD in parentheses; n=6).

	HLB (E1 24h)	MAX (E2 24h)
Bentazon	97% (15)	74% (8)
Chlorsulfuron	95% (5)	81% (5)
Ioxynil	95% (19)	46% (9)
Mecoprop	95% (9)	86% (7)

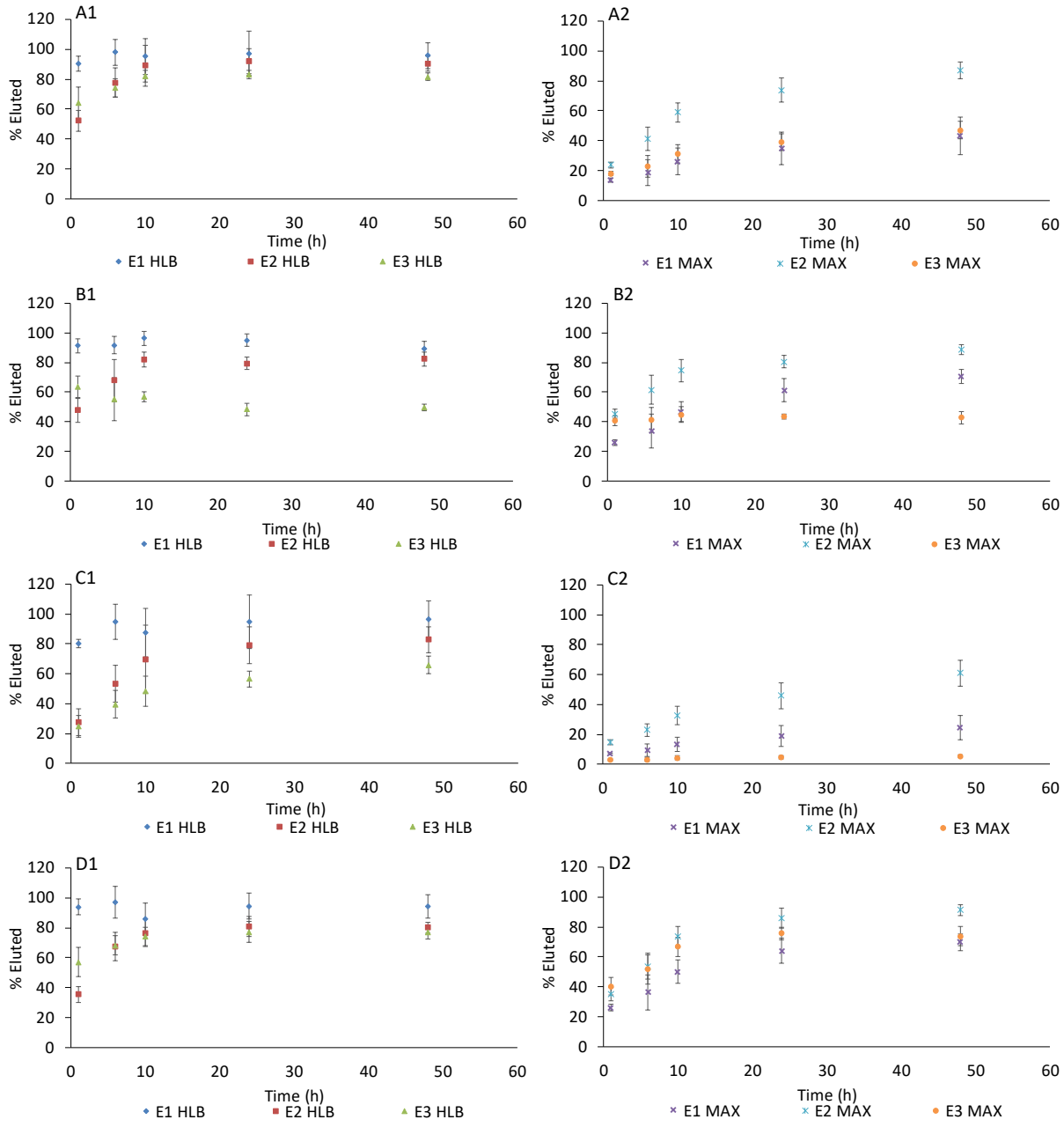

Figure III.5: Elution kinetics (n=6) for bentazon (A), chlorsulfuron (B), ioxynil (C) and mecoprop (D) on HLB-DGT (1) and on MAX-DGT (2). E1: methanol:ethyl acetate mixture (50:50), E2: methanol:1M formic acid mixture (90:10) and E3: methanol:1M NaOH mixture (70:30).

Effective binding capacity.

Accumulation over time of the four studied pesticides in HLB-DGT and MAX-DGT is shown in **Figure III.6** and **Figure III.7**.

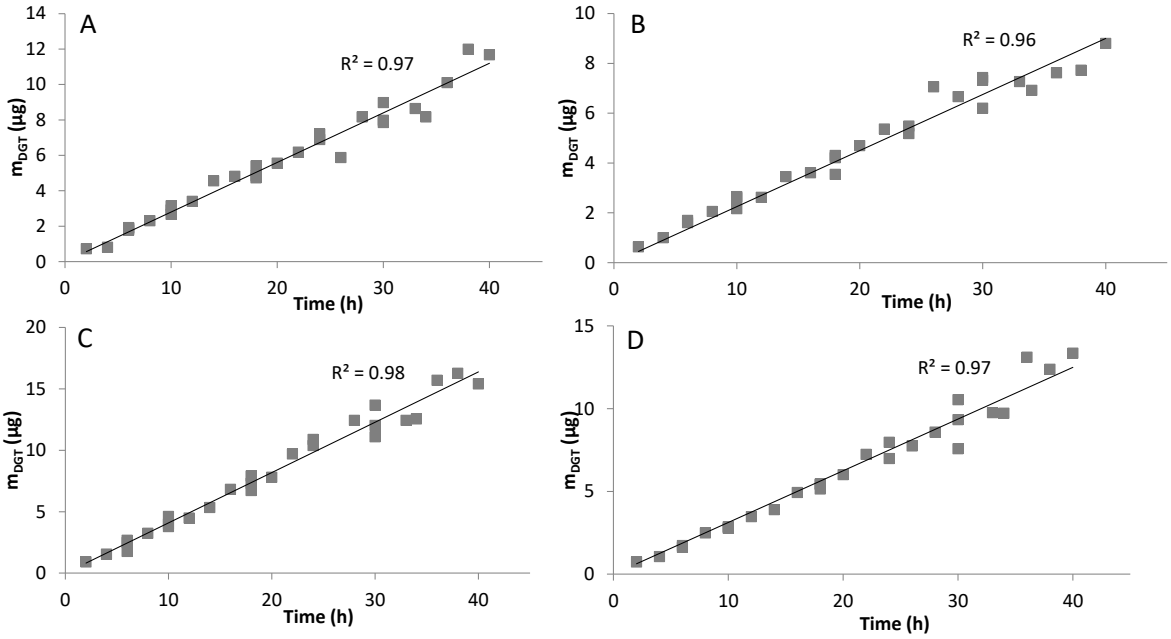

Figure III.6: Accumulation of bentazon (A), chlorsulfuron (B), ioxynil (C) and mecoprop (D) on HLB binding gel (µg per disk) as a function of deployment time (hours).

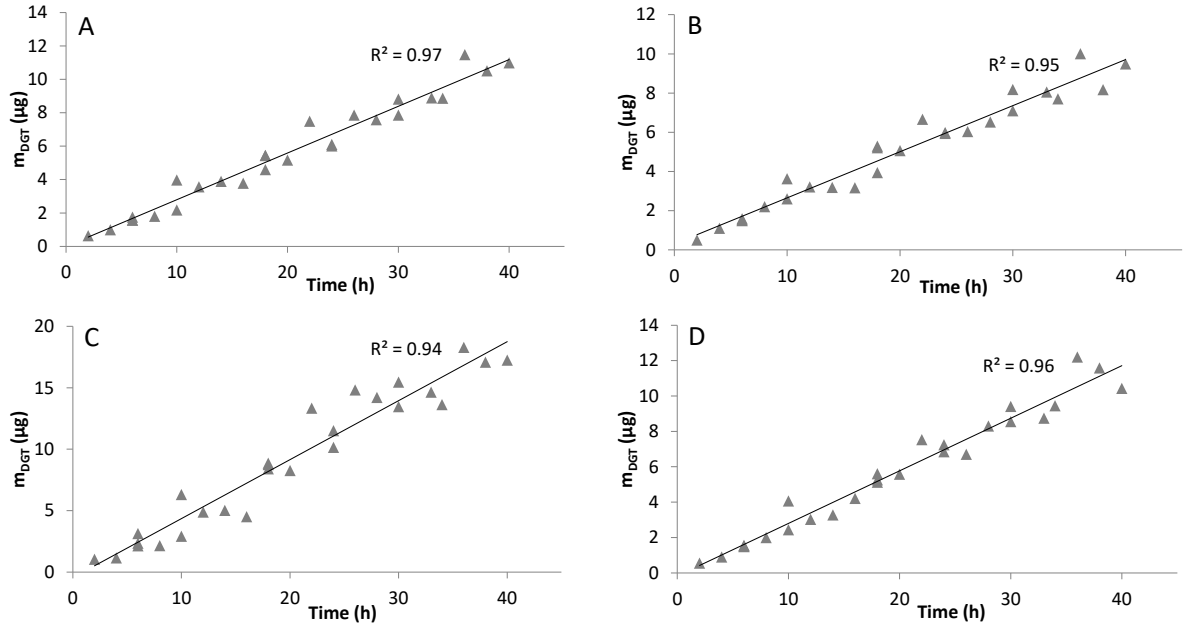

Figure III.7: Accumulation of bentazon (A), chlorsulfuron (B), ioxynil (C) and mecoprop (D) on MAX binding gel (µg per disk) as a function of deployment time (hours).

Plots of *m* versus *t* were found to behave linearly ($r^2 \geq 0.94$) for all the studied pesticides and the two DGT. Because no accumulation rate decrease was observed, effective capacity of the binding gels was not reached. The effective binding capacities are therefore higher than 12, 9, 17 and 14 µg for bentazon, chlorsulfuron, ioxynil and mecoprop, respectively, for HLB-DGT and higher than 11, 10, 17 and 12 µg for MAX-DGT. Accumulated masses following DGT deployments up to the above mentioned values should therefore allow correct conversion into C_{DGT}.

Pesticide concentration in natural waters usually does not exceed 10 µg L^{-1} (99.98% of 7 10^6 data found in the EMPODAT database of the NORMAN network). Considering this a worst case scenario, according to **Equation III.4** , effective binding capacity would not be reached until 43 days of deployment. On this basis, effective binding capacity of the gels should not be limiting for long term deployments (weeks to months) in natural water systems. It should be stressed however, that competition effect can occurs during deployments in natural systems and possibly limit the effective binding capacity of the studied DGT and the above conclusions.

Diffusion coefficients.

Diffusions coefficients for the studied pesticides (**Table III.9**) are of the same order of magnitude as diffusion coefficients previously determined in polyacrylamide gels for sulfamethoxazole (3.6 10^{-6} cm^2 s^{-1} at 20°C) (Chen et al. 2012), glyphosate (3.0 10^{-6} cm^2 s^{-1} at 20°C) (Fauvelle et al. 2015) and metals (1-10 10^{-6} cm^2 s^{-1} at 25°C) (Garmo et al. 2003) and in agarose gels for bisphenols (~5 10^{-6} cm^2 s^{-1} at 25°C) (Zheng et al. 2014). RSD was <13% for all diffusion coefficients which indicates that uncertainty mostly arises from uncertainty of C_s (set at 10%). D_{cell} values were not

significantly different from D_{eff} values for bentazon and ioxynil ($p<0.05$) whereas D_{cell} was significantly higher from 35% for chlorsulfuron and 25% for mecoprop ($p<0.05$). The difference is likely to be caused by the sorption process on the binding gel (involved only in D_{eff} estimation). D_{eff} values were further used for quantification purpose in this study because it will allow correction of such phenomenon. Lower D_{eff} values were systematically obtained for HLB-DGT compared to MAX-DGT. Although the difference is marginal for mecoprop (2%), it reaches 16, 13 and 23% for bentazon, chlorsulfuron and ioxynil, respectively. These differences possibly results from differences in sorption kinetics on HLB or MAX binding gels.

Table III.9: Diffusion coefficients (10^{-6} cm² s^{-1}; corrected to 20 °C) in the diffusive gel (D_{cell}) or derived from uptake capacity experiment (D_{eff}) for HLB-DGT or MAX-DGT (SD is in parentheses).

	D_{cell}	D_{eff} HLB	D_{eff} MAX
Bentazon	4.5 (0.1)	3.6 (0.4)	4.3 (0.5)
Chlorsulfuron	4.2 (0.4)	2.7 (0.3)	3.1 (0.4)
Ioxynil	5.2 (0.5)	4.6 (0.5)	6.0 (0.7)
Mecoprop	5.0 (0.4)	3.8 (0.4)	3.9 (0.5)

Limits of quantification and accuracy.

Elution of 6 binding gel blanks showed the absence of pesticide contamination in HLB and MAX binding gels. Therefore, instrumental limits of quantification (LOQ_i) were used to determine methodological limits of quantification (LOQ_m). For this purpose, LOQ_i were converted to pesticide mass on the binding gel (m) values using eq. 4 and further extrapolated to C_{DGT} values using Eq. 3 considering a standard 14-day deployment at 20°C (**Table III.10**). Values expressed as C_{DGT} indicate that the proposed methodology already allows quantification of concentrations down to approximatively ten ng L^{-1} using 14-day deployment periods. LOQ could be easily improved by using more sensitive analytical tools (*e.g.* HPLC-QqQ), which should allow quantification of concentrations down to one ng L^{-1}. Considering that concentrations of these molecules in water systems typically ranges from few to hundreds of ng L^{-1}, the proposed methodology should allow anionic pesticide monitoring in numerous water systems.

Table III.10: LOQ_m expressed as pesticide concentration in water (C_{DGT}) considering a 14-day deployment at 20° C.

	HLB	MAX
Bentazon	3 ng L^{-1}	4 ng L^{-1}
Chlorsulfuron	4 ng L^{-1}	5 ng L^{-1}
Ioxynil	3 ng L^{-1}	4 ng L^{-1}
Mecoprop	12 ng L^{-1}	13 ng L^{-1}

Accuracy of the entire methodology results from the individual accuracies of analysis and parameters used for C_{DGT} calculations (elution yields and effective diffusion coefficients). For both DGTs, RSD was estimated at approximately 5-20% for f_e (**Table III.8**) and 11% for D_{eff} (**Table III.9**). Therefore, accuracy better than 20% for C_{DGT} estimation is unlikely to be obtained and compound quantification was further considered satisfactory if C_{DGT} was within 20% of the targeted value.

Effect of pH and ionic strength.

Method accuracy was evaluated by differences between solution concentrations determined from spot samples (C_{sol}) and from DGT deployments (C_{DGT}). Satisfactory quantification (<20%) at all pHs was obtained for ioxynil with HLB-DGT and for bentazon and mecoprop with MAX-DGT (**Figure III.8**). Accuracy of chlorsulfuron quantification using both HLB- or MAX-DGT was <30% without any obvious pH effect. Bentazon and mecoprop quantification using HLB-DGT and ioxynil quantification using MAX-DGT were satisfactory in acidic medium but significantly altered ($p<0.01$, Student test) for pH 7 or 8. Given the low pKa values of these molecules (≤ 4), no significant charge shifts are expected at these pH and diffusion alteration is unlikely. Rather, it is hypothesized that pH increase affects binding gels which in turn alter molecule sorption. Indeed, Li et al. (2011) observed an alteration of acidic compound sampling by HLB and MAX sorbents at increased pH.

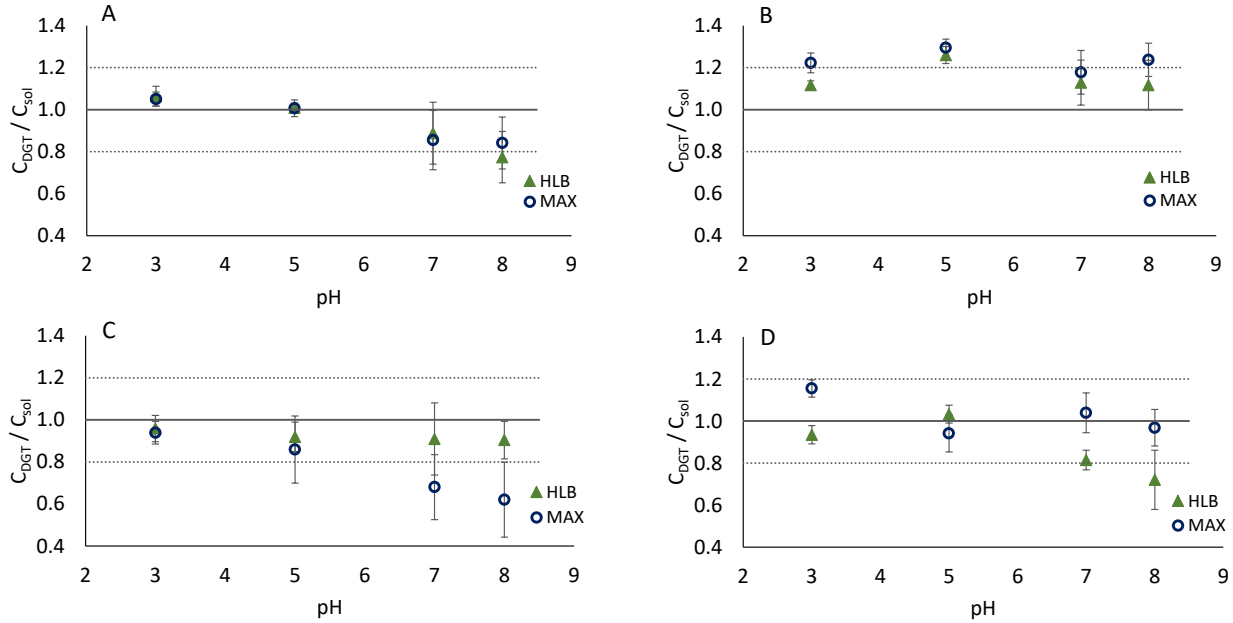

Figure III.8: Effect of pH on the ratio C_{DGT} to pesticide concentration in solution (C_{Sol}) for bentazon (A), chlorsulfuron (B), ioxynil (C) and mecoprop (D).

There was no significant effect of ionic strength on pesticide quantification ($p<0.01$, Student test), except for DGT-HLB with chlorsulfuron and ioxynil and DGT-MAX with chlorsulfuron (**Figure III.9**). Bentazon and mecoprop were satisfactorily quantified (<20%) at all ionic strengths with both HLB- and MAX-DGT. Accuracy was slightly lower for chlorsulfuron and ioxynil quantification at some ionic strengths, but always better than 25%.

Considering the effects of pH and ionic strength, HLB-DGT seems more suitable for ioxynil quantification and MAX-DGT seems more suitable for mecoprop quantification. Both will likely perform similarly for bentazon and chlorsulfuron. As long as the correct DGT configuration is used (HLB or MAX), accuracies are better than 30% for the studied pH (3 to 8) and ionic strength (10^{-2} to 1M) and successful application in most natural waters can be therefore expected (continental, estuarine and sea waters).

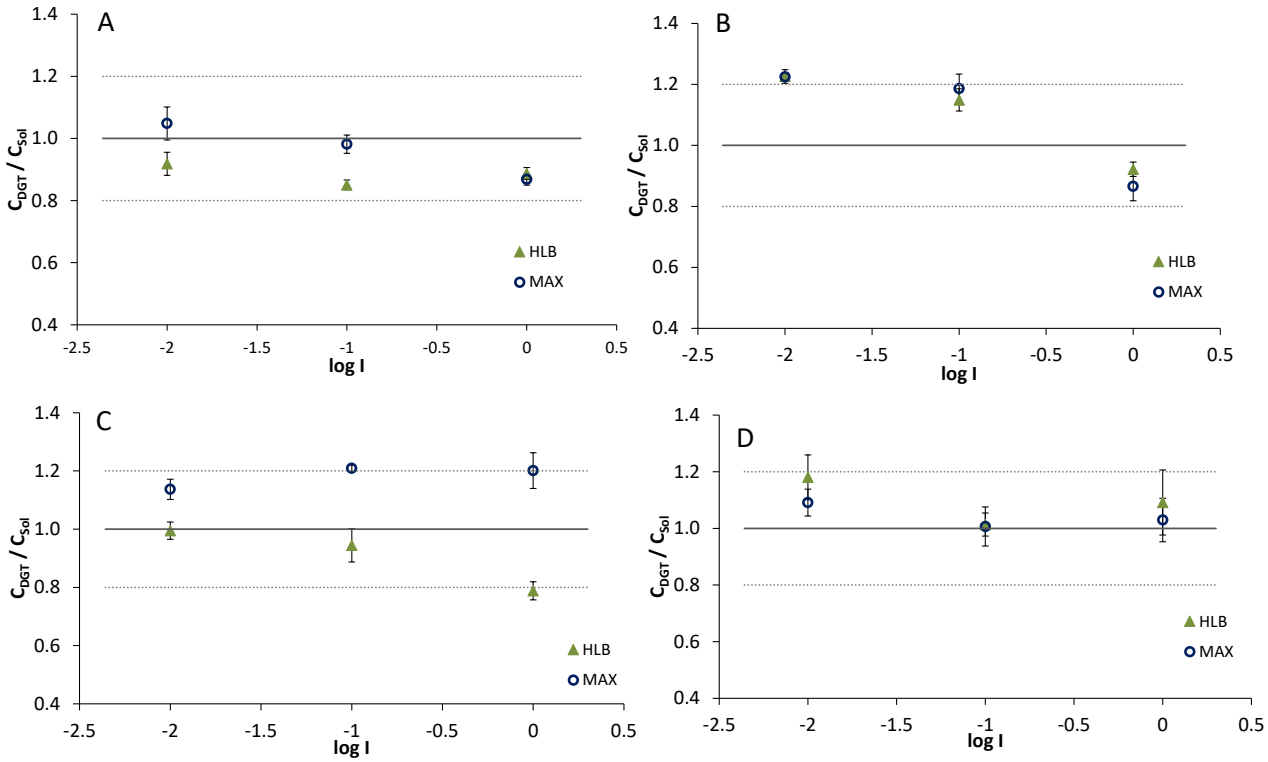

Figure III.9: Effect of ionic strength (simulated with $NaNO_3$ in mol L^{-1}) on the ratio C_{DGT} to C_{Sol} for bentazon (A), chlorsulfuron (B), ioxynil (C) and mecoprop (D).

Effect of stir rate.

Pesticide accumulation was determined for well stirred (140 rpm), moderately stirred (50 rpm) and unstirred (0 rpm) solutions (**Figure III.10**). In general way, accumulation is found to decrease between well stirred and unstirred solutions in HLB-DGT (6-19%) and MAX-DGT (24-48%). Accumulation of bentazon, ioxynil in both HLB or MAX-DGT and accumulation of mecoprop in HLB-DGT were however not significantly different. Conversely, accumulation of chlorsulfuron in both HLB or MAX-DGT and accumulation of mecoprop in MAX-DGT was significantly decreased in unstirred solutions compared to moderately stirred solutions. This is in agreement with the formation of a significant water boundary layer in front of the sampler at low flow rates, well documented phenomenon for metals (Turner et al. 2014, Uher et al. 2013, Warnken et al. 2006) and recently observed for pesticides (Challis et al. 2016). At very low flow rates, TWAC estimation of ionic pesticides could therefore be biased unless water boundary layer length in estimated using DGTs with various thicknesses (Garmo et al. 2006). It should be noticed however that accumulation alteration in HLB-DGT was low (<20%) and TWAC estimation bias could therefore be limited with this tool. This result is surprising because water boundary layer formation is not supposed to be directly linked to binding phase nature.

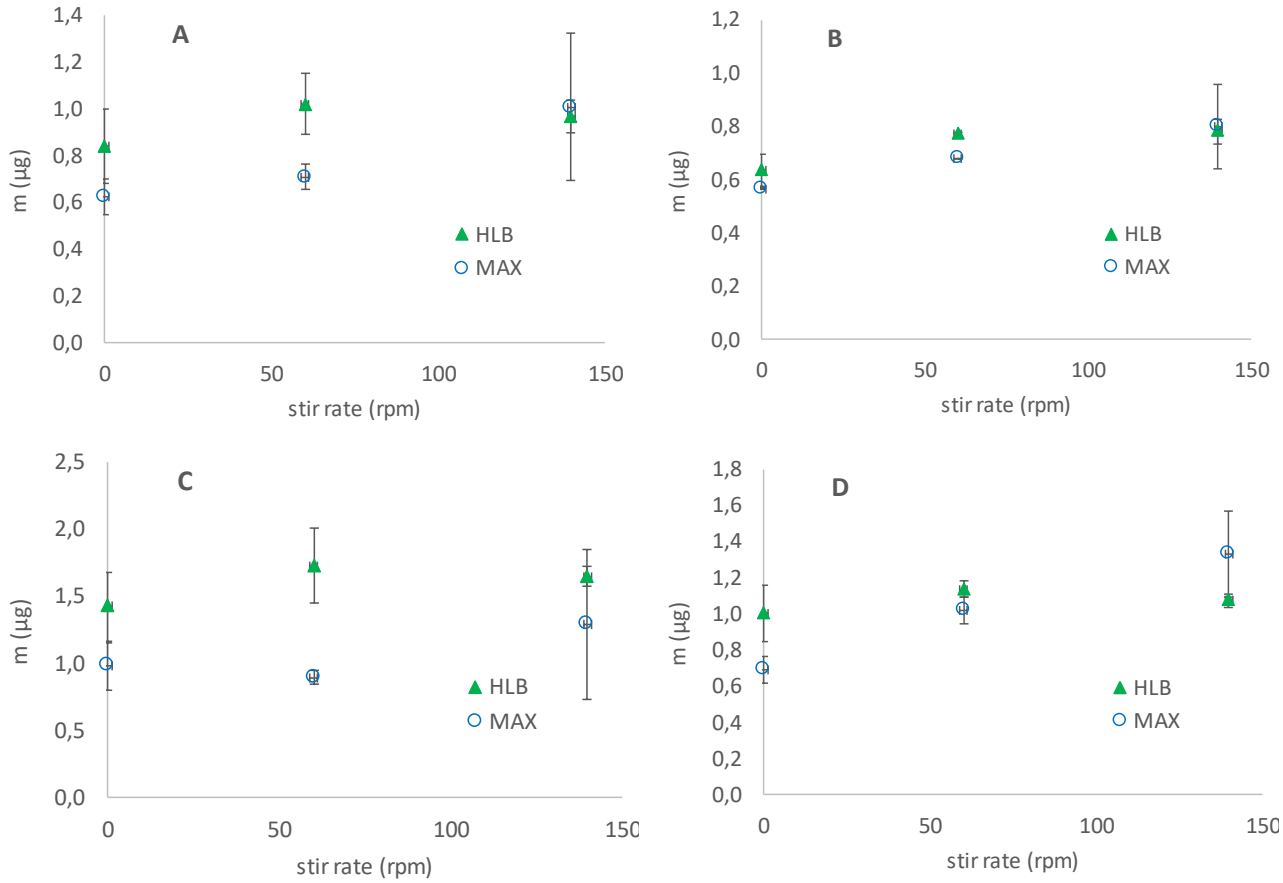

Figure III.10: Influence of stir rate on bentazon (A), chlorsulfuron (B), ioxynil (C) and mecoprop (D) accumulation in DGT samplers.

Validation and application to natural waters.

DGTs accuracy was first tested at moderate concentrations in two spiked natural waters: a subsurface runoff water (acidic and poorly mineralized) and Evian® mineral spring water (neutral and highly mineralized).

Preliminary validation at moderate concentration (5 µg L^{-1}) in two spiked natural water is presented in **Figure III.11**. Application at concentration (0.1 µg L^{-1}) and durations (7 or 14 days) relevant for field exposure have been performed in a spiked natural water (**Figure III.12**). Contrasted behavior are observed between HLB and MAX-DGT. Except for ioxynil, TWAC estimation with HLB-DGT is satisfactory (<20%) following 7 days of exposure. Bentazon and chlorsulfuron were satisfactorily quantified (<20%) in both natural waters with both HLB- and MAX-DGT. Ioxynil was satisfactorily quantified in subsurface runoff water with both DGTs and the mineral water using HLB-DGT. This compound was 47% underestimated in mineral spring water using MAX-HLB, consistent with the pH effect. Ioxynil behavior is possibly linked to its lower robustness over ionic strength (**Figure III.9**). Mecoprop was satisfactorily quantified in mineral spring water using both DGTs and in subsurface runoff water using HLB-DGT but overestimated by 34% using MAX-HLB. Given that mecoprop was satisfactorily quantified with MAX-DGT at pH 5 (**Figure III.18**) and I=10^{-2} M (**Figure III.9**), the 34% overestimation was not expected. It remains unexplained and contradicts the pH and ionic strength study conclusion that MAX-DGT is more suitable for mecoprop quantification. After 14 days of exposure, quantification of on bentazon, chlorsulfuron and mecoprop

was slightly altered (<18%) but still acceptable. It can be concluded that field deployments using HLB-DGT can be expected to provide quantitative results except for ioxynil but deployments longer than 14 days should be considered with caution.

Using MAX-DGT, TWAC estimation was not satisfactory for any exposure duration. This underestimation could be anticipated for ioxynil given the low robustness over pH observed (**Figure III.8**) but was unexpected for the three other compounds. It can be concluded that field deployments using MAX-DGT should lead to non-quantitative results. It should be stressed that underestimation was less pronounced after 14 days of exposure. Given that accumulation rate between the 7th and 14th day of exposure were similar or higher compared to HLB-DGT (**Figure III.13**), satisfactory quantifications cannot be excluded for longer deployments.

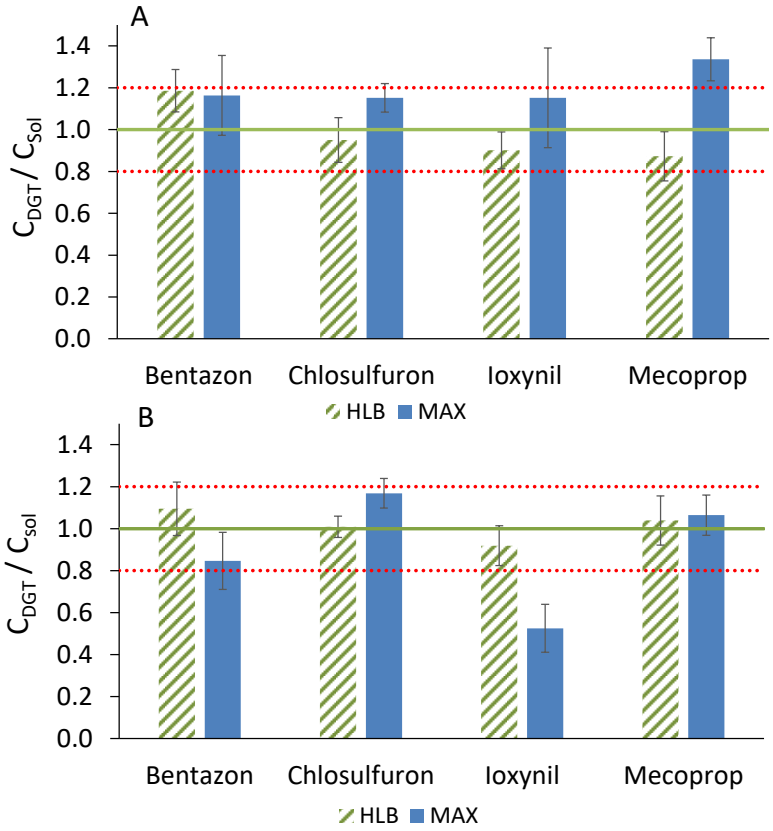

Figure III.11: C_{DGT} to C_{sol} ratio in two spiked natural waters: A subsurface runoff water and B: mineral spring water.

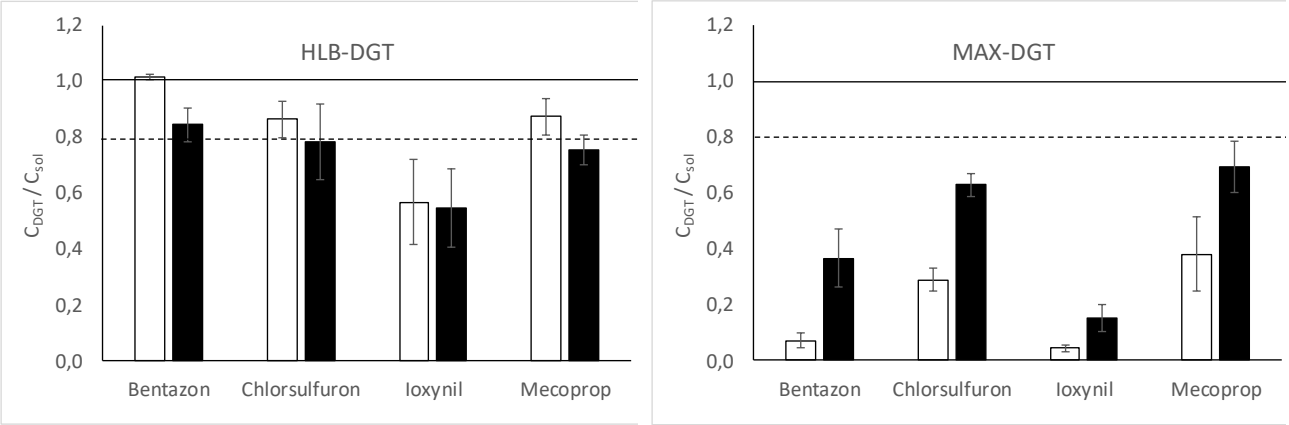

Figure III.12: C_{DGT} to C_{sol} ratio in a spiked natural water (0.1 µg L^{-1}) following 7 days (open bars) or 14 days exposure (filled bars).

After 14 days of *in situ* deployment in R1 River, two anionic pesticides were detected (**Figure III.14A**): bentazon, one of the four studied molecules, and the anionic herbicide mesotrione (pKa = 3.1). No anionic pesticides were detected after *in situ* deployment in R2 River (**Figure III.14B**). TWAC of bentazon obtained with MAX-DGT is about three times higher than TWAC obtained with HLB-DGT. This is not in agreement with laboratory deployment in spiked natural water (**Figure III.12**) and further investigation are needed to explain this behavior. Although some behavior observed with natural waters still have to be better understood (time dependence of TWAC estimation and difference in bentazon TWAC with HLB and MAX-DGT), these applications demonstrates that DGT is already suitable for monitoring of several anionic pesticides in environmental matrixes at relevant concentrations.

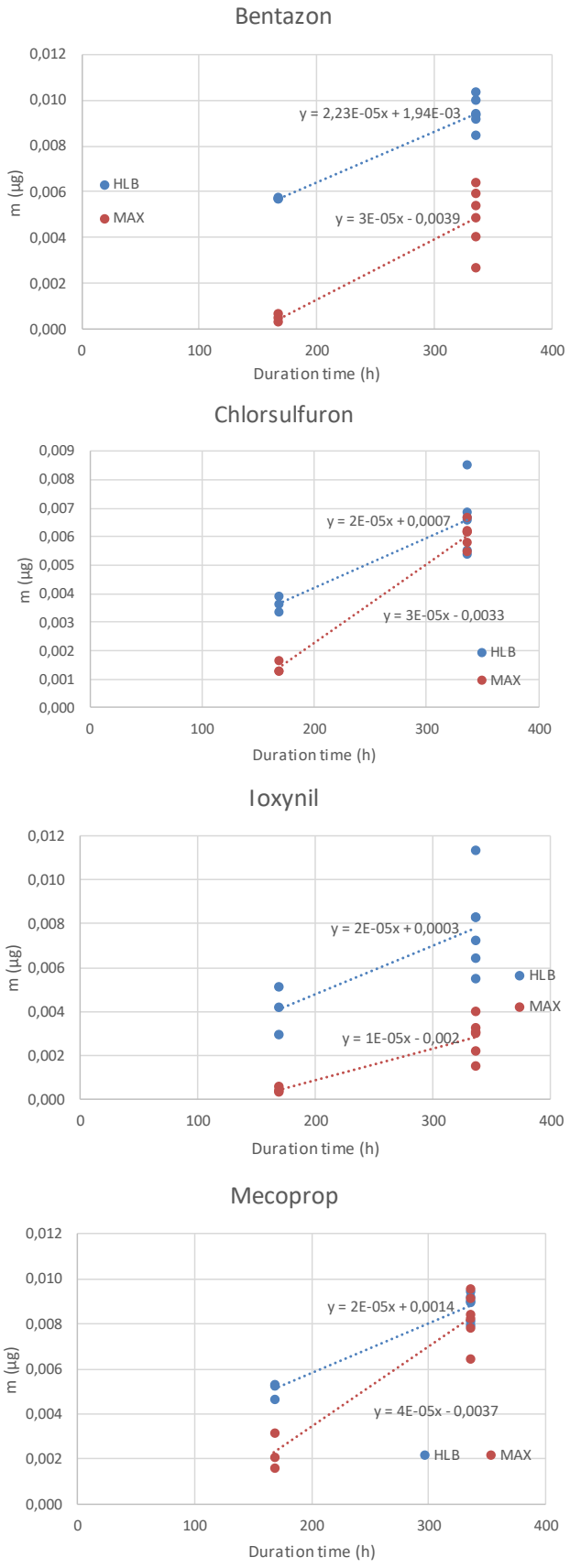

Figure III.13: Accumulation rates between 7 and 14 days in mineral water at low spike (0.1 µg L^{-1}).

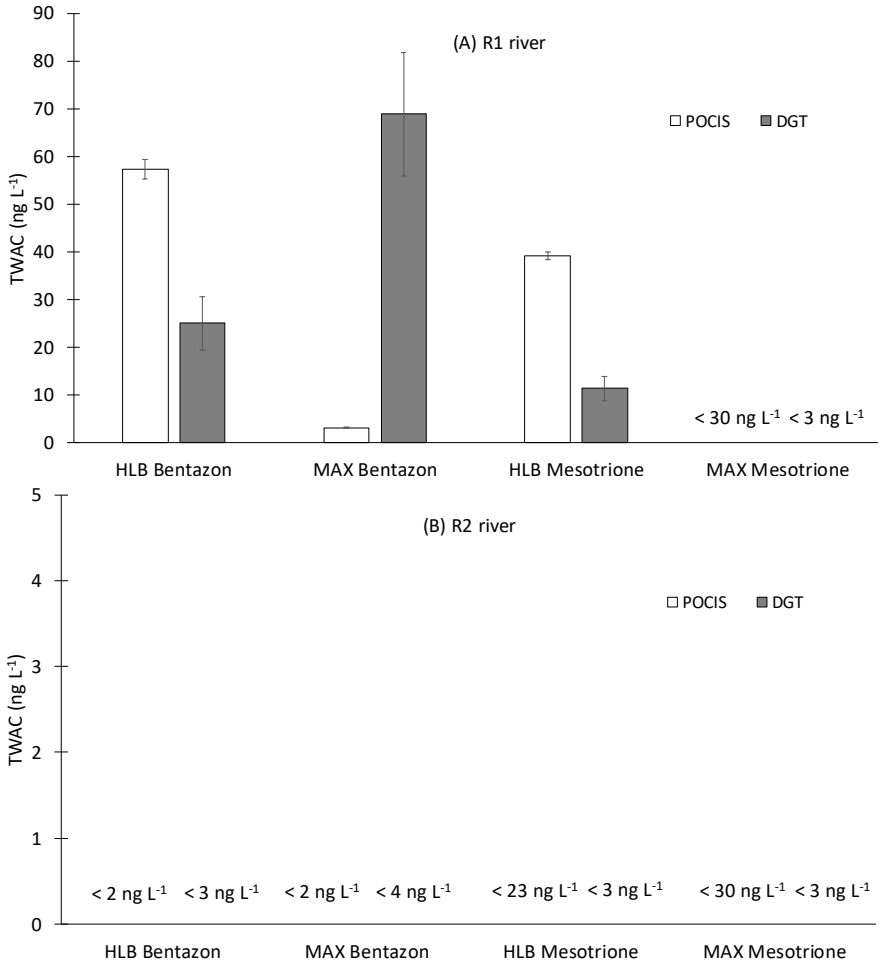

Figure III.14: TWAC of anionic pesticides determined after 14 days deployments of HLB-DGT, HLB-POCIS, MAX-DGT and MAX-POCIS in the R1 (A) and R2 River (B).

Comparison with other passive samplers.

Passive sampling of anionic pesticides is mainly performed by POCIS (Fauvelle et al. 2012) and Chemcatcher (Moschet et al. 2015). DGT and POCIS were deployed alongside in R1 and R2 Rivers give similar results in terms of anionic and neutral pesticide detection (**Table III.11**). Considering anionic pesticides only (**Figure III.14**), bentazon and mesotrione were detected using HLB sorbent and only bentazon was detected when using MAX sorbent in R1 River whereas both DGT and POCIS do not detected any anionic pesticide in R2 River. When TWAC are considered, significant differences are found between DGT and POCIS. DGT lead to lower TWAC when HLB sorbent is used compared to POCIS, whereas DGT lead to higher TWAC when MAX sorbent is used. The differences observed using HLB sorbent (factor 2.3 for bentazon and 3.4 for mesotrione) are probably mostly explained by uncertainty on TWAC estimation as it can reach 100% for POCIS (Poulier et al. 2014) and was recorded up to 23% for HLB-DGT (**Figure III.8**). However, the difference observed using MAX sorbent (factor 22 for bentazon) could not be explained by conventional uncertainty. Because TWAC obtained by MAX-DGT is

in accordance with values obtained by HLB-DGT and HLB-POCIS, TWAC obtained by MAX-POCIS is probably underestimated. Given that low flow velocities were recorded during the deployment (0.07 and 0.04 m s^{-1}), the positioning of MAX-POCIS in the river has possibly limited pesticide transfer in the samplers and thus lead to an underestimation.

The sampling ability of DGT could be compared to other passive samplers using literature through their sampling rates (R_s). R_s found in the literature for the four studied molecules lie between 90 and 400 mL day^{-1} for standard POCIS (Alvarez et al. 2007, Fauvelle et al. 2014, Mazzella et al. 2007) and between 20 and 70 mL day^{-1} for Chemcatchers (Moschet et al. 2015, Vermeirssen et al. 2009, Vermeirssen et al. 2012). This is higher than R_s values found in this study for HLB- and MAX-DGT (calculated according to Moschet et al. (2015): 10 to 15 mL day^{-1}), and likely explained by differences in exposure area. Indeed Fauvelle et al. (2014) used POCIS with the same exposure area as DGT and found a similar R_s for bentazon (8 mL day^{-1}). For comparison, R_s values were therefore standardized to exposure area (**Table III.12**). Values for HLB- and MAX-DGT lie between 3 and 5 mL day^{-1} cm^{-2} and between 1 and 9 mL day^{-1} cm^{-2} for standard POCIS and Chemcatchers. It can be concluded that the sampling ability of HLB- and MAX-DGT is similar to POCIS and Chemcatchers in their standard configuration.

Table III.11: TWAC (ng L^{-1}) of pesticides (anionic and neutral) determined after 14 days deployments of HLB-POCIS, MAX-POCIS, HLB-DGT and MAX-DGT in the R1 River and R2 River (SD is indicated between parentheses).

	R1 River				R2 River			
	HLB-POCIS	MAX-POCIS	HLB-DGT	MAX-DGT	HLB-POCIS	MAX-POCIS	HLB-DGT	MAX-DGT
Mesotrione	39 (3)		11 (23)					
Bentazone	57 (4)	3 (4)	25 (23)	90 (14)				
Carbendazim	3 (5)	1 (39)	2 (65)	4 (6)				
DIA	25 (4)	16 (6)	34 (9)	16 (16)	10 (1)	7 (1)	5 (1)	3.2 (0.1)
Imidacloprid	8 (4)	6 (6)	10 (3)	8 (26)	6 (1)	5 (1)	3 (1)	3 (1)
DEA	24 (2)	14 (7)	37 (9)	28 (6)	47 (1)	24 (3)	43 (4)	33 (2)
Simazine	9 (2)	5 (4)	23 (7)	15 (35)	4 (1)	2 (1)	7 (1)	4 (2)
DET	9 (1)	5 (2)	12 (10)	10 (20)	3 (1)	1 (1)	3 (1)	1 (1)
Chlortoluron	5 (8)	2 (5)	14 (9)	9 (28)	1 (1)	0.8 (0.1)	2 (1)	2 (1)
Atrazine	5 (4)	3 (10)	6 (15)	6 (9)	7 (1)	4 (1)	5 (1)	4 (1)
Metazachlor	22 (7)	11 (2)	76 (5)	52 (48)	6 (1)	4 (1)	14 (4)	9 (3)
Diuron	3 (3)	2 (1)	3 (21)	3 (12)				
Norflurazon	1 (1)	1 (1)	2 (19)	2 (32)				
Dimethanamid	46 (8)	20 (1)	149 (14)	107 (45)	3 (1)	2 (1)	8 (1)	5 (2)
Flurtamone	18 (9)	10 (14)	1 (21)	13 (2)				
Dimetomorph	35 (9)	23 (4)	74 (21)	70 (21)				
Fluorochloridone	17 (2)	9 (2)	8 (33)	12 (29)				
Metolachlor	955 (4)	544 (1)	1094 (10)	1015 (13)	30 (1)	15 (3)	23 (3)	20 (1)
Epoxiconazole	10 (3)	7 (6)	23 (15)	16 (26)	1.55 (0.02)	1.3 (0.1)		
Tebuconazole	44 (7)	4 (8)	40 (16)	42 (6)				

Table III.12: Sampling rates (R_s) standardized to the exposure area calculated for HLB-DGT, MAX-DGT, Polar Organic Chemical Integrative Sampler (POCIS) and Chemcatcher.

	R_s (mL day^{-1} cm^{-2})	Configuration	Conditions	Reference
Bentazon	2.2	POCIS HLB		Alvarez et al. (2007)
	3.5	POCIS HLB	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	4.5	POCIS HLB	River water ; pH 7.8	Fauvelle et al. (2012)
	3.7	POCIS MAX	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	3.7	POCIS MAX	River water ; pH 7.8	Fauvelle et al. (2012)
	8.0	POCIS HLB	Drinking water ; pH 7.6	Fauvelle et al. (2014)
	2.5	µPOCIS HLB	Drinking water ; pH 7.6	Fauvelle et al. (2014)
	3.6	HLB-DGT	pH = 6.8 ; FI = 0,01 M	This study
	4.0	MAX-DGT	pH = 6.8 ; FI = 0,01 M	This study
Chlorsulfuron	2.6	POCIS HLB		Alvarez et al. (2007)
	2.8	POCIS HLB	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	3.1	POCIS HLB	River water ; pH 7.8	Fauvelle et al. (2012)
	2.0	POCIS MAX	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	2.1	POCIS MAX	River water ; pH 7.8	Fauvelle et al. (2012)
	3.4	HLB-DGT	pH = 6.8 ; FI = 0,01 M	This study
	4.1	MAX-DGT	pH = 6.8 ; FI = 0,01 M	This study
Ioxynil	2.7	POCIS HLB		Alvarez et al. (2007)
	4.3	POCIS HLB	Tap water ; pH 7.3	Mazzella et al. (2007)
	7.5	POCIS HLB	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	9.3	POCIS HLB	River water ; pH 7.8	Fauvelle et al. (2012)
	6.6	POCIS MAX	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	5.8	POCIS MAX	River water ; pH 7.8	Fauvelle et al. (2012)
	4.7	HLB-DGT	pH = 6.8 ; FI = 0,01 M	This study
	4.4	MAX-DGT	pH = 6.8 ; FI = 0,01 M	This study
Mecoprop	3.0	POCIS HLB		Alvarez et al. (2007)
	2.1	Chemcatcher (SDB-RPS)	Field Rs ; river water	Moschet et al. (2015)
	4.8	Chemcatcher (SDB-RPS)	Channel ; effluent	Vermeirssen et al. (2009)
	1.4	Chemcatcher (SDB-RPS)	Channel ; river water	Vermeirssen et al. (2012)
	1.2	POCIS HLB	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	1.6	POCIS HLB	River water ; pH 7.8	Fauvelle et al. (2012)
	2.7	POCIS MAX	Drinking water ; pH 7.6	Fauvelle et al. (2012)
	2.6	POCIS MAX	River water ; pH 7.8	Fauvelle et al. (2012)
	3.4	HLB-DGT	pH = 6.8 ; FI = 0,01 M	This study
	4.5	MAX-DGT	pH = 6.8 ; FI = 0,01 M	This study

CONCLUSION

The above literature based discussion combined to experimental results from this study provide first insights regarding passive sampling of anionic pesticides by DGT. Depending on their exposure area, DGT will display similar performances compared to POCIS or Chemcatchers® in terms of anionic pesticide detection. MAX-DGT showed interesting performances under simple conditions but failed to give satisfactory quantifications under relevant field conditions. This tool probably requires better understanding before it can be efficiently used for monitoring studies. HLB-DGT allowed conversely satisfactory quantifications under relevant field conditions and limited impact of flow conditions on pesticide accumulation. Although more work is required to fully establish better robustness over flow conditions of HLB-DGT compared to other passive samplers, this sampler already constitute an alternative for the monitoring of several anionic pesticides. However, this tool will not operate accurately for ioxynil and possibly for other molecules from hydroxybenzonitrile chemical group.

ACKNOWLEDGMENT

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III.3. Publication "Limitation of flow effect on passive sampling accuracy using POCIS with the PRC approach or o-DGT: a pilot-scale evaluation for pharmaceutical compounds".

Cette section est constituée d'une version adaptée d'un article soumis dans la revue « Chemosphere », où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

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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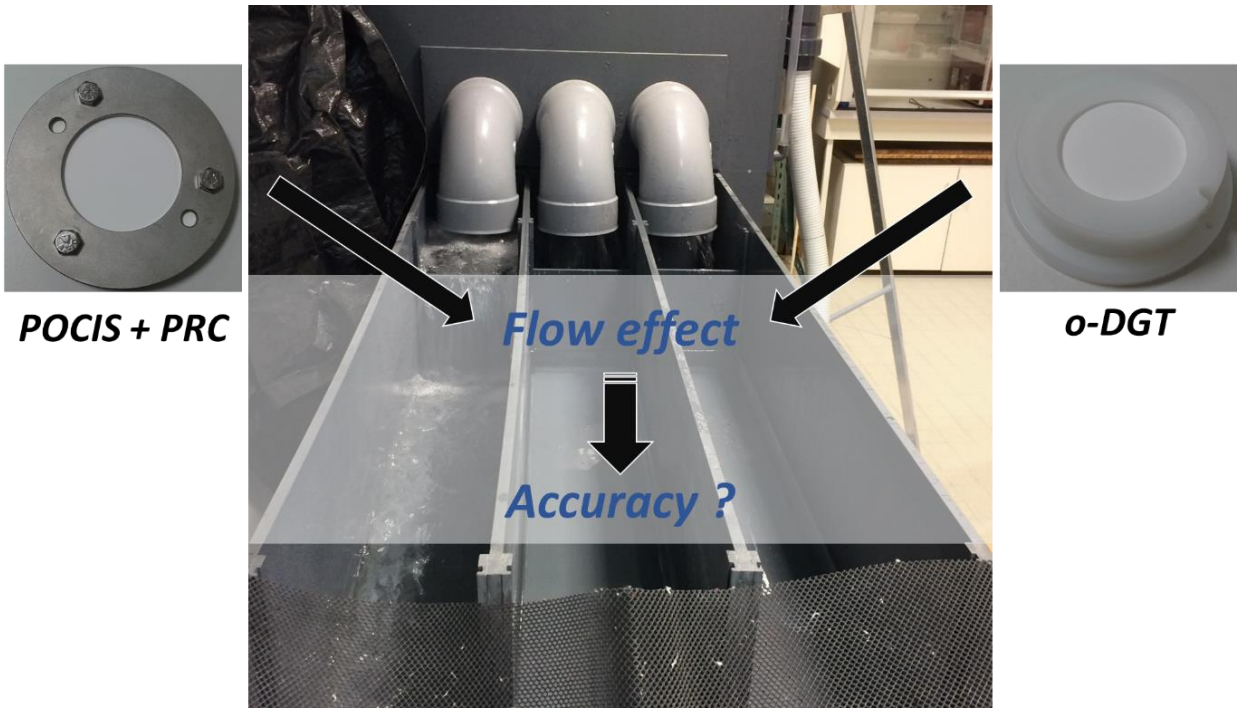
ABSTRACT

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 fourteen pharmaceuticals compounds. 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. Whatever the conditions, POCIS was more accurate than o-DGT for clarithromycin, gemfibrozil and roxithromycin. o-DGT was less efficient for these three compounds because the diffusion coefficients available were inappropriate for the studied conditions probably because of their pH dependency. 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.

GRAPHICAL ABSTRACT



Keywords: Polar Organic Chemical Integrative Sampler (POCIS), Diffusive Gradients in Thin Films (DGT), Time-weighted average concentration, Flow velocity, Accuracy

INTRODUCTION

Passive sampling has been used for 20 years 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). Among them, flow velocity is of particular concern, and conventional calibrations can lead to more than 100% inaccuracy (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. 2010b), 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 Semi-Permeable 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. 2011a). 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. 2017a) (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 14 pharmaceuticals compounds. 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.

MAERIAL AND METHODS

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% except roxithromycin (>91%): atenolol (ATE), carbamazepine (CAR), clarithromycin

(CLA), diclofenac (DIC), erythromycin (ERY), fluoxetine (FLU), gemfibrozil (GEM), ketoprofen (KET), metoprolol (MET), paroxetine (PAR), propanolol (PRO), roxithromycin (ROX), 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 III.13**) were prepared in methanol and stored at -18 C.

Table III.13: Internal standards used and pharmaceuticals after HPLC separation and mass detection.

Pharmaceutical	Retention time (min)	Mass (g mol^{-1})	Internal standard
Atenolol	2.32	266.1630	Salbutamol-d3
Carbamazepine	7.70	236.0950	Carbamazepine-d10
Clarythromycin	8.15	747.4769	Flunixin-d3
Diclofenac	9.07	295.0167	Diclofenac-d4
Erythromycin	7.81	733.4612	Carbamazepine-d10
Fluoxetine	7.88	309.1341	Carbamazepine-d10
Gemfibrozil	10.20	250.1569	Triclabendazole-d3
Ketoprofen	8.08	254.0943	Diclofenac-d4
Metoprolol	6.52	267.1834	Carbamazepine-d10
Paroxetine	6.69	329.1427	Carbamazepine-d10
Propanolol	7.30	259.1572	Propanolol-d3
Roxithromycin	8.22	836.5246	Flunixin-d3
Sulfamethoxazole	5.86	253.0521	Sulfamethoxazole-d4
Trimethoprim	4.75	290.1379	Trimethoprim-d3

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. 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 III.14**) spiked with the 14 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 every two or three days for pharmaceutical analysis (average concentrations are displayed in **Table III.15**). 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). 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.

Table III.14: Major composition of the tap water used in the pilots.

pH	Conductivity µS cm^{-1}	DOC mgC L^{-1}	Cl^- mg L^{-1}	NO_3^- mg L^{-1}	SO_4^{2-} mg L^{-1}	Na^+ mg L^{-1}	K^+ mg L^{-1}	Ca^{2+} mg L^{-1}	Mg^{2+} mg L^{-1}
8.3	275	1.0	19.3	3.6	4.3	8.3	1.2	39.0	0.9

Table III.15: Average concentrations (ng L^{-1}) measured during sampler exposures (n=4) (RSD (%) is indicated in parenthesis).

		ATE	CAR	CLA	DIC	ERY	FLU	GEM	KET	MET	PAR	PRO	ROX	SUL	TRI
o-DGT exposure	Tank (V_0)	393 (8)	426 (11)	204 (34)	457 (13)	275 (22)	47 (23)	435 (13)	483 (9)	395 (9)	62 (34)	394 (12)	168 (73)	414 (12)	427 (12)
	Channels (V_{1-3})	285 (19)	423 (21)	11 (57)	443 (24)	19 (42)	14 (59)	410 (27)	498 (21)	385 (21)	14 (55)	358 (18)	7 (61)	338 (20)	393 (22)
POCIS exposure	Tank (V_0)	248 (13)	263 (15)	75 (29)	284 (21)	128 (21)	33 (17)	279 (15)	304 (16)	241 (13)	37 (23)	242 (12)	52 (31)	234 (9)	262 (14)
	Channels (V_{1-3})	398 (5)	482 (6)	13 (80)	503 (5)	18 (55)	17 (15)	439 (8)	574 (7)	432 (3)	23 (80)	380 (4)	10 (116)	434 (3)	456 (2)

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 cm² 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) were previously washed according to Guibal et al. (2015a). 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 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 cm² 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 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 ≤ 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.

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. Ten µL of a solution with internal standards were added to the water extracts. Extracts were evaporated to dryness under nitrogen flow and then reconstituted with 1 mL of methanol for POCIS extracts or

90:10 UPW:methanol for water extracts. POCIS extracts were diluted 10 times, and 10 µL of internal standards solution was added.

o-DGT binding gel discs were extracted with 3x3 mL of methanol under sonication (210 W for 2 minutes). Extracts were spiked with 10 µL of internal standards solution and evaporated to dryness under nitrogen flow. Extracts were finally reconstituted with 1 mL of 90:10 UPW:methanol.

All samples were analyzed with an HPLC Infinity 1290 coupled with a Q-ToF 6540 equipped with a Jet Stream electrospray ionization source (Agilent). The procedure is fully detailed in Guibal et al. (2018). Briefly, chromatographic separation was performed with a RP18+ Nucleoshell column (Macherey-Nagel), and UPW and methanol (with 5 mM ammonium formate and 0.1% acid formic for both) were used as eluent during a 16 min analytical gradient. Autosampler and column temperatures were kept at 4°C and 30°C, respectively. Mass acquisition was operated in the "all-ions" positive mode (collision energies: 0, 10, 20 and 40 V). QA/QC was used to control any deviations during analysis. Pharmaceutical characteristics after HPLC separation and mass detection are displayed in **Table III.13** and analytical performances in **Table III.16**.

Table III.16: Analytical validation results. Procedures are detailed in Guibal et al. (2015b).

Compound	Linearity		Instrumental LOQ (µg/L)
	Equation	r^2	
Atenolol	y=0.0304x	0.974	0.1
Carbamazepine	y=0.0102x	0.991	0.2
Clarythromycin	y=0.0031x	0.952	0.1
Diclofenac	y=0.0100x	0.993	2.0
Erythromycin	y=0.0043x	0.942	0.2
Fluoxetine	y=0.0056x	0.985	0.2
Gemfibrozil	y=1.0052x	0.998	5.0
Ketoprofen	y=0.0648x	0.990	0.5
Metoprolol	y=0.3050x	0.779	0.1
Paroxetine	y=0.0102x	0.978	0.1
Propanolol	y=0.0118x	0.977	0.5
Roxithromycin	y=0.0009x	0.963	0.5
Sulfamethoxazole	y=0.0127x	0.993	0.2
Trimethoprim	y=0.0106x	0.987	0.2

Exposure concentration estimation.

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

Estimation based on POCIS.

The "standard" estimation of C_W based on POCIS (n=2) was performed using **Equation III.6** (Zhang and Davison 1995):

$$C_w = {}^{m}/_{R_S t} \qquad \textbf{Equation III.6}$$

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 12 references, each using a similar POCIS configuration (200 mg Oasis® HLB) (**Table III.17**). 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.

Table III.17: R_s values (mL d^{-1}) selected for this study (superscript indicated the reference). References (a: MacLeod et al. (2007); b: Harman et al. (2011b); c: Li et al. (2010a); d: Bayen et al. (2014); e: Di Carro et al. (2014) and f: Bailly et al. (2013)).

	ATE	CAR	CLA	DIC	ERY	FLU	GEM	KET	MET	PAR	PRO	ROX	SUL	TRI
V_0	37[a]	112[a]	90[a]	92[a]	183[a]	223[a]	112[a]	83[a]	97[b]	65[c]	147[a]	134[a]	202[b]	90[a]
V_1	51[d]	600[d]	668[a]	69[e]	911[a]	1370[a]	192[a]	80[e]	599[a]	1632[c]	1226[d]	723[a]	153[b]	346[d]
V_2	51[d]	600[d]	668[a]	55[e]	911[a]	1370[a]	192[a]	80[e]	599[a]	883[a]	1226[d]	723[a]	153[b]	360[a]
V_3	101[f]	348[a]	668[a]	53[e]	911[a]	1370[a]	192[a]	206[f]	599[a]	883[a]	980[a]	723[a]	94[f]	360[a]

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. 2018, Mazzella et al. 2010), and corrections were made using the procedure detailed in Mazzella et al. (2010). Briefly, the elimination rate of DIA-d5 (k_{ePRC}) was determined for each flow velocity, and a corrected sampling rate (R_S^{cor}) was calculated using **Equation III.7**:

$$R_S^{cor} = R_S^{ref} \times \left(\frac{k_{ePRC}}{k_{ePRC}^{ref}}\right) \qquad \textbf{Equation III.7}$$

where R_S^{ref} and k_{ePRC}^{ref} are the sampling rate and the PRC elimination rate, respectively, for the reference condition. V_3 was taken as the reference condition and sampling rates determined in this condition (R_S^{ref}) are presented in **Table III.18**. C_W was finally calculated using R_S^{cor} in **Equation III.6**.

Table III.18: R_s values (mL d^{-1}) determined for the V_3 condition (Guibal et al., in prep) and used as references for the PRC approach.

	ATE	CAR	CLA	DIC	ERY	FLU	GEM	KET	MET	PAR	PRO	ROX	SUL	TRI
R_S^{ref}	228	443	351	334	379	514	377	313	346	371	392	404	154	350

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 **Equation III.8** (Zhang and Davison 1995):

$$C_w = \frac{m\Delta_g}{A_g t \mathrm{D}} \qquad \textbf{Equation III.8}$$

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. (2016) and corrected for temperature (T) using the Stokes-Einstein equation (**Equation III.9**) where η is the water viscosity (taken from the NIST chemistry WebBook (Lemmon et al. 2010)):

$$\frac{D_1 T_1}{\eta_1} = \frac{D_2 T_2}{\eta_2} \qquad \textbf{Equation III.9}$$

The "advanced" estimation of C_W was made using a more sophisticated model (**Equation III.10** (Santner et al. 2015)) that considers the thickness of the DBL (δ) and lateral diffusion within the sampler:

$$C_w = \frac{m}{k_{ld} A_g t}\left(\frac{\Delta_g}{D} + \frac{\delta}{D^w}\right) \qquad \textbf{Equation III.10}$$

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 (Schwarzenbach et al. 1993)). C_W was estimated alongside δ through direct adjustment of **Equation III.10** 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).

Quantification bias.

The bias on the estimated with passive samplers of time-weighted average concentrations in pilots (C_w^{est}) was calculated as a percentage relative to the average measured concentration (C_w^{mea}) using **Equation III.11**:

$$\text{bias} = \frac{100 \times |C_w{}^{mea} - C_w{}^{est}|}{C_w{}^{mea}} \qquad \textbf{Equation III.11}$$

To compare two procedures, the estimation improvement was calculated. For example, the estimation improvement using procedure A compared to procedure B was determined as the bias (%) using procedure B minus the bias using procedure A.

Estimation of sampling rates for o-DGT.

R_s were estimated using the formula (**Equation III.12**) found in Challis et al. (2016):

$$R_S = \frac{DA_g}{\Delta_g} \qquad \textbf{Equation III.12}$$

DBL formation alters sampling rate and is significant at V_0. R_S at V_0 was therefore corrected using **Equation III.13**:

$$R_S(V_0) = \frac{DA_g}{(\Delta_g + \delta)} \qquad \textbf{Equation III.13}$$

This equation underlies the approximation $D=D^W$ and will result in underestimated sampling rates. δ was obtained alongside C_w with the advanced procedure.

RESULTS AND DISCUSSION

POCIS C_w estimation without PRC.

Biases made in estimating C_w using R_s from literature ("standard" procedure) are presented in **Figure III.15**. Except for diclofenac, biases were lower than 140%, which agrees with the 138% uncertainty reported by Poulier et al. (2014) during field deployment for pesticide monitoring. The important biases reported for diclofenac indicate that the R_s values chosen were not relevant for our system. Considering that these values were determined in conditions very close to our study (flow velocities, doping level, water matrix and temperature) (Di Carro et al. 2014), the R_s robustness for this compound appears low. For the other compounds, bias was lower than 100% in non-quiescent conditions (V_{1-3}) with few exceptions (atenolol V_1 and V_2, ketoprofen V_2). Moreover, most of biases were between 50 and 75%. These biases are higher than analytical accuracy (typically 20%) and probably arise from differences in calibration conditions compared to our system, although the R_s values were selected with the aim of limiting such differences. Among these differences, flow velocity could be of concern but other parameters should not be excluded. Positioning of the POCIS (*i.e.,* parallel or perpendicular to flow) will affect hydrodynamics but is rarely indicated in the literature. In most cases, our C_w estimations resulted in overestimations, possibly explained by the effect of temperature. This is consistent with the calibrations used; most of the studies were performed at 20-30°C, compared to our study that was performed at 17±2°C. When considering quiescent conditions only (V_0), estimations were satisfactory (bias ≤ 57%, except sulfamethoxazole). Good performance for this condition probably arose from the ease of choice for R_s, since calibrations in quiescent conditions are always available. This highlight the necessity, for the accurate use of POCIS, to utilize calibrations performed in conditions very similar to the studied system.

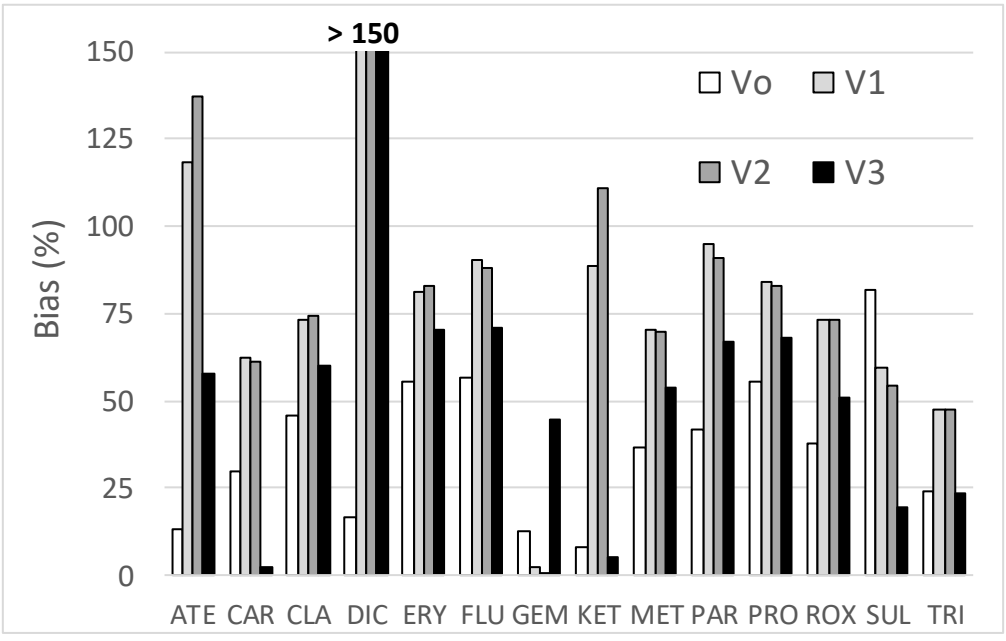


Figure III.15: Bias on C_w estimations using POCIS samplers and the "standard" procedure. Biases for DIC at V_1, V_2 and V_3 reach 152, 237 and 354%, respectively.

PRC approach.

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 ($k_e \sim 0$). 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 consistent with values found in the literature: 0.034 d^{-1} (Carpinteiro et al. 2016), 0.044 d^{-1} (Belles et al. 2014a), 0.046 d^{-1} (Li et al. 2018) 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}). Given that both studies were performed at 17°C, temperature effect is unlikely to be involved in this difference. The discrepancy likely arose from the different methods used for POCIS exposure (parallel to flow in our study and perpendicular to flow for Mazzella et al. study). These results highlight the difficulty in characterizing the hydrodynamic environment of samplers using flow velocity only, especially when variable practices exist.

Estimation bias on C_w using the PRC approach are displayed in **Figure III.16**. For the reference condition (V_3) bias 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.

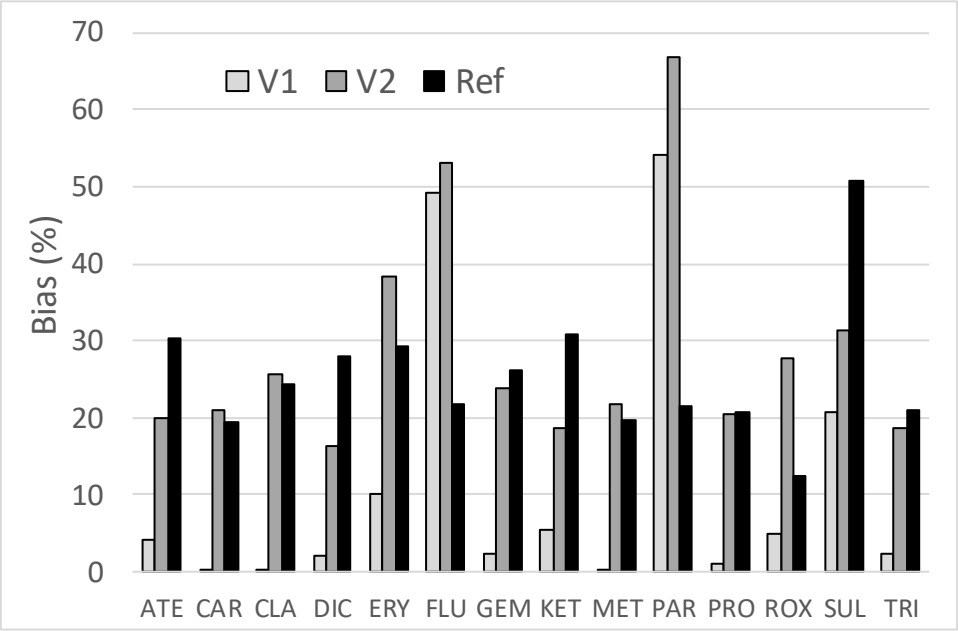


Figure III.16: Bias (%) on C_w estimations using the PRC approach with POCIS samplers.

The use of the PRC approach to correct sampling rate for flow discrepancy increased accuracy both in V_1 and V_2 conditions (**Figure III.17**). Except for fluoxetine and paroxetine, estimation improvement was approximately 25% for V_2 and increased to 45-50% for V_1. 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 III.16**). 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. (2011a) who stressed that the PRC approach has some limitations and might not work for all compounds.

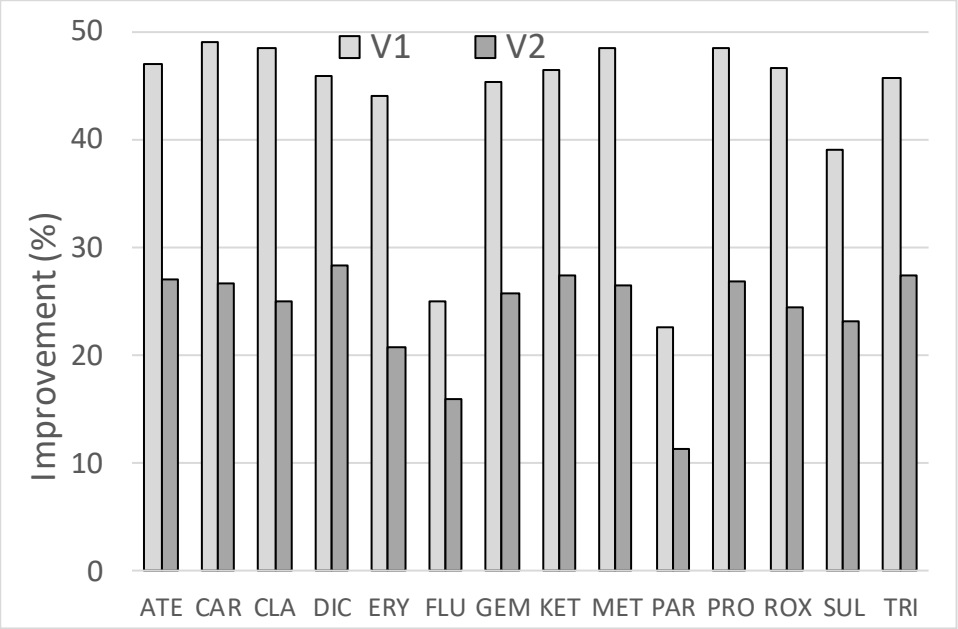


Figure III.17: Accuracy gain (% error) when correction of R_S is made with PRC compared to no correction.

C_w estimation with o-DGT.

Figure III.18 presents biases made in estimating C_w with o-DGT samplers and 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.,* $2 \leq V_{1\text{-}3} \leq 18$ cm s^{-1}), bias was <50% for any compound. Given that most biases 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 bias 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 **Equation III.8**, which does not account for this diffusion path increase.

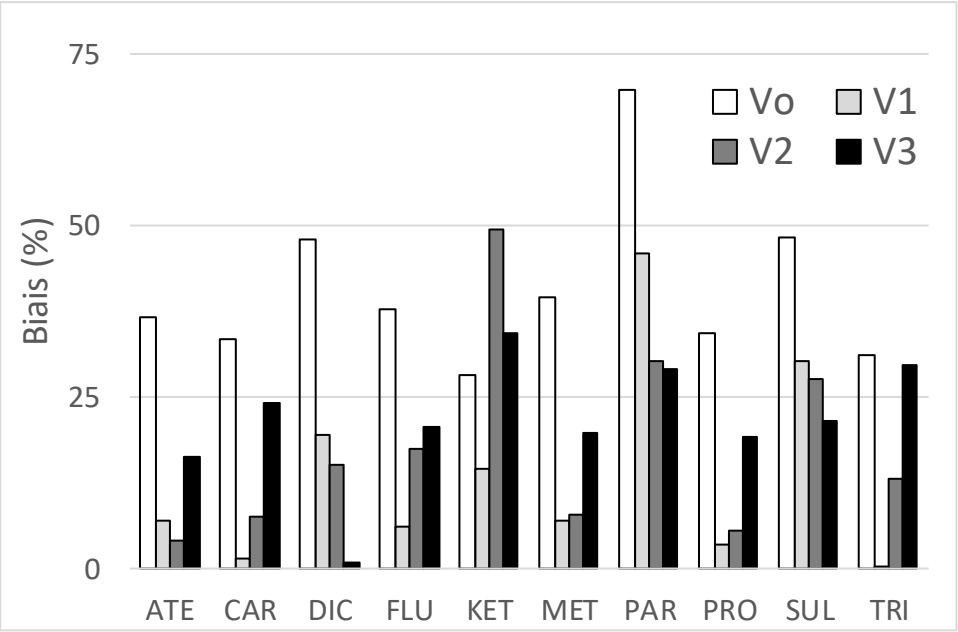


Figure III.18: Error of C_w estimations using o-DGT samplers and the "standard" procedure. Clarithromycin, erythromycin, gemfibrozil and roxithromycin are displayed in Table III.19.

Table III.19: Bias (%) on C_w estimations for clarithromycin, erythromycin, gemfibrozil and roxithromycin using o-DGT samplers and the "standard" or "advanced" procedure.

	Clarithromycin	Erythromycin	Gemfibrozil	Roxithromycin
Standard V_0	39	4	129	107
Standard V_1	149	27	116	922
Standard V_2	243	55	161	1004
Standard V_3	167	66	72	964
Advanced V_0	119	39	253	327
Advanced V_1	344	97	539	3426
Advanced V_2	212	83	261	723
Advanced V_3	226	75	82	1220

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 (**Equation III.10**). Surprisingly, when the system was not quiescent ($V_{1\text{-}3}$), in most cases the "advanced" procedure produced higher biases on C_w estimations (**Table III.20** and **Table III.21**) compared to the "standard" procedure. 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 (**Table III.22**). The "advanced" procedure allows accurate (<30%) estimations except for fluoxetine and paroxetine. Estimations were even highly accurate (<10%) for atenolol, carbamazepine,

propranolol and trimethoprim. Therefore, the "advanced" procedure appears to be promising for producing accurate estimations in quiescent systems.

Table III.20: Bias (%) on C_w estimations using o-DGT samplers and the "advanced" procedure.

	ATE	CAR	DIC	FLU	KET	MET	PAR	PRO	SUL	TRI
V_0	4	1	29	47	29	15	73	2	11	5
V_1	67	56	43	81	105	54	11	50	159	62
V_2	35	33	8	20	60	28	22	24	90	38
V_3	35	32	8	21	66	30	6	25	162	38

Table III.21: Estimation improvement using o-DGT with the "advanced" compared to the "standard" procedure. Negative values indicated a bias increase.

	ATE	CAR	DIC	FLU	KET	MET	PAR	PRO	SUL	TRI
V_0	33	32	19	-9	-1	25	-4	33	37	26
V_1	-60	-55	-24	-75	-91	-47	35	-46	-129	-62
V_2	-32	-26	7	-2	-11	-20	8	-19	-62	-25
V_3	-19	-8	-7	0	-32	-11	23	-6	-140	-8

Table III.22: Bias (%) on C_w estimations for V_0 using o-DGT samplers and the "advanced" procedure, and estimation improvement (%) compared to the "standard" procedure.

	ATE	CAR	DIC	FLU	KET	MET	PAR	PRO	SUL	TRI
error	4	1	29	47	29	15	73	2	11	5
gain	33	32	19	-9	-1	25	-4	33	37	26

Regardless of the procedure, clarithromycin, erythromycin, gemfibrozil and roxithromycin were highly overestimated in most cases (**Table III.19**). Overestimations could arise from the use of inappropriate diffusion coefficients in diffusive gels for the studied conditions. Although the values used in this study (Challis et al. 2016) for clarithromycin, erythromycin and roxithromycin were confirmed by another study (Chen et al. 2013), they were determined at pH 5.5-6.5. Clarithromycin, erythromycin and roxithromycin (pK_a~9, (Babic et al. 2007) were partly deprotonated in our experimental conditions (pH 8.3), which could in turn favor their diffusion within the agarose diffusive gels. However, this hypothesis is not valid for gemfibrozil given its characteristics (pK_a~4.5, (Noorizadeh et al. 2013), which is strengthen by the Stroski et al. (2018) study that showed no significant pH effect on gemfibrozil diffusion in polyacrylamide gels between pH 5 and 8.5.

Comparison of POCIS and o-DGT.

For any flow condition and procedure (except clarithromycin at V_0 with the "standard" procedure), the POCIS allowed more accurate estimations of C_w compared to o-DGT for clarithromycin, gemfibrozil and roxithromycin (**Table III.23**). Limitations of o-DGT for these compounds were discussed above and may arise from the use of inappropriate diffusion coefficients for the studied conditions (possible pH-dependency of the diffusion

coefficient). These results support the current use of POCIS for these three compounds until better calibration is available for o-DGT.

For routine water surveys, simple procedures are required, and "standard" procedures are likely to be used. In this context, o-DGT shows better accuracy (**Table III.23**) in non-quiescent conditions (V_{1-3}) with several exceptions for V_3 (carbamazepine, sulfamethoxazole and trimethoprim). Quiescent conditions (V_0) led to more varied results. POCIS was more accurate for atenolol, diclofenac, ketoprofen and paroxetine whereas o-DGT was more accurate for erythromycin, fluoxetine, propranolol, and sulfamethoxazole. Both tools performed similarly (accuracies differences <10%) 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. 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 (**Table III.22**). Given that in quiescent conditions no improvement was possible for POCIS from the PRC approach (DIA-d5 unable to desorb), o-DGT estimations with the "advanced" procedure were compared to POCIS estimations with the "standard" procedure (**Table III.24**). o-DGT was more accurate for carbamazepine, erythromycin, metoprolol, propranolol, sulfamethoxazole and trimethoprim whereas it was less accurate for diclofenac, ketoprofen and paroxetine. Estimation accuracies were similar (<10%) for atenolol and fluoxetine. Therefore, the most accurate estimations in quiescent conditions are obtained with o-DGT using the "advanced" procedure, except for diclofenac, ketoprofen and paroxetine.

Table III.23: Estimation improvement (%) with the "standard" procedure using o-DGT compared to POCIS.

	ATE	CAR	CLA	DIC	ERY	FLU	GEM	KET	MET	PAR	PRO	ROX	SUL	TRI
V_0	-24	-4	7	-31	52	19	-116	-20	-3	-28	21	-69	33	-7
V_1	111	61	-76	132	54	84	-113	74	64	49	81	-849	29	47
V_2	133	54	-169	222	28	71	-160	62	62	60	78	-930	27	35
V_3	41	-22	-107	353	5	50	-27	-29	34	38	49	-913	-2	-7

Table III.24: Estimation improvement (%) using o-DGT with the "advanced" procedure compared to POCIS in quiescent conditions.

	ATE	CAR	DIC	ERY	FLU	KET	MET	PAR	PRO	SUL	TRI
V_0	9	28	-12	17	9	-21	22	-31	54	70	19

Overall, if implementation of the PRC approach is conceivable for POCIS, both POCIS and o-DGT will suffer from limited flow effects and 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. Moreover, 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). The efficiency of the PRC approach demonstrated in this study for 7 days deployments still have to be confirmed for longer deployments duration. Nevertheless, an important advantage of POCIS compared to o-DGT is its higher sampling rates, especially at high flow velocities (**Table III.25**). This results in a greater POCIS sensitivity (up to 92 times for trimethoprim); therefore POCIS use may be preferred. 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 deployment times longer than 7 days are expected, the choice of o-DGT could be safer until efficiency of DIA-d5 as a PRC has been demonstrated for such durations. Moreover, if quiescent (or nearly quiescent) conditions are expected, then o-DGT should be chosen to achieve better accuracy (except for gemfibrozil and macrolide antibiotics). Anyway, it must be stressed, that flow velocity is not the only condition that affects passive sampling in aquatic systems (*e.g.,* temperature, biofouling), and the above recommendations may be reconsidered in the future.

Table III.25: Sampling rates (mL d^{-1}) for o-DGT (calculated with Equation III.12 and III.13 displayed below) and comparison with POCIS sampling rates calibrated using the same conditions (Guibal at al., in prep). Fluoxetine and paroxetine values were not consistent at V_0 and results for are not displayed.

	ATE	CAR	DIC	FLU	KET	MET	PAR	PRO	SUL	TRI
o-DGT R_S	7	9	10	8	8	7	7	8	9	8
o-DGT R_S (V_0)	3	4	5	ND	3	3	ND	4	3	4
Ratio POCIS/DGT (V_3)	33	47	34	67	38	49	50	50	18	92
Ratio POCIS/DGT (V_0)	19	20	15	ND	36	21	ND	20	18	20

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. Furthermore, when many compounds are targeted, simultaneous implementation of several PRCs will probably be required for extensive flow effect correction. For o-DGT, accurate quantification of clarithromycin, erythromycin, gemfibrozil and roxithromycin was not achieved. Although no reliable hypothesis could be drawn for gemfibrozil, current limitations for macrolide antibiotics are attributed to calibration deficiencies owing to the potential pH-dependence of diffusion coefficients. Investigation of the pH effect of diffusion coefficients is therefore required to allow building a relevant diffusion coefficient database and to increase o-DGT robustness. Moreover, given the failures observed in this study, if compounds that were not investigated here will be targeted, preliminary laboratory tests with the chosen sampler are recommended to identify other potential failures.

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 the unsuitability 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 **Equation III.8**. It was estimated (**Table III.26**) that using 2.5-mm-thick diffusive gels and the "standard" procedure would allow achieving accuracies better than 25% in quiescent systems. Second, the lack of sensitivity of o-DGT compared to POCIS could be overcome. Sensitivity differences are a consequence of sampling rate differences (**Table III.25**). This difference was previously demonstrated for several antibiotics (Chen et al. 2013) and anionic pesticides (Guibal et al. 2017a) to be largely due to sampling area difference. Therefore, increasing the sampling area of o-DGT should result in increased sampling rates (**Equation III.12** and **III.13**) and higher sensitivity. It can be calculated (**Table III.27**) 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.

Table III.26: Diffusive gel thickness needed to achieve 25% accuracy in quiescent systems with the "standard" procedure. Thicknesses were calculated with Equation III.8 and III.10 (lateral diffusion neglected) using DBL thicknesses obtained alongside C_w with the "advanced" procedure. Fluoxetine and paroxetine DBL thicknesses were not consistent and results for these compounds are not displayed.

	ATE	CAR	DIC	KET	MET	PRO	SUL	TRI
Δg (mm)	1.80	1.71	1.50	2.11	1.42	1.65	2.42	1.78

Table III.27: Theoretical areas (cm^2) needed for o-DGT (calculated with Equation III.12 and Equation III.13) to achieve sampling rates that are not lower than POCIS in flowing (2 cm $s^{-1} \leq V \leq 18$ cm s^{-1}; Δ_g=0.84 mm) or quiescent (Δ_g = 2.5 mm) conditions. POCIS sampling rates were taken from Guibal at al. (in prep).

	ATE	CAR	DIC	FLU	KET	MET	PAR	PRO	SUL	TRI
Flowing	104	147	106	212	120	154	158	156	55	133
Quiescent	109	121	94	120	196	126	57	118	94	120

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 found to fail for some compounds. To overcome these failures, it will require development of new PRCs for POCIS whereas, for o-DGT, calibration of diffusion coefficients will be required over the whole pH range of natural waters. 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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III.4. Conclusion intermédiaire

L'échantillonneur, appelé o-DGT (pour DGT organique), développé dans ce chapitre s'est avéré performant avec une robustesse compatible pour l'échantillonnage dans les cours d'eau naturels. Pour cela, deux phases réceptrices ont été développées à partir de deux poudres commerciales Oasis® HLB et Oasis® MAX. Une étape importante a été de tester la robustesse de l'échantillonneur o-DGT dans des gammes de pH allant de 3 à 8 et de force ionique allant de 10^{-2} à 1 M. Les ratios C_{DGT}/C_{sol} ont montré une quantification acceptable sur ces gammes de pH et de force ionique avec des écarts inférieures à 30%. Les résultats ont montré que cet échantillonneur innovant de la famille des o-DGT pouvait donc être utilisé dans la plupart des eaux naturelles (eaux continentales, estuariennes et eaux de mer).

L'échantillonnage de composés organiques a ensuite été testé en laboratoire dans différentes eaux préalablement dopées : une eau minérale (Evian®), une eau naturelle de subsurface peu minéralisée (socle granitique), de l'eau ultrapure avec 10^{-2} M de $NaNO_3$, l'eau du robinet (ville de Limoges) et *in-situ* dans deux rivières (La Seugne et Les Eaux Claires). Différents tests ont été réalisés afin d'étudier l'applicabilité de l'échantillonneur (Evain® et eau naturelle de subsurface), l'effet de la vitesse d'agitation ou vitesse de courant (eau ultrapure contenant 10^{-2} M de $NaNO_3$ et eau de la ville de Limoges). Une comparaison des performances entre POCIS et o-DGT a également été faite en laboratoire grâce à une rivière artificielle (eau de la ville de Limoges) et *in-situ* dans deux rivières.

Une meilleure estimation du TWAC (concentration moyennée) a été obtenue pour le o-DGT avec la phase réceptrice Oasis® HLB (avec une exactitude > 80%) par rapport au o-DGT avec la phase réceptrice Oasis® MAX. L'échantillonneur HLB-DGT semble donc plus approprié pour échantillonner les composés organiques en milieu naturel.

L'effet de la vitesse d'agitation ou vitesse de courant a été testé *via* deux expériences : la première dans un cristallisoir (3 L) en testant les deux phases réceptrices et la deuxième grâce à une rivière artificielle en laboratoire (500 L). Dans cette dernière expérience, des échantillonneurs de type POCIS ont été ajoutés. Plusieurs conditions hydrodynamiques ont donc été testées : milieu sans agitation (« tranquille » ou vitesse de courant nulle) et milieu agité ou turbulent. Dans la première expérience, les deux phases réceptrices (Oasis® HLB et Oasis® MAX) ont été utilisées dans les o-DGT. L'accumulation des pesticides ioniques a été plus faiblement impactée (< 20%) sur l'échantillonneur HLB-DGT que MAX-DGT. Quelle que soit l'expérience, une diminution d'accumulation a été observée dans un milieu non agité. Cela peut s'expliquer par la formation d'une couche limite de diffusion devant l'échantillonneur. Pour avoir une meilleure estimation de la concentration en micropolluant organique dans l'eau lorsque l'échantillonneur est dans un milieu pas ou peu agité (de 0 à 2 $cm.s^{-1}$), les résultats de la deuxième expérience préconisent de prendre en compte la couche limite de diffusion ainsi que la diffusion latérale. Dans ce cas, l'erreur sur l'estimation de la concentration en micropolluant sera inférieure à 30%.

Enfin, la comparaison entre les deux échantillonneurs POCIS et o-DGT a montré qu'en termes de détection, les deux échantillonneurs étaient comparables, cependant, lors des calculs de TWAC, des différences significatives ont été trouvées. Cela peut s'expliquer par les incertitudes liées à chaque échantillonneur. Dans des milieux agités, l'échantillonneur développé dans ce chapitre (HLB-DGT) a une meilleure précision que le POCIS. Pour éviter l'influence des vitesses de courant, il est donc préférable d'utiliser le o-DGT. Dans des milieux non agités, les deux

échantillonneurs passifs (POCIS et o-DGT) obtiennent des niveaux de précision similaires. Cependant, le POCIS a des taux d'échantillonnage plus élevés que ceux du o-DGT. En effet, le taux d'échantillonnage qui traduit la capacité d'un échantillonneur à accumuler les composés d'intérêts est plus grand pour le POCIS grâce à une surface d'exposition plus grande (41 cm^2 pour le POCIS contre 3,1 cm^2 pour le o-DGT). L'échantillonnage par POCIS sera donc plutôt utilisé dans des milieux peu contaminés. Les cours d'eau de tête de bassin versant sont des cours d'eau ayant pour réputation d'être pas ou peu impactés par une pollution anthropique. La concentration en composés organiques de types pesticides ou résidus pharmaceutiques sera donc faible. C'est pour cette raison que le POCIS sera utilisé pour la suite des expériences.

A retenir !

- Un échantillonneur innovant appelé « o-DGT » a été développé dans ce chapitre avec deux phases réceptrices : HLB et MAX
- Utilisable sur des gammes de pH allant de 3 à 8 et des forces ioniques allant de 10^{-2} à 1 M, cette robustesse lui permet d'être utilisé dans la plupart des eaux naturelles.
- HLB-DGT donne la meilleure estimation de la contamination en pesticides (exactitude > 80%) par rapport au MAX-DGT.
- o-DGT est moins sensible aux variations hydrodynamiques du milieu échantillonné par rapport au POCIS.
- Les taux d'échantillonnage du POCIS sont supérieurs aux taux d'échantillonnage du o-DGT.
- L'échantillonnage par POCIS est plus adapté dans des zones faiblement contaminées.

Chapitre IV. Fiabilisation de l'outil POCIS

IV.1. Introduction intermédiaire

Le POCIS est l'échantillonneur passif le plus largement utilisé pour étudier l'état de contamination des eaux par les pesticides et les résidus de médicaments. De plus, l'étude de comparaison entre le POCIS et les récents o-DGT montre que le POCIS mérite toujours d'être considéré pour étudier l'état de qualité des eaux vis à vis des micropolluants organiques. Si le POCIS est un échantillonneur simple à mettre en œuvre, il convient de rester vigilant tout le long de son utilisation (fabrication, déploiement *in situ,* analyses, calculs et interprétation des résultats) pour avoir des concentrations mesurées en composés cibles représentatives de celles circulantes dans le milieu naturel.

En effet, l'échantillonnage passif permet une pré-concentration *in situ* des micropolluants organiques. Cette pré-concentration ne s'arrête pas aux composés d'intérêt mais intègre également les éléments chimiques de la matrice environnementale ou encore les composés pouvant être libérés par les constituants du POCIS. Une étude précédente (Guibal et al. 2015b) a identifié un polymère (polyéthylène glycol – PEG) comme étant responsable d'importants effets de matrice lors de l'analyse d'extraits de POCIS, et par conséquent responsable de biais sur la quantification et donc de la détermination en TWAC. Dans cette même étude, la source de cette contamination en PEG a été identifiée : les membranes en polyéthersulfone (PES) utilisées pour fabriquer un POCIS. L'objectif ici est donc d'améliorer l'échantillonneur en supprimant les effets de matrice issus des membranes PES et de vérifier si le lavage des membranes n'altère pas les capacités de quantification après déploiement en milieu naturel.

Lors du calcul des concentrations moyennes dans l'eau intégrées dans le temps (TWAC), une équation semi-empirique est utilisée et elle ne fait intervenir qu'un seul paramètre inconnu : le taux d'échantillonnage. Ce dernier est spécifique à chaque composé et est généralement calibré en laboratoire où l'on peut contrôler la température, la vitesse de courant et la concentration en composés dans l'eau. Toutefois, ces calibrations sont longues et coûteuses et doivent être faites pour chaque nouveau composé d'intérêt. C'est pourquoi de nombreux auteurs ont entrepris, avec plus ou moins de succès, de prédire ces taux d'échantillonnage à partir de paramètres caractéristiques des molécules parmi lesquels l'hydrophobicité des molécules (*via* le LogP). Cette grandeur, simple d'accès, est souvent utilisée comme descripteur des interactions entre les molécules cibles et la phase fixante (Oasis® HLB) des POCIS (Alvarez et al. 2007, Li et al. 2010a, MacLeod et al. 2007, Togola and Budzinski 2007). Malheureusement, l'absence de conditions normalisées ou de préconisations fortes pour calibrer les échantillonneurs entraine l'utilisation de nombreux modes opératoires dans la littérature avec des conditions environnementales plus ou moins représentatives d'un milieu naturel. Ceci a pour conséquence d'aboutir, pour une même molécule, à des valeurs de Rs très variables jusqu'à un facteur 200 et des modèles prédictifs ou estimatifs des Rs ayant des équations très différentes. La seconde partie de ce chapitre propose de déterminer le taux d'échantillonnage de 44 composés pharmaceutiques (dont 12 non disponibles dans la littérature). Cette détermination sera faite à partir d'un pilote d'une rivière artificielle avec de l'eau du robinet dopée à des concentrations relativement faibles (500 ng/L pour chaque composé). Ce mode de détermination aura l'avantage d'être proche (en termes d'hydrodynamique (vitesse de courant) et de concentration) des conditions environnementales que l'on peut retrouver en rivière. A partir de

ces taux d'échantillonnage, il sera alors intéressant d'établir un lien entre le taux d'échantillonnage et l'hydrophobicité des molécules et ainsi proposer un modèle d'estimation de taux d'échantillonnage.

L'objectif de ce chapitre consiste à améliorer les performances du POCIS et donc de :

- Déterminer un protocole de lavage des membranes PES utilisées dans le POCIS.
- Tester l'accumulation et la quantification de résidus de pesticides dans l'environnement après lavage des membranes.
- Estimer le taux d'échantillonnage de composés pharmaceutiques dans des conditions proches des conditions environnementales.
- Déterminer une relation simple entre le taux d'échantillonnage et le LogP.

IV.2. Publication "Improvment of POCIS ability to quantify pesticides in natural water by reducing polyethylene glycol matrix effects polyethersulfone membranes".

Cette section est constituée d'une version adaptée d'un article publié dans la revue Talanta, où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

Guibal, R., Lissalde, S., Charriau, A. and Guibaud, G. (2015a) Improvement of POCIS ability to quantify pesticides in natural water by reducing polyethylene glycol matrix effects from polyethersulfone membranes. Talanta 144, 1316-1323.

Improvement of POCIS ability to quantify pesticides in natural water by reducing polyethylene glycol matrix effects from polyethersulfone membranes

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ABSTRACT

The presence of polyethylene glycol compounds (PEG) in extracts from polar organic chemical integrative samplers (POCIS) was shown by high resolution time-of-flight mass spectrometry. PEG compounds, which are released by polyethersulfone (PES) membranes used to build POCIS, can induce matrix effects during quantification of performance reference compounds (PRC, DIA-d5) and target pesticides by mass detection, even after chromatographic separation. Dilution of POCIS extracts can reduce this matrix effect, but dilution may induce a decrease in POCIS performance, primarily for quantification limits. To reduce PEG interference during chromatographic analysis, a simple non-damaging washing protocol for PES membranes is proposed. The method consists of 2 successive baths of washing solution (140mL per membrane) of ultrapure water (UPW) and methanol (50/50), stirred at 300 rotations per minute (rpm), followed by a final membrane rinse with UPW (140 mL). The signal from PEG compounds was significantly decreased for washed membranes (between 4 and 6-fold lower). After field deployment, total ion current chromatograms of extracts from POCIS built with washed PES membranes did not display a significant PEG fingerprint. This led to improved quantification accuracy for compounds co-eluting with PEG, i.e. PRC (performance and reference compound, DIA-d5) and some pesticides and metabolites. With washed membranes, an accurate quantification of PRC and pesticides sampled by POCIS was indeed possible without a large extract dilution; 10 times instead of the 25 times needed in unwashed conditions. Assuming that the PRC approach corrects for environmental conditions and sampling rates (Rs), a proper PRC (DIA-d5) quantification significantly improved pesticide time weighted average concentration (TWAC) determination in natural water after field deployment.

Keywords: Passive sampler, matrix effects, PES membranes, washing method

Highlights:

- PEG from PES membranes cause a matrix effect during POCIS extract analysis.
- Washing of PES membranes with MeOH/UPW (50/50), 2 x 1h at 300 rpm was performed.
- Washing improved quantification for molecules with retention times similar to PEG.
- Dilutions 1/10 (washed) or 1/25 (unwashed) are necessary for POCIS extracts analysis.
- Proper PRC (DIA-d5) quantification improved TWAC of pesticides sampled by POCIS.

INTRODUCTION

The need to accurately detect a large range of organic micropollutants e.g. pesticides, PAH, PCB, pharmaceuticals, etc. in natural waters is rapidly intensifying. In recent years, water quality has been predominantly evaluated by collecting grab samples. Field and laboratory methods for this type of sampling are well established and a number of publications are available (Asperger et al. 2002, Barrek et al. 2009, Gervais et al. 2008, Kuster et al. 2009, Masia et al. 2014, Nogueira et al. 2004, Petrovic et al. 2010, Reemtsma 2003, Rodrigues et al. 2007). Pesticide analysis is widely studied in environmental analysis, and the huge number of compounds and diverse array of analytical techniques have provided a range of analytical solutions. Water monitoring requires analytical techniques adapted to trace levels of contaminants. The challenge of reducing quantification limits has resulted in the development of various solutions from sampling to analysis. One of these is passive sampling, which allows detection of organic or inorganic traces of environmental contaminants (Greenwood et al. 2006, Kot-Wasik et al. 2007, Madrid and Zayas 2007, Schopfer et al. 2014, Seethapathy et al. 2008, Vrana et al. 2005, Zabiegala et al. 2010). Passive sampling tools are composed of a sorbent to accumulate compounds and are exposed in rivers for a period of time, generally between one week and one month. This allows contaminant accumulation and substantially decreases the detectable level of contaminants. Indeed, water contamination is very variable and grab sampling can miss episodic events that can noticeably alter pesticide concentration estimates. As passive samplers are continuously immersed in water, a time weighted average concentration can be determined, taking into account pollution events (Alvarez 1999, Alvarez et al. 2005, Mazzella et al. 2008). For polar organic pesticides, the Polar Organic Chemical Integrative Sampler (POCIS) is a well-suited tool (Alvarez et al. 2004, Berho et al. 2013, Lissalde et al. 2011, Mazzella et al. 2010, Metcalfe et al. 2014, Morin et al. 2012, Poulier et al. 2014, Thomatou et al. 2011). A Performance Reference Compound (PRC) can be used to correct exposure conditions. The use of PRC reduces environmental effects and environmental conditions (e.g. flow rate, temperature, fouling) on POCIS sampling rates (Rs) (Mazzella et al. 2010). Despite that, some studies had difficulties achieving a high confidence level for quantification as PRC correction has given very mixed results (Belles et al. 2014b, Charlestra et al. 2012, Harman et al. 2012, Lissalde et al. 2011). Despite these problems, a correct quantification of the PRC is firstly required to not induce an additional bias.

A previous work showed the presence of polyethylene glycol (PEG) in POCIS extracts (Guibal et al. 2015b). As indicate several authors (Keller et al. 2008, Tong et al. 1999, Tong et al. 2002), PEG can induce matrix interference in LC-MS when analytes coelute with PEG. When compounds and PEG were present in the same time in electrospray ion source, there was a competition during the ionization process between the compounds of interest and PEG that can cause suppression or enhancement of the analyte signal (Lissalde et al. 2011, Masia et al. 2014). The present work focuses on PEG release from polyethersulfone (PES) membranes and its impact on LC-ESI-MS/MS analysis, *i.e.* bias in pesticides quantification and one of a bias in PRC quantification (DIA-d5) due to matrix effects.

As confidence in quantification is the key to a satisfactory interpretation of environmental contamination, the present work also highlights the importance of taking some precautions with pesticide, as well as PRC (DIA-d5), quantification in POCIS extracts. In fact, special attention must be paid for the quantification analysis in order to avoid matrix effects (environmental effect and PEG interferences). Environmental matrix effect was site specific

and not investigated in this work. To reduce both of them, POCIS extract dilution was most of the time needed (Guibal et al. 2015b). For PEG interferences (the aims of this work), several washing solutions are investigated for cleaning the PES membranes used to build POCIS and a protocol is proposed to reduce the impact of PEG release on LC-MS/MS analysis. Moreover, a POCIS results (Target pesticides – PRC (DIA-d5)) comparing (after field deployment) between POCIS built with washed membrane (using washing protocol proposed in this work) and POCIS built with unwashed membrane were made.

MATERIALS AND METHODS

Products, reagents and standards.

Ultrapure water (UPW) was produced by a Gradient A10 Milli-Q system from Millipore (Bellerica, Massachusetts, USA). Ethyl acetate, used for the elution step of Solid Phase Extraction (SPE), was obtained from Sigma-Aldrich (Steinheim, Germany) with 99.5% purity. Methanol (MeOH) was purchased from J.T. Baker (Deventer, Netherlands) and was UHPLC-MS quality. Reagents added in eluents (formic acid and ammonium formate with purity >99 %) were purchased from Agilent (Santa Clara, California, USA). The list of pesticides selected for quantification is presented in **Table IV.1**. All standards of pesticide (35), metabolite (9) and internal standards (deuterated pesticides) were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany) with a purity higher than 97% for 40 targeted pesticides and ranging from 94 to 96.5% for the others.

Stock solutions of pesticides, internal standards and calibration solutions were prepared as described in a previous study (Guibal et al. 2015b). Briefly, stock solutions were prepared in acetonitrile and stored at -18°C. Fresh calibration solutions containing pesticide standards (concentrations 1 µg/L, 5 µg/L, 10 µg/L, 25 µg/L and 100 µg/L) and internal standards (concentration 100 µg/L) were prepared daily in a mixture of UPW / MeOH (90/10; v/v).

PES membranes (90 mm diameter, 0.1 µm pore size) used to build POCIS were purchased from Pall; Supor® (100 Membrane Disc Filters – Ann Arbor, USA). POCIS were prepared with Oasis® HLB powder (Waters; Milford, Massachusetts, USA). Two stainless steel rings (Exposmeter; Tavelsjö, Sweden) were used to seal the device (Alvarez et al. 2004).

Pesticide analysis by Ultra High-Pressure Liquid Chromatography (UHPLC) and quadrupole time-of-flight (Q-TOF).

The method used for this study was previously developed and validated (Guibal et al. 2015b). Briefly, a UHPLC 1290 Infinity apparatus from Agilent (Santa Clara, California, USA) was coupled to a quadrupole – time-of-flight (Accurate Mass LC/MS 6540 Agilent). UPW and MeOH with 5 mM ammonium formate and formic acid (0.1 %) were used with a 20 minutes analytical gradient. The mass spectrometer was equipped with an electrospray ionization source (ESI) with an Agilent Jet Stream that was operating in the positive ionization mode. Mass acquisition was performed in the "All-ions" mode.

This method was validated as indicated in the French standard NF T90-210 (AFNOR 2009) and allows detection of pesticides and their metabolites from 0.1 to 5 µg/L in POCIS extracts (Guibal et al. 2015b) (see **Table IV.2**).

Table IV.1: Family, regulatory status and main physicochemical characteristics of the studied pesticides ([1]data from IUPAC, [2]data from INERIS, n.f. not found, n.c. not concerned).

Pesticide	Family	Authorized / Forbidden (In France at 01/08/2014)	pKa	Solubility in water: S_w (mg/L)	$logK_{ow}$ (IUPAC)
3-hydroxy-carbofuran	Metabolite		n.f.	n.f.	0.76[2]
Acetochlor	Herbicide	Authorized	n.c.	282[1]	4.14[1]
Alachlor	Herbicide	Forbidden	0.62[1]	240[1]	3.09[1]
Atrazine	Herbicide	Forbidden	1.7[1]	35[1]	2.70[1]
Azoxystrobin	Fungicide	Authorized	n.c.	6.7[1]	2.50[1]
Benoxacor	Herbicide	Authorized	n.f.	20[1]	2.69[1]
Carbaryl	Insecticide	Forbidden	10.4[1]	9.1[1]	2.36[1]
Carbendazim	Fungicide	Forbidden	4.2[1]	8[1]	1.48[1]
Carbofuran	Insecticide	Forbidden	n.c.	322[1]	1.80[1]
Chlorfenvinphos	Insecticide	Forbidden	n.f.	145[1]	3.80[1]
Chlortoluron	Herbicide	Authorized	n.c.	74[1]	2.50[1]
Cybutryne (Irgarol)	Fungicide	Authorized	n.f.	7[2]	4.00[2]
Cyproconazole	Fungicide	Authorized	n.c.	93[1]	3.09[1]
Dichlorophenyl-methylurea (DCPMU)	Metabolite		n.f.	490[2]	2.09[2]
Dichlorophenyl-urea (DCPU)	Metabolite		n.f.	940[1]	2.35[1]
Atrazine-desethyl (DEA)	Metabolite		n.f.	2700[1]	1.51[1]
Terbuthylazine-desethyl (DET)	Metabolite		n.f.	327.1[1]	2.30[1]
Atrazine-desisopropyl (DIA)	Metabolite		n.f.	980[1]	1.15[1]
Dimethachlor	Herbicide	Authorized	n.c.	2300[1]	2.17[1]
Dimethenamid	Herbicide	Authorized	n.c.	1450[1]	1.89[1]
Dimethoate	Insecticide	Authorized	n.c.	39800[1]	0.70[1]
Dimetomorph	Fungicide	Authorized	-1.3[1]	28.95[1]	2.68[1]
Diuron	Herbicide	Forbidden	n.c.	35.6[1]	2.87[1]
Epoxiconazole	Fungicide	Authorized	n.c.	7.1[1]	3.30[1]
Fluorochloridone	Herbicide	Authorized	n.c.	21.9[1]	3.36[1]
Flurtamone	Herbicide	Authorized	n.c.	10.7[1]	3.20[1]
Flusilazole	Fungicide	Forbidden	2.5[1]	41.9[1]	3.87[1]
Hexazinone	Herbicide	Forbidden	2.2[1]	33000[1]	1.17[1]
Imidacloprid	Insecticide	Authorized	n.c.	610[1]	0.57[1]
Isopropylphenyl-metylurea (IPPMU)	Metabolite		n.f.	n.f.	2.63[2]
Isopropylphenyl-urea (IPPU)	Metabolite		n.f.	n.f.	2.16[2]
Isoproturon	Herbicide	Authorized	n.c.	70.2[1]	2.50[1]
Linuron	Herbicide	Authorized	n.c.	63.8[1]	3.00[1]
Metazachlor	Herbicide	Authorized	n.c.	450[1]	2.49[1]
Methomyl	Insecticide	Forbidden	n.c.	55000[1]	0.09[1]
Metolachlor	Herbicide	Forbidden	n.c.	530[1]	3.40[1]
Metoxuron	Herbicide	Forbidden	n.f.	678[1]	1.60[1]
Norflurazon	Herbicide	Forbidden	n.c.	34[1]	2.45[1]

Norflurazon-desmethyl	Metabolite		n.f.	n.f.	1.72[2]
Pirimicarb	Insecticide	Authorized	4.4[1]	3100[1]	1.70[1]
Simazine	Herbicide	Forbidden	1.62[1]	5[1]	2.30[1]
Tebuconazole	Fungicide	Authorized	5[1]	36[1]	3.70[1]
Terbuthylazine	Herbicide	Forbidden	1.9[1]	6.6[1]	3.40[1]
Thiodicarb	Insecticide	Forbidden	n.c.	22.2[1]	1.62[1]

http://www.iupac.org
http://www.ineris.fr

Table IV.2: Pesticide characteristics after UHPLC separation and mass detection.

Pesticide	Retention Time (min)	LOQ_i	Accurate mass $[M+H]^+$	Internal Standard
3-hydroxy-carbofuran	4.68	2.0	238.1071	Methomyl-d3
Acetochlor	13.59	5.0	270.1245	Metolachlor-d6
Alachlor	13.65	1.0	270.1245	Metolachlor-d6
Atrazine	8.54	0.5	216.1003	Atrazine-d5
Azoxystrobin	11.30	0.1	404.1228	Atrazine-d5
Benoxacor	9.96	0.5	260.024	Diuron-d6
Carbaryl	7.33	0.5	202.0863	Carbaryl-d3
Carbendazim	3.89	0.5	192.0768	Methomyl-d3
Carbofuran	6.73	0.5	222.1125	Carbofuran-d3
Chlorfenvinphos	16.03 and 16.50	0.1	358.9752	Chlorpyrifos-d5
Chlortoluron	8.30	0.1	213.0789	Diuron-d6
Cybutryne (Irgarol)	12.15	0.1	254.1435	Atrazine-d5
Cyproconazole	12.40	0.5	292.1199	Tebuconazole-d6
DCPMU	8.95	0.5	219.0086	Diuron-d6
DCPU	7.95	1.0	204.9930	Diuron-d6
DEA	5.12	0.5	188.0697	DEA-d6
DET	7.26	0.5	202.0855	Atrazine-d5
DIA	4.22	0.5	174.0541	DEA-d6
Dimethachlor	9.53	0.5	256.1091	Diuron-d6
Dimethenamid	11.17	0.1	276.0805	Metolachlor-d6
Dimethoate	4.76	0.1	230.0062	Methomyl-d3
Dimetomorph	11.57 and 12.41	0.5	388.1301	Metolachlor-d6
Diuron	9.30	0.1	233.0239	Diuron-d6
Epoxiconazole	14.18	0.5	330.0806	Tebuconazole-d6
Flurochloridone	12.82	0.5	312.0165	Metolachlor-d6
Flurtamone	11.30	0.1	334.1038	Diuron-d6
Flusilazole	14.84	0.5	316.1061	Tebuconazole-d6
Hexazinone	6.67	0.1	253.1659	Atrazine-d5
Imidacloprid	4.42	0.1	256.0596	Carbofuran-d3
IPPMU	8.54	0.5	193.1335	Diuron-d6
IPPU	7.65	0.5	179.1179	Diuron-d6
Isoproturon	8.95	0.1	207.1492	Diuron-d6
Linuron	10.86	0.1	249.0184	Diuron-d6
Metazachlor	8.74	0.1	278.1046	Metolachlor-d6
Methomyl	3.70	1.0	163.0536	Methomyl-d3
Metolachlor	13.95	0.5	284.1407	Metolachlor-d6
Metoxuron	5.73	0.1	229.0738	Diuron-d6
Norflurazon	9.53	0.1	304.0458	Diuron-d6
Norflurazon-desmethyl	8.30	0.1	290.0288	Diuron-d6
Pirimicarb	5.97	0.5	239.1503	Pirimicarb-d6
Simazine	6.70	0.1	202.0854	Atrazine-d5
Tebuconazole	15.73	0.5	308.1524	Tebuconazole-d6
Terbuthylazine	11.30	0.1	230.1155	Atrazine-d5
Thiodicarb	8.12	0.1	355.0551	Pirimicarb-d6

PEG analysis.

Solutions containing molecules released from PES membranes were analyzed with the Q-TOF (previously described method) and a total ion current chromatogram was displayed. Several peaks (retention time 3.5 – 5.5 minutes) had mass spectra that give a +44 m/z ion series which is characteristic of monomers ($H\text{-}(C_2H_4O)_n\text{-}OH\text{-}NH_4^+$) from the polyethylene glycol polymer (PEG) (Guibal et al. 2015b). The characteristics of different PEG peaks, *i.e.* m/z, retention time and formula, are presented in **Table IV.3**. PEG peak names were assigned by order of retention time.

Table IV.3: PEG peak names and main characteristics (m/z, retention time and formula).

"Name"	m/z	Retention time (min)	Formula
PEG A	300.2014	3.52	$H\text{-}(C_2H_4O)_6\text{-}OH\text{-}NH_4^+$
PEG B	344.2307	3.80	$H\text{-}(C_2H_4O)_7\text{-}OH\text{-}NH_4^+$
PEG C	388.2600	4.06	$H\text{-}(C_2H_4O)_8\text{-}OH\text{-}NH_4^+$
PEG D	432.2886	4.27	$H\text{-}(C_2H_4O)_9\text{-}OH\text{-}NH_4^+$
PEG E	476.3178	4.43	$H\text{-}(C_2H_4O)_{10}\text{-}OH\text{-}NH_4^+$
PEG F	520.3450	4.58	$H\text{-}(C_2H_4O)_{11}\text{-}OH\text{-}NH_4^+$
PEG G	564.3707	4.72	$H\text{-}(C_2H_4O)_{12}\text{-}OH\text{-}NH_4^+$
PEG H	608.3972	4.86	$H\text{-}(C_2H_4O)_{13}\text{-}OH\text{-}NH_4^+$
PEG I	652.4201	4.98	$H\text{-}(C_2H_4O)_{14}\text{-}OH\text{-}NH_4^+$
PEG J	696.4445	5.12	$H\text{-}(C_2H_4O)_{15}\text{-}OH\text{-}NH_4^+$
PEG K	740.4692	5.28	$H\text{-}(C_2H_4O)_{16}\text{-}OH\text{-}NH_4^+$
PEG L	784.4918	5.43	$H\text{-}(C_2H_4O)_{17}\text{-}OH\text{-}NH_4^+$
PEG M	828.5170	5.57	$H\text{-}(C_2H_4O)_{18}\text{-}OH\text{-}NH_4^+$

PES membrane washing procedure.

First tests were carried out in batches where a PES membrane was washed with several pure solvents (140 mL): UPW, MeOH and isopropanol. Batch stirring lasted 15 minutes either by ultrasound, Bioblock Scientific TS 540 (210 watt) or agitation at 300 rotations per minute (rpm) with a magnetic stirrer. Samples were collected in the washing solution at the following times: 1, 3, 5, 8, 11 and 15 min.

To improve membrane cleaning, five UPW/MeOH mixes were investigated as washing solutions: 100/0; 90/10; 70/30; 50/50 and 0/100. Batches (1 membrane in 140mL of solvent mix) were stirred at 300 rpm with a magnetic stirrer (300 rpm) (n=3). An aliquot of washing solution was sampled at different times (1, 3, 5, 10, 26, 52 and 76 hours) to analyze released PEG compounds.

The optimal washing procedure consisted of four successive batches of UPW/MeOH (50/50, 140 mL), each with a 1 hour stirring at 300 rpm. The four washing solutions were collected and the released PEG analyzed. After this cleaning procedure, PES membranes were immediately rinsed with 140 mL of ultrapure water for 1 hour, stirring at 300 rpm.

POCIS: Polar Organic Chemical Integrative Sampler.

Material preparation, construction.

POCIS were composed of a sorbent (200 mg of Oasis® HLB powder) material enclosed between two PES membranes. Two stainless steel rings were used to seal the device (Alvarez et al. 2004). To overcome the effect of environmental factors such as biofouling, water flow rate and temperature on sampling rates, the Oasis® HLB powder was spiked with a performance reference compound (PRC) (Morin et al. 2012). Oasis® HLB powder was spiked with DIA-d5, used as PRC, according to Lissalde et al. (2011).

Elution and sample dilution.

After retrieval, POCIS were carefully opened and the sorbent powder was transferred into an empty 3 mL SPE polypropylene cartridge (Chromabond® Säulen Macherey–Nagel; Düren, Germany) with a previously weighted polyethylene frit, packed under vacuum and dried under nitrogen (Linde Gas France; quality 5.0). To account for sorbent loss during exposure and POCIS treatment, the exact sorbent mass was measured. Cartridges were stored at – 18°C until elution with 3 mL of methanol, followed by 3 mL of a mixture 75/25 (v/v) methanol / ethyl acetate. Internal standards (10 µL of a 1 mg/L solution) were added and the mixture was evaporated to dryness and then reconstituted in 1 mL of MeOH. In order to study matrix effects in extracts from POCIS built with washed and unwashed PES membranes, several dilutions were investigated: 10-times, 25-times, 50-times and 100-times. Dilutions were in a mixture 90/10 (v/v) UPW/MeOH.

Field deployment.

POCIS, spiked with DIA-d5, were exposed for 14 days in 2 rivers located in the southwest of France: the Arnac River (Corrèze) and the La Pude River (Dordogne). La Pude is a small river, 19.7 km long, from here on called Site 1. The La Pude watershed is 91.3 % agricultural surfaces of cereals (maize and wheat) only. The Arnac is a stream, 4.6 km long, and hereafter called Site 2. The Arnac watershed is a small catchment of polycultures (82.2 %) composed of permanent grasslands with extensive cattle breeding and some apple, red fruit and cereal crops. Due to a higher percentage of intensive cereal growth, site 1 has a stronger pesticide pressure than site 2.

At each site, two POCIS triplicates were exposed: one prepared with washed (see part 2.4 for the optimal washing protocol) and a second with unwashed PES membranes. Two POCIS blanks (with washed or unwashed membranes) were prepared like field-exposed samplers to check for any contamination during POCIS preparation, transport or dismantling. No detectable amounts of the targeted pesticides were present in POCIS blanks.

To evaluate the significance of membrane washing and POCIS extract dilution, statistical analyses were performed on average concentrations of PRC and pesticides sampled by POCIS. Analysis of variance (ANOVA) with Fisher's least significant difference (LSD) was done with $\alpha = 0.05$.

Calculation of time-weighted average concentrations in water (TWAC).

An integrative sampler like POCIS is used during the linear sorption phase, and analyte concentration in water (TWAC) can be calculated with the following (**Equation IV.1**) (Alvarez et al. 2004, Mazzella et al. 2007, Morin et al. 2012):

$$C_{POCIS} = C_w \times k_u \times t \qquad \textbf{Equation IV.1}$$

with C_{POCIS} the analyte concentration in the receiving phase (µg/g); C_w the water analyte concentration (µg/L); t the exposure time (days) and k_u the uptake rate (L/g/d) (**Equation IV.2**):

$$k_u = \frac{R_s}{m_{sorbent}} \qquad \textbf{Equation IV.2}$$

with $m_{sorbent}$, the mass of sorbent recovered after POCIS exposure (g) and R_s the sampling rate (L/d). For the present work, R_s values were taken from Lissalde et al. (2011) and Poulier et al. (2015).

Uptake in passive samplers is affected by environmental conditions (*e.g.* temperature, flow rate, biofouling) (Huckins et al. 2002, Vrana et al. 2005). To take into account the variation in sampling rate, PRC can be used (Mazzella et al. 2010) and the in situ R_s calculated following:

$$R_{S\ in\ situ} = \frac{k_{e\ in\ situ}}{k_{e\ lab}} \times R_{s\ lab} \qquad \textbf{Equation IV.3}$$

with R_s the sampling rate (L/day) and k_e the PRC elimination rate constant which is determined (**Equation IV.4**):

$$k_e = \frac{\ln \frac{C_{PRC(t0)}}{C_{PRC}(t)}}{t} \qquad \textbf{Equation IV.4}$$

with $C_{PRC}(t0)$ the concentration spiked in the receiving phase (µg/g), $C_{PRC}(t)$ the residual concentration (µg/g) after an exposure t (in day). During POCIS field deployment, PRC have to release in the range between 20% and 80% (Soderstrom and Bergqvist 2004) to be considered for pesticide TWAC correction.

RESULTS AND DISCUSSION

Release of PEG according to PES membrane washing protocol.

Preliminary tests: choice of stirring mode and washing solvent.

Two stirring modes (sonication and magnetic stirrer) and three pure solvents (UPW, MeOH and isopropanol) were tested. Sonication-aided washing in the three solvents induced membrane deterioration by the formation of holes (**Figure IV.1**). In contrast, 1 h of magnetic stirring at 300 rpm in the same pure solvents showed no tears or holes. Thus, magnetic stirring was chosen to further investigate PEG released by PES membrane under different solvent conditions. Concerning the choice of washing solvent, UPW induced a minor release of PEG by PES membranes. Similar releases of PEG were obtained by MeOH and isopropanol after five minutes of stirring at 300 rpm. Nevertheless, the release of PEG by the PES membrane was slightly faster in the first five minutes with MeOH

than isopropanol. In further cleaning experiments, MeOH was selected instead of isopropanol because it is cheaper and less dangerous. Therefore, MeOH was used, stirring at 300 rpm, alone or in mixture with UPW.

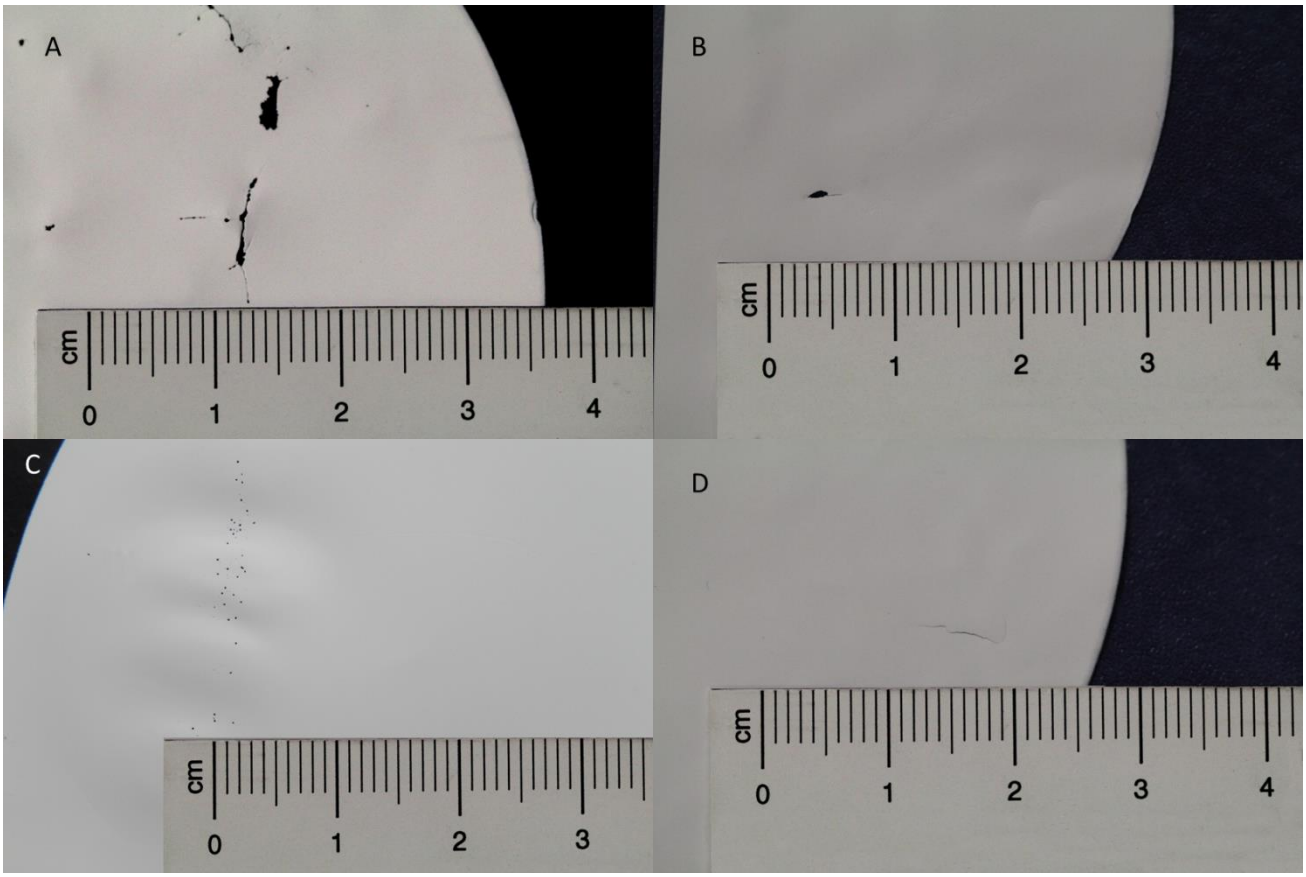

Figure IV.1: Hole formation on PES membranes after different washing; A: UPW with sonication; B: MeOH with sonication; C: isopropanol with sonication and D: MeOH with long agitation (72h).

Effect of MeOH/UPW ratio of the washing solution and effect of successive washing baths.

Firstly, effect of MeOH/UPW ratio of the washing solution was investigated. PEG release, illustrated by the peak area of PEG compounds, is presented as a function of stirring time for different solvent mixtures (**Figure IV.2**). PEG release by PES membrane increased with the addition of MeOH to the washing solvent mixture (**Figure IV.2**). Yet, membranes cleaned with 0/100 (UPW/MeOH) showed holes after 76 hours (**Figure IV.2D**). A significant increase of PEG release with time was noted for 90/10 and 70/30 mixtures. The effect of contact time was less significant for pure MeOH and the 50/50 solvent mixture, thus a 1-hour washing could be sufficient to reduce PEG contamination. To decide on the best washing conditions, a compromise had to be made between washing efficiency, duration and cost. For further experiments, the UPW/MeOH (50/50 ratio) solution was used with an optimal washing time of 1 hour.

Secondly, effect of successive baths with optimal washing solution composition (UPW/MeOH; 50/50) was investigated. According to **Figure IV.3**, the first bath UPW/MeOH (50/50) induced a strong release of all PEG compounds (between 28 and 81 %) and the second bath a slight release, mainly for PEG E to PEG I (between 12

and 17 %). No significant PEG release was shown with baths 3 and 4. In conclusion, for optimal removal of PEG, which are easily released by PES membranes, the following membrane washing procedure was selected: two successive 1-hour baths with 140 mL of UPW/MeOH (50/50) stirring at 300 rpm, followed by immediate rinsing with 140 mL of UPW for 1 hour stirring at 300 rpm. This washing allows removal of 52 to 94 % of PEG (for PEG A and PEG G respectively).

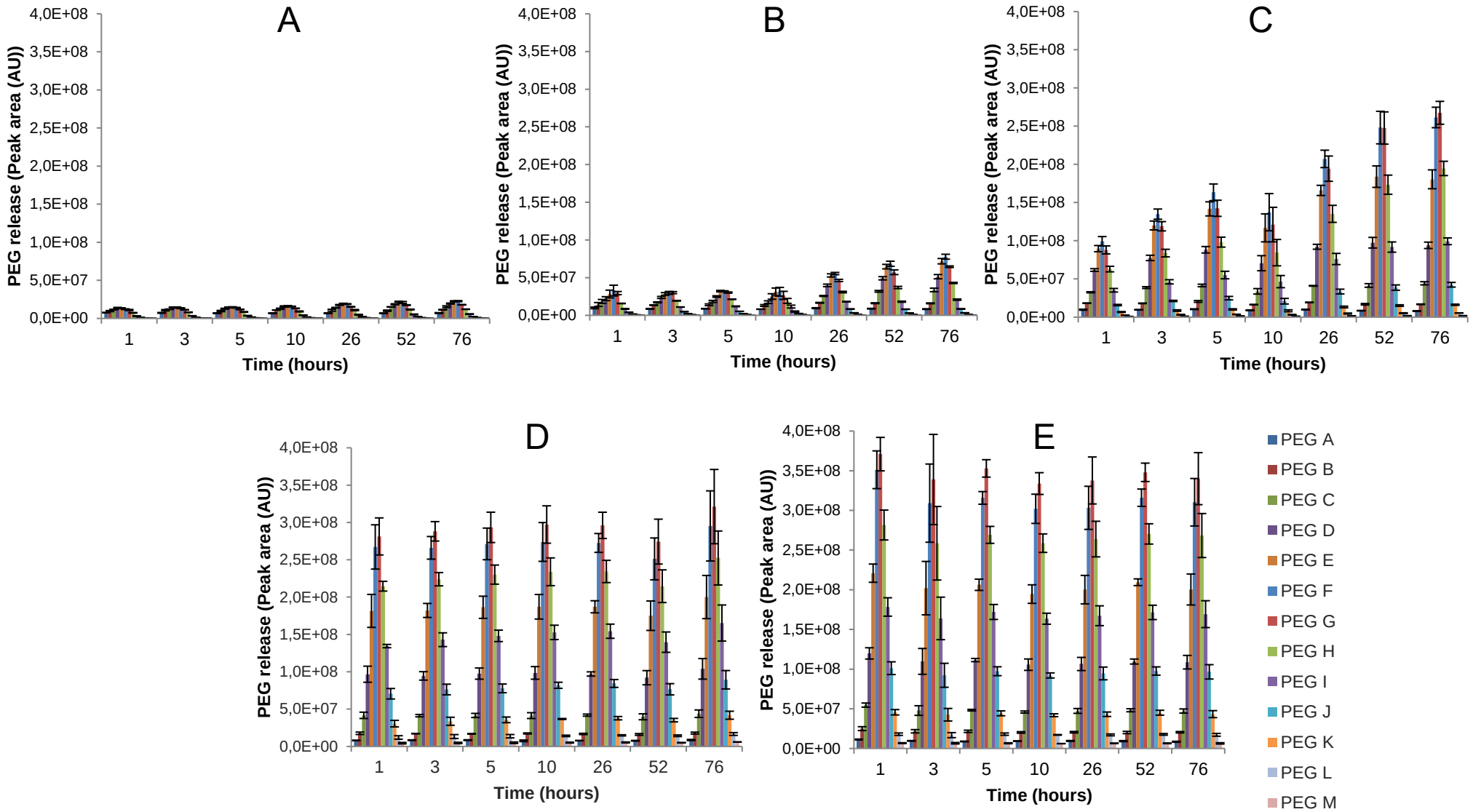

Figure IV.2: PEG release by PES membranes as a function of time and for various washing solution compositions (UPW/MeOH) (n=3): A: 100/0; B: 90/10; C: 70/30; D: 50/50 and E: 0/100.

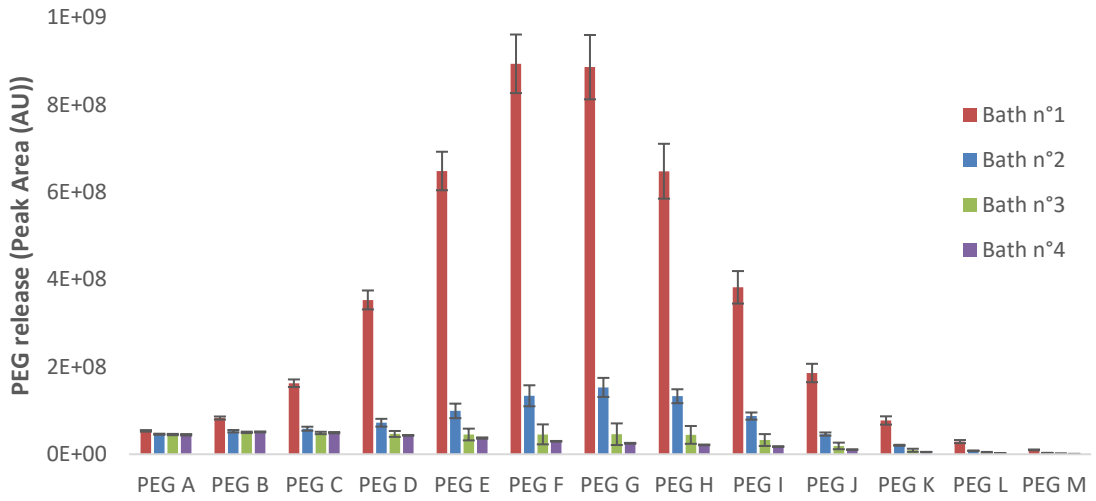

Figure IV.3: PEG release by PES membranes as a function of successive 1-hour baths with a UPW/MeOH (50/50) washing solution (n=3).

Field deployment of POCIS built with washed and unwashed PES membranes.

POCIS extract chromatograms: effect of PES membrane washing and sample dilution.

Total ion current (TIC) chromatograms of POCIS extracts (diluted from 1/10 to 1/100 in UPW) are shown in **Figure IV.4**. POCIS were built with washed and unwashed PES membranes and deployed at site 2.

For POCIS built with unwashed PES membranes, TIC chromatograms displayed an important PEG fingerprint which decreased with extract dilution (**Figure IV.4**). Analyte ionization in LC-MS analysis could be influenced by coeluting PEG compounds (Trufelli et al. 2011). As noted in Guibal et al. (2015b), such PEG contamination could therefore result in erroneous PRC and pesticide quantification.

In contrast, TIC chromatograms of extracts from POCIS built with washed PES membranes did not display PEG fingerprints no matter the dilution (**Figure IV.4**). Nevertheless, for POCIS built with washed PES membranes, a 10-time dilution was associated with an increased TIC baseline compared to UPW. A 25-time dilution was sufficient to reduce TIC baseline to a similar level for POCIS extracts and UPW.

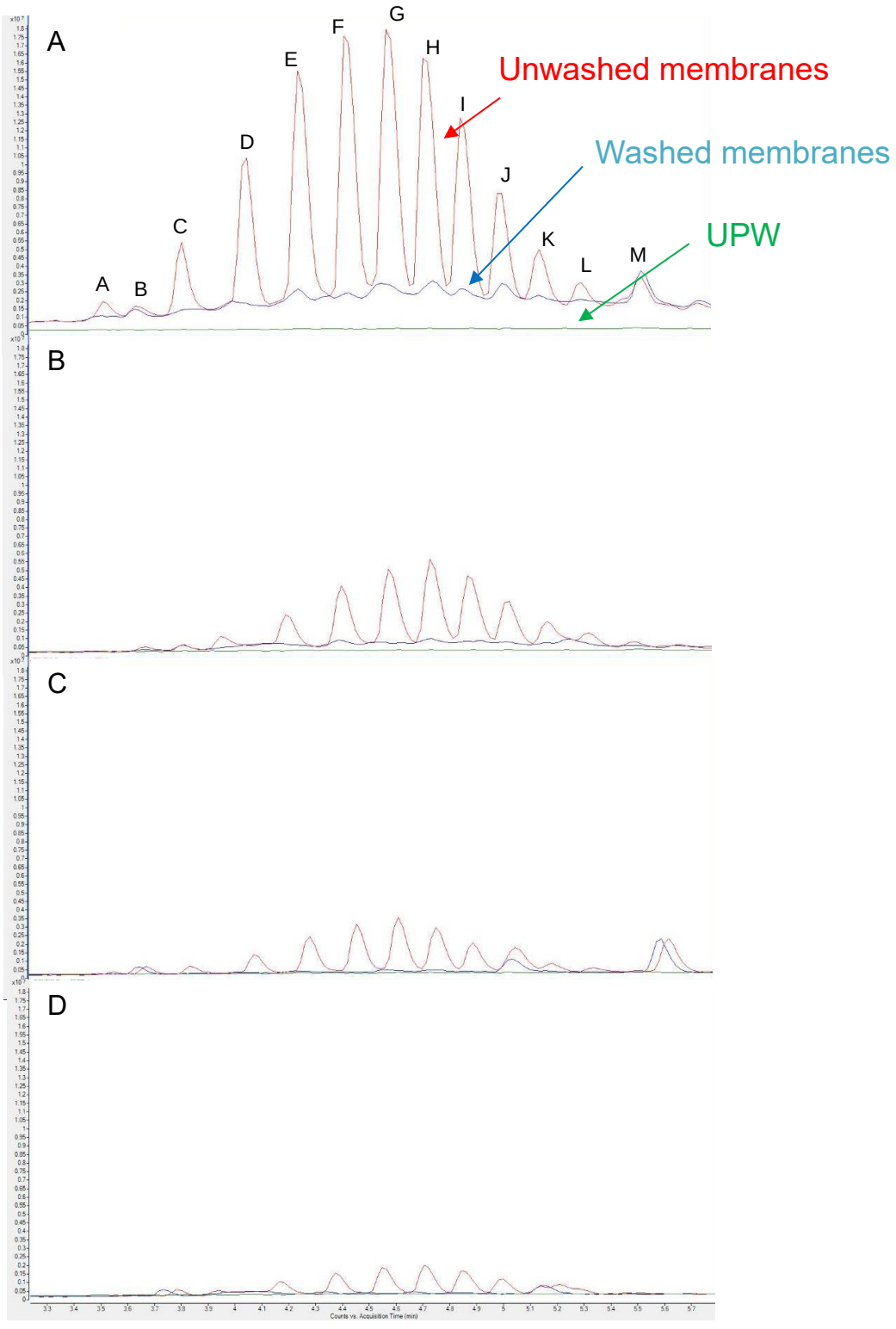

Figure IV.4: Total ion current chromatograms (with PEG peaks names) of UPW (green) and extracts from POCIS built with washed PES membrane (blue) or unwashed PES membrane (red) after field deployment at site 2. POCIS extracts were diluted 10 (A), 25 (B), 50 (C) and 100 (D) times.

Effect of PES membrane washing on PRC (DIA-d5) quantification.

POCIS with washed and unwashed PES membranes were spiked with the PRC DIA-d5 as recommended by Mazzella et al. (2007). DIA-d5 measurements in POCIS extract are shown in **Figure IV.5** as a function of dilution. POCIS built with washed and unwashed PES membranes were deployed at sites 1 and 2. DIA-d5 quantification was corrected by DEA-d6 as an internal standard. DIA-d5, DEA-d6 and PEG had similar retention time ranges, (i.e. 4.3, 5.2 and 3.5 – 5.5 min, respectively), which can cause matrix effects for both analytes.

For POCIS built with unwashed membranes, PEG compounds were still present in the extracts even after a 10-time dilution. This resulted in matrix effects and a significant PRC quantification error which led to an improper calculation of % of PRC desorption (errors of 68 and 95 % for sites 1 and 2, respectively) for the POCIS (**Figure IV.5**). A 25-time dilution was required to obtain a proper quantification of DIA-d5 used as PRC. In contrast, for POCIS built with washed membranes, correction with the DEA-d6 internal standard was efficient and DIA-d5 was properly quantified at every dilution used (**Figure IV.5**). This is in accordance with the lower level of PEG compounds seen in TIC chromatograms after membrane cleaning. To be considered for pesticide TWAC correction, PRC release during POCIS field deployment must be in the range of 20-80% (Soderstrom and Bergqvist 2004). These criteria for minimum and maximum desorption are presented in **Figure IV.5** along with the results for field-deployed POCIS. For a 10-time dilution (unwashed conditions at both sites), PRC desorption was underestimated due to a PEG matrix effect in DIA-d5 quantification. In these conditions, the minimum desorption criterion was not fulfilled and PRC correction could not be carried out. PRC (DIA-d5) quantification at a low dilution level (1/10) is improved following the washing of PES membranes and the concomitant removal of the PEG matrix effect.

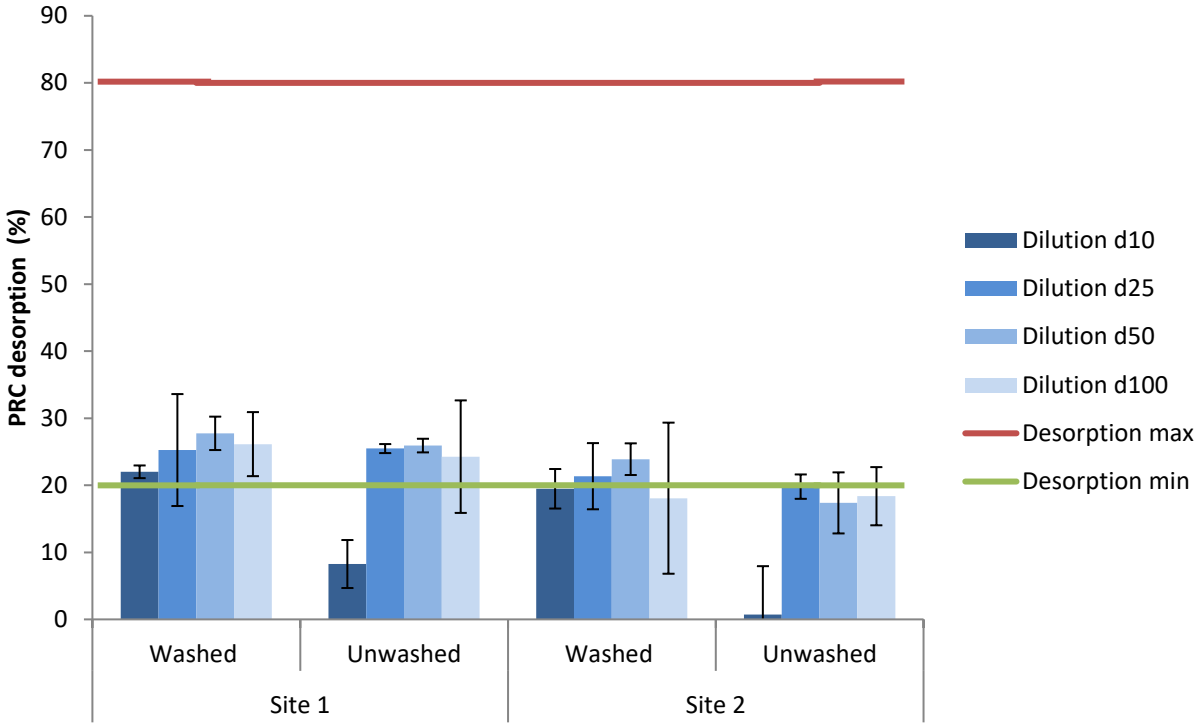

Figure IV.5: PRC (DIA-d5) quantification corrected by DEA-d6 in extracts from POCIS with washed and unwashed PES membranes after field deployment (site 1 or 2) as a function of dilution.

Effect of PES membrane washing on pesticide quantification.

Pesticide quantification (expressed as peak area using an arbitrary unit) in extracts from POCIS built with washed and unwashed PES membranes was performed after field deployment at sites 1 (**Figure IV.6A**) and 2 (**Figure IV.6B**). Statistical analyses (ANOVA LSD) compared i) removal of PEG matrix effects by PES membrane washing and ii) POCIS extract dilutions on molecular quantification.

Seven and six pesticides were quantified at sites 1 and 2, respectively. Among them, atrazine-deisopropyl, imidacloprid and atrazine-desethyl elute in the same retention time range as PEG compounds. For all pesticide quantities and dilutions, the PEG released by PES membranes did not affect peak intensity of DIA and imidacloprid. In contrast, the PEG matrix effect did affect DEA quantification. This matrix effect could be removed by a sufficient dilution (25 times for both sites) alternately, the matrix effect could be removed by washing of the PES membrane. In the latter, a lower dilution of POCIS extract (10 and 25 times for sites 1 and 2, respectively) allowed a proper determination of DEA. To explain such results on pesticide quantification, two assumptions can be made.

First, improvement of pesticide quantification by removal of matrix effects by PES membrane washing is primarily seen for compounds with higher peak signals, *i.e.* DEA (**Figure IV.6**). For compounds with lower chromatographic signals (imidacloprid, DIA), the effect of washing is not significant, which may be due to the low intensity of the chromatographic signal. In this case, the potential error induced by the PEG matrix

effect can be merged with other errors (e.g. sampling and experimental errors) and differences can be hidden in the standard deviation.

Secondly, it is well known that PEG interference occurs in electrospray ionization and this can impact the peak intensity of targeted pesticides (Keller et al. 2008, Tong et al. 2002). We notice here that all compounds were not affected in the same way by co-elution with PEG. We assume that differences are due to chemical formula and /or structure of targeted compounds.

For compounds that elute after PEG (**Figure IV.6A** and **Figure IV.6B**), no differences in pesticide signal were shown and then, as expected, the washing of the PES membrane had no effect.

In sum, this work demonstrates that for targeted pesticide quantification after POCIS field deployment, there are two ways to improve quantification: i) sufficient dilution of the POCIS extract or ii) washing of the PES membrane to limit contamination of Oasis® HLB by PEG. If, as proposed previously by Lissalde et al. (2011) and Guibal et al. (2015b), there is a systematic dilution of passive sampler extract to prevent matrix effects (**Figure IV.6B**), a strong dilution could induce detection difficulties in the case of low pesticide content (*e.g.* imidacloprid, atrazine or diuron**, Figure IV.6B**). Dilutions therefore should be adapted to the studied matrices. Thus, in the case of minimally contaminated water, washing of the POCIS PES membrane is an easy solution to increase the accuracy of pesticide quantification.

For TWAC determination, the washing of PES membranes did not significantly affect chemical and physical properties. In fact, the quantity of accumulated pesticides (**Figure IV.6**), as well as the quantity of desorbed PRC (**Figure IV.5**) were similar for POCIS with or without washed PES membranes (dilutions of 10 and 25, respectively). Consequently, the same sampling rate (Rs) could be used to calculate pesticide time weighted average concentrations in rivers during POCIS field deployment (Alvarez et al. 2004, Morin et al. 2012).

Importance of the removal of PEG matrix effects by washing the POCIS PES membrane.

Looking at i) individual pesticide concentrations (**Figure IV.7**) determined with POCIS extracts diluted 10 (A) and 25 times (B) with POCIS built with washed or unwashed PES membranes and with or without the PRC approach and ii) the TWAC (ng/L) of total pesticides (**Table IV.4**) at sites 1 and 2 calculated according to the dilution of the POCIS extract and from POCIS built with washed or unwashed PES membrane leads to similar conclusions.

A proper dilution of POCIS extracts and/or a washing of PES membranes in order to remove PEG matrix effects during target pesticide analysis is needed. Indeed, an insufficient dilution of the POCIS extract (10 times) will not remove all PEG matrix effects and can result in improper determination of total pesticides TWAC, in our case an overestimation at both sites of about 25%. Washing of PES membranes can remove PEG matrix effects and allow a low dilution of the POCIS extract (10 times); such an approach is needed to quantify those pesticides in very low concentration (ng/L) in natural water.

Additionally, washing of the POCIS PES membrane is interesting from an environmental point of view, as it allows an accurate determination of PRC (DIA-d5) without PEG matrix effects during quantification by

mass spectrometry (**Figure IV.5**). Indeed, a proper determination of PRC (DIA-d5) in POCIS extracts after field deployment allows correction of total pesticide TWAC, assuming that the use of PRC with POCIS can account for environmental effects on Rs (Mazzella et al. 2010). When there is correct DIA-d5 quantification and a sufficient desorption percentage (20-80%), the PRC approach returns a TWAC determined by POCIS that is 4 to 5 times higher than when PRC approach is not possible (**Table IV.4**). Note that a proper PRC approach is also possible, even when PEG is present in the POCIS extract, by a sufficient extract dilution. Indeed, as shown in **Figure IV.7**, a large dilution (25 times) of the POCIS extract from POCIS with unwashed membranes significantly decreased the PEG matrix effect.

The quantification of pesticides using a PRC as proposed in this work, i.e. removing PEG matrix effects by PES membrane washing and use of a proper dilution, confirmed that site 1 had a higher pesticide pressure than site 2: total pesticide TWAC 443 ± 21 and 79 ± 10 ng/L-1 for site 1 and 2, respectively and TWAC for each substance from 30 ± 4 (simazine) to 206 ± 15 ng/L (DEA) and from 5 ± 1 (norflurazon-desmethyl) to 46 ± 7 (DEA) ng/L, for sites 1 and 2, respectively.

Table IV.4: TWAC of total pesticides (ng/L) at site 1 and 2 calculated according the dilution rate of POCIS extract from POCIS built with washed or unwashed PES membrane and with or without PRC approach.

TWAC of total pesticides (ng/L)	Site 1	Site 2	
Washed d10	114 ± 3	23 ± 2	Possible PEG matrix effect without PES membrane washing
Unwashed d10	132 ± 5	22 ± 2	
Washed d25	100 ± 4	15 ± 2	PEG matrix effect was removed by d25 dilution with or without washing of PES membrane
Unwashed d25	110 ± 4	12 ± 1	
Without PRC correction (d25)	100 ± 4	15 ± 2	TWAC correction with proper PRC (DIA-d5) quantification with removing of PEG matrix effect by PES membrane washing
With PRC Correction (d25)	443 ± 21	79 ± 10	

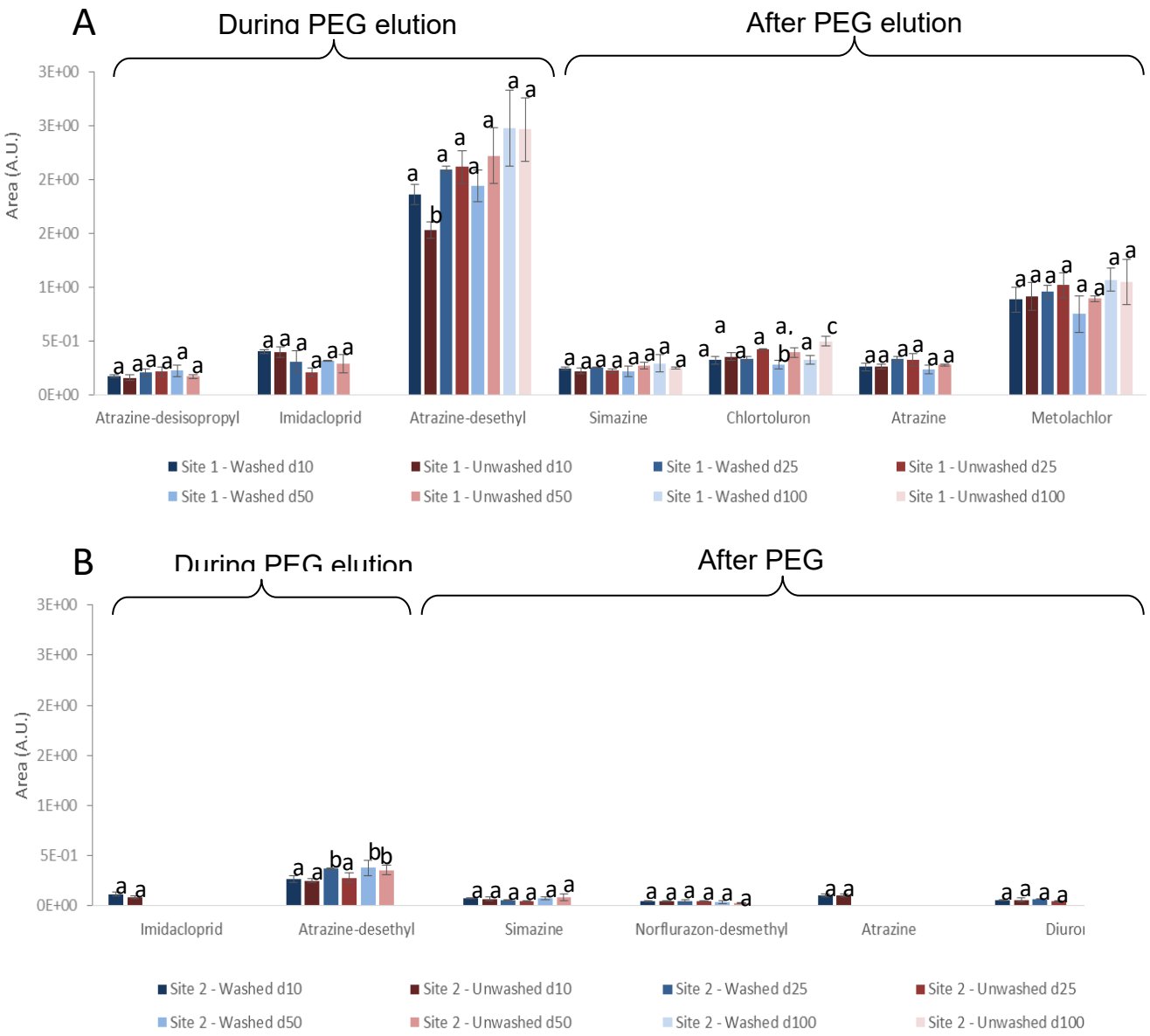

Figure IV.6: Pesticide quantification in POCIS after a 14-day exposure at site 1 (A) and site 2 (B) as a function of extract dilution (10, 25, 50 or 100). Pesticide quantification in extracts from POCIS built with washed (in blue) or unwashed (in red) PES membranes. Pesticides with retention time similar to PEG are specified.

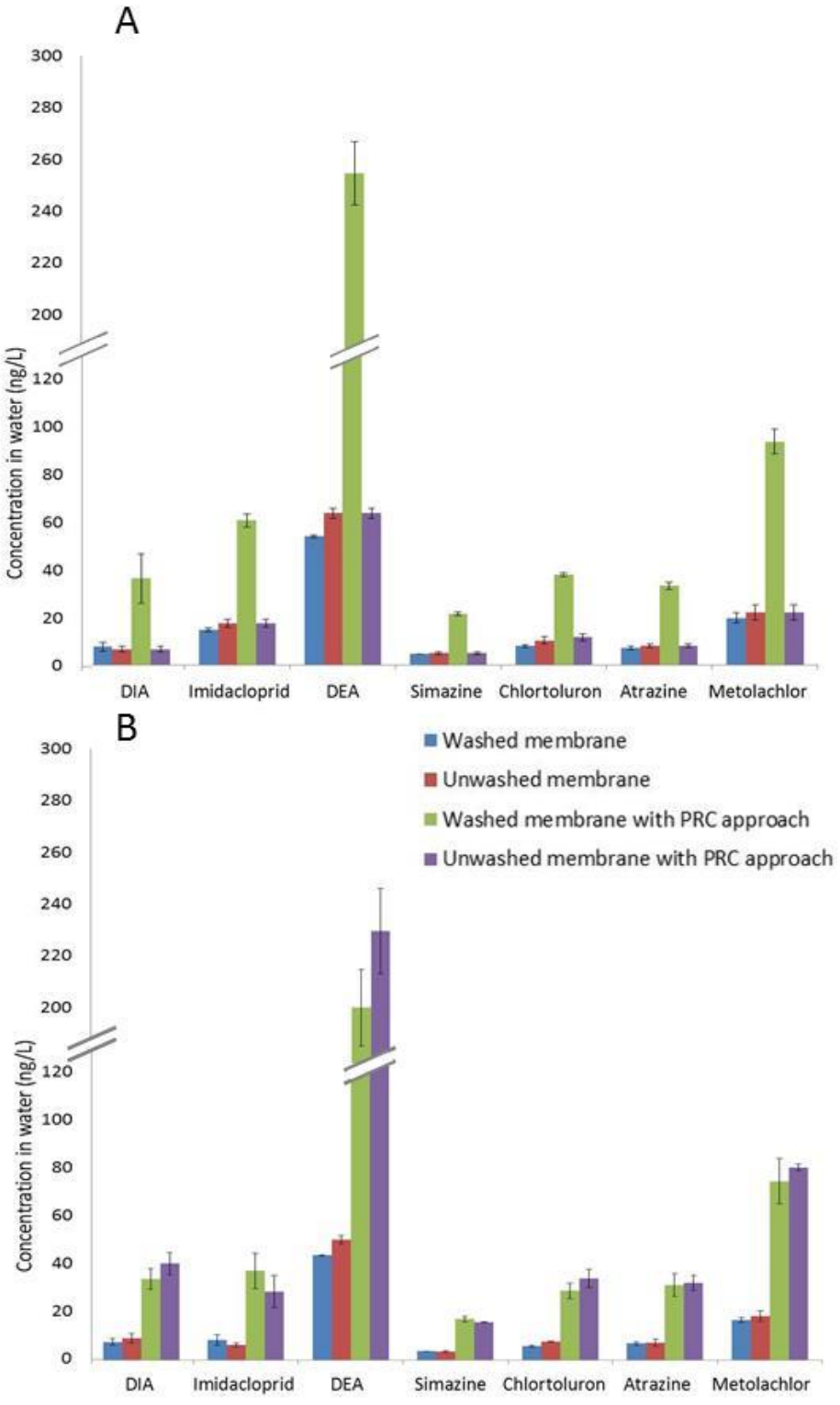

Figure IV.7: Comparison of pesticides concentrations in site 1 determined in different conditions: POCIS extracts diluted 10 times (A) and 25 times (B) with POCIS built with washed and unwashed PES membranes and with or without PRC approach.

CONCLUSION

Analysis of passive sampler extracts by (Q)-TOF detector after chromatographic separation is a powerful tool that allows characterizing some of the molecules responsible for matrix effects, as shown by Guibal et al., (2015b). In the case of POCIS, the primary matrix effect was due to PEG released by PES membranes. A washing procedure consisting of two successive baths with UPW/MeOH (50/50, 140 mL) stirred at 300 rpm, and a final rinse with 140 mL UPW was proposed to limit PEG release (from 52 to 94 % for PEG A and PEG G, respectively). Total ion current chromatograms of extracts from POCIS built with washed PES membranes did not display a significant PEG fingerprint. With a slight extract dilution (10 instead of 25 times for POCIS with unwashed membranes), pesticides at very low concentration can be properly detected and quantified which further improves one of the main passive sampler advantages, i.e. the ability to detect very low concentrations of micropollutants in freshwater. The removal of PEG interference allows correct PRC (DIA-d5) quantification in different dilutions and for the pesticides affected by PEG matrix effects (DEA) during the PEG retention time range and without a strong dilution (10 times is sufficient). For POCIS built with unwashed membrane, extracts needed a larger dilution (25 times for PRC quantification). Washing of PES membranes combined with a 10 times POCIS extract dilution ensured a proper PRC (DIA-d5) quantification which, assuming that use of a PRC minimizes environmental effects on Rs, improved the TWAC of pesticides after POCIS field deployment.

ACKNOWLEDGEMENTS

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IV.3. IV.C. Publication "Measuring POCIS sampling rates (Rs) of 44 pharmaceuticals in lab-scale artificial river with various flow conditions: proposition of mathematical equation to estimate pharmaceuticals Rs".

Cette section est constituée d'une version adaptée d'un article soumis dans la revue « Environmental Toxicology and Chemistry » et en cours de révision suite au processus de reviewing du journal, où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

Measuring POCIS sampling rates (Rs) of 44 pharmaceuticals in lab-scale artificial river with various flow conditions: proposition of mathematical equation to estimate pharmaceuticals Rs

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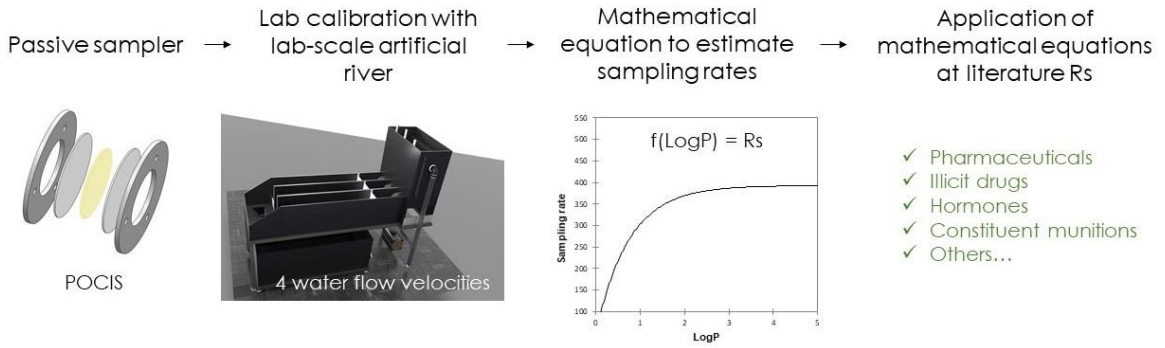
ABSTRACT

This study set out to use the POCIS laboratory calibration to estimate the sampling rates (Rs) of 44 pharmaceuticals. Calibration was performed at 16.0°C ± 1.5 for 4 water flow velocities (0, 2-3, 6-7 and 20 cm/s) in a tank and a lab-scale artificial river filled with 200 and 500 L of tap water spiked with 0.5 µg/L of each compound. Twelve new Rs and 26 Rs already available in the literature were determined, whereas 6 of the pharmaceuticals showed no adsorption on the HLB phase of the POCIS device.

An increase in the Rs with flow velocity was noticed, which is consistent with the decrease in the water boundary layer at the surface of the POCIS membrane. A non-linear relationship between LogP and pharmaceutical sampling rates was observed, and a mathematical equation was proposed to estimate Rs for pharmaceuticals with LogPs ranging from 0 to 5. The accuracy of the mathematical equation was investigated by comparison between calculated Rs and Rs from the literature measured in conditions similar to those in this study on different types of compounds (pharmaceuticals, illicit drugs, hormones, munition constituents and miscellaneous compounds). For approximately 90% of the compounds tested, mathematical equations can estimate an Rs based on LogP by less than a factor of 3, which remains consistent with the semi-quantitative use of POCIS.

GRAPHICAL ABSTRACT



Keywords: POCIS, sampling rate, flow velocity, pharmaceuticals, estimation equation for Rs

INTRODUCTION

Monitoring of organic micropollutants in aquatic environments is performed worldwide. To address the regulation rules via environmental monitoring programs, grab sampling is the most conventional method. However, contamination evolves over time, and this temporal variation in concentrations is not always detected with spot sampling (Guibal et al. 2017b). To overcome this problem, passive samplers have been developed. Passive samplers are deployed from a few days to many weeks in aquatic bodies to determine the time-weighted average concentration (TWAC) of targeted micropollutants. Of all the passive samplers, the Polar Organic Chemical Integrative Sampler (POCIS) has been developed to monitor contamination by semi-polar compounds with LogP values ranging from 0 to 4, such as pesticides, pharmaceuticals and personal care products, in freshwater (Alvarez et al. 2004). Nevertheless, few compounds with lower or higher LogP values can also be sampled by POCIS (Ahrens et al. 2015, Lissalde et al. 2011, Morin et al. 2013, Thomatou et al. 2011).

To determine the TWAC, passive samplers need to be calibrated under controlled exposure concentrations of compounds (Vrana et al. 2005) and sampling rates (Rs) need to be determined. Rs are specific to each compound and are influenced by environmental conditions (*e.g.,* pH, temperature, fouling…) but water flow velocity is often assumed to be the more important parameter to consider (Alvarez et al. 2004, Bailly et al. 2013, Bartelt-Hunt et al. 2011, Harman et al. 2009, Li et al. 2010a, Togola and Budzinski 2007). In the literature, Rs calibrations were sometimes performed *in situ* (Harman et al. 2011b, Ibrahim et al. 2013, Jacquet et al. 2012, Mazzella et al. 2010, Zhang et al. 2008), but this required a labourious experimental procedure. Thus, Rs determinations were made mainly at lab-scale because of the ease of implementation. Calibration experiments varied in a wide range of conditions and sometimes in remote environmental conditions: compound concentrations (from 10 to 10 000 ng/L), different matrixes (*e.g.,* wastewater, tap water, ultrapure water…), temperature and agitation modes to induce a water flow velocity (*e.g.,* magnetic, flow system, quiescent…) and design and volumes of the lab-scale pilot. Indeed, for example, calibrations can be performed in a beaker filled with 1 L (Alvarez et al. 2004, Arditsoglou and Voutsa 2008, Charlestra et al. 2012, Jones-Lepp et al. 2004, Kohoutek et al. 2010, Matthiessen et al. 2006, Thomatou et al. 2011), 1.5 L (Rujiralai et al. 2011), 2 L (Bartelt-Hunt et al. 2011, Martinez Bueno et al. 2009), 3 L (Amdany et al. 2014), or 4.5 L (Magi et al. 2018) of water, a small tank filled with 2 L (Togola and Budzinski 2007), 3 L (Bayen et al. 2014, Li et al. 2010a, MacLeod et al. 2007, Martinez Bueno et al. 2016, Metcalfe et al. 2014, Miller et al. 2016), 7 L (Di Carro et al. 2014), 10 L (Alvarez et al. 2007), 20 L (Bailly et al. 2013, Hernando et al. 2005, Toteu Djomte et al. 2018), 26 L (Vallejo et al. 2013), 27 L (Belles et al. 2014b), 30 L (Zhang et al. 2008), 50 L (Morin et al. 2013), 80 L (Fauvelle et al. 2012, Lissalde et al. 2011, Mazzella et al. 2007, Poulier et al. 2015), 95 L (Ahrens et al. 2015), 250 L (Belles et al. 2014a), 300 L (Harman et al. 2008), or 1 400 L (Kaserzon et al. 2014) of water or more rarely in lab-scale pilots with channels with a large volume of water, such as 120 L (Li et al. 2010b), 480 L (Vermeirssen et al. 2012), or 113 000 L (Lotufo et al. 2018).

It is widely recognized that the Rs factor in the literature can vary. A table including Rs values available in the literature for pharmaceuticals studied in our work is presented in **Annexe 2**. The factor of Rs variation

ranges from 2 to 200. For example, for ketoprofen, 22 Rs values are available with values varying by a factor of 1 to 30 (from 8 (Magi et al. 2018) to 243 (Bailly et al. 2013) mL/d – see **Annexe 2**). With the uncertainty associated with Rs, POCIS can be used as a semi-quantitative tool. When the Rs selected is assumed to be representative of the conditions of rivers where the TWAC of targeted compounds is calculated, Poulier et al. (2014) assumed an error range for the TWAC of a factor of 2.

As previously shown, Rs must be experimentally determined and there are no standardized conditions. To overcome this, some authors investigated the possibility to predict Rs values from physicochemical characteristics of compounds. For pesticides, very few relationships were proposed. Only Alvarez et al. (2007), Mazzella et al. (2007) and Thomatou et al. (2011b) proposed a relationship between Rs and LogP. The first two proposed a Gaussian model (without giving the equation) and the last authors proposed a third-order polynomial function. In contrast, for pharmaceuticals or healthcare products, Alvarez et al. (2007), MacLeod et al. (2007), Togola et al. (2007) and Li et al. (2010a) proposed a relationship between Rs and LogP. Alvarez et al. (2007) suggested the same Gaussian model without any difference between pesticides and pharmaceuticals. MacLeod et al. (2007) also proposed a Gaussian model (without giving the equation). For Togola et al. (2007) and Li et al. (2010a), a linear relationship can be established between pharmaceutical Rs and LogP. Miller et al. (2016) used a more complex modelling approach with artificial neural networks with two models developed in the area of genetic and chromatographic retention using 24 and 15 descriptors, respectively, to predict with more or less success the Rs values for pesticides, endocrine disrupting compounds and pharmaceuticals. To conclude, the type of relationship between Rs and physicochemical parameters of compounds from the literature, mainly LogP, varied in a wide range, perhaps due to experimental conditions where Rs values were measured.

The aim of this study is to determine the POCIS sampling rates (Rs) of 44 pharmaceuticals in conditions as close as possible to environmental conditions using a lab-scale artificial river with different water flow velocities, a temperature of 16°C and a low concentration of compounds (500 ng/L). Laboratory experiments to estimate sampling rates are very expensive in terms of time and money, hence the importance of being able to predict the sampling rate by a mathematical equation. According to flow velocity (range from 2 to 20 cm/s), mathematical equations are proposed to estimate Rs values for compounds with $0 < \text{LogP} < 5$. Mathematical equations are tested and discussed with reference to the literature Rs values.

MATERIALS AND METHODS

Materials and reagents

Ultrapure water (UPW) was produced by a Gradient A10 Milli-Q system from Millipore. All solvents were LC-MS grade. Methanol (MeOH) and ethyl acetate were purchased from Carlo Erba. Formic acid and ammonium formate, reagents added in LC eluents, were obtained from Carlo Erba and Scharlau, respectively. Pharmaceuticals were purchased from HPC (18), Sigma Aldrich (11), Dr. Ehrenstorfer GmbH (9) and Santa Cruz (5) with purities higher than 91%. The characteristics of the pharmaceuticals are presented in **Table IV.5**. A stock pharmaceutical solution, a working solution (containing all pharmaceuticals) and internal standard solution (list of internal standards is presented in **Table IV.6**) were prepared in methanol at concentrations of 100, 1 and 10 mg/L, respectively, and stored at – 18 °C.

Instrumental analysis

All POCIS extracts and water samples were analysed with an HPLC Infinity 1290 from Agilent coupled with a Q-ToF 6540 from Agilent equipped with an Agilent Jet Stream electrospray ionization source (ESI). Liquid chromatographic separation was performed with an RP18+ Nucleoshell column from Macherey-Nagel and with an analytical gradient of 16 min. Eluents were UPW and methanol (with 5 mM ammonium formate and 0.1% acid formic for both eluents) (the linear gradient is presented in **Table IV.7A**). The injected sample volume was 5 µL. Autosampler and column temperatures were maintained at 4°C and 30°C, respectively. Optimized parameters of the HPLC-Q-ToF method are presented in **Table IV.7B**. Characteristics of the pharmaceuticals after HPLC separation and mass detection (retention time, internal standard…) are presented in **Table IV.6**. Mass acquisition was operated in the "all-ions" positive mode (collision energies: 0, 10, 20 and 40 V). The analytical method was validated following the French norm (NF T90-210 (AFNOR 2009)) and the results are presented in **Table IV.8**. QA/QC was used to control any deviations during analysis. Details of the analytical procedure were previously developed and described in Guibal et al. (2015b) and Guibal et al. (2018).

Table IV.5: Action classes and characteristics of the studied pharmaceuticals.

Pharmaceutical	Action class	Purity	CAS	Chemical formula	LogP
Atenolol	β-blocker	99.3	29122-68-7	$C_{14}H_{22}N_2O_3$	0.43
Bezafibrate	Anti-cholesterol	99.6	41859-67-0	$C_{19}H_{20}ClNO_4$	3.99
Bisprolol	β-blocker	98.1	66722-44-9	$C_{18}H_{31}NO_4$	2.20
Caffeine	Human Tracer	98.5	58-08-2	$C_8H_{10}N_4O_2$	-0.55
Carbamazepine	Antibiotic	99.5	298-46-4	$C_{15}H_{12}N_2O$	2.77
Clarythromycin	Antibiotic	99.4	81103-11-9	$C_{38}H_{69}NO_{13}$	3.24
Dexamethasone	Anti-inflammatory	98.0	50-02-2	$C_{22}H_{29}FO_5$	1.68
Diclofenac	Anti-inflammatory	99.5	15307-86-5	$C_{14}H_{11}Cl_2NO_2$	4.26
Econazole	Anti-fungal	99.9	27220-47-9	$C_{18}H_{15}Cl_3N_2O$	5.35
Erythromycin	Antibiotic	97.0	114-07-8	$C_{37}H_{67}NO_{13}$	2.60
Fenbendazole	Antiparasitic	99.5	43210-67-9	$C_{15}H_{13}N_3O_2S$	3.41
Fenofibrate	Anti-cholesterol	99.9	49562-28-9	$C_{20}H_{21}ClO_4$	5.28
Flunixin	Anti-inflammatory	99.9	38677-85-9	$C_{14}H_{11}F_3N_2O_2$	3.69
Fluoxetine	Psychotropic	99.8	59333-67-4	$C_{17}H_{18}F_3NO$	4.17
Gemfibrozil	Anti-cholesterol	99.0	25812-30-0	$C_{15}H_{22}O_3$	4.39
Griseofulvin	Anti-fungal	97.4	126-07-8	$C_{17}H_{17}ClO_6$	2.17
Indomethacin	Anti-inflammatory	99.9	53-86-1	$C_{19}H_{16}ClNO_4$	3.53
Ketoprofen	Anti-inflammatory	99.1	22071-15-4	$C_{16}H_{14}O_3$	3.61
Lincomycin	Antibiotic	99.0	154-21-2	$C_{18}H_{34}N_2O_6S$	-0.32
Metformin	Anti-diabetic	98.2	1115-70-4	$C_4H_{11}N_5$	-0.92
Metoprolol	β-blocker	99.8	56392-17-7	$C_{15}H_{25}NO_3$	1.76
Metronidazole	Antibiotic	99.3	443-48-1	$C_6H_9N_3O_3$	-0.46
Monensin	Antibiotic	98.8	22373-78-0	$C_{36}H_{62}O_{11}$	4.82
Nadolol	β-blocker	99.1	42200-33-9	$C_{17}H_{27}NO_4$	0.87
Omeprazole	Proton Inhibitor	99.9	73590-58-6	$C_{17}H_{19}N_3O_3S$	2.43
Paraxanthine	Metabolite caffeine	99.0	611-59-6	$C_7H_8N_4O_2$	0.24
Paroxetine	Psychotropic	98.3	110429-35-1	$C_{19}H_{20}FNO_3$	3.15
Perindopril	β-blocker	97.0	107133-36-8	$C_{19}H_{32}N_2O_5$	0.63
Praziquantel	Antiparasitic	99.7	55268-74-1	$C_{19}H_{24}N_2O_2$	2.30
Prednisolone	Anti-inflammatory	99.4	50-24-8	$C_{21}H_{28}O_5$	1.27
Propanolol	β-blocker	99.9	318-98-9	$C_{16}H_{21}NO_2$	2.58
Pyrantel	Antiparasitic	95.1	22204-24-6	$C_{11}H_{14}N_2S$	1.96
Roxithromycin	Antibiotic	91.7	80214-83-1	$C_{41}H_{76}N_2O_{15}$	3.00
Salbutamol	Anti-asthma	99.5	51022-70-9	$C_{13}H_{21}NO_3$	0.34
Sotalol	β-blocker	98.5	959-24-0	$C_{12}H_{20}N_2O_3S$	-0.40
Sucralose	Human Tracer	99.0	56038-13-2	$C_{12}H_{19}Cl_3O_8$	-0.47
Sulfadiazine	Antibiotic	99.3	68-35-9	$C_{10}H_{10}N_4O_2S$	0.39
Sulfamerazine	Antibiotic	99.8	127-79-7	$C_{11}H_{12}N_4O_2S$	0.52
Sulfamethoxazole	Antibiotic	99.9	723-46-6	$C_{10}H_{11}N_3O_3S$	0.79
Sulfamethoxypyridazine	Antibiotic	99.0	80-35-3	$C_{11}H_{12}N_4O_3S$	0.47
Terbutaline	Anti-asthma	99.0	23031-32-5	$C_{12}H_{19}NO_3$	0.44
Thioridazine	Psychotropic	99.9	50-52-2	$C_{21}H_{26}N_2S_2$	5.47
Triclabendazole	Antiparasitic	99.8	68786-66-3	$C_{14}H_9Cl_3N_2OS$	5.88
Trimethoprim	Antibiotic	99.5	738-70-5	$C_{14}H_{18}N_4O_3$	1.28

Table IV.6: Pharmaceutical characteristics after HPLC separation and mass detection.

Pharmaceutical	Retention time (min)	Mass (Da)	Internal standard
Atenolol	2.32	266.1630	Salbutamol-d3
Bezafibrate	8.33	361.1081	Flunixin-d3
Bisprolol	7.15	325.2253	Propanolol-d3
Caffeine	5.05	194.0804	Caffeine-c3
Carbamazepine	7.70	236.0950	Carbamazepine-d10
Clarythromycin	8.15	747.4769	Flunixin-d3
Dexamethasone	8.05	392.1999	Carbamazepine-d10
Diclofenac	9.07	295.0167	Diclofenac-d4
Econazole	8.57	380.0250	Triclabendazole-d3
Erythromycin	7.81	733.4612	Carbamazepine-d10
Fenbendazole	8.54	299.0729	Triclabendazole-d3
Fenofibrate	10.88	360.1128	Triclabendazole-d3
Flunixin	8.71	296.0773	Flunixin-d3
Fluoxetine	7.88	309.1341	Carbamazepine-d10
Gemfibrozil	10.20	250.1569	Triclabendazole-d3
Griseofulvin	7.84	352.0714	Carbamazepine-d10
Indomethacin	9.20	357.0768	Diclofenac-d4
Ketoprofen	8.08	254.0943	Diclofenac-d4
Lincomycin	4.30	406.2138	Trimethoprim-d3
Metformin	0.60	129.1015	Salbutamol-d3
Metoprolol	6.52	267.1834	Carbamazepine-d10
Metronidazole	2.25	171.0644	Triclabendazole-d3
Monensin	13.71	670.4292	Triclabendazole-d3
Nadolol	5.62	309.1940	Sulfamethoxazole-d4
Omeprazole	7.51	345.1147	Carbamazepine-d10
Paraxanthine	3.48	180.0647	Caffeine-c3
Paroxetine	6.69	329.1427	Carbamazepine-d10
Perindopril	7.60	368.2311	Carbamazepine-d10
Praziquantel	8.35	312.1838	Flunixin-d3
Prednisolone	7.81	360.1937	Carbamazepine-d10
Propanolol	7.30	259.1572	Propanolol-d3
Pyrantel	4.51	206.0878	Trimethoprim-d3
Roxithromycin	8.22	836.5246	Flunixin-d3
Salbutamol	2.16	239.1521	Salbutamol-d3
Sotalol	1.68	272.1195	Salbutamol-d3
Sucralose	5.72	396.0146	Caffeine-c3
Sulfadiazine	2.39	250.0525	Sulfamethoxazole-d4
Sulfamerazine	3.60	264.0681	Sulfamethoxazole-d4
Sulfamethoxazole	5.86	253.0521	Sulfamethoxazole-d4
Sulfamethoxypyridazine	5.24	280.0630	Sulfamethoxazole-d4
Terbutaline	2.13	225.1365	Salbutamol-d3
Thioridazine	8.24	370.1537	Flunixin-d3
Triclabendazole	10.05	357.9501	Triclabendazole-d3
Trimethoprim	4.75	290.1379	Trimethoprim-d3

Table IV.7: Optimized parameters of the HPLC-Q-ToF method. a: Linear gradient used for the chromatographic separation and b: Q-ToF operational parameters in positive ESI ion mode (*optimized source parameters).

A	Time (min)	UPW + 5mM ammonium formate and 0.1% formic acid (%)	MeOH + 5mM ammonium formate and 0.1% formic acid (%)	Flow (µL/min)
	0	90	10	0.4
	1	90	10	0.4
	5	75	25	0.4
	7	30	70	0.4
	13	10	90	0.4
	16	10	90	0.4

B	Parameter	Value
	Sheath gas temperature*	300°C
	Sheath gas flow*	12 mL/min
	Drying gas temperature*	100°C
	Drying gas flow*	7 mL/min
	Fragmentor voltage*	130 V
	Nebulizer pressure*	35 psi
	Capillary voltage	3500 V
	Skimmer voltage*	65 V
	Mass range	100 – 1500 m/z
	Reference mass	922.0098 Da
	Octopole 1 RF*	750 V
	Nozzle voltage *	300 V

Table IV.8: Analytical validation results (*accuracy for pyrantel were measure for 9.4 and 37.4 µg/L).

Pharmaceutical	Linearity		Instrumental LOQ (µg/L)	Accuracy (%)	
	Equation	r^2		25 µg/L	100 µg/L
Atenolol	y=0.0304x	0.974	0.1	✓	✓
Bezafibrate	y=0.0002x	0.982	0.5	✓	✓
Bisprolol	y=0.0122x	0.994	0.1	✓	✓
Caffeine	y=0.0102x	0.997	0.2	✓	✓
Carbamazepine	y=0.0102x	0.991	0.2	✓	✓
Clarythromycin	y=0.0031x	0.952	0.1	✓	✓
Dexamethasone	y=0.0016x	0.908	0.2	✓	✓
Diclofenac	y=0.0100x	0.993	2.0	✓	✓
Econazole	y=0.0029	0.993	0.1	✓	✓
Erythromycin	y=0.0043x	0.942	0.2	✓	✓
Fenbendazole	y=0.0097	0.983	0.1	✓	✓
Fenofibrate	y=0.0110	0.950	0.1	✓	✓
Flunixin	y=0.0080x	0.977	0.1	✓	✓
Fluoxetine	y=0.0056x	0.985	0.2	✓	✓
Gemfibrozil	y=1.0052x	0.998	5.0	✓	✓
Griseofulvin	y=0.0049x	0.987	0.1	✓	✓
Indomethacin	y=0.0123x	0.967	2.0	✓	✓
Ketoprofen	y=0.0648x	0.990	0.5	✓	✓
Lincomycin	y=0.0030x	0.996	0.1	✓	✓
Metformin	y=0.0197	0.949	0.5	✓	✓
Metoprolol	y=0.3050x	0.779	0.1	✓	✓
Metronidazole	y=0.0045x	0.932	0.2	✓	✓
Monensin	y=0.0112x	0.904	1.0	✓	✓
Nadolol	y=0.0695x	0.997	0.2	✓	✓
Omeprazole	y=0.0029x	0.924	0.1	✓	✓
Paraxanthine	y=0.0040x	0.970	0.5	✓	✓
Paroxetine	y=0.0102x	0.978	0.1	✓	✓
Perindopril	y=0.0057x	0.979	0.1	✓	✓
Praziquantel	y=0.0023x	0.949	0.1	✓	✓
Prednisolone	y=0.0014x	0.917	1.0	✓	✓
Propanolol	y=0.0118x	0.977	0.5	✓	✓
Pyrantel*	y=0.0045x	0.971	0.08	✓	✓
Roxithromycin	y=0.0009x	0.963	0.5	✓	✓
Salbutamol	y=0.0118x	0.994	0.2	✓	✓
Sotalol	y=0.0123x	0.996	0.2	✓	✓
Sucralose	y=0.0012x	0.828	1.0	✓	✓
Sulfadiazine	y=0.0128	0.984	0.1	✓	✓
Sulfamerazine	y=0.0175x	0.988	0.1	✓	✓
Sulfamethoxazole	y=0.0127x	0.993	0.2	✓	✓
Sulfamethoxypyridazine	y=0.0183x	0.991	0.2	✓	✓
Terbutaline	y=0.0126x	0.988	0.1	✓	✓
Thioridazine	y=0.0056	0.979	0.1	✓	✓
Triclabendazole	y=0.0119	0.969	0.2	✓	✓
Trimethoprim	y=0.0106	0.987	0.2	✓	✓

Lab-scale pilot characteristics – POCIS calibration experiment

The POCIS calibration experiment was performed at a temperature of 16,0°C ± 1.5 with two lab-scale pilots filled with tap water from Limoges city (the main physicochemical characteristics of tap water are shown in **Table IV.9**) in an artificial river and in tanks with total volumes of 500 L and 200 L, respectively. Each of the 3 channels (width = 20.3 cm and length = 152 cm) of the artificial river could perform experiments with different flow velocities thanks to the water stock tank of 500 L, a gate system and a pump (flow rate = 13 m^3/h) (**Figure IV.8**).

The tap water from the two lab-scale pilots was spiked with a pharmaceutical cocktail of the 44 compounds at a concentration of 0.5 µg/L. A continuous renewal of 15% of water volume/day of spiked tap water in the 2 lab-scale pilots was performed using a peristaltic pump (Masterflex L/S 7519-10 from Cole-Parmer Instrument Company) for tap water at a flow-rate of 52 and 10 mL/min for the artificial river and for the tanks, respectively, and by a syringe pump (Kd-Scientific) for pharmaceutical spikes at a flow rate of 2.6 µL/min for both lab-scale pilots. The spiking of the stock solution with pharmaceuticals was used at a concentration of 10 and 2 mg/L for the artificial river and for the tanks, respectively.

Table IV.9: Major element composition of the tap water. χ stands for electrical conductivity and DOC for Dissolved Organic Carbon.

	pH	χ µS/cm	DOC mgC/L	Cl^- mg/L	NO_3^- mg/L	SO_4^{2-} mg/L	Na^+ mg/L	K^+ mg/L	Ca^{2+} mg/L	Mg^{2+} mg/L
Tap water	8.3	275	1.0	19.3	3.6	4.3	8.3	1.2	39.0	0.9

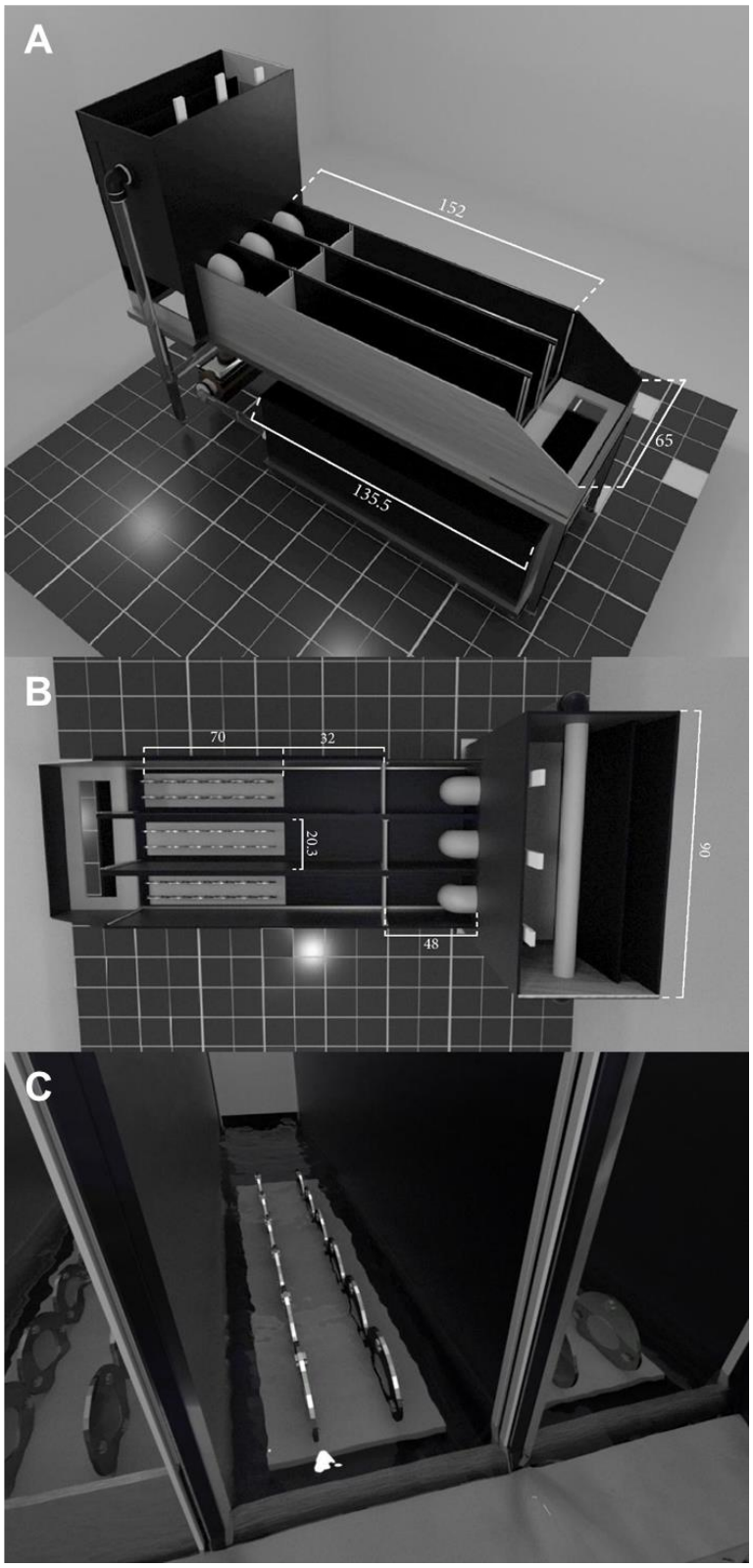


Figure IV.8: Computer image of lab-scale artificial river with dimensions (in cm). A: Three-quarter view; B: top view and C: view of channel.

POCIS deployment and water samples

Before POCIS deployment in the two lab-scale pilots, the concentration of pharmaceuticals was equilibrated for 2 days. Calibration experiments were performed for 21 days. Duplicates of POCIS were exposed for 1, 3, 5, 7, 10, 15 and 21 days. All POCIS were oriented parallel to flow to maintain a steady flow velocity for each POCIS in the river channel. To overcome changing flow conditions, a steady number of POCIS were deployed in each channel using false POCIS (*i.e.,* POCIS without HLB phase) if required (12 POCIS in each channel) (**Figure IV.8C**).

To monitor the concentration evolution of pharmaceuticals in spiked tap water in the storage tanks of the two lab-scale pilots, grab samples (volume 100 mL) were performed in the storage tanks of the 2 lab-scale pilots. Water samples were performed at 0, 3, 5, 7, 10, 12, 14, 17, 19 and 21 days of the experiment (every 2 or 3 days).

Investigation of the flow velocity effect on Rs

Four flow velocities were investigated: 0 (in the tank), 2-3, 7-8 and 20 cm/s (3 channels of the artificial river lab-scale pilot). Flow velocities in artificial river channels were measured with a Marsh-McBirney Flo-Mate 2000 portable velocity flow meter every 2 or 3 days (the same dates as the grab samples) at 2 locations for each channel (orange cross on **Figure IV.8C** – upstream and downstream POCIS).

The temperatures in the tanks and artificial river were measured every 10 min with a Tinytag (TG-4100).

Extraction of pharmaceuticals from spiked water

Pharmaceuticals from water samples were extracted by solid-phase extraction (SPE) with Chromabond® HR-X (60 mg, 3 mL, and 85 µm) purchased from Macherey-Nagel using an automated SPE GX-241 system from Gilson. The SPE step details were described in a previous work (Guibal et al. 2017b). Briefly, 100 mL of water samples were filtered, the pH was adjusted to 7, and then 10 µL surrogates (simazine-d5, monuron-d6 and prometryn-d6) were added to the water sample, which was passed through the cartridge. Cartridges were pre-conditioned with 5 mL of methanol then 5 mL of UPW. Cartridges were dried and stored at -18°C before elution.

POCIS preparation

The receiving phase, 200 mg of Oasis® HLB, was enclosed within two polyethersulfone membranes (PES). PES membranes, 90 mm diameter and 0.1 µm pore size, were previously washed according to Guibal et al. (2015a) and were purchased from Pall Supor®. All membrane-sorbent-membranes were held by two stainless steel rings.

Pharmaceuticals elution from resin sorbent

The elution of water and POCIS extracts stored in SPE cartridges was performed with 3 mL of methanol followed by 3 mL of a mixture of 75:25 *v:v* methanol:ethyl acetate. An internal standards solution (10 µL at

10 mg/L) was added to water samples. Extracts were evaporated to dryness under nitrogen flow. Water samples and POCIS extracts were reconstituted with 1 mL of 90:10 UPW:methanol and 100 % of methanol, respectively. Then, POCIS extracts were diluted 10-fold and 10 µL of internal standard was added. Before analysis, internal standard and surrogate final concentrations were approximately 100 µg/L.

Calculation of the POCIS sampling rate

POCIS were exposed to spiked tap water, and accumulation into POCIS was assumed to be proportional to the concentration of spiked water. A time-weighted average concentration (called C_w or TWAC) can be calculated, following equation (Alvarez et al. 2004):

$$C_{POCIS} = C_w \times k_u \times t \qquad \textbf{Equation IV.5}$$

where C_{POCIS} is the analyte concentration in the sorbent (µg/g), C_w is the water analyte concentration (µg/L), k_u is the uptake rate (L/g/day) and t is the exposure time (days).

The constant Rs is the analyte sampling rate (compound-dependent) in L/d and can be calculated from k_u:

$$k_u = \frac{Rs}{m_{sorbent}} \qquad \textbf{Equation IV.6}$$

where $m_{sorbent}$ is the sorbent mass in g.

For a relatively long exposure time, the uptake becomes curvilinear and an equilibrium regime can be observed. Many studies have proposed a mathematical model wherein the pollutant concentration in the receiving phase can be described by **Equation IV.7** (Alvarez et al. 2004, Mazzella et al. 2007, Vrana et al. 2005):

$$\frac{C_{POCIS}}{C_w} = K_{HLBw} \times (1 - e^{-ke \times t}) \qquad \textbf{Equation IV.7}$$

where K_{HLBw} the receiving phase-water distribution coefficient and ke is the elimination rate (/d).

Determinations of sampling rates were performed using following equation:

$$y = pr1 \times (1 - e^{-pr2 \times X}) \qquad \textbf{Equation IV.8}$$

where y = $\frac{C_{POCIS}}{C_w}$; pr1 = K_{HLBw} ; $pr2 = ke$ and X = t.

Non-linear and linear regression for Rs plotted with LogP

Non-linear **Equation IV.9** and linear **Equation IV.10** regressions were performed between the LogP and the sampling rates.

$$y = pr1 \times e^{-pr2 \times X} + pr3 \qquad \textbf{Equation IV.9}$$

$$y = pr1 \times X + pr2 \qquad \textbf{Equation IV.10}$$

where y = Rs (mL/d) and X = LogP.

All calculations, statistical analyses, modelling and representations were done with XLStat software.

Determinations of the difference between calculated and experimental values were performed with the following equation:

$$\%_{difference} = \frac{Rs_{experimental} - Rs_{calculated}}{Rs_{experimental}} \times 100 \qquad \textbf{Equation IV.11}$$

where $Rs_{experimental}$ is the sampling rate determined by experimental calibration in this study (in mL/d) and $Rs_{calculated}$ is the sampling rate determined by mathematical regression (**Equation IV.12**, **Equation IV.13**, **Equation IV.14**, **Equation IV.15**, **Equation IV.16** and **Equation IV.17**).

RESULTS AND DISCUSSION.

POCIS sampling rate (Rs) determinations.

The sampling rates and uptake profiles of each pharmaceutical for the four flow velocities investigated over the deployment time are given in **Table IV.10** and **Annexe 3**, respectively.

Sampling rate determination succeeded for 38 compounds out of the 44 investigated. The modelling, using equation (4), fitted the experimental data with a range from $r^2 = 0.566$ to 0.995 (adj. $r^2 > 0.90$ for 32, 33, 30 and 35 compounds (out of 38 compounds) for flow velocities V_0, V_1, V_2 and V_3, respectively). The range (mean) of calculated Rs values was 40 – 218 (80), 63 – 375 (206), 62 – 408 (227) and 75 – 539 (309) mL/d for flow velocities V_0, V_1, V_2 and V_3, respectively, and was in the same order as the Rs values available in the literature (Ahrens et al. 2015, Alvarez et al. 2007, Alvarez et al. 2004, Lissalde et al. 2011, Martinez Bueno et al. 2016, Mazzella et al. 2007, Metcalfe et al. 2014, Vermeirssen et al. 2012, Vrana et al. 2005). Uptake experiments to measure the sampling rate were conducted by several authors, but it is difficult to accurately compare sampling rates obtained in this study with those in the literature. Indeed, each POCIS calibration was conducted using different exposure systems. Often, water flow velocity in front of POCIS was measured with difficulty and uncertainty, mainly when an orbital shaker or a magnetic stirrer was used for water agitation. Moreover, for uptake experiments, POCIS were exposed perpendicularly to water flow. In this study, POCIS were exposed parallel to water flow (**Figure IV.8C**) to maintain a steady flow velocity for each POCIS. These differences (positioning, water flow velocity, temperature, fouling…) can affect Rs experimental values (Alvarez et al. 2007, Harman et al. 2009, Li et al. 2010a, Togola and Budzinski 2007) by a factor of 2 to 200. This was also supported by a summary of the data from the literature presented in **Annexe 2**.

This study determined new sampling rates for 12 pharmaceuticals (not available in the literature – in green in **Table IV.10**): dexamethasone, flunixin, griseofulvin, indomethacin, metronidazole, paraxanthine, perindopril, praziquantel, pyrantel, salbutamol, sulfadiazine and sulfamethoxypyridazine.

Whatever the flow velocity, the sampling rates for 6 pharmaceuticals were not determined (in red in **Table IV.10**): econazole, fenbendazole, fenofibrate, metformin, thioridazine and triclabendazole. These compounds showed zero accumulation in POCIS. For these compounds, no Rs and no information about attempts of POCIS calibration were available in the literature except for metformin, where no adsorption on Oasis® HLB (Bauerlein et al. 2012) or in POCIS (MacLeod et al. 2007) was observed. For metformin (LogP = -0.92), the results were consistent with the sampling ability of POCIS, even if few compounds with LogP < 0 (*e.g.,* caffeine, lincomycin, metronidazole and sotalol) can be sampled (Alvarez et al. 2007, Bartelt-Hunt et al. 2011, Morin et al. 2013). Indeed, POCIS was assumed to sample only compounds with 0 < LogP < 4 (Alvarez et al. 2004) or 0 < LogP < 5 (Ahrens et al. 2015, Lissalde et al. 2011). The hydrophobicity of econazole, fenofibrate, thioridazine and triclabendazole, with LogP values higher than 5 can also be hypothesized to explain their lack of sampling by POCIS. Fenbendazole was not sampled by POCIS despite a hydrophobicity (LogP = 3.41) that should have allowed for sampling by POCIS from a theoretical point of view. To explain the non-sampling of fenbendazole by POCIS, we can assume that interactions with the

Oasis® HLB phase are too weak to bind this compound on the lipophilic or hydrophilic sites of the Oasis® HLB. This assumption is consistent with the work of Islam et al. (2013), which achieved successful extraction of modified fenbendazole, *i.e.,* fenbendazole sulfoxide (oxfendazole, LogP = 1.63) and fenbendazole sulfone (LogP = 2.3), with the Oasis® HLB. Regarding the 3D compound configuration and hydrophilic properties of sulfoxide or sulfone moieties, interactions with hydrophilic sites of Oasis® HLB can occur, which is not possible with the single S of fenbendazole. Moreover, the application notes from Waters (Waters 2017) recommends another type of phase (Oasis® PRiME HLB) to extract fenbendazole with efficiency from food.

Table IV.10: Sampling rates (mL/d) for the 4 flow velocities. Rs_0, Rs_1, Rs_2 and Rs_3 obtained for V_0, V_1, V_2 and V_3, respectively. In green, new Rs values (not available in the literature) and in red, (*n.c.* not calculable) values not sampled by POCIS.

Compound	LogP	Rs_0 (V_0 = 0 cm/s)	Rs_1 (V_1 = 2-3 cm/s)	Rs_2 (V_2 = 6-7 cm/s)	Rs_3 (V_3 = 20 cm/s)
Atenolol	0.43	53	145	146	228
Bezafibrate	3.99	63	216	254	276
Bisprolol	2.20	58	180	200	278
Caffeine	-0.55	63	155	170	263
Carbamazepine	2.77	87	290	299	443
Clarythromycin	3.24	150	277	311	351
Dexamethasone	1.68	154	297	304	388
Diclofenac	4.26	75	241	239	334
Econazole	5.35	*n.c.*	*n.c.*	*n.c.*	*n.c.*
Erythromycin	2.60	91	270	266	379
Fenbendazole	3.41	*n.c.*	*n.c.*	*n.c.*	*n.c.*
Fenofibrate	5.28	*n.c.*	*n.c.*	*n.c.*	*n.c.*
Flunixin	3.69	72	273	323	450
Fluoxetine	4.17	91	281	408	514
Gemfibrozil	4.39	115	287	230	377
Griseofulvin	2.17	59	231	250	347
Indomethacin	3.53	75	268	284	365
Ketoprofen	3.61	111	213	222	313
Lincomycin	-0.32	67	207	208	307
Metformin	-0.92	*n.c.*	*n.c.*	*n.c.*	*n.c.*
Metoprolol	1.76	69	228	232	346
Metronidazole	-0.46	89	276	316	462
Monensin	4.82	67	92	119	101
Nadolol	0.87	89	223	193	313
Omeprazole	2.43	*n.c.*	63	62	75
Paraxanthine	0.24	43	107	230	246
Paroxetine	3.15	42	163	266	371
Perindopril	0.63	66	178	170	273
Praziquantel	2.30	65	277	341	422
Prednisolone	1.27	148	268	289	383
Propranolol	2.58	70	249	265	392
Pyrantel	1.96	105	341	328	539
Roxithromycin	3.00	218	375	405	404
Salbutamol	0.34	57	109	103	157
Sotalol	-0.40	58	150	161	231
Sucralose	-0.47	42	142	156	220
Sulfadiazine	0.39	49	89	149	202
Sulfamerazine	0.52	69	130	161	175
Sulfamethoxazole	0.79	53	96	119	154
Sulfamethoxypyridazine	0.47	63	146	162	207

Terbutalin	0.44	40	68	64	103
Thioridazine	5.47	*n.c.*	*n.c.*	*n.c.*	*n.c.*
Triclabendazole	5.88	*n.c.*	*n.c.*	*n.c.*	*n.c.*
Trimethoprim	1.28	74	238	238	350

Effect of the flow velocity on Rs.

Accumulation of pharmaceuticals in POCIS was tested for four flow velocities (0, 2-3, 6-7 and 20 cm/s), and the results are displayed in **Table IV.10** and **Annexe 3**. Water flow velocity in the range investigated (0 – 20 cm/s) induced an increase of the pharmaceutical sampling rates. A greater increase in Rs was observed between flow velocities V_0-V_1 (**Figure IV.9**), on average Rs increase by a factor 3 between stagnant (V_0) and flow condition V_1. For Toteu Djomte et al. (2018), Rs increase by a factor 2 to 5 between stagnant and flow conditions. For these same authors (Toteu Djomte et al. 2018) pesticide Rs were constant over the range of velocities between 6-21 cm/s. The same observation was obtained in our study where pharmaceuticals Rs slightly increase between flow velocities 6-7 and 20 cm/s by an average factor of 1.4. This sampling rate increase was due to a decrease in the thickness of the water boundary layer at the vicinity of the POCIS membrane with an increase of flow velocity. This observation is currently well known and has been discussed for different types of passive samplers (DGT (Buzier et al. 2014, Garmo et al. 2006, Uher et al. 2013), SPMD (Booij et al. 1998, Huckins et al. 2006, Vrana and Schuurmann 2002), Chemcatcher (Kingston et al. 2000, Lissalde et al. 2016, Lobpreis et al. 2008), and POCIS (Alvarez et al. 2004, Charlestra et al. 2012, Harman et al. 2012, Li et al. 2010b).

Table IV.11 shows the determination coefficients between sampling rates obtained at the 4 water flow velocities (linear correlations are presented in **Figure IV.9**). No correlations between Rs values obtained for quiescent (flow velocity = 0 cm/s) and other flow velocities were observed. In contrast, linear correlations between Rs values obtained for V_1, V_2 and V_3 were observed. For these three water flow velocities, uptake rates were less controlled by the water boundary layer than in the first flow velocity (V_0 – 0 cm/s). In this case, uptake rates could be controlled by mass transfer (diffusion through PES membranes), whereas for V_0, adsorption could be mostly controlled by the water boundary layer, and other parameters were negligible (such as sorption on the receiving phase or mass transfer) (Belles et al. 2014a, Booij et al. 2017, Kaserzon et al. 2014).

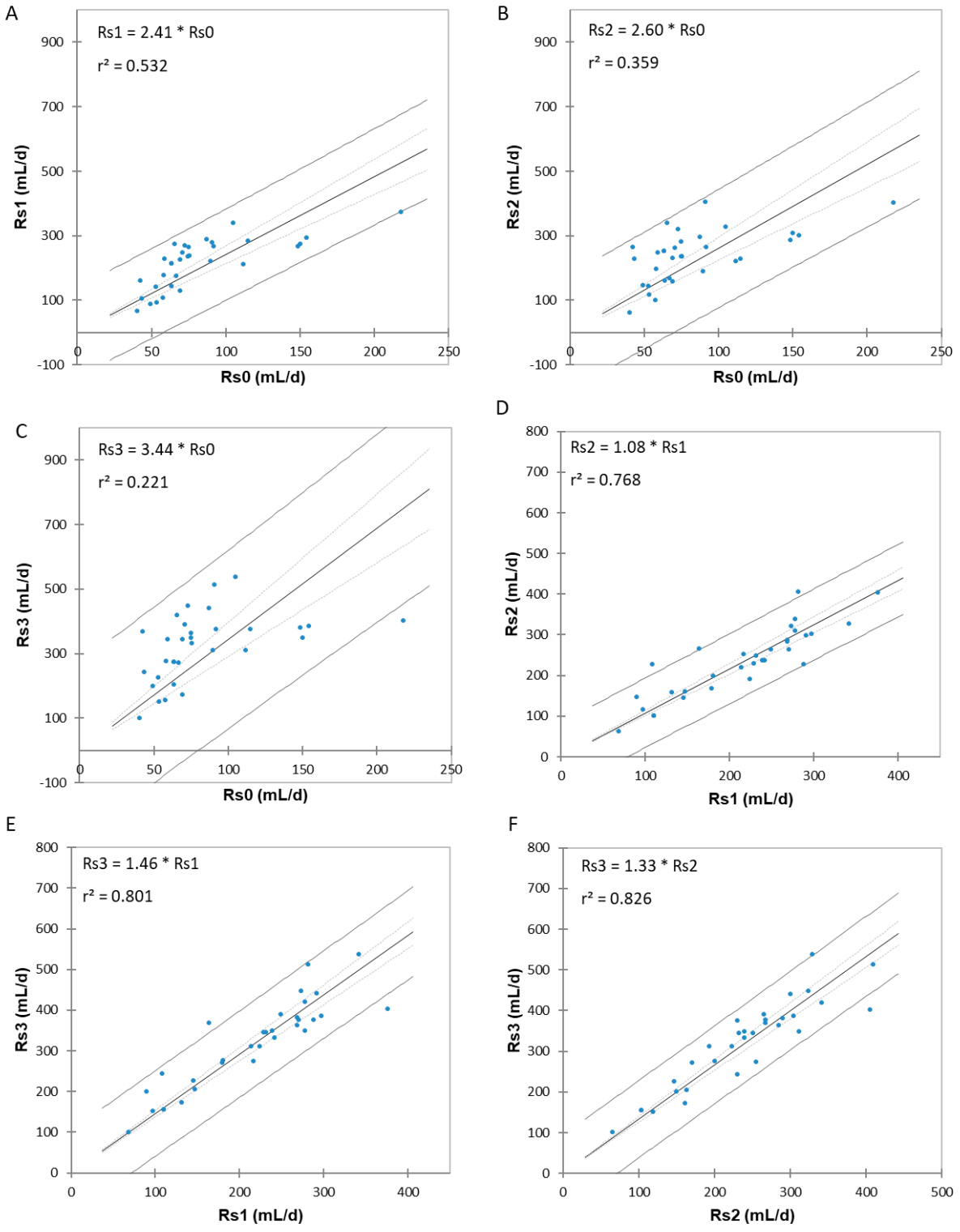


Figure IV.9: Linear correlation between sampling rates obtained at different water flow velocities. A: Rs_1 versus Rs_0 ; B: Rs_2 versus Rs_0 ; C: Rs_3 versus Rs_0 ; D: Rs_2 versus Rs_1 ; E : Rs_3 versus Rs_1 ; F: Rs_3 versus Rs_2.

Table IV.11: Coefficient of determination (r^2) between sampling rates obtained at different flow velocities (Rs_0, Rs_1, Rs_2 and Rs_3 obtained for V_0, V_1, V_2 and V_3, respectively).

	Rs_0	Rs_1	Rs_2	Rs_3
Rs_0	1.00	0.53	0.36	0.22
Rs_1		1.00	0.77	0.80
Rs_2			1.00	0.83
Rs_3				1.00

Estimation of sampling rates.

To determine water quality, accurate determination of the concentrations of target compounds in water bodies is required. A TWAC (Time – Weighted Average Concentration) can be calculated by using POCIS, but a Rs is needed. Currently, for POCIS, Rs are determined experimentally, but a large challenge is to predict Rs values from characteristics of molecules to overcome the lack of reproducibility of Rs mainly due to the wide range of experimental conditions used (Miller et al. 2016). Data from the literature about the relationship between Rs and characteristics of compounds are contrasting. Indeed, Li et al. (2010b), Bartelt-Hunt et al. (2011) and Ahrens et al. (2015) do not find relationships between Rs and simple characteristics of compounds, but this concerns mainly pesticides. Nevertheless, for pharmaceuticals, when we investigate the correlation of Rs values determined in this study in a lab-scale pilot with channels with LogP, a simple relation can be proposed to estimate the Rs of pharmaceutical compounds that display a LogP ranging from 0 to 5. This is consistent with statements by Bauerlein et al. (2012) or Miller et al. (2016), which consider the hydrophobicity of compounds as one of the main parameters to explain sorption onto HLB resin.

Non-linear regression approach to estimate Rs with LogP values.

Figure IV.10 shows the relation between LogP and the sampling rates found for water flow velocities V_1 (2-3 cm/s), V_2 (6-7 cm/s) and V_3 (20 cm/s). A non-linear regression was performed following equation (5). For the non-stirred velocity investigated (V_0), the non-linear model did not fit with experimental data. With the experimental data from this study (31 selected pharmaceuticals), **Equation IV.9** became the following equations, **Equation IV.12** for V_1, **Equation IV.13** for V_2, and **Equation IV.14** for V_3:

For V_1: $Rs1 = -284 \times e^{-1.51 \times LogP} + 270$ $r^2 = 0.593$ **Equation IV.12**

For V_2: $Rs2 = -230 \times e^{-0.96 \times LogP} + 302$ $r^2 = 0.554$ **Equation IV.13**

For V_3: $Rs3 = -340 \times e^{-1.34 \times LogP} + 393$ $r^2 = 0.600$ **Equation IV.14**

With equations **Equation IV.12**, **Equation IV.13** and **Equation IV.14**, differences between experimental Rs and calculated Rs (without terbutalin) are -90 at +50% (equation 7).

Nevertheless, we can notice in **Figure IV.10** that for compounds with LogP values ranging from 0 to 2, Rs increases linearly with the value of LogP. For LogP values ranging from 2 to 5, a steady value of Rs was achieved, *i.e.,* 270, 300 and 390 mL/d for V_1, V_2 and V_3, respectively.

Linear regression approach to estimate Rs with 0 < LogP < 2.

A linear regression was performed for the first part (0 < LogP < 2). Regressions are shown in **Figure IV.10** (A', B' and C'). The linear regression equations are as follows:

For V_1:	$Rs1 = 131 \times \mathrm{LogP} + 64$	$r^2 = 0.803$	**Equation IV.15**
For V_2:	$Rs2 = 106 \times \mathrm{LogP} + 101$	$r^2 = 0.629$	**Equation IV.16**
For V_3:	$Rs3 = 174 \times \mathrm{LogP} + 119$	$r^2 = 0.744$	**Equation IV.17**

For LogP higher than 2, a steady value of Rs was achieved, *i.e.,* 260, 295 and 380 mL/d for V_1, V_2 and V_3, respectively. With linear regressions (11-13), differences between experimental Rs and calculated Rs are -75% to 45%. An increase in the flow velocity results in an increase in the sampling rates. The relationship between parameters from plotting Rs=f(LogP) and water flow velocity was tested. Slopes and y-intercepts (from linear and equilibrium regimes) increase with flow velocity (**Figure IV.11**). These values can be recalculated in various flow rate cases. The linear relationship between parameters (slope and intercept) of **Equation IV.10** and flow velocity allows for the determination of parameters of **Equation IV.10** for velocities from 0 to 20 cm/s (**Figure IV.11A and B**). The determination of the sampling rate for compounds with LogP > 2 can be made with the relationship shown in **Figure IV.11C**. For example for 12 cm/s:

For compound with 0 < LogP < 2:

- Calculation of the slope of linear regression:

$$y = 3.49 \times x + 104.24 = 3.49 \times 12 + 104.24 = 146.12$$

- Calculation of the intercept of linear regression:

$$y = 5.94 \times x + 165.54 = 5.94 \times 12 + 165.54 = 263.82$$

Equation IV.10 become:

$$y = 146 \times LogP + 264$$

For compound with LogP > 2:

- Calculation of the intercept of equilibrium:

$$y = 7.08 \times x + 220.23 = 7.08 \times 12 + 220.23 = 305.19$$

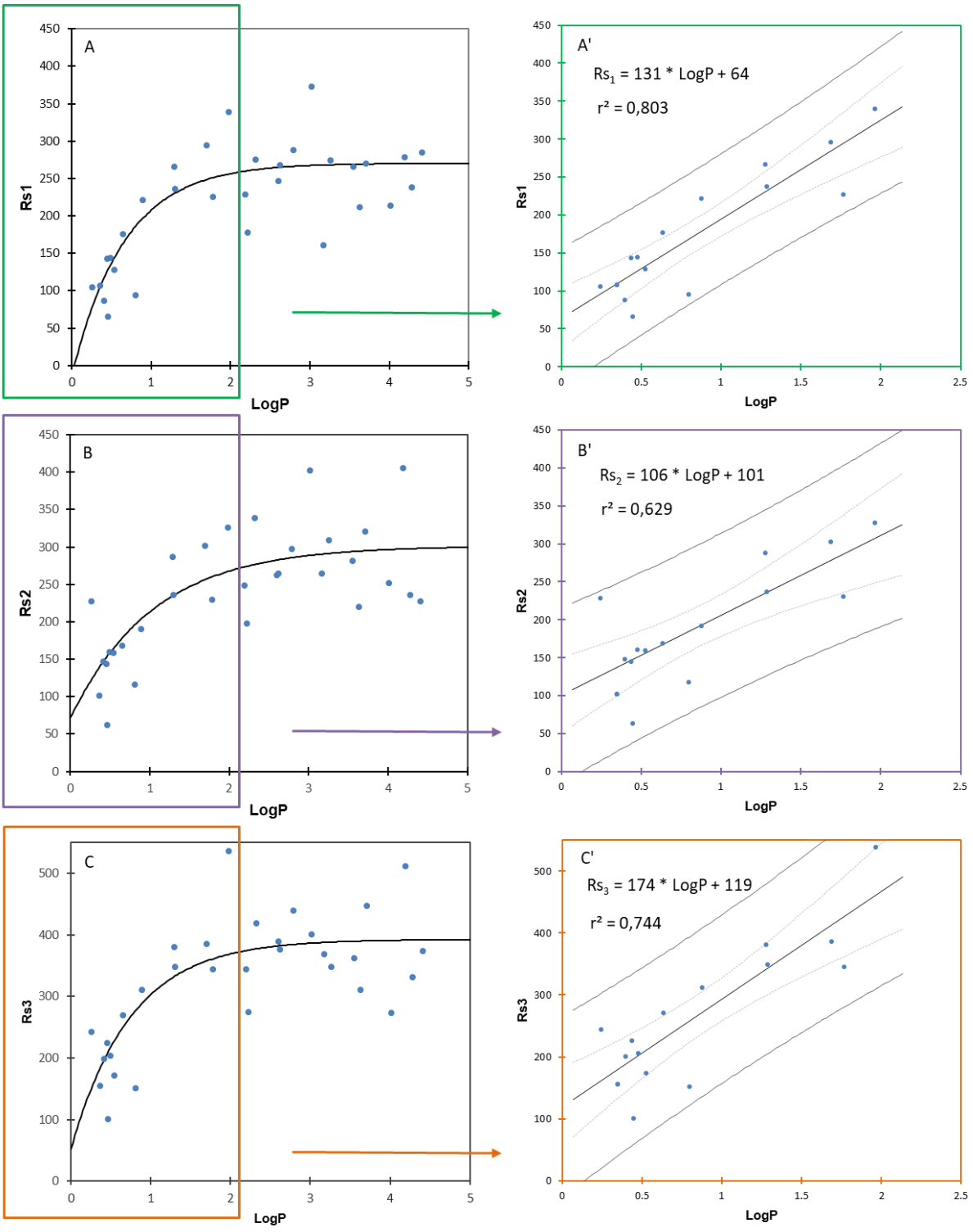


Figure IV.10: Non-linear regression between sampling rates (mL/d) and hydrophobicity (LogP) for various flow velocity. A: 2-3 cm/s; B: 6-7 cm/s and C: 20 cm/s. Linear regression between sampling rates (mL/d) and hydrophobicity (LogP) for various flow velocity. A': 2-3 cm/s; B': 6-7 cm/s and C': 20 cm/s. For A', B' and C': dotted and grey line is confidence interval of 95% (mean and observed, respectively).

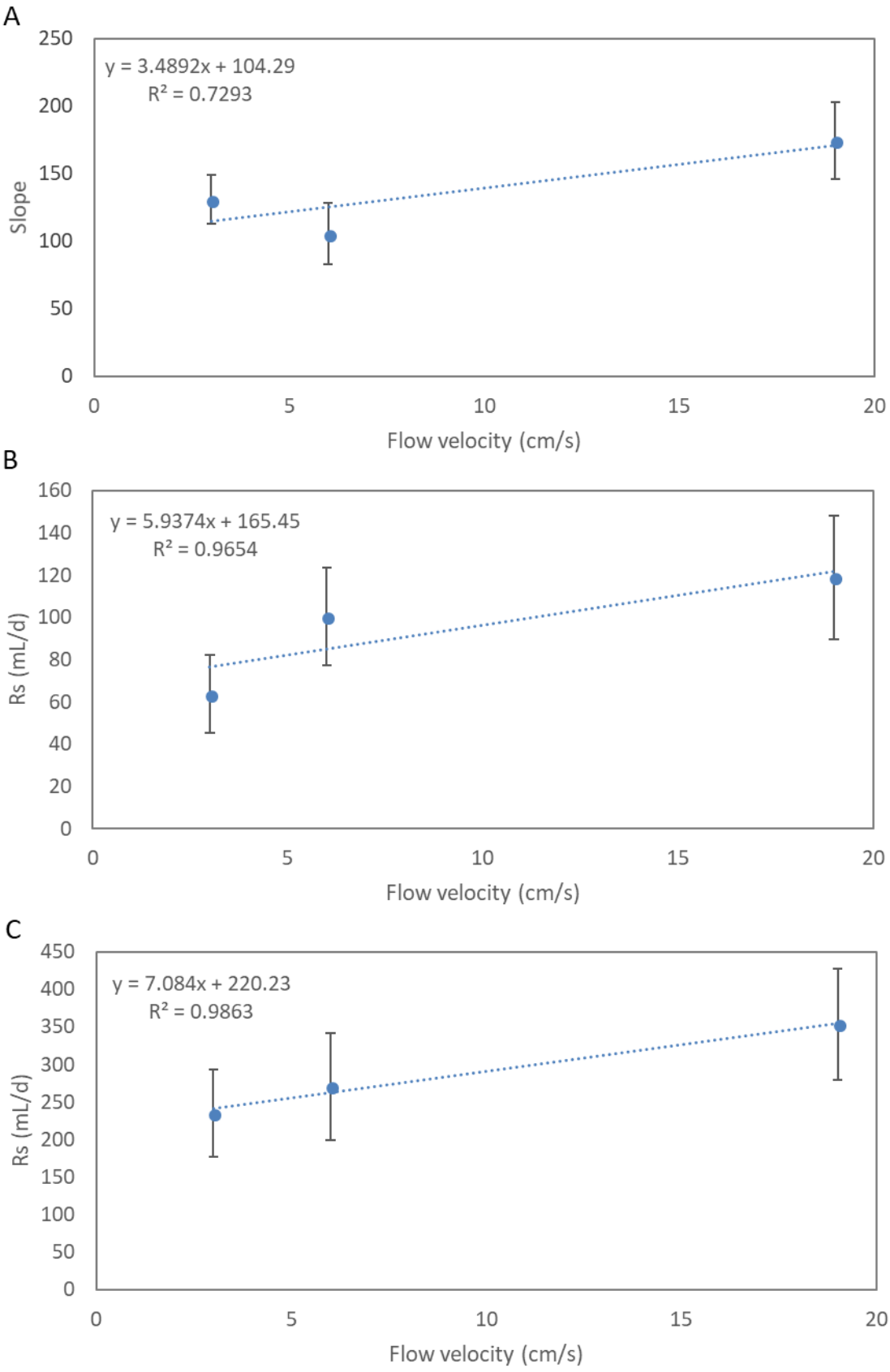


Figure IV.11: A: Slope of linear regressions; B: intercept of linear regression and C: intercept of equilibrium.

Comparison of our relationship with data or models from the literature.

Despite conflicting data from the literature about the possibility to predict Rs from characteristics of compounds, several studies have attempted to propose a simple relationship between Rs and LogP considering different types of regression. For example, Thomatou et al. (2011b) used a third-order polynomial function to establish a relationship between Rs for pesticides and LogP. An Rs increase was observed up to LogP = 3, followed by a decrease after LogP = 3.5.

Togala et al. (2007), proposed a linear relationship (r^2=0.6944) between Rs and LogP ranging from 0 to 5 in freshwater for pharmaceuticals with LogP values ranging from 0 to 5. Later, Li et al. (2010a) determined the Rs for 30 pharmaceuticals and personal care products with LogP values ranging from 0 to 4 and proposed a linear relationship between Rs and LogP (**Equation IV.10**). Calibration was performed in 4 L amber glass bottles using a magnetic stirrer (the speed was set to approximately 850 rpm).

$$Rs = 171 \times \text{LogP} + 196 \qquad r^2 = 0.84 \qquad \textbf{Equation IV.18}$$

As suggested by Togola et al. (2007) and Li et al. (2010a), our study also displays a linear relationship between Rs and LogP for pharmaceuticals, but only for 15 selected pharmaceuticals with 0 < LogP < 2. Moreover, the linear equations of our work (**Equation IV.15**, **Equation IV.16** and **Equation IV.17**) were similar to the equation from Li et al. (2010a) (14). For compounds with LogP values higher than 2, the proposed model from our work and the results of Li et al. (2010a), differ: Rs increases with LogP in Li et al. (2010a), and for our study, Rs reaches a steady value.

However, when we study data from the works of Li et al. (2010a), we can notice that for compounds with LogP values beyond 2.5, the distribution of the Rs value reaches a steady value of approximately 600 mL/d (ranging 400 to 900 mL/d) if we remove the 2 Rs values for triclosan and 4-nonylphenol (**Figure IV.12**).

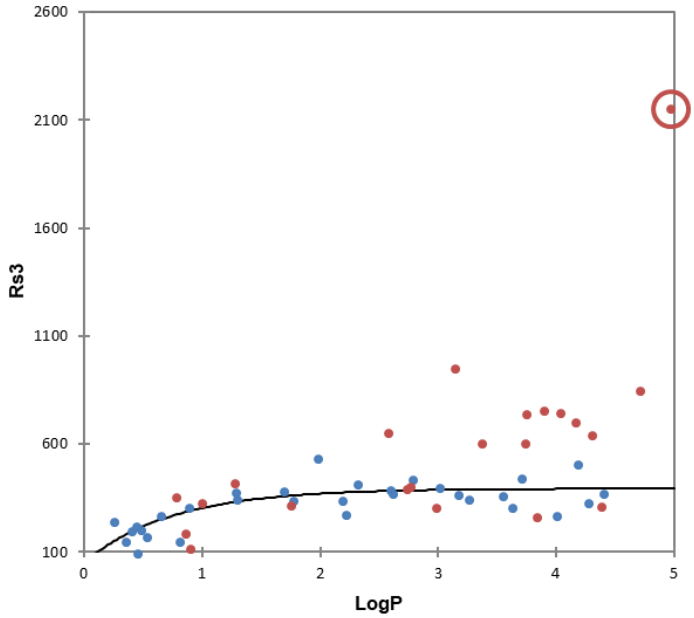


Figure IV.12 : Rs values obtained for the higher flow velocity (V_3) in blue and Rs values obtained in Li et al.(Li et al. 2010a) in red. The dot circled in red corresponds to the Rs value for triclosan from Li et al.(Li et al. 2010a). 4-Nonylphenol has a LogP > 5 and does not appear in this figure.

A steady value of Rs beyond a certain value of LogP is consistent with different works from the literature with different approaches that stated that Rs reaches a maximum or steady value for a LogP values ranging from 1.7 to 3. This observation is consistent with our work. Whatever the class of compound (pesticide, pharmaceutical, hormones, illicit drug…), a Gaussian model was used by Alvarez et al. (2007) to estimate Rs without providing an equation, and this author highlighted that an Rsmax can be achieved for compounds with a LogP higher than 1.7. With a similar approach using a Gaussian model, MacLeod et al. (2007) obtained a maximal Rs value for pharmaceuticals with LogP ≈ 3.

From Mazzella et al. (2007), a quadratic regression (r = 0.924) and an Rsmax (approximately 240 mL/d) was obtained for pesticides with a LogP of approximately 2.5. For endocrine disrupting compounds with LogP values ranging from 2.8 to 4.7, a steady value of Rs (approximately 110 mL/d) was observed but no clear correlation was reported between Rs and LogP (Arditsoglou and Voutsa 2008).

Other authors proposed more complex approaches to predict Rs values from characteristics of compounds, such as Miller et al. (2016), who used artificial neural networks and Rs values from the literature for pesticides, endocrine disrupting compounds and pharmaceuticals (73 compounds). Miller et al. (2016) worked with two models developed in the area of genetic and chromatographic retention using 24 and 15 descriptors, respectively. External model validations were performed with a calibration of six benzodiazepines in a tank filled with 3 L (20 mg/L of $NaHCO_3$) spiked at 200 ng/L. The prediction of Rs was successful, mainly with chromatographic retention approaches with an average absolute error of Rs determination of 43.7±2 mL/d.

Validation of the relationship between Rs and LogP using Rs values from the literature.

To validate our approach to predict Rs for pharmaceuticals, we selected from the literature Rs values measured in similar conditions as our work, i.e., with a lab-scale pilot with a large volume, even if other parameters can affect Rs. The works of Zhang et al. (2008), Harman et al. (2008), Harman et al. (2011b), Jacquet et al. (2012), Morin et al. (2013), Belles et al. (2014a), and Lotufo et al. (2018) were considered. Characteristics of their calibrations (pilot, volume, temperature, flow velocity, doping level and matrix) are presented in **Table IV.12**.

Non-linear regressions (**Equation IV.12**, **Equation IV.13** and **Equation IV.14**) obtained for the non-zero, fairly low velocities proposed in this work to estimate Rs from LogP were tested on various compounds, and calculated Rs values were compared to Rs values determined in this study or proposed by other studies. A summary of calculated Rs values from LogP and their differences from the experimental value of Rs are displayed in **Table IV.13**, and all calculated Rs are presented in**Table IV.14**.

For Rs values from this study, the difference between calculated and experimental Rs values varied by less than a factor of 2 (93%).

For compounds studied here, whatever the origin of the value of Rs (this study or the literature), the difference between calculated and experimental Rs values varied from less than a factor of 2 to less than a factor of 3 (less than a factor of 2 for 86% and less than a factor of 3 for 6% of Rs tested), which is consistent with the use of the POCIS as a semi-quantitative tool (Poulier et al. 2014). Some error values between Rs values calculated and those from the literature are very large (e.g., 8550% for metoprolol with Rs from Harman et al. (2011b)), perhaps due to abnormal values of Rs. For metoprolol, Harman et al. (2011b) indicates a potential underestimation of Rs because of a significant drop in water concentration at the end of the experiment or a competitive adsorption phenomenon with other compounds in solution.

In other table (**Table IV.15**), non-linear models (**Equation IV.12**, **Equation IV.13** and **Equation IV.14**) were also tested to calculate the Rs of other pharmaceuticals (not investigated in this study) and other classes of compounds (illicit drugs, hormones, munition constituents and akylphenols). The differences between experimental and calculated Rs values based on LogP varied from less than a factor of 2 to less than a factor of 3 (less than a factor of 2 for 63% and less than a factor of 3 for 20% of Rs tested). The higher differences between Rs values from the literature and calculated Rs values were obtained for illicit drugs (with the Rs from Harman et al. (2011b). For these different types of compounds, the range of differences between Rs values from literature and calculated Rs values was similar to the difference calculated for pharmaceuticals considered in this study, with a higher proportion differences for Rs values in the range 2-3.

In the literature, for any given compound, the sampling rate can vary in a wide range by a factor f 2 to 200 depending on the calibration conditions, as supported by examples from **Table IV.5**. Therefore, the proposed mathematical **Equation IV.12**, **Equation IV.13** and **Equation IV.14** can be used to estimate the sampling rate for pharmaceuticals, illicit drugs, hormones, alkyphenols and munition constituents with LogP

values ranging from 0 to 5 and allow quick estimation of Rs without intensive laboratory experimentation with an error below a factor of 3.

Table IV.12: Characteristics of POCIS calibration (*n.i.* not indicate and *n.c.* not concerned).

Authors	Pilot	Volume (L)	Temperature (°C)	Flow velocity	Doping level (ng/L)	Matrix
Zhang et al., (2008)	*In-situ* (river)	*n.c.*	15	*n.i.*	*n.c.* (about 1 to 200)	River water
Harman et al., (2008)	PVC tank	300	18	2 cm/s	1 - 10	Drinking water
Jacquet et al., (2008)	*In-situ* (river)	*n.c.*	*n.i.*	*n.i.*	*n.c.* (about < 5)	River water
Morin et al., (2008)	Aquarium	> 50	20	10 cm/s	3000	Tap water
Belles et al., (2008)	Glass tank	250	*n.i.*	*n.i.*	400	Tap water
Lotufo et al., (2008)	Flume	113,000	25	8 ; 14 and 30 cm/s	1000	Dechlorinated and filtered tap water
Harman et al., (2011)	*In-situ* with channel	*n.c.*	6 - 18	stirred	*n.c.* (about 86 to 3137)	Wastewater

Table IV.13: Application of non-linear regressions (Equation IV.12, Equation IV.13 and Equation IV.14) and calculation of differences between literature Rs_{lit} and the model (Equation IV.11).

Type of compound	Number of compounds	Number of Rs	< Factor 2	2 ≤ Factor < 3	≥ Factor 3
		Test with Rs from this study			
Pharmaceuticals from this study	33	99	92	3	4
Total %			93	3	4
		Test with Rs from literature			
Pharmaceuticals common with this study	15	26	16	4	6
Other pharmaceuticals	11	12	9	3	0
Illicit drugs	4	4	0	3	1
Hormones	3	5	4	1	0
Munition constituents	2	6	3	1	2
Alkylphenols	4	4	3	0	1
Others	1	2	2	0	0
Total %			63	20	17

Table IV.14: Application of non-linear regressions (Equation IV.12, Equation IV.13 and Equation IV.14) and calculation of difference between Rs estimate in this study and model (Equation IV.11). Rs were in mL/day.

Compounds	LogP	Rs values calculated with proposed models			Rs value from this study					
		$Rs1_{th}$	$Rs2_{th}$	$Rs3_{th}$	Rs1 (this study)	Diff. (%)	Rs2 (this study)	Diff. (%)	Rs3 (this study)	Diff. (%)
Atenolol	0.43	122	150	202	145	16	146	-3	228	11
Bezafibrate	3.99	269	297	391	216	-25	254	-17	276	-42
Bisprolol	2.2	260	274	375	180	-44	200	-37	278	-35
Carbamazepine	2.77	266	286	385	290	8	299	4	443	13
Clarythromycin	3.24	268	292	389	277	3	311	6	351	-11
Dexamethasone	1.68	248	256	357	297	17	304	16	388	8
Diclofenac	4.26	270	298	392	241	-12	239	-25	334	-17
Erythromycin	2.6	264	283	383	270	2	266	-6	379	-1
Flunixin	3.69	269	295	391	273	1	323	9	450	13
Fluoxetine	4.17	269	298	392	281	4	408	27	514	24
Gemfibrozil	4.39	270	299	392	287	6	230	-30	377	-4
Griseofulvine	2.17	259	273	374	231	-12	250	-9	347	-8
Indomethacin	3.53	269	294	390	268	0	284	-4	365	-7
Ketoprofen	3.61	269	295	390	213	-26	222	-33	313	-25
Metoprolol	1.76	250	260	361	228	-10	232	-12	346	-4
Monensin	4.82	270	300	392	92	-193	119	-152	101	-289
Nadolol	0.87	194	202	287	223	13	193	-5	313	8
Omeprazole	2.43	263	280	380	63	-317	62	-351	75	-407
Paraxanthine	0.24	72	119	147	107	32	230	48	246	40
Paroxetine	3.15	268	291	388	163	-64	266	-9	371	-5
Perindopril	0.63	160	176	247	178	10	170	-4	273	10

Praziquantel	2.3	261	277	377	277	6	341	19	422	11
Prednisolone	1.27	228	234	331	268	15	289	19	383	14
Propranolol	2.58	264	283	382	249	-6	265	-7	392	2
Pyrantel	1.96	255	267	368	341	25	328	19	539	32
Roxithromycin	3	267	289	387	375	29	405	29	404	4
Salbutamol	0.34	100	136	177	109	8	103	-32	157	-13
Sulfadiazine	0.39	112	144	191	89	-26	149	3	202	5
Sulfamerazine	0.52	140	162	224	130	-8	161	-1	175	-28
Sulfamethoxazole	0.79	184	194	275	96	-92	119	-63	154	-79
Sulfamethoxypyridazine	0.47	130	156	212	146	11	162	4	207	-2
Terbutalin	0.44	124	151	204	68	-82	64	-136	103	-98
Trimethoprim	1.28	229	235	332	238	4	238	1	350	5

Table IV.15 : Application of non-linear regressions (Equation IV.12, Equation IV.13 and Equation IV.14) and calculation of difference between Rs_{lit} and model (Equation IV.11). Rs were in mL/day.

Compounds	LogP	Rs values calculated with proposed models			Rs values from literature					
		$Rs1_{th}$	$Rs2_{th}$	$Rs3_{th}$	Rs_{litt}	%	Rs_{litt}	%	Rs_{litt}	%
Pharmaceuticals common with this study										
Atenolol	0.43	122	150	202	60 (Jacquet et al. 2012)	-103	25 (Morin et al. 2013)	-387		
Bezafibrate	3.99	269	297	391	146 (Morin et al. 2013)	-84				
Bisprolol	2.2	260	274	375	161 (Morin et al. 2013)	-61	120 (Jacquet et al. 2012)	-116		
Carbamazepine	2.77	266	286	385	110 (Zhang et al. 2008)	-250	188 (Morin et al. 2013)	-41	140 (Belles et al. 2014a)	-90
Diclofenac	4.26	270	298	392	160 (Zhang et al. 2008)	-145	225 (Morin et al. 2013)	-20		
Fluoxetine	4.17	269	298	392	150 (Belles et al. 2014a)	-80				
Gemfibrozil	4.39	270	299	392	270 (Belles et al. 2014a)	0				
Indomethacin	3.53	269	294	390	300 (Zhang et al. 2008)	-30				
Ketoprofen	3.61	269	295	390	160 (Belles et al. 2014a)	-68	118 (Morin et al. 2013)	-128		
Metoprolol	1.76	250	260	361	3 (Harman et al. 2011b)	-8551	220 (Jacquet et al. 2012)	-14	195 (Morin et al. 2013)	-28
Nadolol	0.87	194	202	287	114 (Morin et al. 2013)	-70				
Propranolol	2.58	264	283	382	220 (Jacquet et al. 2012)	-20	60 (Zhang et al. 2008)	-537	165 (Morin et al. 2013)	-60
Sulfamethoxazole	0.79	184	194	275	460 (Zhang et al. 2008)	40	30 (Morin et al. 2013)	-513		
Terbutalin	0.44	124	151	204	10 (Belles et al. 2014a)	-1139				
Trimethoprim	1.28	229	235	332	162 (Morin et al. 2013)	-41				
Pharmaceuticals										
Acetaminophen	0.91	198	206	293	220 (Jacquet et al. 2012)	-33				
Alprazolam	3.02	267	289	387	200 (Belles et al. 2014a)	-34				
Amitriptyline	4.81	270	300	392	120 (Belles et al. 2014a)	-125				
Bromazepam	2.54	264	282	382	180 (Belles et al. 2014a)	-47				
Cetirizine	0.87	194	202	287	103 (Harman et al. 2011b)	-179				
Doxepin	3.84	269	296	391	160 (Belles et al. 2014a)	-68				
Etopophos	1.16	221	226	321	300 (Belles et al. 2014a)	26				

Ibuprofen	3.84	269	296	391	160 (Belles et al. 2014a)	-68	118 (Morin et al. 2013)	-128		
Imipramine	4.28	270	298	392	180 (Belles et al. 2014a)	-50				
Nordazepam	3.21	268	291	388	180 (Belles et al. 2014a)	-49				
Oxazepam	2.92	267	288	386	226 (Challis et al. 2016)	-18				
Illicit drugs										
Cocaine	2.28	261	276	377	186 (Harman et al. 2011b)	-103				
Morphine	0.9	197	205	291	44 (Harman et al. 2011b)	-562				
Amphetamine	1.8	251	261	363	125 (Harman et al. 2011b)	-190				
Methamphetamine	2.24	260	275	376	128 (Harman et al. 2011b)	-194				
Hormones										
Estrone	4.31	270	298	392	820 (Zhang et al. 2008)	64	230 (Morin et al. 2013)	-17		
17-beta-estradiol	3.75	269	296	391	650 (Zhang et al. 2008)	55	221 (Morin et al. 2013)	-22		
Progesterone	4.15	269	298	392	346 (Morin et al. 2013)	22				
Others										
Munition constituents										
TNT (2,4,6-trinitrotoluene)	2.31	261	277	378	200 (Lotufo et al. 2018)	-38	280 (Lotufo et al. 2018)	-35	520 (Lotufo et al. 2018)	27
2,6-dinitrotoluene	2.37	262	278	379	90 (Lotufo et al. 2018)	-209	110 (Lotufo et al. 2018)	-244	160 (Lotufo et al. 2018)	-137
Alkylphenols										
6-tert-Butyl-2,4-dimethylphenol	4.24	270	298	392	254 (Harman et al. 2008)	-6				
2,4,6-Trimethylphenol	3.21	268	291	388	189 (Harman et al. 2008)	-42				
t-butyphenol	3.21	268	291	388	398 (Morin et al. 2013)	33				
t-octylphenol	4.69	270	299	392	65 (Morin et al. 2013)	-315				
Others										
Bisphenol A	4.04	269	297	391	670 (Zhang et al. 2008)	56	245 (Morin et al. 2013)	-10		

CONCLUSION

Many studies have dealt with intensive laboratory experimentation for POCIS calibration. The result is many sampling rates determined in a wide range of conditions. This study calibrates 44 pharmaceuticals in lab-scale conditions close to environmental conditions (hydrodynamic and temperature). This study proposes 12 new Rs (not available in the literature) and 26 Rs already available in the literature. Six pharmaceuticals were not sampled by POCIS. Calibrations were performed at 4 water flow velocities: 0 (V_0); 2-3 (V_1); 6-7 (V_2); and 20 (V_3) cm/s. Sampling rates ranged from 40 to 218, from 63 to 375, from 62 to 408 and from 75 to 539 mL/d for V_0, V_1, V_2 and V_3, respectively. An increase in the flow velocity decreases the water boundary layer and therefore increases Rs.

A simple relationship between sampling rates and hydrophobicity (*via* LogP) was determined. A non-linear equation can be used to estimate Rs. It is possible to recalculate parameters of the equation to estimate Rs in the range of 2 – 20 cm/s. These equations were tested on Rs from the literature and allowed estimation of the POCIS sampling rate for pharmaceuticals, illicit drugs, hormones, munition constituents and others with an error less than a factor of 3, which is consistent with the semi-quantitative use of POCIS.

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IV.4. Conclusion intermédiaire

Ce travail permet de proposer des solutions pour améliorer les performances du POCIS en se focalisant d'une part sur l'analyse des extraits de POCIS et d'autre part sur la possibilité d'utiliser des Rs déterminés dans des conditions proches de celles du milieu naturel.

Le lavage des membranes PES à base d'un mélange eau/méthanol à 50/50 (v/v) permet de baisser le facteur de dilution des extraits de POCIS de 25 à 10 pour supprimer les effets de matrice dus au PEG relargués par les membranes PES. Les POCIS étant reconnus pour détecter les molécules cibles à de bien plus faibles concentrations que les prélèvements ponctuels, le lavage des membranes PES permet de descendre les limites de quantification d'un facteur 10 environ. De plus, le lavage permet, sans modifier les capacités du POCIS, de s'affranchir d'effet de matrice pouvant conduire à la détermination de concentrations erronées dans les extraits de POCIS.

Pour les POCIS, un des challenges actuels est d'avoir des Rs le plus représentatifs du milieu naturel. Les Rs de 44 résidus de médicaments ont été déterminés à plusieurs vitesses (0, 2-3, 6-7 et 20 cm/s) à 16°C ± 1,5 dans un pilote mimant une rivière artificielle remplie avec de l'eau du robinet et en utilisant des concentrations de 500 ng/L pour chaque molécule. Ce travail confirme que la couche d'eau liée à la membrane impacte la valeur de Rs, surtout à vitesse nulle ou très faible. Les cinétiques d'accumulation des résidus pharmaceutiques dans les POCIS en pilote de rivière artificielle ont permis de déterminer les Rs de 12 molécules pharmaceutiques (dexaméthasone, flunixin, griséofulvine, indomethacine, métronidazole, paraxanthine, perindopril, praziquantel, pyrantel, salbutamol, sulfadiazine et sulfamethoxypyridazine) et de comparer les résultats des 32 autres à ceux de la littérature.

Ce travail a permis d'établir une équation mathématique reliant le Rs à l'hydrophobicité de la molécule (LogP) : $\mathrm{Rs} = a \times e^{-b \times LogP} + c$

Cette équation permet d'estimer un Rs pour 7 types de molécules (composés pharmaceutiques, drogues illicites, hormones, constituant de munition, alkylphénols et autres), ayant un LogP compris entre 0 et 5, avec un facteur inférieur à 3 pour 83 % de molécules testées. Ceci reste en accord avec l'utilisation semi-quantitative reconnu à l'heure actuelle au POCIS.

A retenir !

- Lavage des membranes PES : 2*1h dans 50:50 EUP:MeOH v:v puis 1h dans EUP.

- Analyse des extraits de POCIS : dilution par 10 avec des membranes PES lavées sinon dilution par 25 avec des membranes non lavées.

- 12 nouveaux Rs disponibles : dexaméthasone, flunixin, griséofulvine, indomethacine, métronidazole, paraxanthine, perindopril, praziquantel, pyrantel, salbutamol, sulfadiazine et sulfamethoxypyridazine.

- Estimation des Rs à partir du LogP (pour les molécules avec 0 < LogP < 5) :

$$\mathrm{Rs} = a \times e^{-b \times LogP} + c$$

Chapitre V. Application du POCIS à la contamination des têtes de bassin versant

V.1. Introduction

Le chapitre précédent a permis de fiabiliser le POCIS et d'en améliorer les performances. Il est maintenant intéressant d'appliquer cet échantillonneur dans des cours d'eau supposés relativement peu ou pas contaminés du fait du contexte très rural pour profiter pleinement des seuils de quantifications abaissés des échantillonneurs passifs en plus de leurs capacités intégratrices dans le temps : les têtes de bassin versant (on peut définir une tête de bassin versant pour les cours d'eau ayant un rang de strahler inférieur à 3).

La Directive Cadre sur l'Eau (DCE) requérait d'atteindre un bon état écologique et chimique des masses d'eau pour 2015 (2000/60/CE, (2000)). Cette directive vise, entre autres, à prévenir et à réduire la pollution de l'eau. Pour cela, une liste des substances prioritaires avait été établie. Depuis, des directives filles (2008/105/CE (2008) et 2013/39/CE (2013)) ont réévalué les délais (2021 et 2027) ainsi que la liste des substances prioritaires ajoutant des normes de qualité environnementale (NQE) à ne pas dépasser dans les eaux. A ce jour, 45 substances ou groupes de substances ont été jugés prioritaires dont 26 pesticides et aucun résidu pharmaceutique. Néanmoins, 3 résidus pharmaceutiques (diclofénac, 17-α-éthinylestradiol et 17-β-estradiol) font partie d'une liste de vigilance au niveau de l'UE depuis 2015. Cette directive prévoit un suivi par échantillonnage ponctuel plusieurs fois par an (de 6 à 12 fois). C'est la stratégie d'échantillonnage la plus répandue, pour plusieurs raisons dont la principale est la facilité d'utilisation (Poulier et al. 2014). Cependant, plusieurs auteurs ont montré le manque de représentativité de l'échantillonnage ponctuel par rapport à l'échantillonnage passif. Dans la littérature, ces deux types d'échantillonnage sont toujours comparés et opposés (Allan et al. 2006, Lissalde et al. 2011, Mazzella et al. 2008, Zhang et al. 2016). Il est donc intéressant d'étudier la complémentarité plutôt que l'opposition de ces deux méthodes d'échantillonnage ainsi que les informations apportées par ces dernières.

Ces suivis réglementaires sont souvent effectués sur les cours d'eau principaux ou à l'exutoire de masse d'eau en ne prenant pas en compte l'éventuel chevelu de cours d'eau sur la partie amont. En effet, peu d'études se sont intéressées aux têtes de bassin versant, exceptés Wilkinson et al. (2017) et Van Metre et al. (2017). Sousa et al. (2018) et Jones et al. (2001) affirment que des études plus complètes devraient être menées pour caractériser la pollution de ces zones. En effet, les têtes de bassin versant abritent une biodiversité très importante et il est donc très important de les préserver.

L'objectif de ce chapitre est donc d'évaluer la contamination en pesticides et en résidus pharmaceutiques en tête de bassin versant. Pour cela, des études ont été menées sur les têtes de deux bassins versants situés sur la frange atlantique du massif central : l'Auvézère et l'Aixette. Des suivis « semi-continu » a été réalisé sur les deux bassins versants et ont duré 3 ans pour le premier et 1 an pour le second. C'est-à-dire que, tous les 14 jours, l'échantillonneur déployé est retiré du milieu à échantillonner et qu'un nouvel échantillonneur est déployé. Grâce à ce mode de suivi, l'évolution de la contamination de la rivière est évaluée par pas de 14 jours sur l'ensemble de la période de suivi (3 ans ou 1 an). Cela permet de voir l'évolution de la contamination au cours de l'année, de calculer des flux de composés et d'identifier les zones contributrices à la pollution en composés organiques.

Deux types de contamination ont été évalués : la contamination en produits phytopharmaceutiques (bassin versant de l'Auvézère) et en résidus pharmaceutiques (bassin versant de l'Aixette). Sur chaque bassin versant, les POCIS

ont été déployés sur 3 sites différents (sur le cours d'eau principal et sur un affluent) permettant d'étudier l'occurrence spatiale des composés d'intérêts. L'échantillonnage ponctuel a été fait durant les 3 ans de suivi sur le bassin versant de l'Auvézère.

Enfin, une dernière étape est de voir si un lien peut être établi entre l'occupation du sol sur ces bassins versants et la contamination détectée en termes de quantité et de qualité. En effet, ce sont deux bassins versants ruraux où l'on pratique l'élevage extensif d'ovins et de bovins. A cela s'ajoute de plus en plus la présence de cultures céréalières (maïs, blé et orge) pour rendre les exploitations autonomes en alimentation du bétail et ainsi améliorer leur rentabilité économique.

L'objectif de ce chapitre consiste à étudier les têtes de bassin versant et donc de :

- Étudier la complémentarité des échantillonnages ponctuel et passif.
- Utiliser l'échantillonneur POCIS sur deux bassins versants : l'Auvézère et l'Aixette.
- Déterminer l'occurrence temporelle (saisonnalité) et spatiale des composés (pesticides et résidus pharmaceutiques) grâce aux suivis semi-continus.
- Tenter de lier occupation du sol et contamination des eaux de rivière.

V.2. Publication "Two sampling strategies for an overview of pesticides contamination in agricultural-extensive headwater stream".

Cette section est constituée d'une version adaptée d'un article publié dans la revue « Environmental Science and Pollution Research », où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

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Two sampling strategies for an overview of pesticide contamination in an agriculture-extensive headwater stream.

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ABSTRACT

Two headwaters located in southwest France were monitored for three and two years (Auvézère and Aixette watershed, respectively) with two sampling strategies: grab and passive sampling with POCIS. These watersheds are rural and characterized by agricultural areas with similar breeding practices, except that the Auvézère watershed contains apple production for agricultural diversification and the downstream portion of the Aixette watershed is in a peri-urban area. The agricultural activities of both are extensive *i.e.* with limited supply of fertilizer and pesticides. The sampling strategies used here give specific information: grab samples for higher pesticide content and POCIS for contamination background noise and number of compounds found. Agricultural catchments in small headwater streams are characterized by a background noise of pesticide contamination in the range 20-70 ng/L, but there may also be transient and high peak pesticide contamination (2000-3000 ng/L) caused by rain events, poor use of pesticides and/or the small size of the water body. This study demonstrates that between two specific runoff events contamination was low, hence the importance of passive sampler use. While the peak pesticide concentrations seen here are a toxicity risk for aquatic life, the pesticide background noise of single compounds do not pose obvious acute nor chronic risks, however this study did not consider the risk from synergistic "cocktail" effects. Proper tools and sampling strategies may link watershed activities (agricultural, non-agricultural) to pesticides detected in the water, and data from both grab and passive samples can contribute to discussions on environmental effects in headwaters, an area of great importance for biodiversity.

Keywords: POCIS, Passive sampling, grab sampling, pesticides, headwater stream, organic pollutants

INTRODUCTION

The diversity of human activities leads to a wide range of organic micropollutants in the environment (*e.g.* pesticides, pharmaceuticals, PCBs). Pesticide use exists in several activities (*e.g.* industry, agriculture, private consumers) and is one of the main sources of pollution of water resources (Dalton et al. 2014, Loos et al. 2009). These compounds can cause problems for flora and fauna (Mahmood et al. 2016, Mason et al. 2003, Solomon et al. 1996) and human health can also be affected (Damalas and Eleftherohorinos 2011, Kim et al. 2016) through, for example, cancers, hormonal disturbances or allergies (Van Maele-Fabry et al. 2010). The source of a river (headwater stream) is the upstream of the watershed composed of ponds, swamps, wetlands or small lakes. It plays a huge role in biodiversity protection, containing numerous species of high biological value, and also in water quality and quantity of the downstream (Finn et al. 2011, Lowe and Likens 2005, Meyer et al. 2007) and, until recently, these areas have often been overlooked by scientists and water management authorities (Biggs et al. 2017, Rasmussen et al. 2013).

In the European Union (EU), the Water Framework Directive (WFD) required good ecological and chemical status of water bodies from 2015 (2000/60/EC 2000); it was updated for 2021 to 2027 by WFD (2013/39/EC 2013). To evaluate water quality regarding micropollutants, the WFD dictates water monitoring with reliable sampling and analysis protocols, and the monitoring of 45 compounds including 20 pesticides as priority substances to meet Environmental Quality Standards (EQS). Water quality studies for different types of compounds (e.g. pesticides, PCBs, PAHs, heavy metals) are also implemented by water management at the watershed scale to identify origins of water pollution and take remediation actions in order to meet objectives of the WFD.

Currently, grab sampling is the most widespread sampling strategy for several reasons, including the simplicity of implementation and use (Poulier et al. 2014). However, this technique presents some disadvantages, of which the best known is the lack of temporal representativeness (Allan et al. 2006). For the WFD water quality monitoring network, the solution proposed by the EU is to increase sampling frequency (especially during spring), but this solution also increases the cost of the monitoring program and is therefore not suitable for the majority of water management agencies. To overcome the lack of temporal representativeness, new devices were created about twenty years ago; including Diffusive Gradient in Thin film (DGT) for inorganics (Davison and Zhang 1994, Zhang and Davison 1995), Polar Organic Chemical Integrative Sampler (POCIS) for organic compounds with a $0 \leq \log Kow \leq 5$ (Alvarez 1999, Alvarez et al. 2004), Semi-Permeable Membrane Device (SPMD) for organic compounds with a $\log Kow \geq 4$ (Booij et al. 1998, Huckins et al. 1993, Vrana and Schuurmann 2002) and Chemcatcher® for organic compounds with a $1 \leq \log Kow \leq 7$ (Charriau et al. 2016, Kingston et al. 2000, Vrana et al. 2007). Briefly, in each of these, a receiving phase (liquid or solid) is exposed for a few days to several weeks (usually 14 days (Alvarez 1999, Mazzella et al. 2010)). Thus, there is a continuous accumulation of contaminants, pre-concentration occurs in the sampler and allows lower quantification limits (LOQ) (Lissalde et al. 2011, Zhang et al. 2008). Moreover, a time-weighted averaged concentration (TWAC) can be calculated to give a better estimate of overall contamination (Alvarez et al. 2004, Gorecki and Namienik 2002, Vrana et al. 2005). However, if the period of exposure is short, some compounds can have a TWAC below LOQ and therefore be non-detectable, when a grab sampling could have detected them (Schafer et al. 2008). Differences between passive and grab sampling have been reviewed (Lissalde et al. 2011, Mazzella et al. 2008, Zhang et al. 2016). Indeed, Zhang et al. (2016) calculated pesticide fluxes

with a passive sampler and improved pesticide monitoring under operational constraints, concluding that both techniques give the same results on most compounds, except for low concentrations, thus supporting the findings of several other studies (Poulier et al. 2015, Poulier et al. 2014). POCIS was also shown efficient for studying pesticide and metabolite contamination in 100 small streams across the Midwest, an agricultural area of the USA (Van Metre et al. (2017)).

The objective of this work is to evaluate the occurrence of pesticides in a poorly studied type of watershed, *i.e.* headwater, using an extensive data set that combines grab and POCIS passive sampling. Headwater streams are considered important for natural biodiversity preservation in the EU but may be vulnerable to pesticide contamination (small body water), even if the use of pesticides in the watershed is assumed low or moderate (Ccanccapa et al. 2016) based on agricultural practices. The combined sampling approach was applied to improve our understanding of pesticide contamination of small headwater streams in a mixed agricultural setting and the ability of the two sampling methods to detect pesticides at low or high levels is considered. The toxicity risks of detected pesticides are also discussed, using EQS proposed by WFD or chronic and acute toxicity data for aquatic organisms available in literature.

MATERIALS AND METHODS

Main characteristics of headwaters.

The study was done on two headwaters located in southwest France: the Auvézère and Aixette rivers (geographic localization of the watersheds on **Figure V.1**). The Strahler number of the main rivers (Auvézère; Aixette) was 3 in the study area considered, which is representative of a headwater stream. Some tributaries were also considered: the Arthonnet tributary for the Aixette watershed and the Arnac tributary for the Auvézère watershed, both have a Strahler number of 2. As shown in **Figure V.1**, these watersheds are characterized by a high density of very small streams. Both catchments were located on crystalline bedrock (granite and gneiss) with slight groundwater *i.e.* in the alterites (first few meters of depth) and in the cracks of bedrock up to a depth of 50-60 m. The climate is degraded Atlantic (continental influence) oceanic.

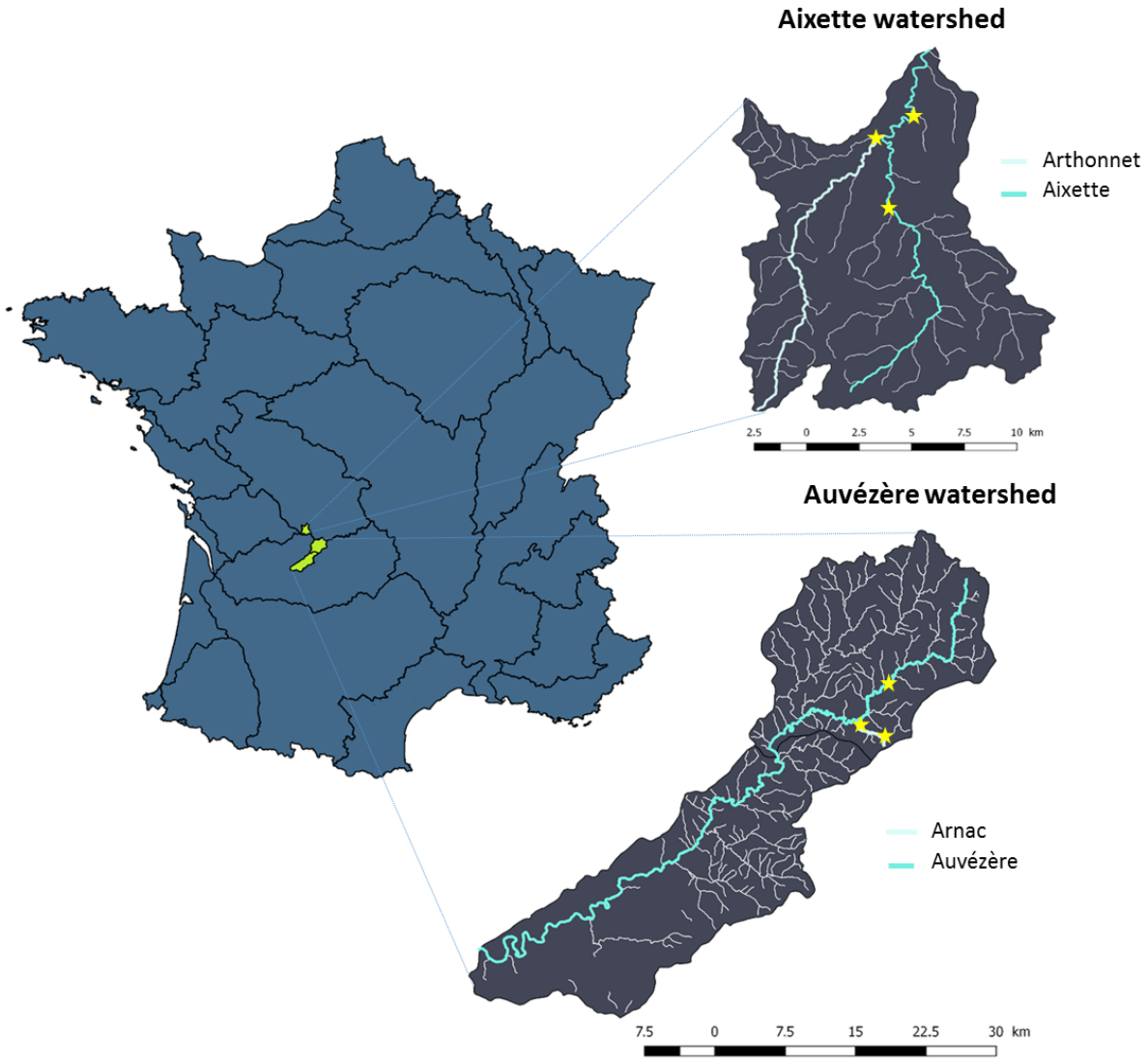

Figure V.1: Aixette and Auvézère watersheds localizations and sampling points.

Three sampling points were chosen for each watershed. On the Auvézère River watershed, the first one was at Quatre-Moulins (coordinates - Lambert 93, kilometers: X 574.57, Y 6486.31) and the two others were in the Arnac stream (called Arnac upstream and Arnac downstream, coordinates - Lambert 93, kilometers: Arnac upstream – X

573.02, 6480.22, Arnac downstream – X 570.91, Y 6481.03), a tributary of the Auvézère River. On the Aixette river watershed, two sampling points were located on the Aixette River. The first one was 13.5 km from the spring at Lavignac, called Aixette upstream (coordinates - Lambert 93, kilometers: X 554.01, Y 6515.79), and the second one 5 km before the confluence with the Vienne River at La Pouette, called Aixette downstream, (coordinates - Lambert 93, kilometers: X 554.98, Y 6520.56). The last sampling point was located on the Arthonnet River, a tributary of the Aixette River, and located between the first two sampling points at Pont Péry mill (coordinates - Lambert 93, kilometers: X 553.39, Y 6519.36).

The Auvézère River flows 112 km in a rural area (Corrèze and Dordogne) and drains a catchment of 900 km². The principal land use in the Auvézère watershed is agricultural (74% of the watershed surface), with extensive cattle breeding grassland (67% of the utilized agricultural area), arable land (23% of the utilized agricultural area) with mainly cereal crops or cultivated grassland but also with apple and red fruit orchards (about 1% of the utilized agricultural area) (**Figure V.2**). The Aixette River flows 27.6 km in the area of Haute-Vienne and drains a catchment of 163 km². The end of the Aixette watershed is in the peri-urban area of Limoges (Haute-Vienne, France). The 3 sampling spots on the Aixette watershed were located in the rural and agricultural parts of the watershed, where agricultural lands were grassland (37%) with extensive cattle breeding, cereal crops (37%), forest (16%) and urban areas (3%) (**Figure V.3**). The two watersheds are geographically close and agricultural practices are similar, with extensive breeding of the Limousin cow (exception is apple orchards in the Auvézère watershed but covering only about 1% of the utilized agricultural area). The agricultural practices in both watersheds are extensive, aiming to secure financial profitability with the lowest possible costs for feeding and pesticides.

Materials and chemicals.

Solvents were all HPLC-MS quality. Methanol (MeOH) and ethyl acetate were purchased from J.T. Baker and Sigma Aldrich, respectively. Reagents added in eluents (formic acid and ammonium formate) were obtained from Agilent and had a purity >99%. Ultrapure water (UPW) was produced by a Gradient A10 Milli-Q system from Millipore.

The list of pesticides is presented in **Table V.1**, including main pesticide properties. Briefly, all pesticides (35) and metabolites (9) were purchased from Dr. Ehrenstorfer GmbH, with a purity higher than 94%. Stock pesticide solutions at concentrations of 100 mg/L were prepared in methanol and stored at -18°C for no more than 6 months. A working solution at a concentration of 1 mg/L containing all compounds was prepared in methanol with a dilution of stock solutions and stored in the same conditions (-18°C and no more than 6 months).

Internal standard solutions at a concentration of 10 mg/L were prepared in methanol and stored at -18°C. The list of internal standards (deuterated pesticides) is presented in **Table V.2**.

Fresh calibration solutions containing pesticide standards (1 to 100 µg/L) and internal standards (100 µg/L) were prepared daily in a mixture of UPW:MeOH (90:10 v:v).

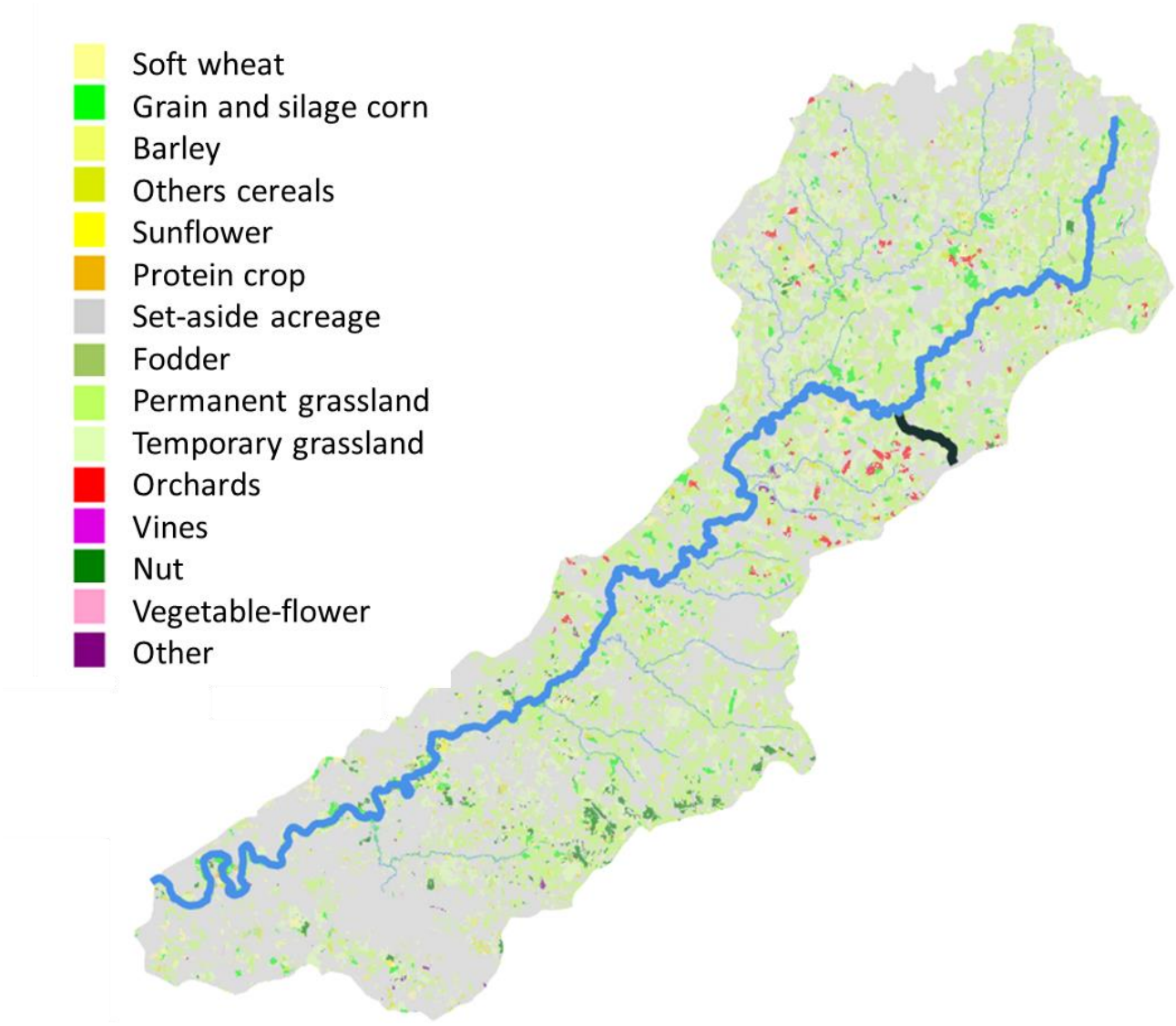

Figure V.2: Auvézère watersheds land-use (RPG, 2012, Géoportail).

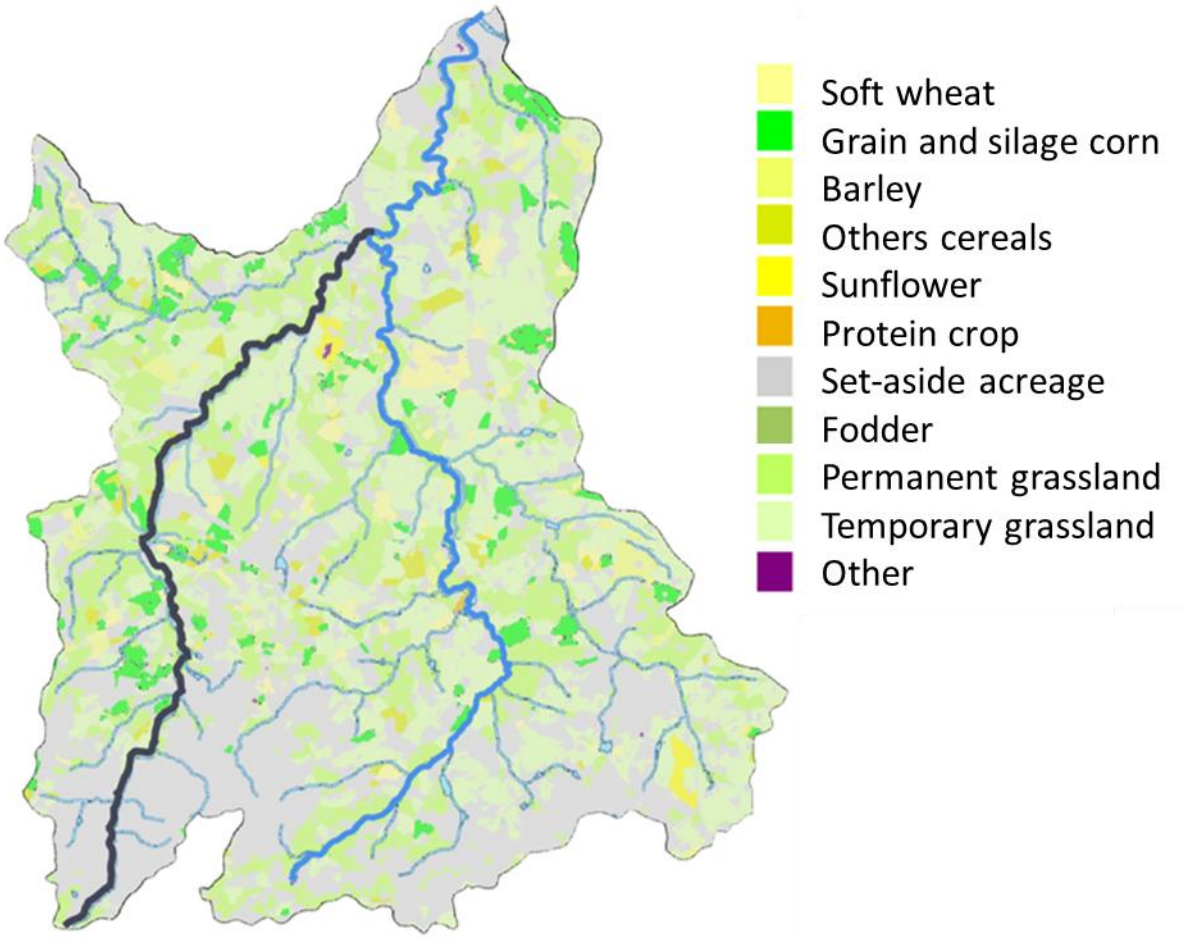

Figure V.3: Aixette watersheds land-use (RPG, 2012, Géoportail).

POCIS preparation.

POCIS consists of a sorbent (200 mg of Oasis® HLB powder from Waters) enclosed between two polyethersulfone membranes (PES) of 90 mm diameter and 0.1 µm pore size, purchased from Pall Supor® (Alvarez et al. 2004). PES membranes were previously washed with two successive 1h baths in 50:50 MeOH:UPW followed by two 30 min baths in UPW (Guibal et al. 2015a). The POCIS assembly is held by two stainless steel rings. Oasis® HLB powder was spiked with a performance and reference compound (PRC) which was deisopropylatrazine-d5 or DIA-d5 at 4 µg/g. PRC is used to overcome environmental effects (Lissalde et al. 2011, Mazzella et al. 2010), although it does not fully correct TWAC (Fauvelle et al. 2017, Harman et al. 2012). In this study, PRC was used as an indicator of environmental status and not to calculate a corrected R_s and PRC desorption was monitored to verify proper pesticide accumulation, with PRC release required to be between 20 and 80% (Soderstrom and Bergqvist 2004).

Table V.1: Family, regulatory status and main physicochemical characteristics of the studied pesticides ([1]data from IUPAC, [2]data from INERIS, n.f. not found, n.c. not concerned). (Source: http://www.iupac.org and http://www.ineris.fr)

Pesticide	Family	Authorized / Forbidden (In France at 01/08/2014)	pKa	Solubility in water: S_w (mg/L)	logK_{ow} (IUPAC)
3-hydroxy-carbofuran	Metabolite		n.f.	n.f.	0.76[2]
Acetochlor	Herbicide	Authorized	n.c.	282[1]	4.14[1]
Alachlor	Herbicide	Forbidden	0.62[1]	240[1]	3.09[1]
Atrazine	Herbicide	Forbidden	1.7[1]	35[1]	2.70[1]
Azoxystrobin	Fungicide	Authorized	n.c.	6.7[1]	2.50[1]
Benoxacor	Herbicide	Authorized	n.f.	20[1]	2.69[1]
Carbaryl	Insecticide	Forbidden	10.4[1]	9.1[1]	2.36[1]
Carbendazim	Fungicide	Forbidden	4.2[1]	8[1]	1.48[1]
Carbofuran	Insecticide	Forbidden	n.c.	322[1]	1.80[1]
Chlorfenvinphos	Insecticide	Forbidden	n.f.	145[1]	3.80[1]
Chlortoluron	Herbicide	Authorized	n.c.	74[1]	2.50[1]
Cybutryne (Irgarol)	Fungicide	Authorized	n.f.	7[2]	4.00[2]
Cyproconazole	Fungicide	Authorized	n.c.	93[1]	3.09[1]
Dichlorophenyl-methylurea (DCPMU)	Metabolite		n.f.	490[2]	2.09[2]
Dichlorophenyl-urea (DCPU)	Metabolite		n.f.	940[1]	2.35[1]
Atrazine-desethyl (DEA)	Metabolite		n.f.	2700[1]	1.51[1]
Terbuthylazine-desethyl (DET)	Metabolite		n.f.	327.1[1]	2.30[1]
Atrazine-desisopropyl (DIA)	Metabolite		n.f.	980[1]	1.15[1]
Dimethachlor	Herbicide	Authorized	n.c.	2300[1]	2.17[1]
Dimethenamid	Herbicide	Authorized	n.c.	1450[1]	1.89[1]
Dimethoate	Insecticide	Authorized	n.c.	39800[1]	0.70[1]
Dimetomorph	Fungicide	Authorized	-1.3[1]	28.95[1]	2.68[1]
Diuron	Herbicide	Forbidden	n.c.	35.6[1]	2.87[1]
Epoxiconazole	Fungicide	Authorized	n.c.	7.1[1]	3.30[1]
Fluorochloridone	Herbicide	Authorized	n.c.	21.9[1]	3.36[1]
Flurtamone	Herbicide	Authorized	n.c.	10.7[1]	3.20[1]
Flusilazole	Fungicide	Forbidden	2.5[1]	41.9[1]	3.87[1]
Hexazinone	Herbicide	Forbidden	2.2[1]	33000[1]	1.17[1]
Imidacloprid	Insecticide	Authorized	n.c.	610[1]	0.57[1]
Isopropylphenyl-metylurea (IPPMU)	Metabolite		n.f.	n.f.	2.63[2]
Isopropylphenyl-urea (IPPU)	Metabolite		n.f.	n.f.	2.16[2]
Isoproturon	Herbicide	Authorized	n.c.	70.2[1]	2.50[1]
Linuron	Herbicide	Authorized	n.c.	63.8[1]	3.00[1]
Metazachlor	Herbicide	Authorized	n.c.	450[1]	2.49[1]
Methomyl	Insecticide	Forbidden	n.c.	55000[1]	0.09[1]
Metolachlor	Herbicide	Forbidden	n.c.	530[1]	3.40[1]
Metoxuron	Herbicide	Forbidden	n.f.	678[1]	1.60[1]
Norflurazon	Herbicide	Forbidden	n.c.	34[1]	2.45[1]

Norflurazon-desmethyl	Metabolite		n.f.	n.f.	1.72[2]
Pirimicarb	Insecticide	Authorized	4.4[1]	3100[1]	1.70[1]
Simazine	Herbicide	Forbidden	1.62[1]	5[1]	2.30[1]
Tebuconazole	Fungicide	Authorized	5[1]	36[1]	3.70[1]
Terbuthylazine	Herbicide	Forbidden	1.9[1]	6.6[1]	3.40[1]
Thiodicarb	Insecticide	Forbidden	n.c.	22.2[1]	1.62[1]

Table V.2: Pesticide characteristics after UHPLC separation and mass detection.

Pesticide	Retention Time (min)	Mass (Da)	Accurate mass $[M+H]^+$	Internal Standard
3-hydroxy-carbofuran	4.68	237.1001	238.1071	Methomyl-d3
Acetochlor	13.59	269.1183	270.1245	Metolachlor-d6
Alachlor	13.65	269.1183	270.1245	Metolachlor-d6
Atrazine	8.54	215.0938	216.1003	Atrazine-d5
Azoxystrobin	11.30	403.1168	404.1228	Atrazine-d5
Benoxacor	9.96	259.0167	260.024	Diuron-d6
Carbaryl	7.33	201.079	202.0863	Carbaryl-d3
Carbendazim	3.89	191.0695	192.0768	Methomyl-d3
Carbofuran	6.73	221.1052	222.1125	Carbofuran-d3
Chlorfenvinphos	16.03 and 16.50	357.9695	358.9752	Chlorpyrifos-d5
Chlortoluron	8.30	212.0716	213.0789	Diuron-d6
Cybutryne (Irgarol)	12.15	253.1361	254.1435	Atrazine-d5
Cyproconazole	12.40	291.1138	292.1199	Tebuconazole-d6
DCPMU	8.95	218.0014	219.0086	Diuron-d6
DCPU	7.95	203.9857	204.9930	Diuron-d6
DEA	5.12	187.0625	188.0697	DEA-d6
DET	7.26	201.0781	202.0855	Atrazine-d6
DIA	4.22	173.0468	174.0541	DEA-d6
Dimethachlor	9.53	255.1026	256.1091	Diuron-d6
Dimethenamid	11.17	275.0747	276.0805	Metolachlor-d6
Dimethoate	4.76	228.9996	230.0062	Methomyl-d3
Dimetomorph	11.57 and 12.41	387.1237	388.1301	Metolachlor-d6
Diuron	9.30	232.0170	233.0239	Diuron-d6
Epoxiconazole	14.18	329.0731	330.0806	Tebuconazole-d6
Flurochloridone	12.82	311.0092	312.0165	Metolachlor-d6
Flurtamone	11.30	333.0977	334.1038	Diuron-d6
Flusilazole	14.84	315.1003	316.1061	Tebuconazole-d6
Hexazinone	6.67	252.1586	253.1659	Atrazine-d5
Imidacloprid	4.42	255.0523	256.0596	Carbofuran-d3
IPPMU	8.54	192.1263	193.1335	Diuron-d6
IPPU	7.65	178.1106	179.1179	Diuron-d6
Isoproturon	8.95	206.1419	207.1492	Diuron-d6
Linuron	10.86	248.0119	249.0184	Diuron-d6
Metazachlor	8.74	277.0982	278.1046	Metolachlor-d6
Methomyl	3.70	162.0463	163.0536	Methomyl-d3
Metolachlor	13.95	283.1339	284.1407	Metolachlor-d6
Metoxuron	5.73	228.0666	229.0738	Diuron-d6
Norflurazon	9.53	303.0386	304.0458	Diuron-d6
Norflurazon-desmethyl	8.30	289.0230	290.0288	Diuron-d6
Pirimicarb	5.97	238.143	239.1503	Pirimicarb-d6
Simazine	6.70	201.0781	202.0854	Atrazine-d5
Tebuconazole	15.73	307.1451	308.1524	Tebuconazole-d6
Terbuthylazine	11.30	229.1094	230.1155	Atrazine-d5
Thiodicarb	8.12	354.049	355.0551	Pirimicarb-d6

Field deployment for grab and passive sampling.

Two sampling types were used for measuring levels of chemical pollutants at both watersheds: The commonly used grab sampling, and passive sampling (POCIS). A summary of sampling strategy is presented in **Table V.3**.

Table V.3: Summary of field deployments for grab and passive sampler.

			2012	2013	2014	2015	2016
Auvézère	Grab samples	Our lab	26 samples/station – 3 stations	25 samples/station – 3 stations	24 samples/station – 3 stations		
		AEAG	14 samples on Arnac sampling point	6 samples on Arnac sampling point	5 samples on Arnac sampling point		
	Passive samples	Our lab	26 POCIS/station – 3 stations	24 POCIS/station – 3 stations	26 POCIS/station – 3 stations		
Aixette	Grab samples	SABV				4 samples/station	
	Passive samples	Our lab				5 POCIS/station – 3 stations	19 POCIS/station – 3 stations

Grab samples, which consist of a single sample of 1 to 3L taken in the sub-surface water in the mid-channel when possible, were taken at the 3 sampling points on the Auvézère watershed at each POCIS deployment from 2012 to 2014 (*i.e.* every 2 weeks). At this watershed, grab samples at Arnac downstream were also taken by the French water agency (5 to 14 grab samples per year for their own monitoring for the WFD). Grab samples at the Aixette watershed were only taken by the Syndicat d'Aménagement du Bassin de la Vienne (SABV), an independent governmental organization (5 samples in 2015).

POCIS were exposed for 14 days in both watersheds, every 14-days from January 2012 to December 2014 at the Auvézère watershed (75 POCIS exposures) and from January 2015 to October 2016 at the Aixette watershed (5 POCIS exposures in 2015 in parallel with the grab sampling; 19 POCIS exposures in 2016). POCIS were exposed in plastic cages or nets depending on the exposure site. Generally, one single POCIS was exposed per site and date, but triplicates were periodically done to control standard deviation.

Water samples and POCIS were transported in a cool box from the field to the laboratory and stored at 4°C until extraction.

Extraction of pesticides from POCIS.

After field deployment, each POCIS was rinsed with UPW. Briefly, POCIS were disassembled and the receiving phase was transferred into an empty 3 mL SPE polypropylene cartridge with polyethylene frits (purchased from Chromabond® Säulen from Macherey-Nagel), packed under vacuum and dried under nitrogen (Lissalde et al. 2011). Elution of passive sampler extracts was performed with 3 mL of methanol followed by 3 mL of a mixture of 75/25 v/v methanol/ethyl acetate (Lissalde et al. 2011). 10 µL of internal standards solution was added to the extracts collected from the grab samples. The final concentration of the internal standards was about 100 µg/L (before

analysis). The collected extracts were evaporated to dryness under nitrogen flow then reconstituted with 1 mL of 0:100 UPW:MeOH. Passive sampler extracts were diluted 10-times.

POCIS extract instrumental analysis.

An HPLC ultimate 3000 apparatus from Dionex was used (solvent rack SRD-3600 6 degasser channels, DGP-3600 M pump, WPS-3000 TSL Micro autosampler, TCC-3100 HP 1xRH 2P—6P thermostated column oven) for analyzing the Auvézère POCIS samples from January 2012 to September 2013. Chromatographic separation was performed with a Gemini-NX C18 3 µm, 110 Å, 110 mm x 2 mm with a SecurityGuard cartridge Gemini-NX C18 4 mm x 2.0 mm, both from Phenomenex. The injected sample volume was 40 µL. Column and autosampler temperatures were maintained at 40°C and 10°C, respectively. Acetonitrile and UPW with 5 mM ammonium acetate were used with an analytical gradient of 15 min. More information is in a previous work (Lissalde et al. 2011) and in **Table V.4**. The detector was a mass spectrometer: an API 2000 triple quadrupole (QqQ) from Applied Biosystems/MDS/SCIEX.

Table V.4: Optimized parameters of the HPLC-QqQ method.

Linear gradient used for the chromatographic separation.

Time (min)	UPW (%)	MeOH + 5mM ammonium formate and 0.1% formic acid (%)	Flow (µL/min)
0	90	10	400
1	90	10	400
4	70	30	400
8	60	40	400
9.5	20	80	400
10.5	20	80	400
11	90	10	400
15	90	10	400

A UHPLC 1290 Infinity apparatus from Agilent was used for the Auvézère POCIS samples from November 2013 to December 2014 and for all Aixette POCIS samples. Chromatographic separation was performed with a Zorbax Eclipse Plus C18 Rapid Resolution High Definition column 150 mm x 2.1 mm 1.8 µm from Agilent. The injected sample volume was 5 µL. Column and autosampler temperatures were maintained at 30°C and 5°C, respectively. MeOH with 5 mM ammonium acetate and 0.1% formic acid and UPW were used with an analytical gradient of 20 min (see **Table V.5A** for gradient). The detector was a tandem mass spectrometer composed of a quadrupole combined with a time-of-flight (Accurate Mass LC/MS 6540 Agilent).

Both mass spectrometers were equipped with an electrospray ionization source (ESI) and were operated in the positive ionization mode. For the QqQ, mass acquisition was performed in the SRM mode. QqQ parameters are presented in a previous work (Lissalde et al. 2011). For the Q-TOF, mass acquisition was performed in the "All-ions" mode with 0, 10, 20 and 40 eV as collision energies. Source parameters and other TOF-MS parameters were optimized as shown in a previous paper (Guibal et al. 2015b) and are presented in **Table V.5B**. The instrumental limit of quantification (LOQ) and injected mass are presented for both analytical methods in **Table V.6**. Similarly,

analytical gradients for the HPLC ultimate 3000 and the UHPLC 1290 infinity were presented in Lissalde et al., (2011) and Guibal et al., (2015b), respectively.

Table V.5: Optimized parameters of the UHPLC-Q-TOF method.

A: Linear gradient used for the chromatographic separation.

Time (min)	UPW (%)	MeOH + 5mM ammonium formate and 0.1% formic acid (%)	Flow (µL/min)
0	90	10	400
0.5	90	10	400
3.5	50	50	400
14	30	70	400
17	10	90	400
20	10	90	400

B: Linear gradient used for the chromatographic separation.

Parameter	Value
Sheath gas temperature*	375°C
Drying gas temperature*	130°C
Drying gas flow*	13 L/min
Fragmentor voltage*	120 V
Nebulizer pressure*	35 psi
Capillary voltage	3500 V
Skimmer voltage	65 V
Mass range (m/z)	100 – 1500
Reference mass	922.0098 Da
Octopole 1 RF	750 V
Nozzle voltage	300 V

Table V.6: Instrument limit of quantification (in µg/L and injected mass in pg) for the both mass spectrometry (n.c. not calculated).

Pesticide	UHPLC-(Q)-ToF (Guibal et al. 2015b)		HPLC-QqQ (Lissalde et al. 2011)	
	LOQ (µg/L)	Injected mass (pg)	LOQ (µg/L)	Injected mass (pg)
3-hydroxy-carbofuran	2	10	2	80
Acetochlor	5	25	1	40
Alachlor	1	5	2	80
Atrazine	0.5	2.5	1	40
Azoxystrobin	0.1	0.5	1	40
Benoxacor	0.5	2.5	n.c.	n.c.
Carbaryl	0.5	2.5	5	200
Carbendazim	0.5	2.5	1	40
Carbofuran	0.5	2.5	1	40
Chlorfenvinphos	0.1	0.5	1	40
Chlorpyrifos	n.c.	n.c.	1	40
Chlortoluron	0.1	0.5	2	80
Cybutrine (Irgarol)	0.1	0.5	1	40
Cyproconazole	0.5	2.5	n.c.	n.c.
DCPMU	0.5	2.5	2	80
DCPU	1	5.0	5	200
DEA	0.5	2.5	1	40
DET	0.5	2.5	1	40
DIA	0.5	2.5	1	40
Dimethachlor	0.5	2.5	n.c.	n.c.
Dimethenamid	0.1	0.5	n.c.	n.c.
Dimethoate	0.1	0.5	1	40
Dimethomorph	0.5	2.5	1	40
Diuron	0.1	0.5	1	40
Epoxiconazole	0.5	2.5	n.c.	n.c.
Flurochloridone	0.5	2.5	n.c.	n.c.
Flurtamone	0.1	0.5	n.c.	n.c.
Flusilazole	0.5	2.5	n.c.	n.c.
Hexazinone	0.1	0.5	1	40
Imidacloprid	0.1	0.5	n.c.	n.c.
IPPMU	0.5	2.5	1	40
IPPU	0.5	2.5	1	40
Isoproturon	0.1	0.5	1	40
Linuron	0.1	0.5	1	40
Metazachlor	0.1	0.5	1	40
Methomyl	1.0	5.0	1	40
Metolachlor	0.5	2.5	2	80
Metoxuron	0.1	0.5	1	40
Norflurazon	0.1	0.5	n.c.	n.c.

Norflurazon-desmethyl	0.1	0.5	n.c.	n.c.
Pirimicarb	0.5	2.5	1	40
Simazine	0.1	0.5	1	40
Tebuconazole	0.5	2.5	n.c.	n.c.
Terbuthylazine	0.1	0.5	1	40
Thiodicarb	0.1	0.5	1	40

Quality control.

All experiments were performed with quality controls. For sample analysis, QA/QC were used to control any deviations. Triplicates of POCIS were deployed twice at the Auvézère watershed at the Quatre-Moulins sampling point: 04/10/2012 - 06/18/2012 and 05/13/2013 – 07/08/13. The deviations in pesticide TWAC were in accordance with the study of Poulier et al. (2014).

Additionally, POCIS blanks were used as field and laboratory controls during all trials at the Aixette and Auvézère watersheds. POCIS blanks were taken to the sampling sites and opened when POCIS samplers were manipulated (controlling for contamination during storage, transportation, processing and analytical procedures). POCIS blank were eluted and analyzed with POCIS samplers.

Calculation of time-weighted average concentration (TWAC) with POCIS.

POCIS is considered an integrative sampler and is typically used during the linear sorption phase; analyte concentrations in water (*i.e.* a time-weighted average concentration, TWAC) can be calculated by the following equation (Alvarez et al. 2004, Mazzella et al. 2007, Morin et al. 2012):

$$C_{POCIS} = C_W * k_u * \mathrm{t} \qquad \textbf{Equation V.1}$$

with C_{POCIS} the analyte concentration in the receiving phase (µg/g); C_w the water analyte concentration (µg/L); t the exposure time (days) and k_u the uptake rate (L/g/d). The constant k_u can be calculated from the analyte sampling rate R_s (L/d):

$$k_u = \frac{R_s}{m_{sorbent}} \qquad \textbf{Equation V.2}$$

with $m_{sorbent}$ the mass of sorbent recovered inside the POCIS (g). R_s is a specific constant for each analyte and, for this work, R_s values were taken from Lissalde et al. (2011) and Poulier et al. (2015).

All statistical analyses and representations were done with XLSTAT software (**Figure V.9**, **Figure V.13** and **Figure V.14**).

Extraction and analysis of pesticides from grab samples.

Grab samples from the Auvézère and Aixette watersheds taken by the French water agency or the SABV were analyzed by the Corrèze Analysis Laboratory (France), accredited by a French accreditation organization (COFRAC – Comité d'Accréditation Français) under agreement n°1-0782.

Grab samples for this study were extracted by solid phase extraction (SPE) using Chromabond® HR-X 60 mg, 3 mL 85 µm purchased from Macherey-Nagel. The SPE step was performed as follows: 100 mL of water samples were filtered with 0.7 µm GF/F filters (Whatman), water pH was adjusted to 7 with 1M acidic or basic solution, HCl or NaOH, respectively. Cartridges were conditioned with 5 mL of MeOH then 5 mL of UPW. 10 µL of surrogates (simazine-d5, prometryn-d6 and monuron-d6) were added to 100 mL of water sample and were passed through the cartridge, then dried under nitrogen stream and stored at 4°C before elution.

Elution of grab extracts was performed with 3 mL of methanol followed by 3 mL of a mixture of 75/25 v/v methanol/ethyl acetate. 10 µL of internal standards solution was added to the extracts collected from the grab

sampler. The collected extracts were evaporated to dryness under nitrogen flow then reconstituted with 1 mL of 90:10 UPW:MeOH. The final concentrations of the internal standards and surrogate were about 100 µg/L (before analysis).

The method for analyzing pesticides in grab water extracts was the same as the method described previously for POCIS extracts.

RESULTS AND DISCUSSION

Contribution of the two sampling techniques.

Figure V.4 presents three years of sampling at the Auvézère watershed (at Arnac Downstream) with two sampling techniques: grab sampling (from the French water agency and from our laboratory) and passive sampling with POCIS. Three POCIS samples (two in 2012 and one in 2013) were unusable (POCIS lost or damaged). During 14-day stream deployment samplers can experience varied environmental conditions (high flow, plant debris, animal or human presence) and can be damaged. Nevertheless, the percentage of lost POCIS samples is very low *c.a.* 1.4% (4 POCIS lost for 282 deployed).

Grab sample data were highly variable, as samples were taken at different time frequencies by the French water agency and our laboratory, making it difficult to understand true pesticide contamination of these waters. Nevertheless, when grab samples were taken by both groups in the same period, the pesticide content of the waters was similar.

Figure V.4 suggests three scenarios when comparing pesticide contamination in headwater streams using a grab sample strategy or a POCIS strategy: i) when pesticide concentrations determined by grab sampling were largely above those measured by passive samplers; ii) when pesticide concentrations were similar and iii) when pesticide concentrations were below LOQ.

The first case (i) was seen several times: *e.g.* (for more than 300%) 10/04/2012, 26/11/2012, 17/12/2012, 08/07/2013, 14/10/2013 27/10/2014 and 10/11/2014 with grab sampling 660, 480, 400, 345, 315, 330 and 345% higher than POCIS, respectively. In headwater streams, studies have shown peaks of pesticide concentration lasting 1 to 4 days, likely due to the periodic use of pesticides and the small size of the streams (Kreuger 1998, Liess et al. 1999, Williams et al. 1995). Passive samplers are deployed for several days (14 in our study), and if there is a concentration peak during this time it will be averaged over the deployment period. Thus, if a grab sample is taken during the peak, it will naturally have a higher concentration than POCIS, as noticed by Schafer et al. (Schafer et al. 2008). Differences in pesticide content between sampling methods can also result from cut-off thresholds of the filters used (0.1µm for POCIS membranes and 0.7 µm for grab samples), with the larger grab sample pore size resulting in more consideration of pesticides linked to particulate materials (Boithias et al. 2014, Poulier et al. 2014).

The second scenario (ii), when concentrations measured by POCIS samples are similar to those measured by grab samples (performed in WFD recommendations or our laboratory), was seen for 10 samples (difference ≤ 20%) and less so for 24 samples (difference ≤ 50%). Similar results were reported by Poulier et al. (Poulier et al. 2014) for four quantified pesticides (atrazine, dimethenamid, DEA and metolachlor) sampled by POCIS and grab sampling (dissolved fraction), and by Novic et al. (Novic et al. 2017) where passive and grab sampling had a mean difference

less than a factor of 1.5. Such similarities are likely due to steady pesticide concentrations in the water stream during the 2 weeks of passive sampler exposure.

When pesticides are at very low concentrations in water (the third case, iii), the two sampling strategies do not give the same information. Here, the advantage of POCIS is seen: It accumulates compounds during its deployment and allows lower quantification limits, as already described by Zhang et al. (Zhang et al. 2008) and Lissalde et al. (Lissalde et al. 2011). This benefit is obvious in **Figure V.4**, where the contamination background noise of the headwater stream was systematically quantified by POCIS. Thus, passive sampling allows sampling of sporadic contamination but only gives TWAC and not peaks. In the monitoring of a small watershed, the two sampling techniques are complementary and the choice of sampling strategy depends on the desired information and the budget available.

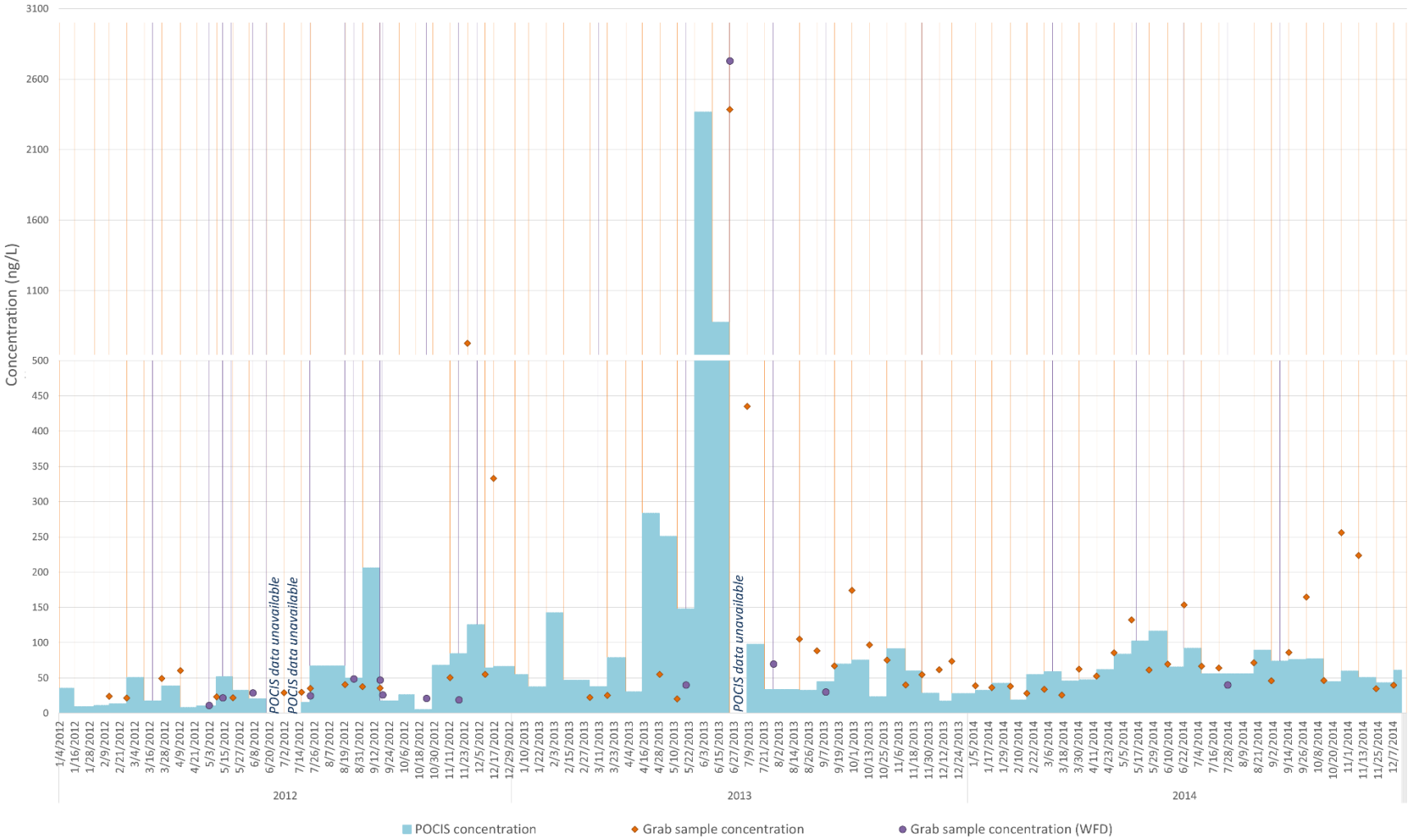

Figure V.4: Monitoring by both passive and grab sampling at the Auvézère watershed, Arnac downstream sampling point from 2012-2014 (total pesticide concentration). Orange bars indicate grab samples and orange spots the concentration of these grab samples from our laboratory analysis. Purple bars indicate grab samples and purple spots the concentration of these grab samples from regulatory monitoring networks. Blue bars indicate POCIS concentration. Lost or damaged passive samplers are indicated « POCIS data unvailable ».

Sensitivity of analytical methods.

Currently, a wide range of LC-MS equipment is available for pesticide quantification and all have different limits of quantification (LOQ). While the majority are sufficiently sensitive for mildly contaminated rivers, quality of monitoring is still dependent on the mass spectrometry detector used, especially in very mildly polluted freshwaters. **Figure V.5** shows POCIS and grab monitoring of the Auvézère River at Quatre-Moulins from 2012-2014. For the first 21 months, POCIS extracts and grab samples were analyzed on a different LC-MS compared to the following months, clearly leading to more sporadic results with the less sensitive equipment (LOQ higher by a factor of 2 to 10, **Table V.6**). This makes interpretation of the contamination more difficult. A lower LOQ with a passive sampler allows definition of pesticide contamination background noise (in the range 20-70 ng/L); for grab samples, only 7 were above LOQ with the less sensitive LC-MS apparatus. Thus, both sampling method and analytical choice are important for monitoring success, and natural spaces with very low background contamination need at least a mid-range LC-MS.

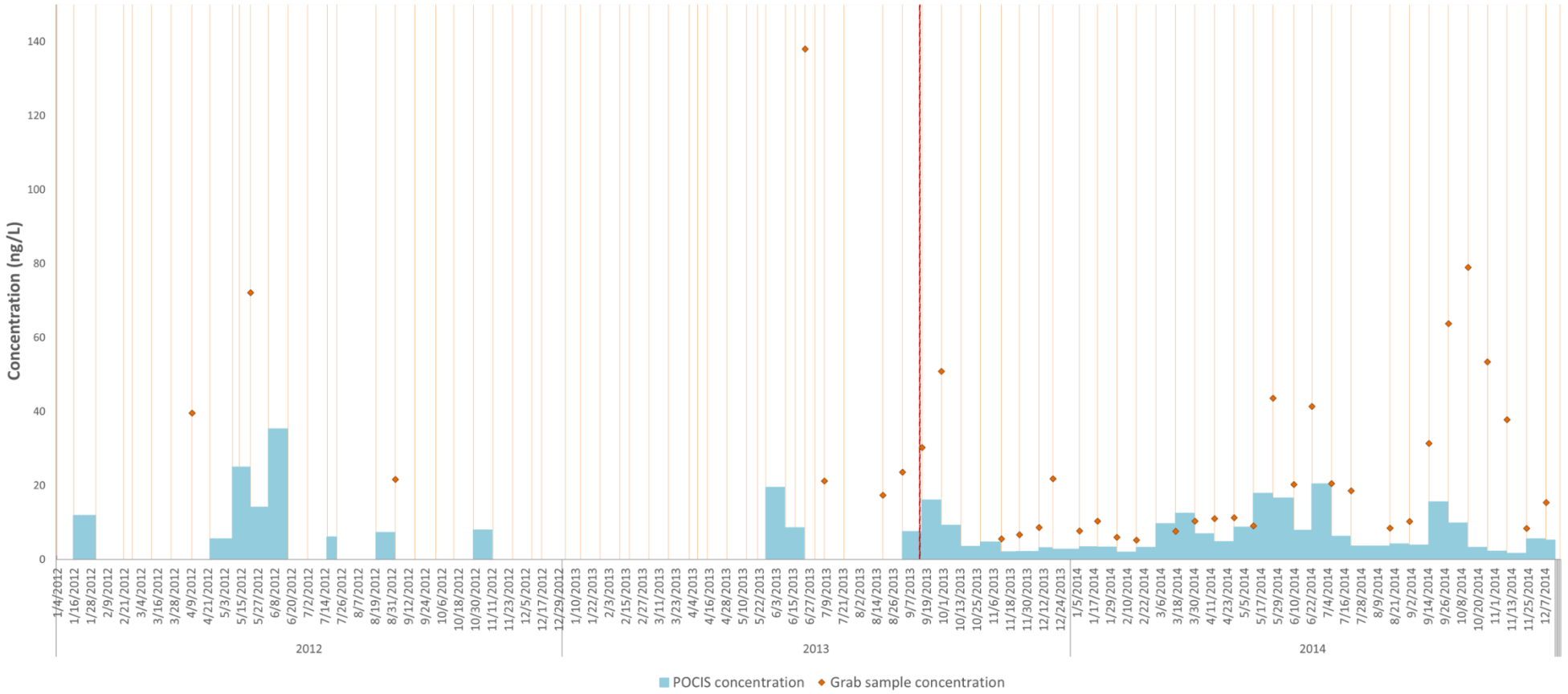

Figure V.5: Monitoring at the Auvézère watershed from 2012-2014 (total pesticide concentration). The red dotted line represents the change in LC-MS apparatus for POCIS and grab sample analysis. Total pesticide content was calculated when pesticide concentrations were above the LOQ (blue bars) in POCIS samples. Orange bars indicate when grab sampling was performed and diamonds show total pesticide content when detection was above LOQ.

Headwater stream contamination.

Detection frequency and maximum concentration with passive samplers.

The detection frequencies of the different pesticides (with action classes) and their highest concentrations are reported in **Figure V.6** and **Figure V.7**. First, observation of pesticide classes (herbicides, insecticides or fungicides) in the river catchments give an indication of the treatments used on local cultures and is important for characterizing contamination. Herbicides were prevalent in both watersheds and this can be explained by plurality of use (weed control, inter-row weeding in orchards or non-agricultural treatments). Similar results were recently obtained by Van Metre et al. (Van Metre et al. 2017) in a study of contamination of 100 small streams in the Midwest of the USA. These authors also showed that herbicides are prevalent compounds in small rivers in agricultural areas. In both watersheds of this study, 60% of the compounds found were common compounds and their presence can be explained by land use and practices found in extensive agricultural breeding of Limousin cattle. Some disparities between the years were observed (**Figure V.8A** et **B**), easily explained by the seasonality of treatments and by hydrological disparities from one year to another. For example, fungicides were observed at Arnac downstream throughout 2013, a very rainy year which induced an increase in treatment to prevent apple disease.

Detection frequencies are not correlated (**Figure V.9**) with maximum concentrations. A compound with a high detection frequency can be detected at a low maximum level (*e.g.*, norflurazon in Arnac downstream, 40% and 1 ng/L) whereas a compound not often detected can be present at relatively high concentrations (carbaryl in Arnac downstream, 1% and 40 ng/L).

Among the top six detected pesticides, DEA, atrazine and diuron were systematically present in all rivers with detection frequencies between 20 and 100%. At the Aixette catchment, metolachlor and chlortoluron were also among the top in detection frequency, whereas at Auvézère, norflurazon-desmethyl, imidacloprid, DIA, simazine and dimethenamid were among the most detected pesticides, depending on sampling point. The different watersheds had different numbers of detected pesticides. The most contaminated was Arnac stream with 23 pesticides and metabolites detected downstream and 20 upstream. At the Auvézère watershed, the tributary was more contaminated than the main river (higher detection frequencies, higher number of compounds, higher maximal concentrations) (**Figure V.6**). In contrast, the Arthonnet tributary of the Aixette catchment was less contaminated than the main river; 14 compounds detected at Arthonnet compared to 20 at the Aixette River but Aixette Upstream were more contaminated than Aixette Downstream.

Figure V.6: Pesticide detection frequencies and highest concentrations determined with POCIS at the Aixette watershed in 2016 (POCIS exposures=19): A: Aixette Upstream, B: Aixette Downstream and C: Arthonnet. Herbicides, fungicides and insecticides are in purple, blue and yellow, respectively.

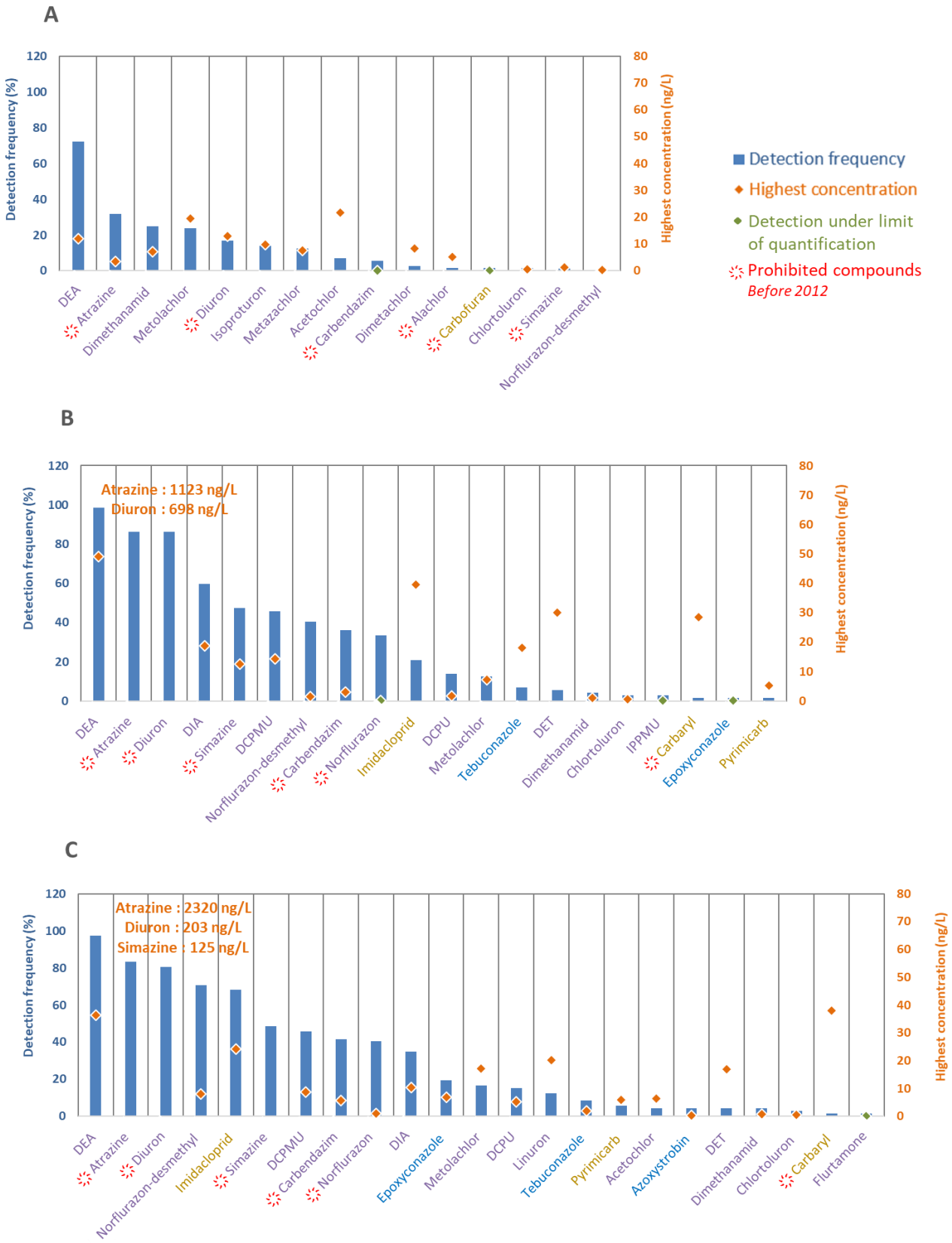

Figure V.7: Pesticide detection frequencies and highest concentrations determined with POCIS at the Auvézère watershed from 2012-2014 (POCIS exposures=75): A: Auvézère, B: Arnac Upstream and C: Arnac Downstream. Herbicides, fungicides and insecticides are in purple, blue and yellow, respectively.

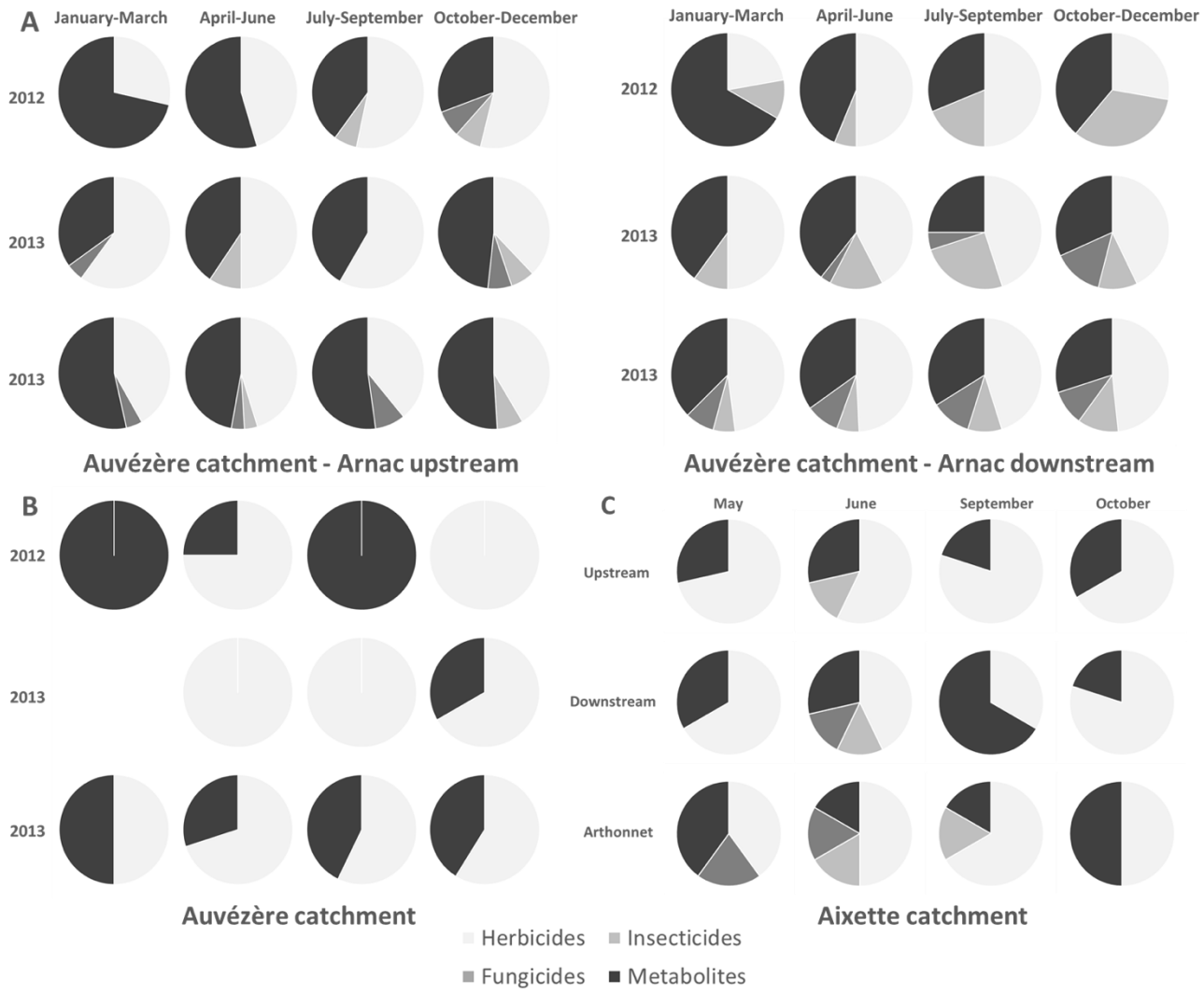

Figure V.8: Pesticide classes retrieved at the Auvézère watershed from 2012-2014, A : Arnac watershed (upstream on left and downstream on right) and B : Auvézère watershed. Pesticide classes retrieved at the Aixette watershed in 2016, C : Aixette upstream, Aixette downstream and Arthonnet tributary.

At the Auvézère catchment (**Figure V.7**), there was significant atrazine and diuron contamination: Total concentrations (obtained by POCIS) of 1100 and 2300 ng/L for atrazine upstream and downstream, respectively and 200 and 700 ng/L for diuron upstream and downstream, respectively. We might conclude that contamination tends to be higher in small catchments, where contamination concentrations can reach µg/L.

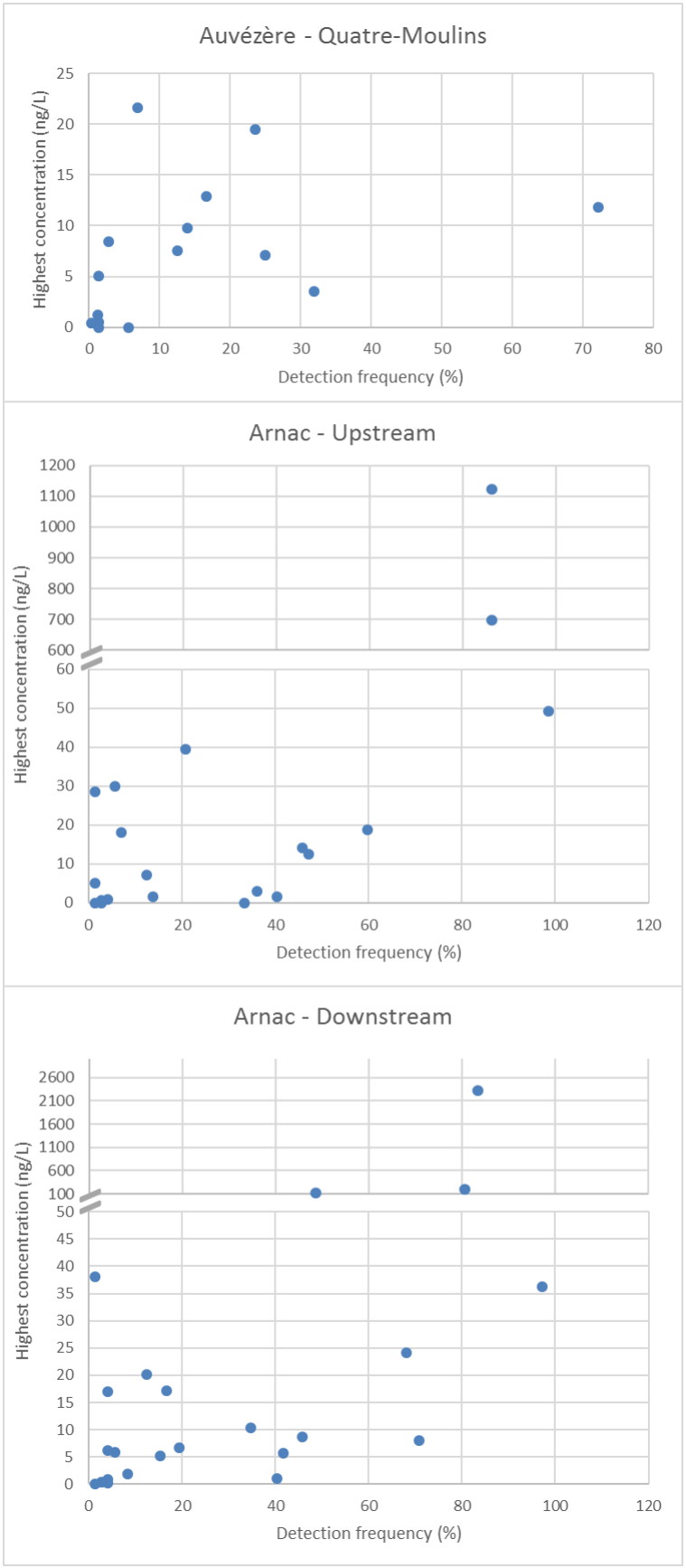

Figure V.9: Correlation between the highest concentrations and the detection frequencies of the pesticides retrieved on Auvézère catchment.

Relationship between water contamination and pesticide use.

Regarding allowed *vs* prohibited pesticides detected in the two catchments, it seems that some prohibited compounds are still being used (**Figure V.10** and **Figure V.11**). The top five prohibited pesticides at the Arnac watershed were atrazine, simazine, carbendazim, norflurazon and diuron (**Figure V.7B** and **C**). At the Aixette, diuron was the most common, with 100 % quantification, and triazines (atrazine, simazine and terbuthylazine) were the other prohibited pesticides detected (**Figure V.6**).

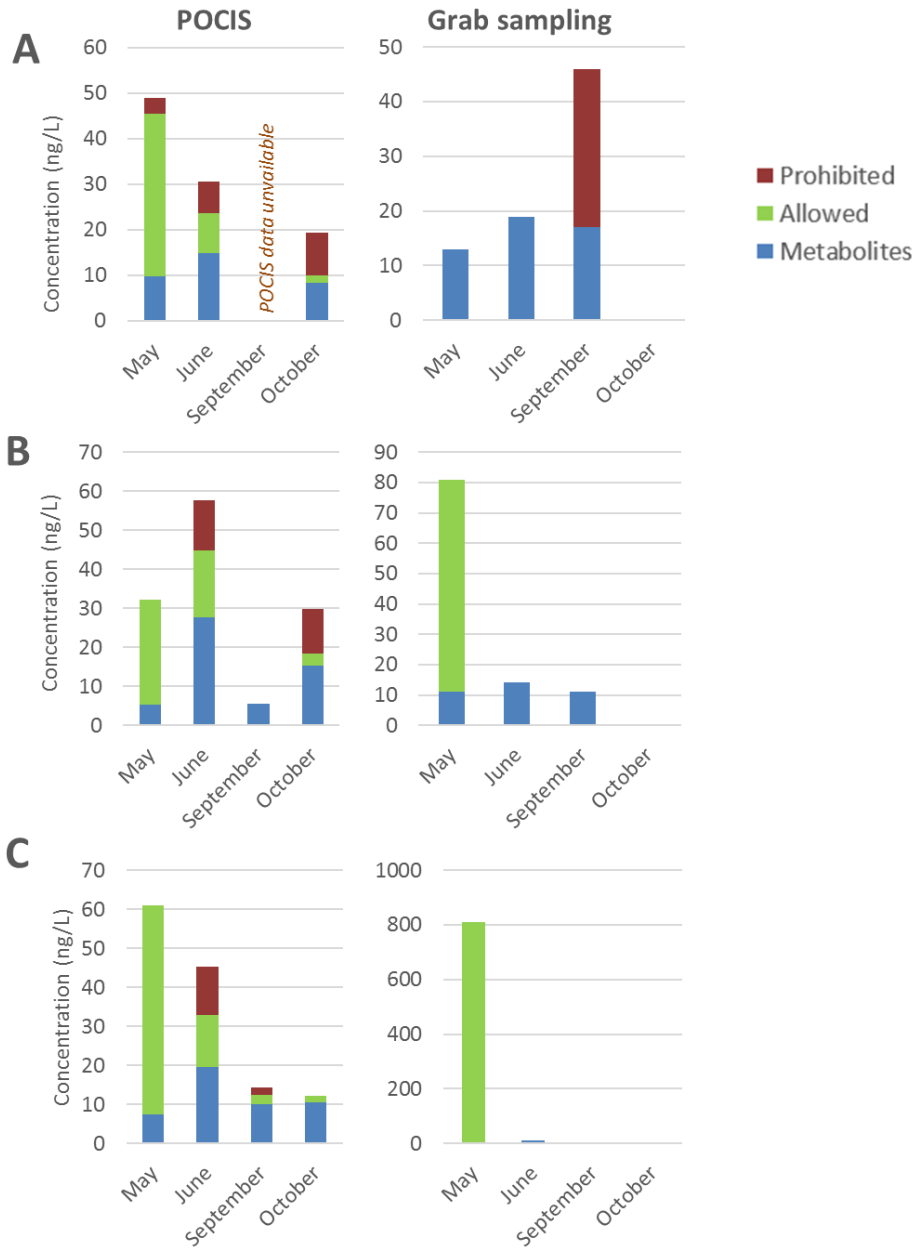

Figure V.10: Monitoring at the Aixette watershed in 2015, POCIS sampling on the left and grab sampling from the regulatory monitoring on the right, A: Aixette upstream sampling point, B: Aixette downstream sampling point and C: Arthonnet sampling point. Compounds are shown as prohibited (red) and allowed (green) concentrations in France and metabolites of pesticides (blue).

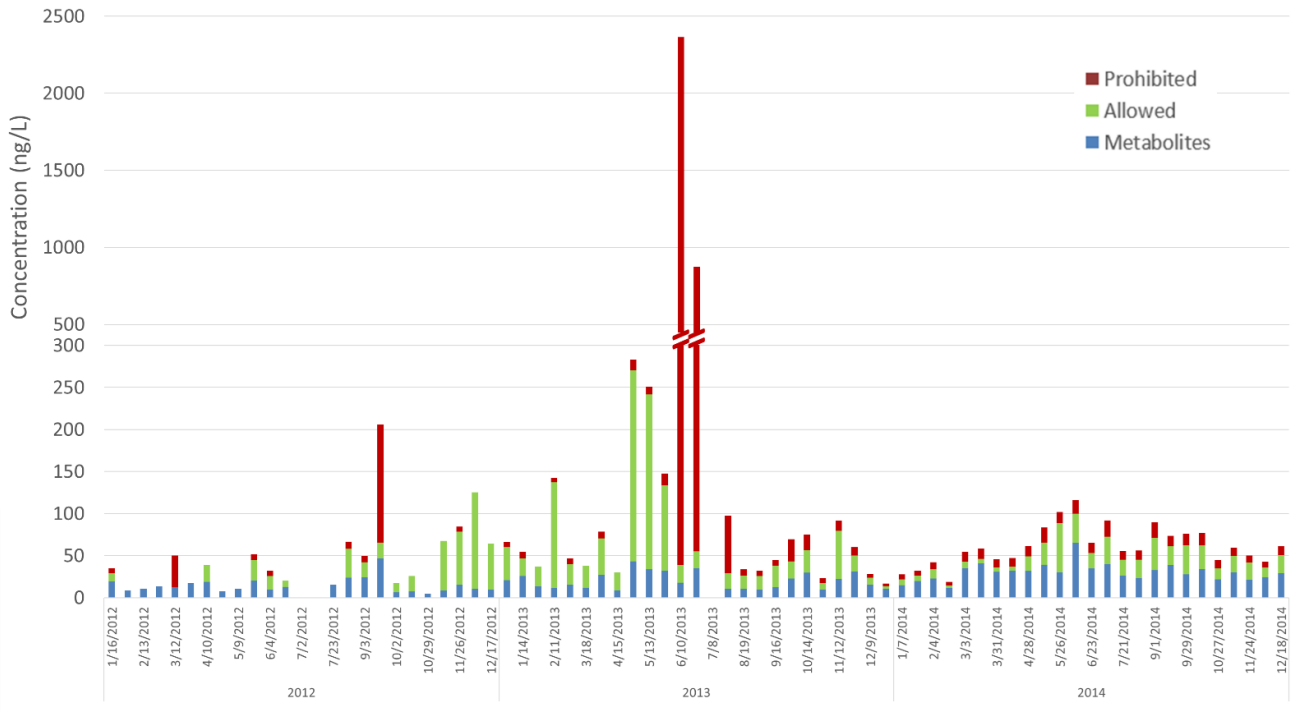

Figure V.11: Monitoring at the Auvézère watershed, Arnac downstream sampling point from 2012-2014. Compounds are shown as prohibited (red) and allowed (green) concentrations in France and metabolites of pesticides (blue).

Atrazine was prohibited in France in 2003, thus its quantification could only be explained by release from soil or illegal use. An important atrazine contamination peak (2300, 2300 and 2700 ng/L for POCIS sample, grab sample by our laboratory and by water agencies, respectively) occurred in 2013 at Arnac downstream in mid-June. Such a high release of atrazine from groundwater is not consistent with the crystalline geology (granite, gneiss) of the area nor the low quantity of groundwater. Moreover, the DEA/atrazine ratio, an efficient indicator of time since contamination as DEA is an atrazine metabolite, was between 0.01 and 0.2 in May-July 2013 and between 2-4 at other times and a low ratio indicates recent atrazine use rather than soil release (Shipitalo and Owens 2003, Thurman and Fallon 1996). Thus, the high atrazine contamination in spring 2013 can most likely be attributed to illegal use (**Figure V.12**). At Aixette, the detection frequency of atrazine was 100 % but concentrations were lower than 5.5 ng/L. DEA is the main metabolite of atrazine and it was quantified with the highest frequency (100 % at Aixette and over 72 % at Auvézère) but concentrations were relatively low, with values under 50 ng/L for Auvézère and 30 ng/L for Aixette. This metabolite is the most quantified compound in France for the past several years (CGDD/SOeS 2015, IFEN 2006).

Simazine, from the same family as atrazine, was also prohibited in 2003 in France and it was detected at the two catchments at low levels (<10 ng/L, except one peak of 124 ng/L at Arnac downstream in September 2012). Even at the low levels detected, simazine presence can be due to low levels of recent use; especially likely considering that in this watershed, as discussed above, simazine soil release is expected to be below 10ng/L. Simazine detection frequencies were moderate, 50% at the Arnac and Aixette and less than 3% at Arthonnet and Auvézère.

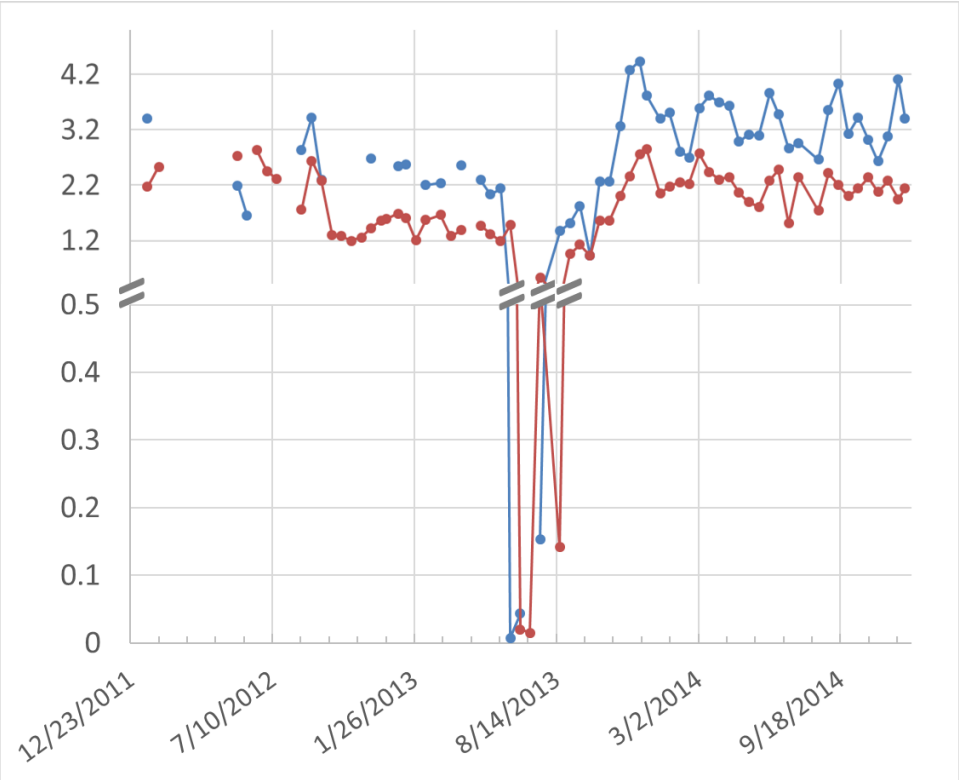

Figure V.12: DEA/Atrazine ration on Arnac watershed (downstream in blue and upstream in red).

Carbendazim, previously used in orchards, was prohibited in 2009 in France. This compound was only detected at the Auvézère catchment, which is characterized by apple orchards (0.7% of utilized agricultural land). Detection frequencies at Arnac were about 40% but levels were steady and very low (< 6 ng/L), most likely indicating a release from soil.

Norflurazon and its metabolite norflurazon-desmethyl were detected only at the Arnac catchment. This herbicide was prohibited in 2004 and was previously used in orchards to control germinating weeds. It was stable in soil and its key metabolite norflurazon-desmethyl is formed in soil. The metabolite was more common, with detection frequencies between 40 and 70%, but at steady and very low levels (maximum of 8 ng/L).

Authorized pesticides detected in the main river (Auvézère) were different from those in the tributary (Arnac) on Auvézère wartershed. Chloroacetamids (acetochlor, metazachlor, metolachlor, dimethenamid, dimethachlor) and isoproturon were either in lower concentration or not detected at all in the Arnac stream. These compounds are typically used in crop weed control or cultivated grassland (23% of the utilized agricultural land), commonly found in the Auvézère watershed.

Diuron was present in the Arnac watershed with 3 peaks: December 2012 (100 and 273ng/L), February 2013 (120 and 326 ng/L) and April-May 2013 (200 and 698 ng/L) at downstream and upstream sampling stations, respectively. This herbicide is currently authorized only for roof treatment in France and could have been used in treatment of animal housing roofs.

Imidacloprid was detected only on the Arnac watershed with 21 and 68% for detection frequencies with 40 and 24 ng/L for maximal concentrations (for Arnac Upstream and Arnac Downstream, respectively) and came from agricultural use due to the presence of apple orchard but also from none-agricultural use (e.g. garden).

At the Aixette catchment, the pesticides detected were mainly chloroacetamids (metolachlor, dimethenamid, metazachlor), sulfonylureas (diuron, chlortoluron, isoproturon and their metabolites DCPMU and IPPMU) and triazoles (epoxiconazole, tebuconazole, cyproconazole). The first and second classes are used as herbicides on crop cultures or cultivated grassland and the third class are fungicides for wheat, barley and rye.
The presence of these compounds is likely an indicator of changes in agricultural practices at the Aixette and Auvézère watersheds. Both watersheds are in areas where Limousin cows are raised extensively and the desire to improve meat quality has pushed farmers to become self-sufficient in producing cereal for livestock feed and cultivating grasslands directly on their farms. This change was put in place in 2010 by the Regional Agricultural Chamber for economic reasons (encourage economically sustainable rural agricultural for young farmers).

Headwater stream biodiversity preservation and pesticide contamination.

Several authors have studied pesticide effects on aquatic habitats (Cooper 1993, Heckman 1982, Liess and Schulz 1999, Schafer et al. 2007), particularly important here because headwater streams play a huge role in biodiversity (Finn et al. 2011, Lowe and Likens 2005, Meyer et al. 2007). There are two approaches to estimate the risk of pesticide impact on organisms in headwaters: chronic toxicity based on guide values of the AA-EQS (Annual Average-Environmental Quality Standards) and using the WFD or NOEC (No Observed Effect Concentration) literature values for different aquatic organisms and acute toxicity based on guide values of the MAC-EQS (Maximum Annual Concentration-Environmental Quality Standards) and using the WFD or LC50 (Half maximal Lethal Concentration) or EC50 (Half maximal Effective Concentration) literature values for different aquatic organisms.

Figure V.13 illustrates annual average concentrations obtained by passive and grab sampling with a box and whiskers graphic for atrazine and imidacloprid. Two other examples, diuron and metolachlor, are shown in **Figure V.14**.

In 2013, both passive and grab sampling showed an important contamination for atrazine in 2013. The grab sampling value (2700 ng/L from the French water agency) was higher than the French Environmental Quality Standard Maximal Admissible Concentration (MAC-EQS), which is used to estimate acute toxicity in the context of WFD and is 2000 ng/L; such a high atrazine concentration can pose an acute toxic risk for aquatic life. This result shows that the grab sampling data were useful to obtain the maximal concentration when the grab sample was done at the right time and could be used for the WFD environmental quality of rivers.
For chronic toxicity, the AA-EQS is the guide value in WFD and **Figure V.13** shows that three years of POCIS estimates of annual averages were more realistic than grab samples. It is inherent in the principle of operation of the POCIS sampler, that is to give time-weighted average concentrations calculated over long durations, to provide more reliable annual averages than grab samples. For all the compounds detected with an AA-EQS value, the POCIS sampling average was under the guide values which suggests no risk of chronic toxicity for aquatic life. Schafer et al. (Schafer et al. 2007) suggest that's effects may also occur below levels that are commonly thought to be protective.

Table V.7 gives the NOEC for the 21 compounds (without metabolites) detected at the two watersheds. For all compounds, both average and peak concentrations detected in this study were well below NOEC. Nevertheless, there were 20 and 23 compounds at the Aixette and Auvézère watersheds, respectively, and potentially others not looked for here (*e.g.* other pesticides, pharmaceuticals, heavy metals), and these "cocktails" can change the toxicity of the individual compounds (synergism or antagonism) and may affect biodiversity (Belden et al. 2007, Schulz and Liess 1999, Villeneuve et al. 2011). For example, a mixture of four herbicides, (atrazine, diuron, metolachlor and cybutryne - the first three of which were detected at the Auvézère catchment) had chronic effects on photosynthesis or on effective quantum yield in the seagrass *Zostera noltei* (Diepens et al. 2017). Effective quantum yield was inhibited 95, 98 and 99% following exposure to mixture of 100 µg/L of each pesticide for 6, 24 and 96 h, respectively. A less important effect (10, 37 and 41% inhibition) was observed at 10 µg/L. Relyea et al. (Relyea 2009) tested a cocktail of contaminants (*e.g.* atrazine, acetochlor or metolachlor for herbicides and carbaryl or chlorpyrifos for insecticides) at low concentrations (the nominal concentration was 10 µg/L) on aquatic communities including zooplankton, phytoplankton or larval amphibians and showed that some cocktails can eliminate 99% of leopard frogs while the same compounds alone result in more limited mortality (24% for the same aquatic communities). In this study, the impact of a pesticide mix on zooplankton was close to the impact of individual effects while for phytoplankton, effects of a pesticide mix were predictable (summation) from individual effects.

Taken together, the above data indicate that in headwaters, individual pesticide peaks can pose an acute toxicity risk for aquatic life, but it is more difficult to evaluate the risk of chronic toxicity from the background noise of a cocktail of pesticides. Specific studies on fauna and flora should be conducted in watershed headwaters to validate if, for example, the Pesticide Toxicity Index (PTI) (Nowell et al. 2014), is suitable for assessing toxicity.

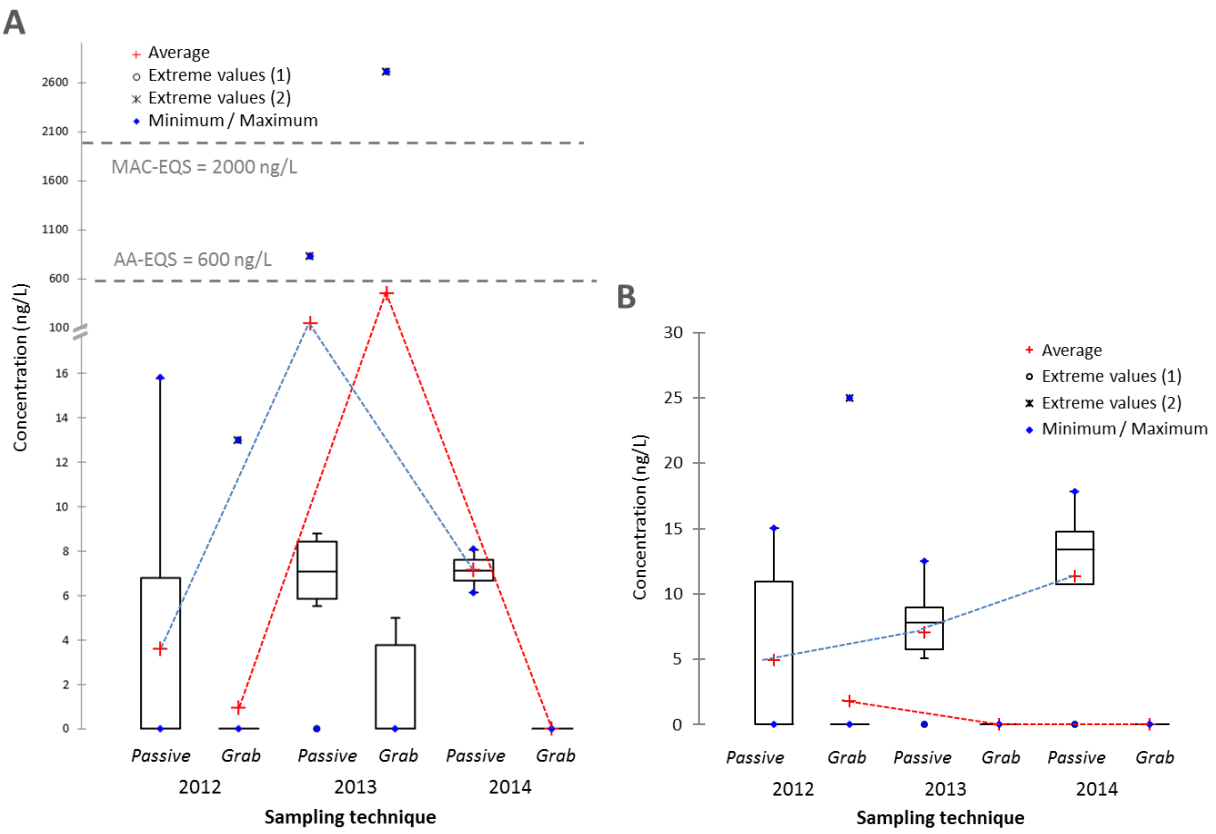

Figure V.13: Comparison of data distribution and yearly average concentrations (2012-2014) for atrazine (A) and imidacloprid (B) at the Arnac downstream sampling point. Only grab data from French water agency and passive sampling data with common dates were used. The French Environmental Quality Standard Annual Average and Maximal Admissible Concentration – (AA – EQS and MAC – EQS) are indicated for atrazine. Boxes represent median values and quartiles.

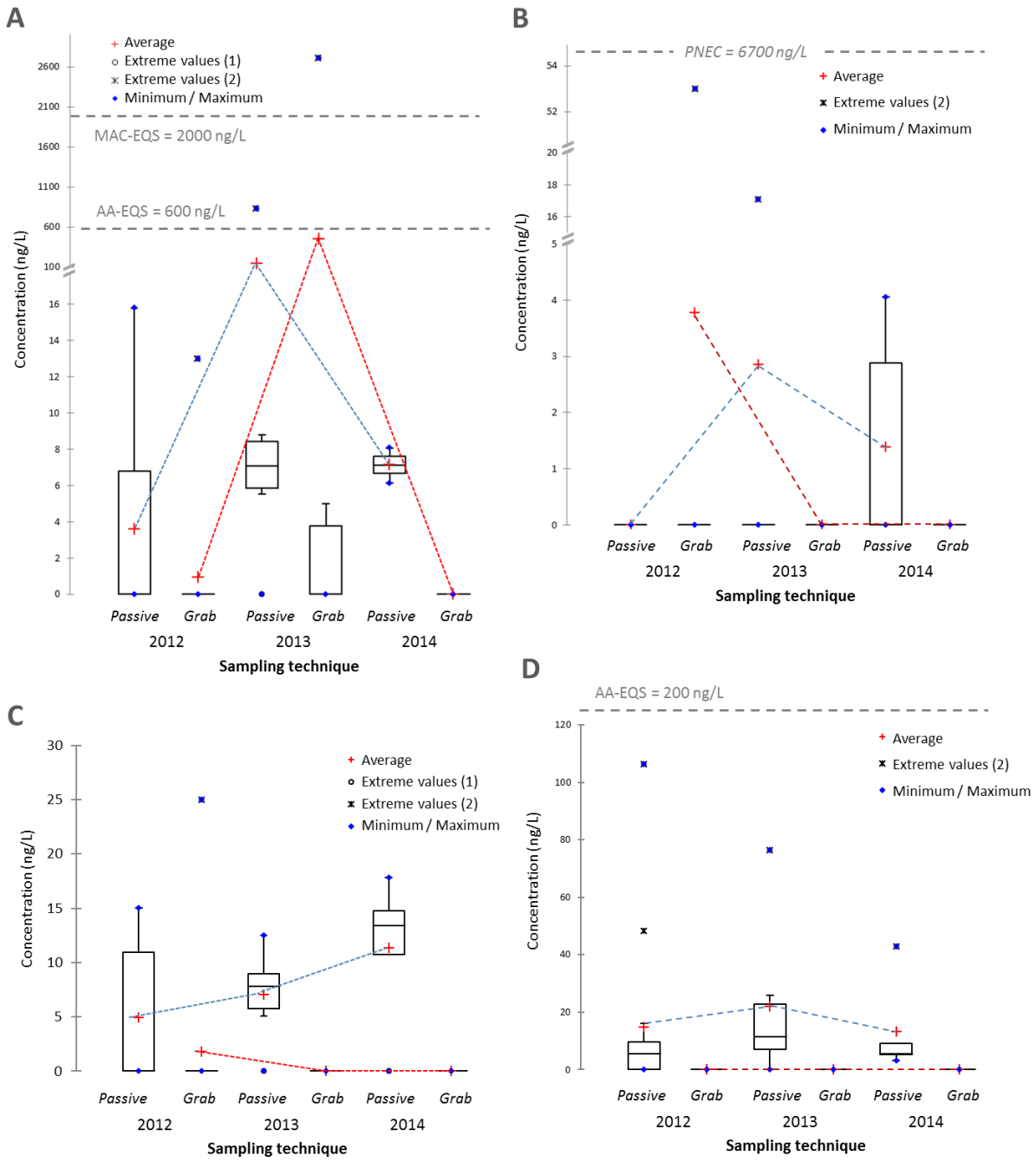

Figure V.14: Comparison of data distribution and yearly average concentrations (2012-2014) for atrazine (A), metolachlore (B), imidacloprid (C) and diuron (D) at the Arnac downstream sampling point. The French Environmental Quality Standard – Annual Average (EQS-AA) is indicated for atrazine and diuron and the Predictive No Effect Concentration (PNEC) is indicated for metolachlor. Boxes represent median values and quartiles.

Table V.7: Toxicity of pesticides detected on both watersheds. Values (NOEC and acute toxicity) obtained from Pesticides Properties Database (http://sitem.herts.ac.uk/aeru/ppdb/en/index.htm) **in ng/L** (*n.a.* not available and *n.c.* not concerned).

	Maximal concentration (Auvézère watershed)		Maximal concentration (Aixette watershed)		NOEC			Acute toxicity			AA-EQS	MAC-EQS
	TWAC	Grab	TWAC	Grab	Fish	Aquatic invertebrates	Algae	Fish (LC50)	Aquatic invertebrates (EC50)	Algae (EC50)		
Acetochlor	21.67	72	-	-	1.30E+05	2.20E+03	5.90E+02	3.60E+05	8.60E+06	2.70E+02	*n.c.*	*n.c.*
Alachlore	5.04	<20	-	-	1.90E+05	2.20E+05	2.00E+04	1.80E+06	1.00E+07	9.66E+05	300	700
Atrazine	2320	2300	5.3	34.94	2.00E+06	2.50E+05	1.00E+05	4.50E+06	8.50E+07	5.90E+04	600	2000
Carbendazim	5.66	145.13	-	-	3.20E+03	1.50E+03	*n.a.*	1.90E+05	1.50E+05	>7.70E+06	*n.c.*	*n.c.*
Carbofuran	<0.8	<5	18.7	23.09	2.20E+03	8.00E+03	3.20E+06	1.80E+05	9.40E+03	6.50E+06	*n.c.*	*n.c.*
Chlortoluron	0.56	<1	13.7	20.38	4.00E+05	1.67E+07	1.00E+03	2.00E+07	6.70E+07	2.40E+04	*n.c.*	*n.c.*
Cyproconazole	-	<5	2.5	-	6.50E+05	2.90E+05	2.00E+04	1.90E+07	>2.20E+07	9.90E+04	*n.c.*	*n.c.*
Dimetachlor	8.4	-	-	-	8.50E+05	2.30E+06	*n.a.*	3.90E+06	2.40E+07	6.50E+03	*n.c.*	*n.c.*
Dimethanamid	7.13	18.53	0.5	2.28	2.50E+06	1.25E+06	*n.a.*	2.60E+06	3.20E+06	6.20E+04	*n.c.*	*n.c.*
Diuron	698	2020	73.5	17.32	4.10E+05	9.60E+04	*n.a.*	6.70E+06	5.70E+06	2.70E+03	200	1800
Epoxiconazole	6.74	-	1.3	-	1.00E+04	6.30E+05	7.80E+03	3.14E+06	8.69E+06	1.19E+06	*n.c.*	*n.c.*
Flurtamone	<0.2	-	<0.2	<1	6.30E+05	7.10E+04	*n.a.*	7.00E+06	1.30E+07	2.00E+04	*n.c.*	*n.c.*
Imidacloprid	39.48	313	8.8	31.91	9.02E+06	1.80E+06	1.00E+07	>8.30E+07	8.50E+07	>1.00E+07	*n.c.*	*n.c.*
Isoproturon	9.74	<1	11.1	157.35	1.00E+06	1.20E+05	5.20E+04	1.80E+07	5.80E+05	1.30E+04	300	1000
Metazachlor	7.51	<1	0.7	-	2.15E+06	1.00E+05	3.40E+05	8.50E+06	3.30E+07	1.62E+04	*n.c.*	*n.c.*
Metolachlor	19.49	138	49.49	88	*n.a.*	7.07E+05	*n.a.*	3.90E+06	2.35E+07	5.71E+07	*n.c.*	*n.c.*
Norflurazon	0.97	1.83	-	-	*n.a.*	*n.a.*	*n.a.*	8.10E+06	1.50E+07	1.76E+04	*n.c.*	*n.c.*
Pyrimicarb	5.84	40.7	-	-	<1.80E+07	9.00E+02	5.00E+07	>1.00E+08	1.70E+04	1.40E+08	*n.c.*	*n.c.*
Simazine	124.58	5.48	9.23	7.6	7.00E+05	2.50E+06	6.00E+05	9.00E+07	1.10E+06	4.00E+04	*n.c.*	*n.c.*
Tebuconazole	18.15	43.6	8.27	-	1.20E+04	1.00E+04	1.00E+05	4.40E+06	2.79E+06	1.96E+06	*n.c.*	*n.c.*
Terbuthylazine	0.2	<1	0.2	-	9.00E+04	1.90E+04	*n.a.*	2.20E+06	2.12E+07	1.20E+04	*n.c.*	*n.c.*

CONCLUSION

This study demonstrates that to detect and quantify low pesticide content at the headwater of a watershed, a combination of specific materials is required. An LC-MS/MS with a high quality LOQ combined with the use of grab and/or a passive sampler (*e.g.* POCIS) allows detection and quantification of pesticides and their metabolites on the order of ng/L. This work used a combined approach of grab and passive sampling and demonstrated that watershed tributaries can display strong pesticide pollution often by only one compound, whereas the main river, due to its dilution ability, displays only slight pollution. Grab samples were suitable for detecting stronger pesticide concentrations, which result mainly from poor agricultural pesticide deployment but also from non-agricultural use. Passive samplers were more appropriate for detecting a pool of pesticides and metabolites at low concentration and demonstrated the presence of a background pesticide noise between 20 and 70 ng/L. In the extensive agricultural cattle breeding context studied here, the primary compounds detected at the headwater were herbicides, likely due to the development of self-feeding for local breeders. The lesser presence of fungicides and insecticides is likely linked to the particularities of this headwater – the presence of apple orchards and the proximity of a town and therefore non-agricultural use of these compounds. Headwaters are a high biodiversity area and, if polluted by persistent low concentrations (around 50 ng/L) and sometimes pesticides peaks (more than 1000 ng/L) as reported here, then continued monitoring is important. Pesticide peaks are a known toxicity risk for aquatic life but the toxic effect of background pesticides is currently not clear and must consider synergies from "combined" or "cocktail effects".

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V.3. Publication "Semi-continuous pharmaceutical and human tracer monitoring by POCIS sampling at watershed-scale in an agricultural rural headwater river".

Cette section est constituée d'une version adaptée d'un article publié dans la revue « Journal of Hazardous Materials », où les informations complémentaires (« supplementary materials ») ont été intégrées au corps de l'article.

Guibal, R., Lissalde, S., Brizard, Y. and Guibaud, G. (2018) Semi-continuous pharmaceutical and human tracer monitoring by POCIS sampling at the watershed-scale in an agricultural rural headwater river. Journal of Hazardous Materials 360(15), 106-114.

Semi-continuous pharmaceutical and human tracer monitoring by POCIS sampling at the watershed-scale in an agricultural rural headwater river.

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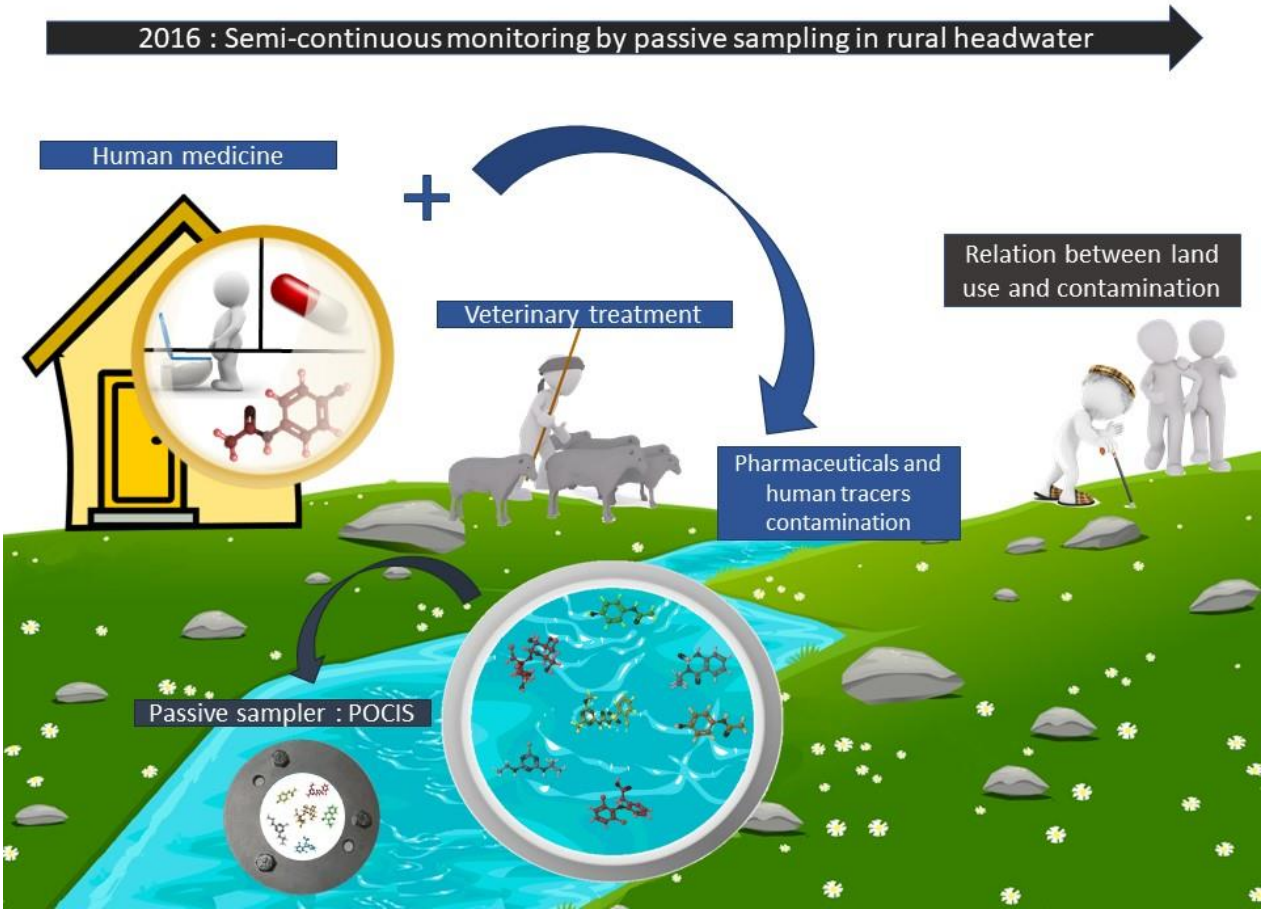
GRAPHICAL ABSTRACT



Keywords: Pharmaceuticals, passive sampler, watershed analysis, WWTP, headwater streams.

INTRODUCTION

The presence of pharmaceuticals, veterinary drugs and hormones in freshwater has been reported by numerous studies (*e.g.* (Mandaric et al. 2017, Sousa et al. 2018, ter Laak et al. 2010, Wilkinson et al. 2017) but more research is required for establishing occurrence, exposure and effects (Jones et al. 2001, Sousa et al. 2018). These compounds pollute aquatic environments in various ways, but WasteWater Treatment Plants (WWTP) are the major contamination pathway (Jones et al. 2001). Pharmaceuticals have been widely detected in waters all around the world with concentrations ranging from ng to µg/L, depending on regions and seasons (Homem and Santos 2011, Kunkel and Radke 2012, Mandaric et al. 2017, Paiga et al. 2016).

Headwater streams were, for a long time, considered the less contaminated areas (for organic and inorganic compounds) because of low human pressure (*e.g.* low population density, extensive farming (*i.e.* with a low density of cow in the meadows and with limited supply of fertilizer and pesticides – see **Figure V.15**), numerous forests). This type of watershed plays a huge role in biodiversity, containing numerous species of high biological value (Finn et al. 2011). Headwater streams are characterized by wetlands, low flow rates and rapid contaminant transfer due to the presence of numerous very small streams. Thus, small and often old, WWTP from nearby small towns can represent a significant part of the water flow and may result in pollution by pharmaceutical contaminants.

In addition to pharmaceuticals, anthropogenic markers can be monitored, such as caffeine or sucralose, which are very frequently detected in water (Peeler et al. 2006). By their high human consumption, caffeine and sucralose have been monitored as human tracers in water (Peeler et al. 2006). These compounds are found in drinks (*e.g.* coffee, tea, soft drinks), food products (*e.g.* chocolate, candies…) and also, for caffeine, in psychoactive stimulant drug. Depending on study region, other compounds can be monitored as human tracers, such as some illicit drugs (amphetamine, methamphetamine, cocaine and benzoylecgonine) (Mastroianni et al. 2016, Wilkinson et al. 2017) or hormones (estrone, estradiol, progesterone or derivates) (Rodayan et al. 2016, Wilkinson et al. 2017). Nevertheless, due to the ability of WWTP to remove hormones from wastewater, only estrone was more interesting as a tracer of treated wastewater discharge in rivers (Servos et al. 2005).

Traditionally, grab sampling has been used to evaluate the presence of pharmaceuticals in aquatic environments. This technique does not perform well enough when pharmaceuticals are present at low concentration in freshwaters. Moreover, this technique presents other disadvantages such as the lack of temporal representativeness (Allan et al. 2006). Passive samplers such as the Polar Organic Chemical Integrative Sampler (POCIS) appear to be a very interesting alternative to grab sampling (Alvarez et al. 2004). POCIS continuously accumulates pharmaceuticals and allows lower quantification limits (Lissalde et al. 2011). A better estimation of contamination with time-weighted averaged concentrations (TWAC) can be calculated (Alvarez et al. 2004, Vrana et al. 2005). From TWAC, real load of compounds can be estimated if flow rate at the sampling site is available (Poulier et al. 2015). Poulier et al. (2014) estimate TWAC uncertainty about factor 2 because of accumulation on POCIS could be influenced by environmental conditions (*e.g.* temperature, flow velocity…).

Currently, headwater plays an important role in aquatic biodiversity and river quality must be better characterized (Aubertheau et al. 2017). Nevertheless, this water quality, regarding for example organic micropollutants, is under-researched. To our knowledge, pharmaceutical contamination of such watersheds is poorly documented, except for Wilkinson et al. (2017) who reported slight contamination downstream of a WWTP. To better specify the pharmaceutical contamination state of headwaters, a 1-year study using POCIS semi-continuous sampling was performed at the watershed-scale (Aixette watershed in south-west France). This headwaters watershed, like numerous rural headwaters watershed in France, is characterized by a low population density, an elderly population and extensive agricultural activities (mainly cattle breeding).

Figure V.15: Example of extensive agriculture with a low number of cattle of headwater area.

MATERIALS AND METHODS

Materials and chemicals.

Ultrapure water (UPW) was produced by a Gradient A10 Milli-Q system from Millipore. Organic solvents (HPLC-MS quality) were obtained from Carlo Erba for methanol (MeOH), Sigma Aldrich for ethyl acetate, J.T. Baker for formic acid and Scharlau for ammonium formate. The list of pharmaceuticals (37 compounds) and human tracers (3 compounds – caffeine, sucralose and a caffeine metabolite: paraxanthine) with purity, CAS number and chemical formula is presented in supplementary materials (**Table V.8**). Action classes and use of the studied pharmaceuticals and human tracers are presented in **Table V.9** (16 compounds were only used for humans, 3 were only used for animals and 20 were common to human and animals). Compounds were purchased from HPC Standards GmbH (16), Ehrenstorfer GmbH (10), Sigma-Aldrich (8), Dr. Santa Cruz Biotechnology (5), or Neochema (1) with a purity ≥ 91.7% (Table S1). Stock pharmaceutical solutions at concentrations of 100 mg/L were prepared in MeOH and stored at -18°C. A working solution containing all compounds was prepared at 1 mg/L in MeOH with a dilution of stock solutions and stored at -18°C for no more than 6 months.

Internal standards are presented in **Table V.10**. Internal standard solutions were prepared in MeOH at 10 mg/L and stored at -18°C. Fresh calibration solutions containing pharmaceutical standards (1, 2, 5, 10, 25, 50 and 100 µg/L) and internal standards (100 µg/L) were prepared before analysis in a mixture of UPW:MeOH (90:10 v:v).

Table V.8: Main data and sampling rates of the studied pharmaceuticals and human tracers. Sampling rates were from unpublished results and from a = Li et al. (2010a) and b = Belles et al. (2014a).

Pharmaceutical	Purity	CAS	Chemical formula	R_s (L/d)
Acetaminophen	99.9	103-90-2	$C_8 H_9 N O_2$	0.111[a]
Atenolol	99.3	29122-68-7	$C_{14} H_{22} N_2 O_3$	0.228
Bezafibrate	99.6	41859-67-0	$C_{19} H_{20} Cl N O_4$	0.276
Bisprolol	98.1	66722-44-9	$C_{18} H_{31} N O_4$	0.278
Caffeine	98.5	58-08-2	$C_8 H_{10} N_4 O_2$	0.263
Carbamazepine	99.5	298-46-4	$C_{15} H_{12} N_2 O$	0.443
Clarythromycin	99.4	81103-11-9	$C_{38} H_{69} N O_{13}$	0.351
Dexamethasone	98.0	50-02-2	$C_{22} H_{29} F O_5$	0.388
Diazepam	99.9	439-14-5	$C_{16} H_{13} Cl N_2 O$	0.160[b]
Diclofenac	99.5	15307-86-5	$C_{14} H_{11} Cl_2 N O_2$	0.334
Erythromycin	97.0	114-07-8	$C_{37} H_{67} N O_{13}$	0.379
Flunixin	99.9	38677-85-9	$C_{14} H_{11} F_3 N_2 O_2$	0.450
Fluoxetine	99.8	59333-67-4	$C_{17} H_{18} F_3 N O$	0.514
Gemfibrozil	99.0	25812-30-0	$C_{15} H_{22} O_3$	0.377
Griseofulvin	97.4	126-07-8	$C_{17} H_{17} Cl O_6$	0.347
Indomethacin	99.9	53-86-1	$C_{19} H_{16} Cl N O_4$	0.365
Ketoprofen	99.1	22071-15-4	$C_{16} H_{14} O_3$	0.313
Lincomycin	99.0	154-21-2	$C_{18} H_{34} N_2 O_6 S$	0.307
Metoprolol	99.8	56392-17-7	$C_{15} H_{25} N O_3$	0.346
Metronidazole	99.3	443-48-1	$C_6 H_9 N_3 O_3$	0.462
Monensin	98.8	22373-78-0	$C_{36} H_{62} O_{11}$	0.101
Nadolol	99.1	42200-33-9	$C_{17} H_{27} N O_4$	0.313
Omeprazole	99.9	73590-58-6	$C_{17} H_{19} N_3 O_3 S$	0.075
Paraxanthine	99.0	611-59-6	$C_7 H_8 N_4 O_2$	0.246
Paroxetine	98.3	110429-35-1	$C_{19} H_{20} F N O_3$	0.371
Perindopril	97.0	107133-36-8	$C_{19} H_{32} N_2 O_5$	0.273
Praziquantel	99.7	55268-74-1	$C_{19} H_{24} N_2 O_2$	0.422
Prednisolone	99.4	50-24-8	$C_{21} H_{28} O_5$	0.383
Propanolol	99.9	318-98-9	$C_{16} H_{21} N O_2$	0.392
Pyrantel	95.1	22204-24-6	$C_{11} H_{14} N_2 S$	0.539
Roxithromycin	91.7	80214-83-1	$C_{41} H_{76} N_2 O_{15}$	0.404
Salbutamol	99.5	51022-70-9	$C_{13} H_{21} N O_3$	0.157
Sotalol	98.5	959-24-0	$C_{12} H_{20} N_2 O_3 S$	0.231
Sucralose	99.0	56038-13-2	$C_{12} H_{19} Cl_3 O_8$	0.220
Sulfadiazine	99.3	68-35-9	$C_{10} H_{10} N_4 O_2 S$	0.202
Sulfamerazine	99.8	127-79-7	$C_{11} H_{12} N_4 O_2 S$	0.175
Sulfamethoxazole	99.9	723-46-6	$C_{10} H_{11} N_3 O_3 S$	0.154
Sulfamethoxypyridazine	99.0	80-35-3	$C_{11} H_{12} N_4 O_3 S$	0.207
Terbutaline	99.0	23031-32-5	$C_{12} H_{19} N O_3$	0.103
Trimethoprim	99.5	738-70-5	$C_{14} H_{18} N_4 O_3$	0.350

Table V.9: Action classes and use of the studied pharmaceuticals and human tracers.

Pharmaceutical	Action class	Use
Acetaminophen	Anti-inflammatory	Human
Atenolol	β-blocker	Human and Veterinary
Bezafibrate	Anti-cholesterol	Human
Bisprolol	β-blocker	Human
Caffeine	Human Tracer	Human and Veterinary
Carbamazepine	Antiepileptic	Human
Clarythromycin	Antibiotic	Human
Dexamethasone	Anti-inflammatory	Human and Veterinary
Diazepam	Psychotropic	Human and Veterinary
Diclofenac	Anti-inflammatory	Human and Veterinary
Erythromycin	Antibiotic	Human and Veterinary
Flunixin	Anti-inflammatory	Veterinary
Fluoxetine	Psychotropic	Human and Veterinary
Gemfibrozil	Anti-cholesterol	Human
Griseofulvin	Anti-fungal	Human and Veterinary
Indomethacin	Anti-inflammatory	Human
Ketoprofen	Anti-inflammatory	Human and Veterinary
Lincomycin	Antibiotic	Human and Veterinary
Metoprolol	β-blocker	Human
Metronidazole	Antibiotic	Human and Veterinary
Monensin	Antibiotic	Veterinary
Nadolol	β-blocker	Human
Omeprazole	Proton Inhibitor	Human and Veterinary
Paraxanthine	Metabolite caffeine	-
Paroxetine	Psychotropic	Human
Perindopril	β-blocker	Human
Praziquantel	Antiparasitic	Human and Veterinary
Prednisolone	Anti-inflammatory	Human and Veterinary
Propanolol	β-blocker	Human
Pyrantel	Antiparasitic	Human and Veterinary
Roxithromycin	Antibiotic	Human
Salbutamol	Anti-asthma	Human
Sotalol	β-blocker	Human
Sucralose	Human Tracer	Human
Sulfadiazine	Antibiotic	Human and Veterinary
Sulfamerazine	Antibiotic	Veterinary
Sulfamethoxazole	Antibiotic	Human and Veterinary
Sulfamethoxypyridazine	Antibiotic	Human and Veterinary
Terbutaline	Anti-asthma	Human and Veterinary
Trimethoprim	Antibiotic	Human and Veterinary

Table V.10: Pharmaceutical and human tracer characteristics after UHPLC separation and mass detection.

Pharmaceutical	Retention time (min)	Mass (Da)	Internal standard
Acetaminophen	2.04	151.0633	Salbutamol-d3
Atenolol	2.32	266.1630	Salbutamol-d3
Bezafibrate	8.33	361.1081	Flunixin-d3
Bisprolol	7.15	325.2253	Propanolol-d3
Caffeine	5.05	194.0804	Caffeine-c3
Carbamazepine	7.70	236.0950	Carbamazepine-d10
Clarythromycin	8.15	747.4769	Flunixin-d3
Dexamethasone	8.05	392.1999	Carbamazepine-d10
Diazepam	8.33	284.0716	Flunixin-d3
Diclofenac	9.07	295.0167	Diclofenac-d4
Erythromycin	7.81	733.4612	Carbamazepine-d10
Flunixin	8.71	296.0773	Flunixin-d3
Fluoxetine	7.88	309.1341	Carbamazepine-d10
Gemfibrozil	10.20	250.1569	Triclabendazole-d3
Griseofulvin	7.84	352.0714	Carbamazepine-d10
Indomethacin	9.20	357.0768	Diclofenac-d4
Ketoprofen	8.08	254.0943	Diclofenac-d4
Lincomycin	4.30	406.2138	Trimethoprim-d3
Metoprolol	6.52	267.1834	Carbamazepine-d10
Metronidazole	2.25	171.0644	Triclabendazole-d3
Monensin	13.71	670.4292	Triclabendazole-d3
Nadolol	5.62	309.1940	Sulfamethoxazole-d4
Omeprazole	7.51	345.1147	Carbamazepine-d10
Paraxanthine	3.48	180.0647	Caffeine-c3
Paroxetine	6.69	329.1427	Carbamazepine-d10
Perindopril	7.60	368.2311	Carbamazepine-d10
Praziquantel	8.35	312.1838	Flunixin-d3
Prednisolone	7.81	360.1937	Carbamazepine-d10
Propanolol	7.30	259.1572	Propanolol-d3
Pyrantel	4.51	206.0878	Trimethoprim-d3
Roxithromycin	8.22	836.5246	Flunixin-d3
Salbutamol	2.16	239.1521	Salbutamol-d3
Sotalol	1.68	272.1195	Salbutamol-d3
Sucralose	5.72	396.0146	Caffeine-c3
Sulfadiazine	2.39	250.0525	Sulfamethoxazole-d4
Sulfamerazine	3.60	264.0681	Sulfamethoxazole-d4
Sulfamethoxazole	5.86	253.0521	Sulfamethoxazole-d4
Sulfamethoxypyridazine	5.24	280.0630	Sulfamethoxazole-d4
Terbutaline	2.13	225.1365	Salbutamol-d3
Trimethoprim	4.75	290.1379	Trimethoprim-d3

Main characteristics of the headwater.

The study was done on one headwater streams located in southwest France (Haute-Vienne, Nouvelle Aquitaine): the Aixette watershed. The Aixette watershed localization and sampling point is presented in **Figure V.16**. The climate is characterized as degraded Atlantic oceanic (continental influence) with mild and wet seasons. Three sampling points were chosen: two on the Aixette River (Aixette Upstream and Downstream) and another on a tributary of the Aixette River, the Arthonnet. The first sampling point (Aixette Upstream) was located 13.5 km from the spring at Lavignac, the second (Aixette Downstream) was located 5 km before the confluence with the Vienne River and 8.4 km after the Aixette Upstream sampling point. The last point (Arthonnet) was located before the outlet of the tributary' "The Arthonnet" which meets the Aixette between the first two sample points at Pont Péry. The size of the watershed is 163 km². The end of the Aixette watershed is in a peri-urban area of the city of Limoges. The 3 sampling points were located in the rural agricultural part of the Aixette watershed where agricultural lands were composed of grassland (37%) with extensive cattle breeding (a picture of extensive agriculture are shown in **Figure V.15**), cultures (37%), forest (16%), arable land (3%) and urban area (3%) (see Aixette watershed land-use in **Figure V.16**). In this extensive agriculture watershed, the density of cow is 280 and 210 cow/km² for Arthonnet and Aixette watershed, respectively.

The population density is low (from 23.2 to 63.6 inhabitants/km² in the main municipalities of the watershed, the average in France is 118 inhabitant/km², Table S4). The population distribution in Haute-Vienne (French department where headwaters watershed of Aixette is located) in 2016 was: 22% [0-19 years old], 22% [20-39 years old]; 26% [40-59 years old]; 18% [60-74 years old]; 12% [>75 years old] (INSEE 2016). The population density is low with 30% of the population are over 60, which is significantly more than the French average (25% >60 years old). Six small WWTP are located in the Aixette watershed and are presented in **Figure V.16**. Two WWTP are before the Aixette Upstream sampling point: 1350 population equivalent (PE – In wastewater treatment is a measure of pollution representing the organic biodegradable load per person per day. In UE, 1 PE is the organic biodegradable load having a five-day biochemical oxygen demand (DBO5) of 60 g of oxygen per day. In addition, in France, it is also a wastewater volume of 120 L/day in rural area) and 217 PE. One WWTP of 367 PE is before the Arthonnet sampling point. Three supplementary WWTP (300, 400 and 533 PE) are before the last sampling point (Aixette Downstream). WWTP characteristics are presented in **Table V.11**.

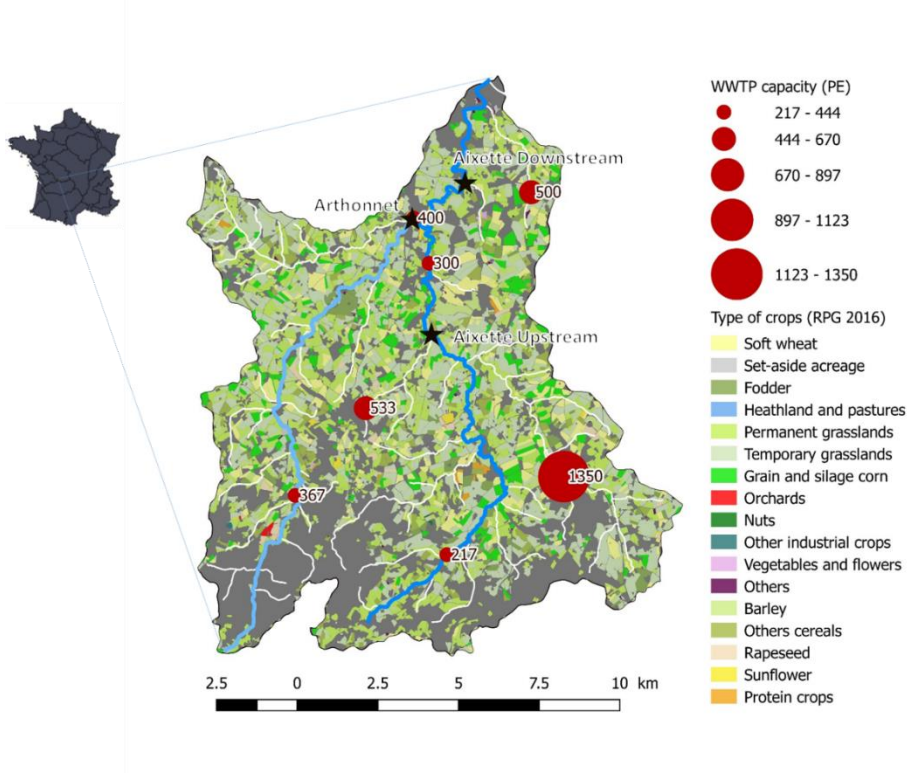


Figure V.16: Aixette watershed localization with land-use (RPG, 2012, Géoportail)**. Localization of sampling points (black stars) and wastewater treatment plant (red circle).**

Table V.11: Municipality and WWTP characteristics on the Aixette watershed.

	Flavignac	Les Cars	Rilhac Lastours	Saint Martin Le Vieux – Bourg	Saint Martin Le Vieux - Poueix	Nexon
Area of the municipality (km^2)	30.79	16.72	16.32	17.49		40.79
Population of the municipality (INSEE, December 2016)	1 058	633	378	930		2 596
Population density (inhabitant/km^2)	34.4	37.9	23.2	53.2		63.6
Watershed	Aixette	Arthonnet	Aixette	Aixette	Arthonnet	Vanelle
Localization	Downstream of "Aixette Upstream"	Upstream of "Arthonnet tributary"	Upstream of "Aixette Upstream"	Downstream of "Aixette Upstream"	Downstream of "Arthonnet tributary"	Upstream of "Aixette Upstream"
Capacity (population equivalent)	533	367	217	300	400	1350
Reference flow (m^3/d)	90	60	38	45	96	225
Charge DBO_5 (kg/d)	33	24	15	18	24	84
2015 linked residents number	850	70	130	30	140	1090
Mean Flow (m^3/d)	43	26	16	6	25	227
Treatment	Pre-treatment Activated sludge, extended aeration	activated sludge, extended aeration	Lagoon	Reedbed wastewater treatment	Reedbed wastewater treatment	Pre-treatment Activated sludge, extended aeration
Initial start-up date	1974	1982	1994	2005	2006	1972

Field deployment of passive sampler

Passive samplers (Polar Organic Compound Integrative Sampler: POCIS) were used for measuring levels of pharmaceuticals and human tracers in water. POCIS were exposed at the three sampling points for every 14-day period from January to December 2016 (24 POCIS exposures). This field deployment duration was chosen because compound uptakes were linear (or curvilinear) more than 14 days of exposure and were not in equilibrium regime (Alvarez et al. 2004, Bailly et al. 2013, Belles et al. 2014a, Li et al. 2010a, Morin et al. 2013). For each period, two POCIS were exposed per site in plastic nets. POCIS blanks were used as laboratory and field controls for all trials (one POCIS blank per 14-day period). POCIS blanks were taken to the sampling site and unpacked (at one sampling site – Arthonnet) when POCIS samplers were manipulated. Blanks evaluated the level of contamination during storage, transportation or processing and analytical procedures. All POCIS (blanks and samples) were eluted and analyzed at the same time.

At the field deployment, physicochemical measurements were taken and results are presented in **Table V.12**.

Table V.12: Physicochemical measurements and TSS of field deployment.

	Aixette Upstream			Aixette Downstream			Arthonnet Tributary		
	Min	Max	Average	Min	Max	Average	Min	Max	Average
pH	6.8	8.0	7.4	7.1	8.6	7.6	7.0	7.7	7.4
Water temperature (°C)	3.3	18.8	10.9	2.7	18.7	11.1	3.1	18.0	10.9
Air temperature (°C)	4.0	24.7	14.4	4.0	24.8	14.3	4.0	24.0	14.4
Conductivity (µs/cm)	100.2	229.0	160.4	105.2	344.0	164.9	96.6	162.0	126.6
Oxygen (mg/L)	8.2	13.0	10.4	7.2	13.1	10.6	9.0	13.3	10.7
Oxygen Saturation (%)	84.5	111.7	95.3	87.1	126.4	98.7	92.8	104.0	98.3
TSS (mg/L)	2.0	130.5	20.2	1.9	128.0	17.4	1.2	62.9	16.4

POCIS preparation and extraction.

POCIS are home-made and are composed of a sorbent (200 mg of Oasis® HLB powder from Waters) maintained between two polyethersulfone (PES) membranes of 90 mm diameter and 0.1 µm pore size obtained from Pall Supor® (Alvarez et al. 2004). PES membranes were previously washed following recommendations (Guibal et al. 2015a). The assembly was held by two stainless steel rings.

After exposure, each POCIS was rinsed with UPW and opened. The sorbent phase was transferred into an empty 3 mL SPE tube with polyethylene frits (previously weighed) obtained from Macherey–Nagel, packed under vacuum and dried under nitrogen stream for 30 min (Lissalde et al. 2011). Cartridge were weighted to measure the recovered mass of receiving phase.

Analytes were eluted with 3 mL of MeOH followed by 3 mL of a mixture of 75:25 v:v MeOH:ethyl acetate (Lissalde et al. 2011). POCIS extracts were collected and evaporated to dryness under nitrogen flow then reconstituted with 1 mL of MeOH. Then, samples were diluted 10-times (Guibal et al. 2015b) and internal

standards solution was added (10 µL) for an internal standards final concentration of 100 µg/L before analysis.

Instrumental analysis.

A UHPLC 1290 Infinity apparatus from Agilent coupled with a tandem mass spectrometer composed of a quadrupole combined with a time-of-flight Accurate Mass LC/MS 6540 from Agilent equipped with an Agilent Jet Stream electrospray ionization source (ESI) was used for POCIS extract analysis. Chromatographic separation was performed with a Nucleoshell RP18+ column (100 mm length, 3 mm internal diameter) from Macherey – Nagel. Column and autosampler temperatures were maintained at 30°C and 4°C, respectively. The injected volume was 5 µL. Analytical gradient and source parameters of the detector are presented in **Table V.13A** and **B**, respectively. Mass acquisition was performed in the "All-ions" mode and collision cell energies were: 0, 10, 20 and 40 V.

All field deployment and analysis were performed with quality controls. Analytical method was validated following the French norm NF T90-210 and well descripted in a previous work (Guibal 2015a). Results are presented in **Table V.14**.

Table V.13: Optimized parameters of the UHPLC-Q-TOF method. A: Linear gradient used for the chromatographic separation and B: : UHPLC-TOF-MS operational parameters in positive ESI ion mode (*Optimized source parameters).

A

Time (min)	UPW + 5mM ammonium formate and 0.1% formic acid (%)	MeOH + 5mM ammonium formate and 0.1% formic acid (%)	Flow (µL/min)
0	90	10	0.4
1	90	10	0.4
5	75	25	0.4
7	30	70	0.4
13	10	90	0.4
16	10	90	0.4

B

Parameter	Value
Sheath gas temperature*	300°C
Sheath gas flow*	12 mL/min
Drying gas temperature*	100°C
Drying gas flow*	7 mL/min
Fragmentor voltage*	130 V
Nebulizer pressure*	35 psi
Capillary voltage	3500 V
Skimmer voltage*	65 V
Mass range	100 – 1500 m/z
Reference mass	922.0098 Da
Octopole 1 RF*	750 V
Nozzle voltage *	300 V

Table V.14: Analytical validation results (*accuracy for pyrantel were measured for 9.4 and 37.4 µg/L). Linearity was tested from 1 to 100 µg/L.

Pharmaceutical	Linearity		Instrumental LOQ (µg/L)	LOQ_{POCIS} (ng/L)	Accuracy	
	Equation	r^2			25 µg/L	100 µg/L
Acetaminophen	y=0.0197x	0.988	0.1	0.6	✓	✓
Atenolol	y=0.0304x	0.974	0.1	0.3	✓	✓
Bezafibrate	y=0.0002x	0.982	0.5	1.3	✓	✓
Bisprolol	y=0.0122x	0.994	0.1	0.3	✓	✓
Caffeine	y=0.0102x	0.997	0.2	0.5	✓	✓
Carbamazepine	y=0.0102x	0.991	0.2	0.3	✓	✓
Clarythromycin	y=0.0031x	0.952	0.1	0.2	✓	✓
Dexamethasone	y=0.0016x	0.908	0.2	0.4	✓	✓
Diazepam	y=0.0070x	0.988	0.1	0.4	✓	✓
Diclofenac	y=0.0100x	0.993	2.0	4.3	✓	✓
Erythromycin	y=0.0043x	0.942	0.2	0.4	✓	✓
Flunixin	y=0.0080x	0.977	0.1	0.2	✓	✓
Fluoxetine	y=0.0056x	0.985	0.2	0.3	✓	✓
Gemfibrozil	y=1.0052x	0.998	5.0	9.5	✓	✓
Griseofulvin	y=0.0049x	0.987	0.1	0.2	✓	✓
Indomethacin	y=0.0123x	0.967	2.0	3.9	✓	✓
Ketoprofen	y=0.0648x	0.990	0.5	1.1	✓	✓
Lincomycin	y=0.0030x	0.996	0.1	0.2	✓	✓
Metoprolol	y=0.3050x	0.779	0.1	0.2	✓	✓
Metronidazole	y=0.0045x	0.932	0.2	0.3	✓	✓
Monensin	y=0.0112x	0.904	1.0	7.1	✓	✓
Nadolol	y=0.0695x	0.997	0.2	0.5	✓	✓
Omeprazole	y=0.0029x	0.924	0.1	1.0	✓	✓
Paraxanthine	y=0.0040x	0.970	0.5	1.5	✓	✓
Paroxetine	y=0.0102x	0.978	0.1	0.2	✓	✓
Perindopril	y=0.0057x	0.979	0.1	0.3	✓	✓
Praziquantel	y=0.0023x	0.949	0.1	0.2	✓	✓
Prednisolone	y=0.0014x	0.917	1.0	1.9	✓	✓
Propanolol	y=0.0118x	0.977	0.5	0.9	✓	✓
Pyrantel*	y=0.0045x	0.971	0.08	0.1	✓	✓
Roxithromycin	y=0.0009x	0.963	0.5	0.9	✓	✓
Salbutamol	y=0.0118x	0.994	0.2	0.9	✓	✓
Sotalol	y=0.0123x	0.996	0.2	0.6	✓	✓
Sucralose	y=0.0012x	0.828	1.0	3.2	✓	✓
Sulfadiazine	y=0.0128	0.984	0.1	0.4	✓	✓
Sulfamerazine	y=0.0175x	0.988	0.1	0.4	✓	✓
Sulfamethoxazole	y=0.0127x	0.993	0.2	0.9	✓	✓
Sulfamethoxypyridazine	y=0.0183x	0.991	0.2	0.7	✓	✓
Terbutaline	y=0.0126x	0.988	0.1	0.7	✓	✓
Trimethoprim	y=0.0106x	0.987	0.2	0.4	✓	✓

QA/QC.

Analytical methods (calibration, linearity and limit of quantification) were validated for the 56 compounds followed the French norm (NF T90-210) (AFNOR 2009). The detailed methodology was presented in a previous work (Guibal 2015a). Results were presented in **Table V.14**. Accuracy was performed on 2 level (25 and 100 µg/L) with a minimum of five series (analyzed in intermediate precision conditions) in two repetitions minimum (prepared in repeatability conditions). A Cochran test ($\alpha = 0.01$) to check variance was performed, then anova test ($\alpha = 0.01$) was performed. Accuracy was validated when:

$$[C]r - x[C]r < [C]a - 2\sigma \quad \text{and} \quad [C]r + x[C]r < [C]a + 2\sigma \qquad \textbf{Equation V.3}$$

With $[C]_r$: the reference concentration (spiked concentration in µg/L), x: the admissible percentage, $[C]_a$: the average concentration found (µg/L), σ: the standard deviation of the analyses (n=10). This procedure was developed in Guibal et al., (2015).

All field deployment and analysis were performed with quality controls. For sample analysis, QA/QC were used to control any deviations with standard each ten samples.

Duplicates of POCIS were deployed at the three sampling points. The deviations in pharmaceutical TWAC were calculated following **Equation V.4**. Errors on TWAC were calculated with the estimated concentrations in POCIS duplicate. Error on sampling rates was not considered in this study.

$$\sigma_{[Ct]} = \sqrt{\sum_{i=1}^{n} \left(\frac{\partial [Ct]}{\partial x_i}\right)^2 \sigma_i^2} = \sqrt{\sum_{i=1}^{n} \sigma_i^2} \qquad \textbf{Equation V.4}$$

Where $((\partial[C_t])/(\partial x_i))$ is the partial derivative of $[C_t]$ (total concentration) with respect to x_i, σ_i is the standard deviation of x_i and where n = 22, 22 and 20 for Aixette Upstream, Downstream and Arthonnet, respectively and corresponding at molecules detected in duplicate exposed. Error bars were performed following this equation and were calculated for each site.

Additionally, POCIS blanks were used as field and laboratory controls during all trials at the Aixette watersheds. POCIS blanks were taken to the sampling sites and opened when POCIS samplers were manipulated (controlling for contamination during storage, transportation, processing and analytical procedures). POCIS blank were eluted and analyzed in the same time of POCIS samplers.

Calculation of time-weighted average concentration (TWAC) in water using POCIS.

POCIS is an integrative sampler and is typically used during the linear sorption phase (Vrana et al. 2005), and analyte concentration in water (*i.e.* time-weighted average concentration, TWAC) can be calculated by the following equation (Alvarez et al. 2004, Morin et al. 2012):

$$TWAC = \frac{C_{POCIS} * m_{sorbent}}{R_s * t} \qquad \textbf{Equation V.5}$$

with TWAC the water analyte concentration (µg/L); C_{POCIS} the analyte concentration in the receiving phase (µg/g); $m_{sorbent}$ the mass of sorbent recovered inside the POCIS (g); R_s the sampling rate (L/d) and t the exposure time (days). R_s is a specific constant for each analyte and, for this work, R_s values were taken from unpublished work from our laboratory (article in preparation – POCIS calibration experiment are detailed

in next section) and from Belles et al. (2014b) and Li et al. (2010a). When different R_s were available in the literature, the R_s from the environmental conditions closest to those at the Aixette watershed was selected. The Rs calibration must performed with POCIS containing 200 mg of receiving phase (Oasis® HLB) with the PES membrane at, about, 15°C in stirred tap water (R_s are available in **Table V.8**).

Determination of sampling rates.

POCIS calibration was performed in an artificial river filled with 500 L of tap water and spiked at 500 ng/L. Flow velocity was about 20 cm/s and temperature was about 17°C. The artificial river had three channels. Each channel had width of 20.3 cm and a length of 152 cm (**Figure V.17** and **Figure V.18**). Duplicate of POCIS were exposed during 1, 3, 5, 7, 10, 15 and 21 days. The water concentration in pilot was monitored every 2 or 3 days.

Determination of Rs was performed using equation:

$$\frac{C_{POCIS}}{C_w} = K_{HLBw} \times (1 - e^{-ke \times t}) \qquad \textbf{Equation V.6}$$

Where C_{POCIS} is the analyte concentration in the receiving phase (µg/g), C_w is the water pharmaceutical concentration, K_{HLBw} is the receiving phase-water distribution coefficient, k_e is the elimination rate (/d) and t the time (in days). POCIS calibration experiment are full descripted on Guibal et al. (in prep).

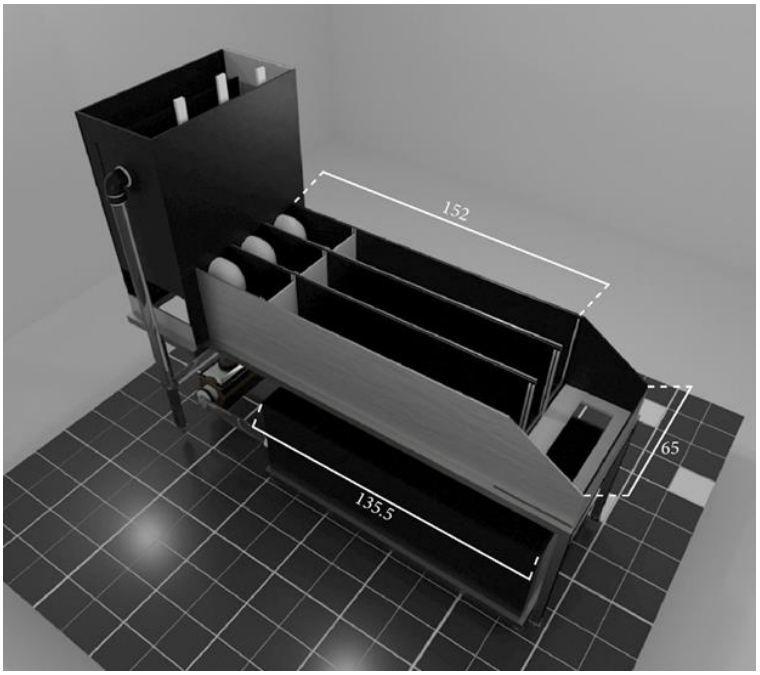


Figure V.17: Computer image of lab-scale artificial river with dimension (cm).

Figure V.18: View of channels during POCIS calibration.

Estimation of pharmaceutical load at each sampling site.

To estimate the pharmaceutical loads, the flow rate at each sampling point was calculated with the specific average daily flow-rate value (expressed in L/s/km²) of a similar neighboring watershed of the Gorre River (Watershed 192 km²) extracted from the Banque Hydro (HYDRO-MEDDE/DE 2017). The estimated flow rate was calculated at the outlet of Aixette watershed, then the flow rate at each sampling points was calculated proportionally at the size of sampling point watershed (75, 145 and 55 km² for Aixette Upstream, Aixette Downstream and Arthonnet, respectively).

The pharmaceutical loads were estimated considering the volume of water during the POCIS deployments and the TWAC of POCIS.

RESULTS AND DISCUSSION

Headwaters watershed contamination state.

Total concentrations measured in waters.

Figure V.19 shows the sum of targeted compounds (37 pharmaceuticals and 3 human tracers) concentrations quantified for each site (3) and each POCIS exposure (average of POCIS duplicates) during the year 2016. Throughout the year, a pharmaceutical contamination of the headwaters was highlighted. Our study, at the watershed scale, clarify the work of Wilkinson et al. (2017) on headwaters, which only noticed a water contamination by pharmaceuticals at the downstream WWTP discharge.

Average (and maximum) total quantified compounds TWAC for the three sampling sites were 139 (241), 75 (153) and 37 (120) ng/L for Aixette Upstream, Downstream and Arthonnet, respectively. Regarding total concentrations measured in the headwaters investigated in this study, it was quite difficult to compare these values with literature: the sum of pharmaceutical concentrations depends on the studied region, the season, the list of targeted compounds, the location of sampling area in the watershed and sampling method (grab or passive sampling) (Sousa et al. 2018). According to Homem and Santos (2011), pharmaceuticals in the surface waters are quantified at low concentration (about few ng/L) such as concentrations found in our study.

Contamination by pharmaceuticals and human tracers, could arise from WWTP discharges with treated effluent or not treated effluent from by-pass of sewage network in Aixette River and Arthonnet tributary. The investigated headwaters watershed displayed six small WWTP (localization and main characteristics are shown in **Figure V.16** and **Table V.11**, respectively). Moreover, to highlight the presence of WWTP discharge treated or not in rivers, the caffeine/carbamazepine ratio, can be use (Daneshvar et al. 2012, Ma et al. 2017). In this study, the average (and maximum) ratios were 13 (90), 13 (40) and 9 (20) for Aixette Upstream, Downstream and Arthonnet, respectively. Influent of WWTP have a ratio about 100 and effluent of WWTP have a ratio less than 10 (Ma et al. 2017). According to Daneshvar et al. (2012) and Ma et al. (2017), ratio found in our study indicated there are is, regularly, a greater proportion of raw sewage *versus* treated wastewater. According to the characteristics summarized in **Table V.11** and WWTP location (**Figure V.16**), the type of treatment (activated sludge or lagoon) and the distance to the sampling point played an important role in the contamination state. This can induce, firstly technical malfunctioning of WWTP but also by-pass of raw wastewater into the river. Moreover, in rural area, non-collective sanitations were wildly present, and wastewater poorly treated by old septic tank could reach easily the river by ditches and contribute significantly to water contamination by pharmaceuticals. In this area, the non-collective sanitation corresponded about a half of the domestic sewage water to treat (about 1600 non-collective sanitation (which correspond to *c.a.* 4800 population equivalent) on Aixette watershed). Moreover, a part of the non-collective sanitation contained only septic tank without efficient treatment.

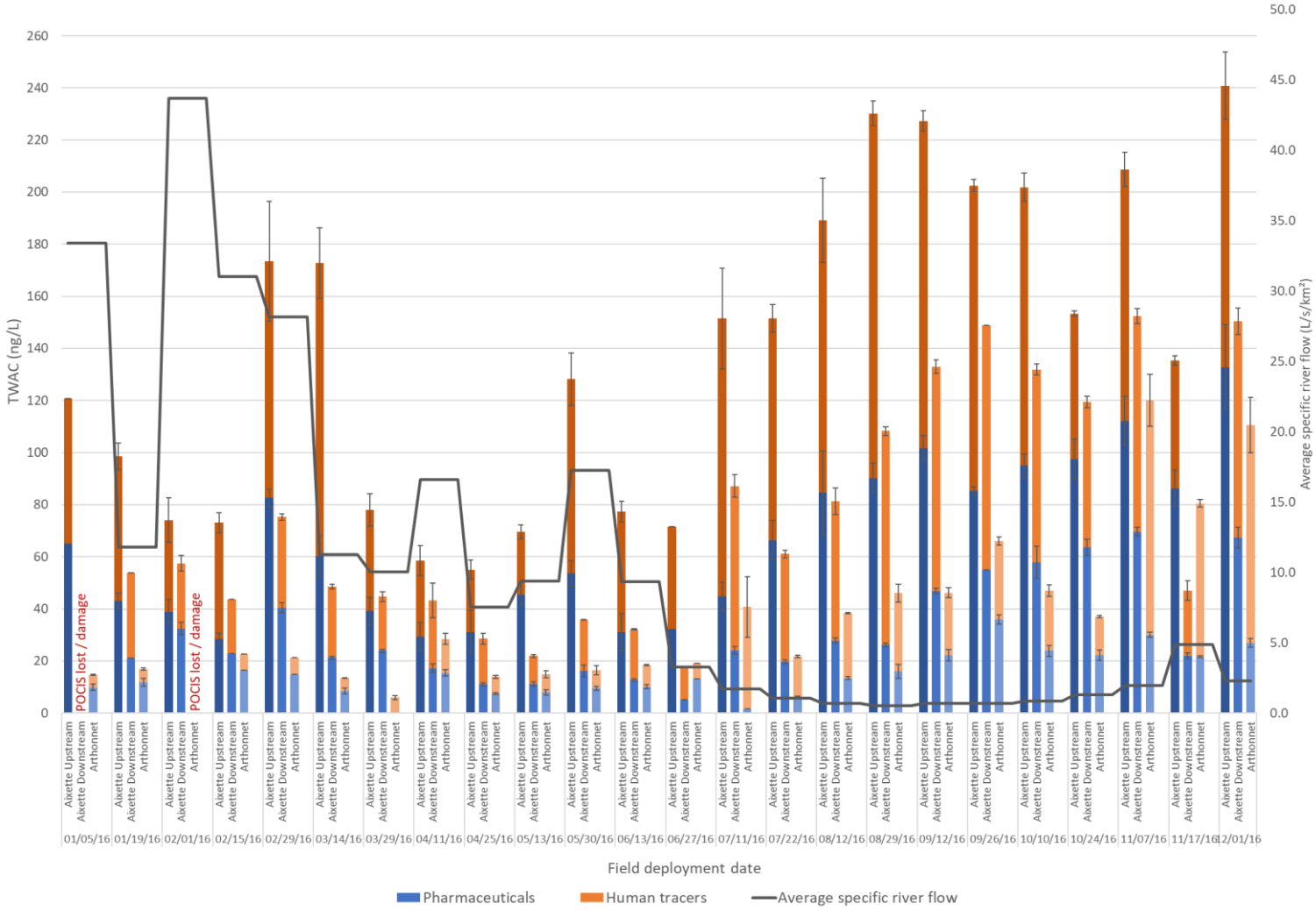


Figure V.19: Total targeted pharmaceuticals and human tracers TWAC (ng/L) for the three sampling points (48 POCIS exposure for each site – duplicate per date – error bars corresponds to the standard deviation). Average specific river flow in grey. Field deployment dates corresponds to the first deployment day.

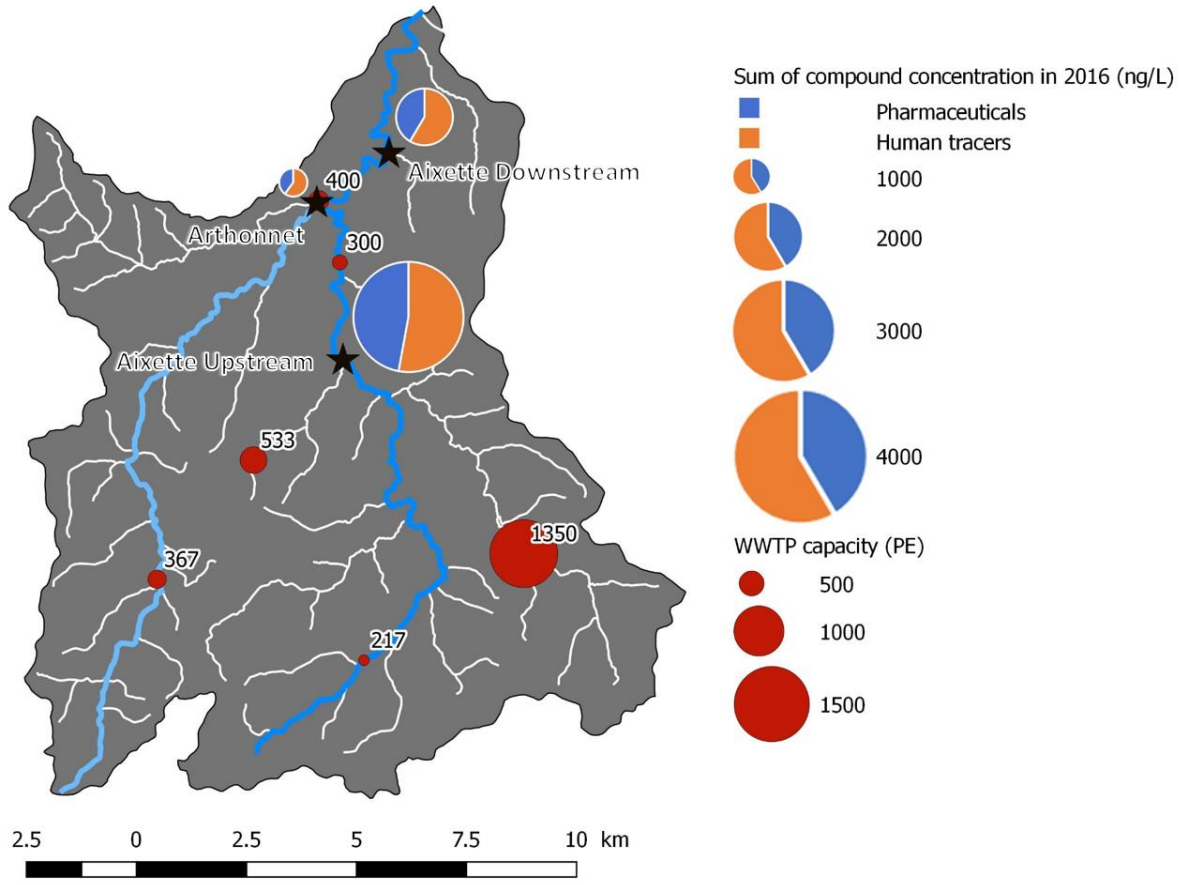


Figure V.20: Localization of WWTP and sampling sites (black stars) in the Aixette watershed and sum of the compounds concentration in 2016.

Spatial distribution.

Regarding the spatial distribution, at a watershed-scale, it is widely recognized that upstream areas are usually less contaminated than downstream (Dai et al. 2015, Paiga et al. 2016, Wu et al. 2009). In contrast, in this study, the Aixette upstream was more contaminated by pharmaceuticals and human tracers than the downstream (**Figure V.20**). The tributary (Arthonnet) of Aixette, except for two periods (06/27 to 07/11/2016 and 11/17 to 12/01/2016), was the less contaminated river.

In the Aixette watershed, three smalls supplementary WWTP (300, 400 and 533 population equivalents with reed bed wastewater treatment for the first two and biological system (activated sludge) with filtration and coagulation – floculation – see supplementary material for more information **Figure V.20** and **Table V.11**) are located between the upstream and downstream sampling sites of the Aixette river. Thus, downstream, should be more contaminated than upstream but the results obtained in this study show the opposite (Figure 2). Three hypothesis can be proposed:(i) dilution by less contaminated tributaries (such as Arthonnet) can occur at the upstream Aixette site; (ii) the biggest WWTP (1350 PE) was localized in a small tributary above Aixette Upstream sampling station and contribute significantly to the contamination of the upstream sampling site; (iii) pharmaceuticals could be biodegradated and/or photodegraded into the river between

the two sampling sites. This study demonstrates that discharge of poorly or not treated sewage waters, the size and number of WWTP, the type of treatment, and mainly the location of discharge point is important to consider understanding the content of pharmaceuticals and human tracers in rivers. This last statement is in accordance with Lindholm-Lehto et al. (2016) and Chonova et al. (2017). Indeed, these authors (Chonova et al. 2017, Lindholm-Lehto et al. 2016) found a higher pharmaceutical concentration near a WWTP which was the main local source of pharmaceuticals.

Temporal distribution.

Whatever sampling point, maximum total concentrations of targeted compounds were quantified in rivers the second part of 2016 (July-December), except on Aixette upstream in March. The year 2016 was characterized by an atypical trend for the rivers flow rate. Based on the rainfall pattern, on this watershed, the first part of the year (January-June) is characterized by high river flow rate (monthly average specific flow rate from 9.0 to 36.8 L/s/km²) and the second part of the year by low flow rate (monthly average specific flow rate from 0.6 to 3.2 L/s/km²) (**Figure V.19** and **Figure V.21** show average specific discharge in L/s/km² and water average temperature, respectively).

River dilution capacity was an important parameter to understand trend of pharmaceutical concentration in river water, especially in small rivers from headwaters, maximum concentrations of pharmaceuticals and human tracers were found during rivers low flow conditions. Indeed, the flow of the treated effluent from wastewater can contribute significantly to the flow of little stream during their low flow rate. Nevertheless, for a better contamination understanding, a data representation in pharmaceuticals specific loads in rivers should be determined.

Seasonal patterns for pharmaceuticals and human tracers.

Concentrations were determined at the different sampling sites, different sampling dates and specific flow rates were used to calculate specific loads in order to overcome concentration variabilities (presented in **Figure V.19**) based on water flow rate. Results are presented in **Figure V.21**.

For the three sampling sites on the Aixette watershed, results showed the same patterns. Minimal loads of targeted compounds (pharmaceuticals and human tracers) were observed for three consecutive months (July- September).

Firstly, already underlined by Koba et al. (2018), decreased loads can be explained by the seasonal decrease in consumption of some pharmaceuticals, *e.g.* antibiotics. Indeed, there were fewer antibiotics in the Aixette and Arthonnet rivers in summer than in cold or wet season due to infectious diseases are less common in summer.

Secondly, the population on the watershed decreases in summer because this is not a tourist area and, in fact, peoples leave for holidays elsewhere. This is consistent with the decrease of human tracers' concentration in river waters (**Figure V.21**).

Thirdly, a better degradation of targeted compounds by different ways can be increased in summer (Baena-Nogueras et al. 2017, Lindholm-Lehto et al. 2016, Vieno et al. 2005). Indeed, high temperature could

increase bacteria activity and therefore biodegradation rates in surface water and mostly in WWTP processes. Indeed, temperature influence were tested on removal rates of pharmaceutical and hormones by Gabet-Giraud et al. (2010) and Vieno et al. (2005). They demonstrated that removal rates increased with temperature but/or also compound-dependent. During summer with decrease of population on the watershed, wastewater residence times in WWTP increased and a higher removal of pharmaceuticals can be achieved according to Kunkel et al. (2012). Moreover, sunlight intensity is also higher in summer and pharmaceutical photodegradation may be increased (Zhou et al. 2016). Concerning the specific case of caffeine, despite conflicting data on its degradation possibilities (Baena-Nogueras et al. 2017, Benotti and Brownawell 2009, Edwards et al. 2015), its decreased concentration was potentially due to transformation by microbial degradation according to Benotti et al. (2009).

Fourth, in warm water, biofilm increase on the sediments and stones in the rivers. Biofilms can contribute to removal of organic compounds, *e.g* pharmaceuticals from water by sorption mechanism or biodegradation (Chonova et al. 2017).

In October, important loads were observed due to heavy rains that induced a leaching of wastewater networks and an overflow of WWTP. A sediment stirred up was also observed inducing a huge increase of water turbidity limiting strongly photodegradation (Babin et al. 2003). We can also assumed that stirred up of sediment could also induce a release of sorbed compounds.

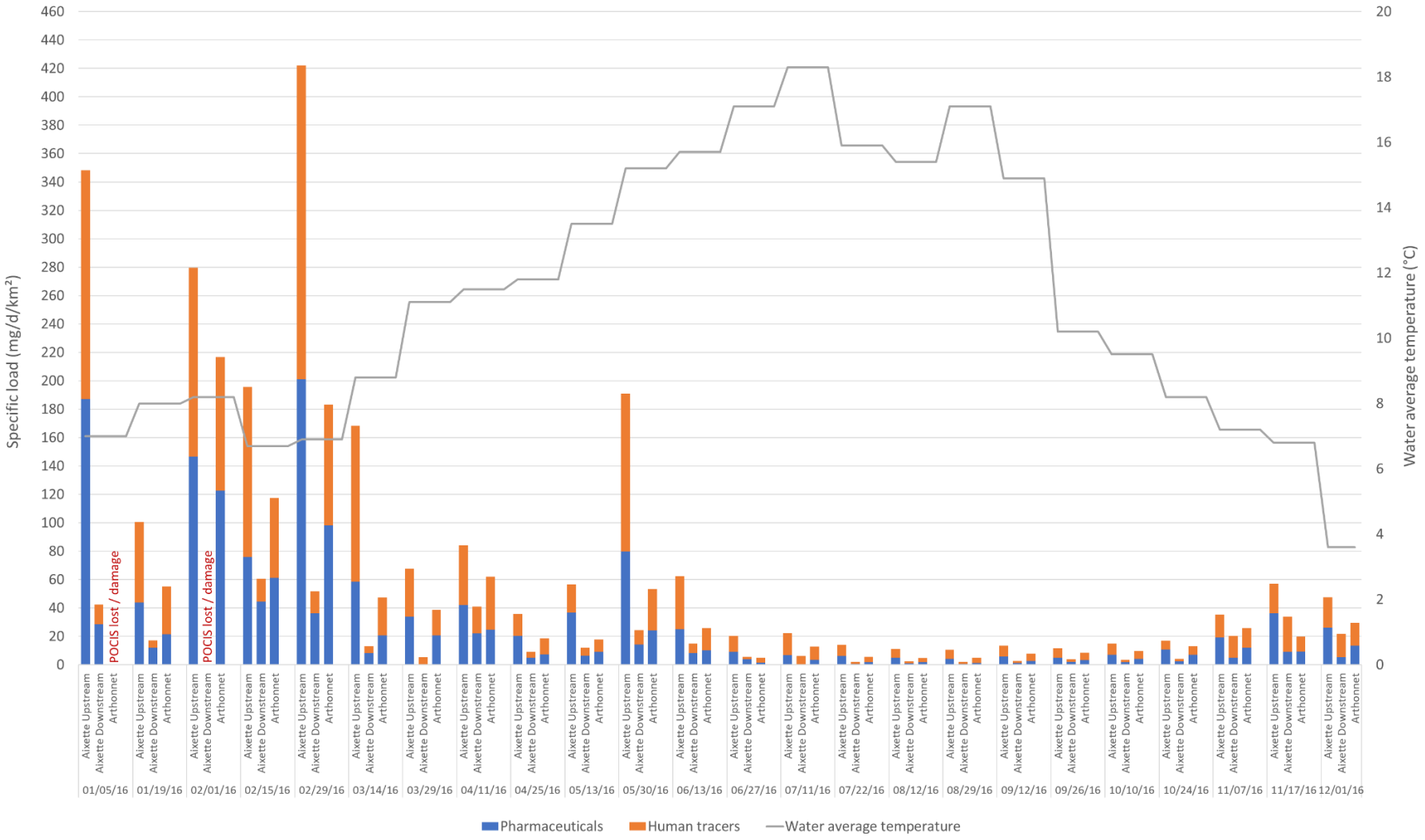


Figure V.21: Temporal load variation of pharmaceuticals and human tracers at the Aixette watershed in 2016 (POCIS exposure = 24) and water average temperature.

Individual targeted compounds distribution over the year 2016.

Pharmaceutical and human tracer detection frequencies and highest concentrations on headwater watershed investigated are reported in **Figure V.22**.

Number of compounds detected/quantified.

At the watershed scale, 20 pharmaceuticals and 3 human tracers out of the 40 tested were detected/quantified at least once in 2016.

At Aixette Upstream and Downstream, 8 pharmaceuticals and 2 human tracers were detected/quantified with a frequency of 100%. 15 and 14 compounds (pharmaceuticals and human tracers) were detected/quantified, respectively with a frequency higher than 80% (out of 22 total targeted compounds detected). In contrast, at Arthonnet, only 4 and 9 targeted compounds were detected/quantified with 100% and > 80% frequency, respectively (out of 20 pharmaceuticals detected/quantified).

Human tracers (caffeine, sucralose, paraxanthine).

At all sampling sites, human tracers were detected with a frequency equal (Aixette) or close (tributary Arthonnet) to 100%. Due to their high human consumption, caffeine and sucralose are two commonly monitored as human tracer compounds in water (Peeler et al. 2006). Average human tracers proportion were more than 50% (52, 58 and 53 % for Aixette Upstream, Downstream and Arthonnet, respectively) of all targeted compounds. Caffeine and sucralose show also the highest concentrations of targeted compounds measured in water.

Caffeine, an ubiquitous compound in raw domestic wastewater (Buerge et al. 2006), was detected in the studied headwaters freshwater. The concentration of caffeine detected in waters from Aixette wathershed (ranging from 5 to 90 ng/L) are similiar to the survey of Buerge et al. (2006) (ranging from 30 to 400 ng/L) performed in a swiss lake but located in densely populated catchment area. Paraxanthine, a caffeine metabolite, was detected with frequency > 63% on the Aixette River and > 13% on the Arthonnet tributary. This relatively low occurrence of the primary caffeine metabolite, may be explained by a low degradation (Baena-Nogueras et al. 2017) or a high stability of the mother compound (caffeine) at acidic and neutral pH, perhaps due to its aromaticity (Edwards et al. 2015).

Figure V.22: Detection frequencies and highest TWAC determined with POCIS at the Aixette watershed in 2016 (POCIS exposure = 24), A: Aixette Upstream, B: Aixette Downstream and C: Arthonnet tributary.

Human pharmaceuticals.

For 15 of the detected/quantified pharmaceuticals in our study out of the 23 (acetaminophen, atenolol, bezafibrate, carbamazepine, clarithromycin, diclofenac, erythromycin, lincomycin, metoprolol, propranolol, salbutamol, sotalol, sulfadiazine, sulfamethoxazole and trimethoprim), the mean detection frequencies in waters varied from 40 to 96% which meet the data from the review of Hughes et al. (2013) and their list of the 61 compounds the most studied with their detection frequencies.

Salbutamol was detected (but not quantified) at Aixette Downstream only while bisprolol and propranolol were quantified at both Aixette river sites and sulfadiazine was only quantified at Aixette Upstream and Arthonnet.

Acetaminophen was the pharmaceutical found at the highest concentration for Aixette river sites (63 and 28 ng/L for Aixette Upstream and Downstream respectively) which was consistent to its consumption to treat pain and fever. Acetaminophen is fully removed by WWTP (Miège et al. 2009), so its presence was originated from discharge of poorly or not treated sewage water.

For both sampling spots on Aixette river, sotalol was the second pharmaceutical found at the highest concentration. Sotalol was frequently detected in surface water (Aminot et al. 2016, ter Laak et al. 2010). Some of the compounds detected/quantified here, *e.g.*, β-blockers (sotalol, atenolol and metoprolol) which are used to manage cardiac arrhythmia and to protect the heart from a second heart attack, are commonly prescribed to elderly persons. The presence of these types of compounds was consistent with the area population (Haute-Vienne, French department): low population density and an elderly population (30% > 60 years old *vs. c.a.* 25% in France).

Comparison with literature data.

Our study highlighted that pharmaceutical families found in headwaters streams were similar to the compounds found in other studies available in literature performed on river in a large range of size reported in **Table V.15** and **Table V.16**. Despite, difference in sampling mode, targeted compounds, 80% of the concentrations found in our work were lower than other studies performed in different region or country (mean values were from 0.5 to 30 ng/L for this work). The type of area where the study was performed, *i.e.* a rural headwater watershed with extensive agricultural practices, can explain the range of concentration measured in freshwater. Indeed, the studies used for comparison of freshwaters pharmaceuticals contents (**Table V.15**) were carried out in urban and/or agricultural watersheds.

In literature, analgesics or psychiatric drug were the most quantified (**Table V.15** and **Table V.16**). Moreover, Hughes et al. (2013) specified that carbamazepine and acetaminophen were the most pharmaceuticals quantified in water. Our study performed in headwaters showed also that analgesics (*e.g.* acetaminophen in our study) is one the most quantified pharmaceuticals compounds. Nevertheless, for our study in a rural headwater watershed, human tracers and β-blockers were compounds the most quantified at the highest concentrations.

Table V.15: Mean concentration on river basin (ng/L). *graphically estimated; **graphically estimated and calculated with our Rs ; n.d. not detected.

	Our study	Aminot et al. (2016)	Jacquet et al. (2012)		Criquet et al. (2017)	Vieno et al. (2007)
River watershed	**Aixette**	Gironde	Seine	Bourbre	Marque	Vantaa
Country	**France**	France	France	France	France	Finland
Number of sites	**3**	6	1	2	1	1
WWTPs influenced sites	**Yes**	Yes	Yes	Yes	Yes	Yes
Number of sampling	**24**	11 or 18	1	1	2	6
Type of sampling	**POCIS**	grab samples	POCIS*	POCIS**	POCIS*	grab samples
Human tracers						
Caffeine	**20**	92				
Sucralose	**29.7**				145	
ß-blockers						
Atenolol	**0.8**	3	48	15		32.8
Sotalol	**13**	16	38	12.4		58.5
Propranolol	**1**	1.3	12	2.4		
Metoprolol	**1.5**	0.8	7	1.4		68.7
Bisprolol	**0.8**	0.9	10	3		
Analgesics / Anti-inflammatories						
Paracetamol	**8.6**	125.6				
Diclofenac	**8**	9.7			214	30.5
Psychatric drugs						
Carbamazepine	**3.6**	12			63	51
Paroxetine	**1.1**					
Antibiotics						
Sulfamerazine	**2.9**					
Sulfamethoxazole	**5.3**					
Trimethoprim	**0.7**					
Clarithromycin	**0.5**					

	Our study	Ashton et al. (2004)	Wilkinson et al. (2017)	Mandaric et al. (2017)	Metcalfe et al. (2014)		Jaimes-Correa et al. (2015)
River watershed	**Aixette**		Thames	Adige	Drinking water treatment plants		Shell Creek
Country	**France**	Southeast of England	England	Italy	Ontario, Canada		Nebraska, US
Number of sites	**3**	10	26	12	10	10	7
WWTPs influenced sites	**Yes**	Yes	Yes	Yes	Yes	Yes	Yes
Number of sampling	**24**	1	3 or 4	2	2	3	5
Type of sampling	**POCIS**	grab samples	grab samples	grab samples	POCIS	grab samples	POCIS
Human tracers							
Caffeine	**20**						
Sucralose	**29.7**				8.3	64.8	
ß-blockers							
Atenolol	**0.8**			1.5			
Sotalol	**13**			12.6			
Propranolol	**1**	25.5		6.2			
Metoprolol	**1.5**			17.4			
Bisprolol	**0.8**						
Analgesics / Anti-inflammatories							
Paracetamol	**8.6**		21.9	17.8			
Diclofenac	**8**	154	50.6	95.5			
Psychatric drugs							
Carbamazepine	**3.6**			35.2	1.5	3.2	
Paroxetine	**1.1**						
Antibiotics							
Sulfamerazine	**2.9**						
Sulfamethoxazole	**5.3**	< 50		22.3	0.03	0.6	0.07
Trimethoprim	**0.7**	12		23.7	0.4	0.7	
Clarithromycin	**0.5**			25			

	Our study	Lindholm-Lehto et al. (2016)		ter Laak et al. (2010)	Kunkel et al. (2012)	Carmona et al., (2014)
River watershed	**Aixette**	Vantaa		Rhin	Gründlach	Turia
Country	**France**	Finland		The Netherlands	Germany	Spain
Number of sites	**3**	4	4	4	2	22
WWTPs influenced sites	**Yes**	Yes	Yes	Yes	Yes	Yes
Number of sampling	**24**	2	2	72	51 to 55	1
Type of sampling	**POCIS**	Chemcatcher	grab samples	grab samples	automated grab samples	grab samples
Human tracers						
Caffeine	**20**					
Sucralose	**29.7**					
ß-blockers						
Atenolol	**0.8**			15		
Sotalol	**13**			67	110.5	
Propranolol	**1**				2.3	
Metoprolol	**1.5**			70	197	
Bisprolol	**0.8**					
Analgesics / Anti-inflammatories						
Paracetamol	**8.6**					
Diclofenac	**8**	20.5	60.55	55	410	49
Psychatric drugs						
Carbamazepine	**3.6**	11.85	27.75	122	400	
Paroxetine	**1.1**					
Antibiotics						
Sulfamerazine	**2.9**					
Sulfamethoxazole	**5.3**			32	235	
Trimethoprim	**0.7**			8		
Clarithromycin	**0.5**			15		

Table V.16: Median concentration in river basin (ng/L). n.d.: not detected; <LOD: under limit of detection; <LOQ: under limit of quantification.

	Our study	ter Laak et al. (2010)	Paiga et al. (2016)	Wu et al. (2009)	Veach et al. (2011)	Dai et al. (2015)			Hughes et al. (2013)
River watershed	**Aixette**	Rhin	Lis	Lake Erie	White river	Beiyun-March	Beiyun-June	Beiyun-September	**Review paper**
Country	**France**	The Netherlands	Portugal	Ohio, US	Indiana, US		China		
Number of sites	**3**	4	1	27	2	15	30	30	**50 references**
WWTPs influenced sites	**Yes**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Number of campaigns	**24**	72	11	6	12	1	1	1	
Type of sampling	**POCIS**	grab samples	grab samples	grab samples	grab samples	grab samples	grab samples	grab samples	
Human tracers									
Caffeine	**12.7**			188	400	4200	2340	1280	
Sucralose	**16.8**								
ß-blockers									
Atenolol	**0.9**	14							90.9
Sotalol	**8.4**	70							101.6
Propranolol	**1.1**					10.5	n.d.	n.d.	18.8
Metoprolol	**1.4**	60				181.5	66.3	93.5	104.5
Bisprolol	**0.9**								
Analgesics / Anti-inflammatories									
Paracetamol	**4.7**		34.4		460				148.2
Diclofenac	**9.1**	50	38	n.d.		67	67.8	57.3	136.5
Psychatric drugs									
Carbamazepine	**2.6**	110	31.7	2	2.7	78	45.1	64.2	174.2
Paroxetine	**0.9**		25.6	n.d.					
Antibiotics									
Sulfamerazine	**2.2**								
Sulfamethoxazole	**4.5**	30	43	n.d.					83
Trimethoprim	**0.6**	7	n.d.	n.d.		204	52.1	46.4	53.4
Clarithromycin	**0.5**	13	< LD	< LQ					

About origin of pharmaceutical in headwaters.

As underlined in the first part, the presence of pharmaceuticals in the headwater watershed of Aixette is linked to the presence of small WWTP and discharge in the small streams of treated or untreated domestic effluent. Currently, it is known that a part of substances was not or little removed by activated sludge process from WWTP, such as atenolol, metoprolol, trimethoprim (removal rate < 20 %), diclofenac, clarithromycin (removal rate < 40 %) (Miège et al. 2009). In Gabet-Giraud et al. (2010), sotalol had a median removal rate ranging from 20% to 60%. In the same way, sulfamethoxazole (a pharmaceutical use for human and veterinary treatment) detected over 78% of the time in this study) was considered non-biodegradable by Richardson and Bowron (Richardson and Bowron 1985) and was removed less than 60% according to Miège et al. (2009). Other compounds detected/quantified in this study, such as bezafibrate and propanol were reported to be removed by more than 60 and 90%, respectively (Miège et al. 2009). A part of compounds present in rivers of Aixette watershed are consistent with the removal rate of pharmaceuticals of biological treatment of wastewater. We keep in mind that the removal rate is process-dependent as underlined by Gabet-Giraud et al. (2010) and small WWTP can display various process (**Table V.11**). We should also consider that a significant part of domestic sewage water is not treated in a WWTP (non-collective sanitation, effluent by-pass) as discussed in the first part with high caffeine/carbamazepine ratio or supported by a strong presence of acetaminophen, a compound removed at 100% by WWTP (Miège et al. 2009). To conclude, it is difficult to assess water contamination by considering only pharmaceuticals' removal rate by WWTP.

Moreover, the watershed displays agricultural activities of cattle breeding. Even if the cattle breeding is performed in an environmental friendly extensive way, the medical care of cow can contribute in a weak part of contamination. Indeed, flunixin, a non-steroidal anti-inflammatory drug, analgesic, and antipyretic used for horses, cattle and pigs medication, was detected at the three sampling points but always below the LOQ. Sulfamerazine, an antibiotic characteristic of cattle breeding sites, was also detected in 100 % of the POCIS extracts at all sampling sites. On Aixette river, the profile of pharmaceuticals quantified shows the same trend: sotalol and acetaminophen were the two pharmaceuticals the most quantified. Those are two human pharmaceuticals whereas on the Arthonnet river, sulfamerazine and sulfamethoxazole were the both compounds were the most quantified. Those two main compounds are veterinary use (sulfamethoxazole can be used for human and veterinary care). The presence of these compounds is linked to the agricultural activities of the watershed, *i.e.* extensive cow cattle breeding. The fingerprint of extensive cattle breeding was more important on Arthonnet sampling point because of the density of head of cattle was more important (*c.a.* 280/km² for Arthonnet and 215/km² for Aixette river).

CONCLUSION

To conclude, during one year, semi-continuous monitoring of three sites on one rural head watershed with extensive cow breeding as agricultural activities was performed with 24 POCIS duplicates exposures for consecutive 14-day periods. A total of 23 compounds were detected/quantified out of 37 targeted. The maximum sum of pharmaceuticals and human tracers concentrations (for one deployment) reached 241, 153 and 120 ng/L on Aixette Upstream, Downstream and Arthonnet, respectively. Pharmaceutical classes detected/quantified were linked to the characteristics' watershed population and agricultural activities. Indeed, an elderly population in an agricultural and cattle breeding zone yielded β-blockers, and veterinary medicines. Seasonal variations of pharmaceuticals were observed and could be due to changes in consumption (*e.g.* antibiotics) and environmental conditions (*e.g.* temperature, sunlight intensity which can affect photo-biodegradation or capacity of river dilution).

Nevertheless, it is clear that on small rivers of headwaters, pharmaceuticals contamination by treated or untreated sewage water is similar to the other type of rivers, with a slight contribution of the extensive agricultural activities.

Currently, headwater stream are considered to play a major role in biodiversity and in the presence of heritage species. The presence of pharmaceutical in these areas can induce toxic damages which should be studied in future investigations.

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V.4. Conclusion intermédiaire

Ce travail a permis de mettre en évidence la contamination en pesticides et en résidus pharmaceutiques des petits cours d'eau situés en tête de bassin versant. En effet, quelle que soit la période de l'année et quel que soit le type de contaminant (pesticide ou résidu pharmaceutique), la contamination s'échelonne de quelques nanogrammes par litre à plusieurs centaines de nanogrammes par litre.

L'échantillonnage ponctuel et l'échantillonnage passif n'apportent pas les mêmes informations. Le premier renseigne sur la contamination dissoute du cours d'eau au moment du prélèvement alors que le second rend compte de la concentration moyenne pendant le temps d'exposition. La contamination d'un cours d'eau peut suivre plusieurs *scenarii* : (i) pic de contamination, (ii) contamination stable ou (iii) contamination faible. Ces cours d'eau étant très petits, les volumes d'eau qui y transitent sont faibles et les capacités de dilution limitées. De plus, ils sont souvent en contact direct avec les sources de contamination à cause de la densité importante de chevelus en tête de bassin versant ou du grand nombre de zones humides. Il peut donc y avoir des contaminations très fortes et très rapides (*scenario* (i)) sans qu'il y ait forcément traitement de grandes surfaces. Ce type de contamination est détectable par l'échantillonnage ponctuel s'il est effectué au bon moment. Cette situation s'est produite sur l'Auvézère avec des concentrations allant jusqu'à 2,7 µg/L. En revanche, l'échantillonnage passif aura une information lissée sur les jours d'exposition. Dans le cas du *scenario* (ii), une information similaire sur la qualité va être obtenue par les deux types d'échantillonnage à la condition que la concentration soit stable pendant le temps de déploiement de l'échantillonneur passif. Enfin, dans le dernier *scenario* (iii), si la contamination est faible, l'échantillonnage passif aura l'avantage de pré-concentrer *in situ* les contaminants et donc de pouvoir détecter des molécules, alors qu'avec l'échantillonnage ponctuel la contamination ne sera pas détectable ou quantifiable.

Dans ce chapitre, deux têtes de bassin versant ont été étudiées (l'Auvézère et l'Aixette) et, pour chacune, 3 points de prélèvement ont été suivis. Sur l'Auvézère, un tributaire (le Rau d'Arnac) est plus contaminé en pesticides que le cours d'eau principal (l'Auvézère) : davantage contaminé en termes de concentration (concentration moyenne de la somme des TWAC sur les 3 ans de suivi : 120, 104 et 5 ng/L pour Arnac Amont, Arnac Aval et l'Auvézère, respectivement), en termes de fréquence de détection et de variété de molécules phytopharmaceutiques (20 et 23 molécules pour le Rau d'Arnac Amont et Aval et 15 molécules pour l'Auvézère). Sur l'Aixette, le point le plus en amont (appelé « Aixette Amont ») est l'endroit le plus contaminé en termes de concentration (concentration moyenne de la somme des TWAC : 38 ng/L pour les pesticides et 140 ng/L pour les résidus pharmaceutiques) et de variété de molécules (19 composés phytopharmaceutiques et 22 résidus pharmaceutiques).

Sur ces deux bassins versants, une pollution plus importante est détectée sur les sites en amont car un effet de dilution est observé pour les sites situés en aval. Il a également été remarqué que la part des résidus vétérinaires était plus faible que la part des résidus pharmaceutiques utilisés pour soigner les humains. Contrairement aux sources de contamination par les composés utilisés pour soigner les humains, les sources de contamination par les composés vétérinaires sont diffuses. Les composés peuvent donc se dégrader avant d'arriver dans le compartiment aquatique.

Ces travaux ont donc permis de mettre en évidence une pollution de deux têtes de bassin versant. Cette pollution, certes faible (de l'ordre du ng/L), reste toutefois questionnable puisque des pics de pollution ont été détectés. Lors de leurs occurrences, le milieu aquatique peut subir une pression importante. De même, l'effet « cocktail », avec la présence d'une grande variété de composés (41 molécules par exemple pour l'Aixette amont), reste à étudier.

A retenir !

- Echantillonnage ponctuel : pic de contamination (utile pour l'estimation de la toxicité aigüe).
- Echantillonnage passif : bruit de fond de la contamination autour de 20 ng/L (apporte des éléments à l'évaluation de la toxicité chronique).
- Sur les têtes de BV, existence de pics de contamination pouvant aller jusqu'à 2700 ng/L sur les sites étudiés.
- Des variations saisonnières de contamination par les résidus pharmaceutiques sont observées (changement de consommation, photo-dégradation des composés selon la température ou l'intensité lumineuse, capacité de dilution de la rivière…).
- Rejets d'eaux usées peu ou non traitées dans la rivière.

Conclusions, discussion et perspectives

Les travaux réalisés au cours de cette thèse ont été construits autour de trois grands objectifs.

Le premier volet de ce travail était de développer un échantillonneur innovant pour l'échantillonnage de pesticides ioniques, d'en connaître la robustesse et de comparer la justesse de ce nouvel échantillonneur à celle du POCIS. Le choix de l'adaptation du DGT pour en faire un échantillonneur pour composés organiques a été validé très rapidement par rapport aux avancées et au fort potentiel du o-DGT pour échantillonner les résidus médicamenteux (Chen et al. 2012). Des avantages du POCIS et du DGT ont ainsi été rassemblés en utilisant les phases réceptrices couramment utilisées dans le POCIS (Oasis® HLB et MAX) et en y appliquant le modèle diffusif du DGT. Deux phases réceptrices (Oasis® HLB ou MAX) ont été incorporées dans un hydrogel permettant ainsi une facilité de manipulation. Quatre pesticides ioniques tests issus de quatre familles chimiques différentes ont été également choisis pour étudier l'échantillonneur. Les tests sur la robustesse de l'échantillonneur (pH et force ionique) ont permis de montrer que cet échantillonneur était utilisable dans les eaux naturelles dans une gamme de pH et force ionique de 3 à 8 et de 0,01 à 1 $mol.L^{-1}$, respectivement.
Le deuxième axe de travail de cette partie a été de déterminer quel était l'outil le plus adapté à l'étude des eaux des têtes de bassin versant, à partir d'expérimentations contrôlées de laboratoire en rivière artificielle. Ces travaux ont démontré qu'au vu des concentrations attendues (milieu supposé faiblement contaminé par les pesticides et les résidus pharmaceutiques), le DGT, dans sa configuration actuelle, présentait des limites de quantification (LQ) pouvant être trop élevées par rapport au POCIS, ceci étant dû à des taux d'échantillonnage plus faibles. L'échantillonnage par le POCIS a donc été choisi pour la suite de ces travaux. De plus, l'ancienneté de cet échantillonneur, créé en 1999 (Alvarez 1999, Alvarez et al. 2004), permet de disposer d'une bibliographie abondante donnant un bon historique des utilisations, mais aussi de la connaissance des biais de quantification.

Le deuxième objectif de ce travail de thèse a été de fiabiliser l'utilisation de l'échantillonneur sélectionné. Lors des premières analyses d'extraits de POCIS sur l'analyseur ToF (Time-of-Flight), le signal mettait en évidence la présence importante de matrice pouvant engendrer un effet de matrice sur l'analyse des extraits d'échantillonneurs. Une étude complète sur les effets de matrice a donc été initiée. Cette étude permettait aussi de répondre à un des quatre volets (la linéarité, l'exactitude, la limite de quantification ainsi que les effets de matrice) nécessaires pour valider les méthodes analytiques développées et utilisées dans ce travail de thèse selon la norme française NF T90-210 (AFNOR 2009). Les effets de matrice ont été étudiés avec des extraits de POCIS exposés en rivière pendant 14 jours. Ainsi, l'étude des effets de matrice a été réalisée avec une matrice environnementale proche des extraits analysés dans les travaux de cette thèse. Dans le cadre de cette fiabilisation, l'effet de matrice le plus important s'est avéré venir, non pas de l'environnement, mais de l'échantillonneur lui-même et plus particulièrement des membranes utilisées. En effet, du polyéthylène glycol (PEG) était relargué par les membranes en polyéthersulfone (PES) et adsorbé par la phase réceptrice. Un protocole de lavage des membranes PES avant assemblage des POCIS a été développé pour permettre de supprimer ce relargage de PEG. Finalement, un lavage des membranes par deux bains successifs d'un mélange

méthanol:eau ultrapure (50:50 v:v) puis d'un rinçage à l'eau ultrapure permettait de supprimer fortement le relargage de PEG. Une dilution minimale par 10 des extraits de POCIS, avant l'étape de quantification des molécules cibles par chromatographie liquide couplée à la spectrométrie haute résolution en masse, a été ajoutée pour supprimer tous les effets de matrices (matrice résiduelle de PEG et matrice environnementale).
Pour estimer la pollution en composés organiques d'un cours d'eau grâce à l'échantillonnage par POCIS, des calibrations doivent être réalisées. En effet, les taux d'échantillonnage (Rs) de chaque composé, servant au calcul de concentration moyennée, doivent être préalablement déterminés. Ce travail de thèse a donc estimé les Rs de 44 molécules pharmaceutiques, en pilote de laboratoire, dans des conditions proches de celles de l'environnement. Dans ce travail, la calibration de POCIS a été réalisée dans une rivière artificielle remplie avec de l'eau du robinet (matrice comprise entre l'eau distillée et une eau naturelle), dopée à une concentration relativement faible (0,5 $\mu g.L^{-1}$) et à une température moyenne de 16°C. Ce travail a permis de mettre à disposition de la communauté des utilisateurs des échantillonneurs passifs des Rs pour 12 composés pharmaceutiques jusqu'à présent non disponibles. De plus, l'effet de la vitesse de courant sur les taux d'échantillonnage a été étudié avec des vitesses de courant allant de 0 à 20 $cm.s^{-1}$. Ce travail montre une variation des Rs déterminés en fonction de la vitesse de courant, en accord avec la présence d'une couche limite de diffusion (DBL) non négligeable aux plus faibles vitesses étudiées (0 et 2-3 $cm.s^{-1}$, principalement). Les taux d'échantillonnage déterminés à 20 $cm.s^{-1}$ ont été utilisés pour le calcul des concentrations moyennes en micropolluants organiques mesurées en milieu naturel, en accord avec les vitesses de courant mesurées dans les cours d'eau étudiés.

Le troisième et dernier objectif de cette thèse s'est attaché à déterminer la concentration en pesticides et résidus pharmaceutiques dans les cours d'eau de deux têtes de bassin versant situées sur la frange ouest du Massif-central au nord-est de la région Nouvelle-Aquitaine en appliquant l'échantillonnage classique ponctuel et passif avec le POCIS. Les avantages de la combinaison de ces deux types d'échantillonnage ont ainsi pu être mis en avant. En effet, ces cours d'eau de tête de bassin versant ont la particularité d'être de petits cours d'eau avec un faible volume d'eau et de se trouver en contact direct avec les sources de pollution du fait de leur densité ou de leurs interactions avec les très nombreuses zones humides présentes sur le bassin versant. La réactivité de ces zones est très rapide et forte. En effet, l'utilisation de faible quantité de polluant (pesticides) peut engendrer de fortes concentrations (supérieures aux $\mu g.L^{-1}$). Cela a pu être mis en évidence grâce aux prélèvements ponctuels, qui, lorsqu'ils sont réalisés au « bon » moment peuvent détecter le pic de pollution, sans cependant assurer que l'on mesure les concentrations maximales ayant transitées dans la rivière. Les concentrations de micropolluants enregistrées à l'aide de prélèvements ponctuels permettent d'estimer ou, à défaut, de discuter les risques de toxicité aigüe qui, avec le POCIS ou un autre échantillonneur passif, n'auraient pas été détectés à ce niveau de concentration, l'information obtenue avec ces dispositifs étant lissée sur les 14 jours de déploiement. Cependant, l'utilisation de l'échantillonneur passif est très bénéfique quand le prélèvement ponctuel n'est pas réalisé au « bon » moment. Un composé transitant seulement une ou deux journées pourra être accumulé dans l'échantillonneur passif et une concentration moyenne sur les 14 jours de déploiement pourra alors être

déterminée. D'un point de vue écotoxicologique, ces informations pourront aussi servir à discuter d'une exposition chronique d'organismes aquatiques à des micropolluants, même si la discussion reste très limitée du fait de la non prise en compte de la multi-exposition à toutes les molécules potentiellement actives circulant dans le milieu aquatique.

Le suivi « semi-continu » réalisé sur deux territoires ont ainsi permis de mettre en évidence l'existence d'une pollution des têtes de bassin versant par les pesticides et les résidus pharmaceutiques, contrairement à ce qui était couramment admis. De plus, du fait de seuils règlementaires existants, les pesticides sont les composés les plus surveillés contrairement aux résidus pharmaceutiques qui à l'heure actuelle ne font pas l'objet de réelle réglementation concernant leur concentration dans les eaux. Il apparait dans ces études que si l'on compare les teneurs entre les pesticides et les résidus pharmaceutiques, par rapport aux molécules ciblées (44 pesticides et métabolites ; 40 résidus de médicaments), les résidus pharmaceutiques sont dans des concentrations moyennes comparables à celles des pesticides dans les cours d'eau. Leurs fréquences de détection sont même plus élevées que celles des pesticides. Ceci peut s'expliquer par le fait que les molécules à usage thérapeutique peuvent être utilisées de manière récurrente sur l'année hydrologique par la population d'un territoire, alors que les usages de pesticides se font à certaines périodes de l'année, leur exportation vers le milieu aquatique dépendant d'une multitude de paramètres (qualité de l'épandage, dégradation, pluviométrie, mobilité du sol vers l'eau…). De même, il a été montré que la contamination en pesticides et résidus pharmaceutiques peut être plus importante à l'amont du cours d'eau qu'en aval, ce qui peut être imputé aux capacités de dilution faibles de l'amont des cours d'eau de tête de bassin.

Un des autres avantages de l'échantillonnage passif est la possibilité de calculer des flux réels grâce au débit moyen journalier. En effet, la concentration déterminée par le POCIS étant une moyenne sur les 14 jours, il est facile de recalculer le flux transitant dans le cours d'eau. L'information obtenue par les flux est complémentaire à celle issue des concentrations car cela permet de s'affranchir du niveau d'eau qui évolue tout au long de l'année. L'utilisation des flux permet d'estimer la quantité de molécules transitant au niveau du bassin versant ou du sous bassin versant. Ceci permet d'accéder, par exemple, aux périodes d'utilisation des substances ou aux zones du bassin versant les plus contributives à la contamination des eaux. Ces deux têtes de bassin versant ont la particularité d'être situées en milieu rural et dans une zone d'élevage extensif avec de la polyagriculture (production de céréales et fourrages permettant aux éleveurs d'être autonomes pour l'alimentation du bétail). Ces évolutions récentes des pratiques agricoles (*i.e.* depuis 2010) ont un impact sur les pesticides que l'on détecte, majoritairement des herbicides. Certaines molécules pharmaceutiques détectées dans les eaux, comme l'antibiotique sulfamérazine, sont aussi en lien avec cette principale activité économique de ces territoires. Ce résidu de médicament à usage vétérinaire fait partie du top 5 des molécules détectées sur le bassin versant étudié, l'Aixette. Un lien a aussi pu être remarqué entre les caractéristiques des populations habitant ces zones et les résidus pharmaceutiques détectés dans les eaux. En effet, le top 5 des molécules détectées (traceurs humains (caféine et sucralose), β-bloquants (sotalol et métoprolol) et résidu vétérinaire (sulfamérazine) ne sont pas les mêmes que celles détectées majoritairement en France ou dans le monde (carbamazépine, acétaminophène, diclofénac, métoprolol et sotalol). Cela peut s'expliquer par la présence d'élevage, comme expliqué

précédemment, mais également par la présence d'une proportion de personnes âgées plus importante que la moyenne nationale (+5% pour la tranche des personnes âgées de plus de 60 ans).

Pour conclure ce travail thèse, il apparait important de discuter spécifiquement les différentes techniques d'échantillonnages. Depuis le développement des échantillonneurs passifs, des améliorations ainsi qu'une meilleure connaissance de leur utilisation ont été apportées pour permettre une bonne évaluation de la pollution environnementale par les micropolluants. Jusqu'ici, les deux grands types d'échantillonnage disponibles, ponctuel et passif, étaient toujours opposés. Cependant, avec deux décennies d'utilisation, plusieurs utilisateurs dans les congrès annuels de l'IPSW (International Passive Sampling Workshop) s'accordent récemment à dire que ces deux approches d'échantillonnage n'apportent pas les mêmes informations et présentent chacune des avantages et des faiblesses. Par ailleurs, comme rappelé dans la première partie de cette conclusion, ce travail montre que la combinaison des échantillonnages passifs et ponctuels des pesticides apporte des informations complémentaires. Cette évolution va être discutée plus spécifiquement avec les deux échantillonneurs passifs (POCIS et o-DGT) utilisés dans ce travail et les échantillons ponctuels d'eau.

L'échantillonnage de substances cibles par POCIS ou o-DGT peut être influencé par les facteurs environnementaux (*e.g.* vitesse de courant, température) lors des déploiements *in-situ* (Harman et al. 2012). En effet, les milieux aquatiques, dans lesquels les échantillonneurs sont placés, peuvent évoluer lors des campagnes d'échantillonnage (*e.g.* débit, physico-chmie) et peuvent induire des changements sur l'accumulation des composés et donc des biais sur la quantification moyenne des analytes cibles ayant transités dans le milieu. Ainsi une bonne connaissance du milieu échantillonné et de la matrice environnementale dans laquelle l'échantillonneur est placé est importante. Il est aussi important d'avoir une connaissance de l'échantillonneur lui-même, sur les mécanismes mis en jeu lors de l'échantillonnage et les influences des différents paramètres physico-chimiques ou hydrodynamiques du milieu sur cet échantillonnage. De plus, le traitement des échantillonneurs avant et après déploiement, tout comme le traitement des extraits d'échantillonneurs passifs avant analyse, sont des étapes cruciales pour avoir un résultat juste. Une réflexion sur l'échantillonneur à sélectionner peut aussi être développée avant de procéder à l'échantillonnage des substances cibles dans le milieu. Ainsi, le **Tableau 1** présente les paramètres clés à examiner pour choisir le mode de prélèvement le plus adapté à l'application visée ou envisager une combinaison des deux modes d'échantillonnage, même si cette dernière stratégie est pour le moment peu pratiquée, du fait de l'opposition historique des deux approches d'échantillonnage.

Tableau 1 : Paramètres à vérifier lors de l'échantillonnage (Données issues de a : Gimpel et al. (2001), b : cette thèse avec 48 pesticides et 46 résidus pharmaceutiques étudiés ([b1] : calculs avec formule standard et [b2] : calculs avec formule développée) , c : Poulier et al. (2014) et d : Belles et al. (2018); ✖ : non étudié, ✓ : applicable, n.c. non concerné, n.d. non déterminé).

		POCIS	o-DGT	Ponctuel
Molécules cibles		0 < LogKow < 5	-3,4 < LogKow < 7,5	*n.c.*
Déploiement terrain	Durée	14 à 21 jours	7 à 21 jours	*n.c.*
	Niveau de contamination du site	+	++	++
	Agitation	> 2 cm.s^{-1}[(b)]	> 2 cm.s^{-1}[(a)] 0 cm.s^{-1}[(b)]	*n.c.*
	Encrassement (biofilm)	✖ (peu étudié hors Harman et al. (2009))	✖	*n.c.*
Détermination des concentrations du milieu	Concentration déterminée	Moyennée dans le temps	Moyennée dans le temps	Concentration à l'instant t (instantanée)
	Calculs	Une seule formule	A adapter selon milieu	Une seule formule
	Justesse	100%[(c)] 35% (0 cm.s^{-1})[(b)] 50 – 75% (2 à 20 cm.s^{-1})[(b)] 25% (2 à 20 cm.s^{-1} avec PRC)[(b)]	23%[(d)] 30 – 70%[(b1)] ou 20%[(b2)] (0 cm.s^{-1}) 20%[(c1)] ou 30 – 70%[(b2)] (2 à 20 cm.s^{-1})	*n.d.* 20%[(c)]
	Limite de quantification (ng.L^{-1})	0,2 à 19,3[(b)]	1,1 à 52,6[(b)]	1,0 à 50,0[(b)]

Dans l'évaluation de la qualité des milieux, il faut aussi considérer l'incertitude sur les résultats apportés par la technique d'échantillonnage utilisée ainsi que les erreurs issues de l'étape analytique et discuter sur l'ensemble des incertitudes.

Considérant les incertitudes liées au POCIS, l'utilisation de cet échantillonneur permet de faire une évaluation « semi-quantitative » des micropolluants avec une incertitude de 100% (Poulier et al. 2014). L'incertitude calculée dans notre travail, résulte d'une expérience dans un pilote de grande taille mimant un écoulement en rivière, avec un contrôle de la vitesse de courant, de la concentration en analytes et de la température. Grâce à ces conditions expérimentales, une erreur moins importante a été calculée (en moyenne de 50 à 70% ou de l'ordre de 30% avec l'utilisation de PRC), mais elle dépend du composé suivi. L'utilisation prometteuse d'un PRC pour améliorer les performances du POCIS (Mazzella et al. 2010) est actuellement remise en cause (Booij and Chen 2018), néanmoins ces travaux de thèse montrent qu'elle présente encore un intérêt pour certaines molécules, à condition d'avoir testé au préalable l'applicabilité de la correction PRC (avec une désorption de 20 à 80% (Soderstrom and Bergqvist 2004)). Enfin, un point faible du POCIS identifié à travers les travaux de cette thèse résulte surtout dans les taux d'échantillonnage (Rs) disponibles dans la littérature. En effet, du fait des conditions de détermination non harmonisées, parfois très éloignées des conditions réelles du milieu naturel, ils peuvent varier d'un facteur allant jusqu'à 200 d'un auteur à l'autre, ce qui fait varier les concentrations moyennes de micropolluants du milieu échantillonné du même facteur. Il serait souhaitable d'arriver à des conditions harmonisées de détermination des Rs pour fiabiliser avant tout les concentrations moyennes déterminées dans les eaux à l'aide des POCIS.

Quant au o-DGT, une incertitude de 23% a été calculée par Belles et al. (2018). Les travaux réalisés dans cette thèse montrent également une incertitude de l'ordre de 20%. En effet, la formule la plus couramment utilisée pour la détermination de la concentration en micropolluants organiques dans l'eau par la technique DGT repose sur un modèle avec 5 hypothèses ou approximations. Ainsi, selon le milieu échantillonné (milieu agité ou non), il peut être intéressant d'utiliser une formule mathématique plus avancée afin d'augmenter la justesse et la précision de la quantification de la pollution par les composés organiques.

Par ailleurs, la récente adaptation du DGT pour l'échantillonnage de composés organiques de type pesticides ou résidus pharmaceutiques implique un manque de recul sur la technique qui peut potentiellement être influencée par de nombreux paramètres environnementaux (*e.g.* « biofouling ») qui restent encore à tester si on se réfère à la connaissance acquise depuis près d'un quart de siècle sur les DGT pour les composés minéraux.

Concernant l'échantillonnage ponctuel, les incertitudes vont être liées à l'étape d'extraction-concentration en laboratoire des composés cibles ainsi qu'à leur quantification par séparation chromatographique liquide couplée à la spectrométrie de masse. Les processus normalisés et l'amélioration des matériels analytiques font que les incertitudes sont largement acceptables (*c.a.* 20%). La principale faiblesse reconnue de l'échantillonnage ponctuel, malgré une mise en œuvre aisée, est principalement liée à son manque de représentativité temporelle, sauf à multiplier le nombre de mesure ce qui peut être économiquement difficilement réalisable.

Concernant les échantillonneurs passifs, les poursuites de travaux sont importantes.

Dans le cadre de l'adaptation du DGT pour l'échantillonnage de composés ioniques, le travail réalisé consistait à développer l'outil. Des études plus approfondies méritent d'être mises en place. Une partie de la bibliographie y est d'ailleurs consacrée. Le potentiel de cet échantillonneur a été largement démontré dans le chapitre III et les différents articles de la littérature l'ont aussi démontré. En effet, sa robustesse devant les variations de vitesse de courant, et surtout lors de déploiements dans des systèmes peu turbulents, lui donne une place privilégiée. Sa potentielle application à d'autres compartiments environnementaux comme le sol ou les sédiments en font un outil très complet. Comme nous l'avons rappelé, il n'a pas été choisi dans notre étude du fait de ses taux d'échantillonnage plus faibles, dans sa configuration actuelle, comparé au POCIS. Pour pallier à cette faiblesse, plusieurs solutions peuvent être envisagées. Un nouveau design avec une surface d'exposition plus grande lui permettrait d'obtenir des taux d'échantillonnage identiques au POCIS. Une autre alternative serait de laisser l'échantillonneur déployé dans le milieu plus longtemps mais dans ces conditions, l'échantillonneur serait susceptible de voir se développer à sa surface du biofouling. L'impact de cette couche supplémentaire de diffusion sur le transfert des composés cibles du milieu à échantillonner vers la phase fixante n'a pas encore été étudié pour les composés organiques. Si on se réfère aux quelques études sur l'impact du biofouling sur la quantification de composés inorganiques par DGT, il existe des formes d'interaction entre les métaux et le biofilm qui affectent fortement la diffusion de certain métaux comme le Cu ou le Pb (Devillers et al. 2017). Il peut donc y avoir des réactions similaires avec les composés organiques, d'autant plus s'ils sont ioniques comme les éléments métalliques. Ceci implique que les coefficients de diffusion devront être mesurés systématiquement ou recalculés si un modèle arrive à être établi afin d'avoir une estimation de la concentration la plus juste. De

plus, le biofouling n'étant pas identique et ne se développant pas de la même manière (*e.g.* épaisseur, matières inertes le composant, types de microorganismes…) sur chaque site d'étude ou au fil des saisons, il serait intéressant de caractériser les interactions possibles entre une molécule et des biofilms avec différentes caractéristiques de manière à cerner l'impact sur les capacités d'échantillonnage de la o-DGT.
En l'absence de la connaissance des mécanismes exacts de fixation des molécules cibles sur les phases fixantes, l'étude de l'influence du pH et de la force ionique est réalisée assez systématiquement pour tester la robustesse de chaque échantillonneur. Une caractérisation des mécanismes d'interaction phase fixante-molécules serait alors un gain de temps important dans le développement d'autres échantillonneur de type o-DGT dédiés à d'autres classes de molécules. Pour déterminer les interactions majoritairement mises en jeu (*e.g.* liaisons de Van der Waals, intéractions π-π, liaisons hydrogènes…) il faudrait utiliser différentes catégories de molécules (des molécules neutres avec différentes fonctions impliquant des polarités différentes ainsi que des molécules chargées positivement et négativement) et les tester sur différentes phases fixantes.

Une standardisation des procédures de calibration des échantillonneurs devrait être menée pour permettre d'obtenir les paramètres clés de calcul des concentrations moyennes fiables et homogènes d'une étude à l'autre. En effet, toutes les étapes de calibration sont concernées. Ainsi, pour le o-DGT, les coefficients de diffusion devraient être déterminés à la même température et à partir de la même méthode. Il semblerait que le coefficient de diffusion effectif serait celui le plus proche du coefficient de diffusion réel. Cela peut s'expliquer car il est déterminé à partir d'expériences utilisant l'intégralité de l'échantillonneur. De la même manière, les calibrations pour le POCIS, qui sont plus lourdes à mettre en place et qui sont demandeuses en temps et en argent, devraient être faites dans des conditions proches de celles de l'environnement afin d'obtenir des taux d'échantillonnage comparables. Ce travail a mis en avant la possibilité d'approcher des Rs de POCIS à partir d'une méthode de calcul simple en utilisant des Rs issus de calibration en rivière artificielle pour établir une équation. L'établissement d'un modèle d'estimation des Rs serait alors une avancée importante facilitant l'utilisation des techniques d'échantillonnage passif en évitant cette étape de calibration.

Ces travaux apportent une meilleure connaissance des têtes de bassin versant grâce à l'utilisation améliorée d'échantillonneurs passifs et de prélèvements ponctuels. Au-delà du transfert des résultats acquis vers les gestionnaires, qui pourront envisager des mesures correctives sur les territoires pour protéger les milieux aquatiques et les usages de l'eau, de futurs travaux sur les zones comme les têtes de bassin versant peuvent cibler d'autres types de molécules en rapport avec les activités du bassin versant. Par exemple, le suivi de la contamination par les hormones naturelles des bovins pourrait être envisagé car la population bovine, dans ces zones rurales, est importante et les vaches sont gestantes tous les ans, ce qui accentue la sécrétion d'hormone. En effet, les hormones font partie d'une classe de composés chimiques réputés pour causer la féminisation des poissons (Yamamoto 1969), et leur présence dans les têtes de bassin versant, où des espèces patrimoniales sont présentes, n'est pas documentée.

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Annexes

Annexe 1. Liste des composés organiques échantillonné par le o-DGT avec les caractéristiques de mise en œuvre et la configuration correspondante de l'échantillonneur.

Table A.1: Compounds tested with corresponding receiving phase and diffusive coefficient (calculated for 25°C) and elution protocol (a: Chen et al. (2013), b: Challis et al. (2016), c: D'Angelo and Starnes (2016) and *n.i.* not indicate).

Compound	Diffusive gel	Receiving phase	Diffusive coefficient ($x10^{-6}$ cm^2 s^{-1})	Elution protocol	Reference
17-α-ethynylestradiol	Agarose	HLB	3.33	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
17-α-ethynylestradiol	Agarose	HLB	3.40	5 mL acetonitrile + 30 min US	Chen et al. (2018)
17-α-ethynylestradiol	Agarose	HLB	3.33[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
17-α-ethynylestradiol	Agarose	XAD18	5.08	acetone:n-hexane 50:50 by ASE: 50°C, 1000 psi during 11 min	Guo et al. (2017b)
17-α-ethynylestradiol	Agarose	XAD18	4.01	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018b)
17-α-ethynylestradiol	Polyacrylamide	Sepra ZT	3.53	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
17-β-estradiol	Agarose	HLB	3.13	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
17-β-estradiol	Agarose	HLB	3.13[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
17-β-estradiol	Agarose	HLB	3.13[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
17-β-estradiol	Agarose	XAD18	5.17	acetone:n-hexane 50:50 by ASE: 50°C, 1000 psi during 11 min	Guo et al. (2017b)
17-β-estradiol	Agarose	XDA-1	3.75	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018b)
17-β-estradiol	Polyacrylamide	Sepra ZT	2.97	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
2.4-D	Agarose	HLB	4.77	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
2.4-D	Agarose	HLB	4.77[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
2.4-D	Agarose	HLB	4.77[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
2.4-D	Polyacrylamide	Sepra ZT	3.88	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
4-chlorophenol	Nylon membrane	Molecular imprinted polymers (MIP)	0.91	5 mL methanol during 12h	Dong et al. (2014)
4-hydroxybenzoic acid	Agarose	HLB	7.30	5 mL acetonitrile + 30 min US	Chen et al. (2017)
4-tert-octylphenol	Agarose	HLB	4.34	5 mL acetonitrile + 30 min US	Chen et al. (2018)
Acetochlor	Agarose	XDA-1	4.32	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018b)
AMPA	Polyacrylamide	TiO_2	4.02	1 mL NaOH during 24h	Fauvelle et al. (2015)

Amphetamine	Agarose	XAD18	8.38	10 mL methanol during 6h	Guo et al. (2017a)
Atenolol	Agarose	HLB	3.85	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Atenolol	Agarose	HLB	3.85[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Atenolol	Agarose	HLB	3.85[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Atenolol	Agarose	HLB	3.85[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Atenolol	Polyacrylamide	Sepra ZT	2.86	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Atrazine	-	-	-	5 mL acetonitrile	Lin et al. (2018)
Atrazine	Agarose	HLB	3.73	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Atrazine	Agarose	HLB	3.73[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Atrazine	Agarose	HLB	3.73[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Atrazine	Agarose	Strata-X	4.58	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Atrazine	Agarose	Strata-X	5.13	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Atrazine	Agarose	XDA-1	4.95	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018b)
Atrazine	Polyacrylamide	Sepra ZT	3.13	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Atrazine-desethyl	Agarose	Strata-X	4.58	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Azithromycin	Agarose	XDA-1	1.32	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Balofloxacin	Agarose	PCM	1.55	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Bentazon	Polyacrylamide	HLB	4.14	5 mL methanol:ethyl acetate 50:50 (v/v) during 24h	Guibal et al. (2017a)
Bentazon	Polyacrylamide	MAX	4.94	5 mL methanol:formic acid (1 M) 90:10 (v/v) during 24h	Guibal et al. (2017a)
Benzophenone	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Benzylparaben	Agarose	HLB	4.97	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Bisphenol A	Agarose	Activated charcoal	5.03	10 mL methanol:NaOH (1 M) 70:30 (v/v) during 24h or 10 mL methanol during 24h	Zheng et al. (2014)
Bisphenol A	Agarose	HLB	4.80	5 mL acetonitrile + 30 min US	Chen et al. (2018)
Bisphenol A	Agarose	XDA-1	5.21	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018b)
Bisphenol B	Agarose	Activated charcoal	4.44	10 mL methanol:NaOH (1 M) 70:30 (v/v) during 24h or 10 mL methanol during 24h	Zheng et al. (2014)
Bisphenol F	Agarose	Activated charcoal	5.64	10 mL methanol:NaOH (1 M) 70:30 (v/v) during 24h or 10 mL methanol during 24h	Zheng et al. (2014)

Butylated hydroxyanisole	Agarose	HLB	4.25	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Butylated hydroxytoluene	Agarose	HLB	3.67	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Butylparaben	Agarose	HLB	5.61	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Carbadox	Agarose	XAD18	3.79	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Carbadox	Agarose	XAD18	3.79[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Carbamazepine	Agarose	HLB	5.14	(3 mL dichloromethane:hexane 50:50 (v/v) + 1 min vortex + 5 min US) x2	Amato et al. (2018)
Carbamazepine	Agarose	HLB	5.01	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Carbamazepine	Agarose	HLB	5.01[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Carbamazepine	Agarose	HLB	5.01[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Carbamazepine	Agarose	HLB	5.01[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Carbamazepine	Polyacrylamide	Sepra ZT	4.12	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Chloramphenicol	Agarose	XDA-1	4.57	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Chlorpyrifos	Agarose	HLB	3.42	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Chlorpyrifos	Agarose	HLB	3.42[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Chlorpyrifos	Agarose	HLB	3.42[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Chlorpyrifos	Polyacrylamide	Sepra ZT	1.36	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Chlorsulfuron	Polyacrylamide	HLB	3.10	5 mL methanol:ethyl acetate 50:50 (v/v) during 24h	Guibal et al. (2017a)
Chlorsulfuron	Polyacrylamide	MAX	3.56	5 mL methanol:formic acid (1 M) 90:10 (v/v) during 24h	Guibal et al. (2017a)
Ciprofloxacin	Agarose	PCM	1.55	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Ciprofloxacin	Agarose	XAD18	2.75	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Ciprofloxacin	Agarose	XAD18	2.75[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Ciprofloxacin	Agarose	XAD18	1.16	10 mL acetonitrile:HCl (0.15 M) 50:50 (v/v) + 30 min US	D'Angelo and Starnes (2016)
Ciprofloxacin	Agarose	XDA-1	2.50	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Clarithromycin	Agarose	HLB	3.42	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Clarithromycin	Agarose	HLB	3.42[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Clarithromycin	Agarose	XAD18	1.95	(5 mL methanol + 20 min US) x2	Chen et al. (2013)

Clarithromycin	Agarose	XAD18	1.95[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Clarithromycin	Agarose	XDA-1	1.32	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Clofibric acid	Agarose	HLB	4.28	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Clofibric acid	Agarose	HLB	4.28[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Clofibric acid	Agarose	HLB	4.28[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Clofibric acid	Polyacrylamide	Sepra ZT	3.43	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Clothianidin	Agarose	HLB	4.22	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Clothianidin	Agarose	HLB	4.22[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Clothianidin	Agarose	HLB	4.22[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Clothianidin	Polyacrylamide	Sepra ZT	3.35	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Danofloxacin	Agarose	XAD18	Poor linearity	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Danofloxacin	Agarose	XAD18	-	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Diazinon	Agarose	HLB	3.80	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Diazinon	Agarose	HLB	3.80[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Diazinon	Agarose	HLB	3.80[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Diazinon	Polyacrylamide	Sepra ZT	2.23	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Diclofenac	Agarose	HLB	4.44	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Diclofenac	Agarose	HLB	4.44[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Diclofenac	Agarose	HLB	4.44[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Diclofenac	Agarose	HLB	4.44[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Diclofenac	Polyacrylamide	Sepra ZT	3.53	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Diethylstilbestrol	Agarose	HLB	4.83	5 mL acetonitrile + 30 min US	Chen et al. (2018)
Difloxacin	Agarose	XAD18	3.20	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Difloxacin	Agarose	XAD18	3.20[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Diflufenican	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Diflufenican	Agarose	Strata-X	4.27	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Diuron	Agarose	HLB	5.24	(3 mL dichloromethane:hexane 50:50 (v/v) + 1 min vortex + 5 min US) x2	Amato et al. (2018)
Enrofloxacin	Agarose	HLB	2.96[a]	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Enrofloxacin	Agarose	HLB	*2.96[a]*	(3 mL methanol + 2 min US) x3	Challis et al. (2018)

Enrofloxacin	Agarose	HLB	2.96[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Enrofloxacin	Agarose	PCM	1.41	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Enrofloxacin	Agarose	XAD18	2.96	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Enrofloxacin	Agarose	XAD18	2.96[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Enrofloxacin	Agarose	XDA-1	2.62	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Enrofloxacin	Polyacrylamide	Sepra ZT	3.49	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Ephedrine	Agarose	XAD18	6.62	10 mL acetonitrile (5% NH_3) during 24h	Zhang et al. (2018)
Erythromycin	Agarose	HLB	1.76	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Erythromycin	Agarose	HLB	1.76[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Erythromycin	Agarose	HLB	1.76[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Erythromycin-H2O	Agarose	XAD18	1.85	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Erythromycin-H2O	Agarose	XAD18	1.85[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Erythromycin-H2O	Agarose	XDA-1	1.44	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Estriol	Agarose	HLB	4.59	5 mL acetonitrile + 30 min US	Chen et al. (2018)
Estriol	Agarose	XAD18	5.20	acetone:n-hexane 50:50 by ASE: 50°C, 1000 psi during 11 min	Guo et al. (2017b)
Estriol	Agarose	XDA-1	5.00	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018b)
Estrone	Agarose	HLB	3.83	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Estrone	Agarose	HLB	4.80	5 mL acetonitrile + 30 min US	Chen et al. (2018)
Estrone	Agarose	HLB	3.83[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Estrone	Agarose	XAD18	5.17	acetone:n-hexane 50:50 by ASE: 50°C, 1000 psi during 11 min	Guo et al. (2017b)
Estrone	Polyacrylamide	Sepra ZT	3.43	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Ethofumesathe	Agarose	Strata-X	6.61	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Ethylparaben	Agarose	HLB	-	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Fenoprofen	Agarose	HLB	4.13	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Fenoprofen	Agarose	HLB	4.13[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Fenoprofen	Agarose	HLB	4.13[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Fenoprofen	Polyacrylamide	Sepra ZT	3.05	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Fleroxacin	Agarose	PCM	1.86	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)

Fleroxacin	Agarose	XAD18	1.03	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Fleroxacin	Agarose	XAD18	1.03[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Flofenicol	Agarose	XDA-1	4.61	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Fluoxetine	Agarose	HLB	4.38	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Fluoxetine	Agarose	HLB	4.38[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Fluoxetine	Agarose	HLB	4.38[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Fluoxetine	Agarose	HLB	4.38[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Fluoxetine	Polyacrylamide	Sepra ZT	3.01	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Flutolanil	Agarose	Strata-X	6.77	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Galaxolide	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Galaxolide	Agarose	Strata-X	4.58	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Gatifloxacin	Agarose	PCM	2.35	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Gemfibrozil	Agarose	HLB	3.58	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Gemfibrozil	Agarose	HLB	3.58[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Gemfibrozil	Agarose	HLB	3.58[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Gemfibrozil	Agarose	HLB	3.58[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Gemfibrozil	Polyacrylamide	Sepra ZT	2.65	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Glyphosate	Polyacrylamide	TiO_2	3.39	1 mL NaOH during 24h	Fauvelle et al. (2015)
Heptylparaben	Agarose	HLB	4.83	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Ibuprofen	Agarose	HLB	4.07	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Ibuprofen	Agarose	HLB	4.07[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Ibuprofen	Agarose	HLB	4.07[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Ibuprofen	Polyacrylamide	Sepra ZT	3.13	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Imidacloprid	Agarose	HLB	4.59	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Imidacloprid	Agarose	HLB	4.59[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Imidacloprid	Agarose	HLB	4.59[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Imidacloprid	Polyacrylamide	Sepra ZT	-	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Ioxynil	Polyacrylamide	HLB	5.29	5 mL methanol:ethyl acetate 50:50 (v/v) during 24h	Guibal et al. (2017a)

Ioxynil	Polyacrylamide	MAX	6.90	5 mL methanol:formic acid (1 M) 90:10 (v/v) during 24h	Guibal et al. (2017a)
Irgarol	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Isopropylparaben	Agarose	HLB	5.91	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Isoproturon	Agarose	HLB	4.93	(3 mL dichloromethane:hexane 50:50 (v/v) + 1 min vortex + 5 min US) x2	Amato et al. (2018)
Ketamine	Agarose	XAD18	8.83	10 mL methanol during 6h	Guo et al. (2017a)
Ketoprofen	Agarose	HLB	3.31	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Ketoprofen	Agarose	HLB	3.31[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Ketoprofen	Agarose	HLB	3.31[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Ketoprofen	Agarose	HLB	3.31[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Ketoprofen	Polyacrylamide	Sepra ZT	2.74	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Leucomycin	Agarose	XAD18	1.43	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Leucomycin	Agarose	XAD18	1.43[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Lilial	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Lincomycin	Agarose	XAD18	3.10	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Lincomycin	Agarose	XAD18	3.10[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Lincomycin	Agarose	XDA-1	3.07	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Lomefloxacin	Agarose	PCM	1.93	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Lomefloxacin	Agarose	XAD18	1.43	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Lomefloxacin	Agarose	XAD18	3.07[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Marbofloxacin	Agarose	XAD18	Poor linearity	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Marbofloxacin	Agarose	XAD18	-	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Mecoprop	Polyacrylamide	HLB	4.37	5 mL methanol:ethyl acetate 50:50 (v/v) during 24h	Guibal et al. (2017a)
Mecoprop	Polyacrylamide	MAX	4.48	5 mL methanol:formic acid (1 M) 90:10 (v/v) during 24h	Guibal et al. (2017a)
Metazachlor	Agarose	Strata-X	4.58	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Methamphetamine	Agarose	XAD18	9.28	10 mL methanol during 6h	Guo et al. (2017a)
Methcathinone	Agarose	XAD18	7.60	10 mL acetonitrile (5% NH_3) during 24h	Zhang et al. (2018)
Methylparaben	Agarose	HLB	6.85	5 mL acetonitrile + 30 min US	Chen et al. (2017)

Metolachlor	Agarose	Strata-X	4.58	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Metolachlor	Agarose	Strata-X	6.46	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Metoprolol	Agarose	HLB	4.38	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Metoprolol	Agarose	HLB	4.38[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Metoprolol	Agarose	HLB	4.38[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Metoprolol	Agarose	HLB	4.38[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Metoprolol	Polyacrylamide	Sepra ZT	2.70	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Monensin	Agarose	XAD18	0.58	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Monensin	Agarose	XAD18	0.58[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Moxifloxacin	Agarose	PCM	1.43	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Naphtalene	Water	Activated charcoal	94.5	5 mL CS_2 + 30 min US	Bodarenko et al. (2011)
Naproxen	Agarose	HLB	4.37	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Naproxen	Agarose	HLB	4.37[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Naproxen	Agarose	HLB	4.37[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Naproxen	Polyacrylamide	Sepra ZT	3.41	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Nonylphenol	Agarose	HLB	4.13	5 mL acetonitrile + 30 min US	Chen et al. (2018)
Norfloxacin	Agarose	XAD18	2.46	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Norfloxacin	Agarose	XAD18	2.46[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Norfloxacin	Agarose	XDA-1	2.66	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Novobiocin	Agarose	XAD18	0.80	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Novobiocin	Agarose	XAD18	0.80[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Octicizer	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Ofloxacin	Agarose	PCM	1.68	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Ofloxacin	Agarose	XAD18	2.24	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Ofloxacin	Agarose	XAD18	2.24[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Ofloxacin	Agarose	XDA-1	2.04	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Oleandomycin	Agarose	XAD18	1.66	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Oleandomycin	Agarose	XAD18	1.66[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Ormetoprim	Agarose	XAD18	3.94	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Ormetoprim	Agarose	XAD18	3.94[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)

ortho-phenylphenol	Agarose	HLB	5.18	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Paroxetine	Agarose	HLB	4.60	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Paroxetine	Agarose	HLB	4.60[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Paroxetine	Agarose	HLB	4.60[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Paroxetine	Agarose	HLB	4.60[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Paroxetine	Polyacrylamide	Sepra ZT	4.31	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Pefloxacin	Agarose	XAD18	1.92	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Pefloxacin	Agarose	XAD18	1.92[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Propanolol	Agarose	HLB	4.46	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Propanolol	Agarose	HLB	4.46[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Propanolol	Agarose	HLB	4.46[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Propanolol	Agarose	HLB	4.46[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Propanolol	Polyacrylamide	Sepra ZT	3.14	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Propazine	Agarose	Strata-X	3.63	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Propylparaben	Agarose	HLB	5.92	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Roxithromycin	Agarose	HLB	2.43	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Roxithromycin	Agarose	HLB	2.43[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Roxithromycin	Agarose	XAD18	1.49	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Roxithromycin	Agarose	XAD18	1.49[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Salinomycin	Agarose	XAD18	0.61	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Salinomycin	Agarose	XAD18	0.61[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sarafloxacin	Agarose	PCM	1.75	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sarafloxacin	Agarose	XAD18	Poor linearity	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sarafloxacin	Agarose	XAD18	-	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Simazine	Agarose	Strata-X	5.76	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Sparfloxacin	Agarose	PCM	2.04	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfacetamide	Agarose	PCM	4.60	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfacetamide	Agarose	XAD18	4.76	(5 mL methanol + 20 min US) x2	Chen et al. (2013)

Sulfacetamide	Agarose	XAD18	4.76[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfachlorpyridazine	Agarose	HLB	4.90	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Sulfachlorpyridazine	Agarose	HLB	4.90[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Sulfachlorpyridazine	Agarose	HLB	4.90[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfachlorpyridazine	Agarose	XAD18	3.59	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfachlorpyridazine	Agarose	XAD18	3.59[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfachlorpyridazine	Polyacrylamide	Sepra ZT	3.37	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfachlropyridazine	Agarose	XDA-1	4.63	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfadiazine	Agarose	PCM	4.20	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfadiazine	Agarose	XAD18	4.23	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfadiazine	Agarose	XAD18	4.23[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfadiazine	Agarose	XDA-1	4.41	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfadimethoxine	Agarose	HLB	3.81	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Sulfadimethoxine	Agarose	HLB	3.81[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Sulfadimethoxine	Agarose	HLB	3.81[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfadimethoxine	Agarose	XAD18	3.84	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfadimethoxine	Agarose	XAD18	3.84[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2014)
Sulfadimethoxine	Agarose	XAD18	3.84[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfadimethoxine	Agarose	XAD18	3.84[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015a)
Sulfadimethoxine	Agarose	XDA-1	4.30	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfadimethoxine	Polyacrylamide	Sepra ZT	3.36	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfadimidine	Agarose	PCM	3.68	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfadoxine	Agarose	PCM	3.93	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfadoxine	Agarose	XAD18	3.85	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfadoxine	Agarose	XAD18	3.85[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfaguanidine	Agarose	XAD18	4.51	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfaguanidine	Agarose	XAD18	4.51[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfamerazine	Agarose	PCM	3.95	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfamerazine	Agarose	XAD18	3.79	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfamerazine	Agarose	XAD18	3.79[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfameter	Agarose	XAD18	4.01	(5 mL methanol + 20 min US) x2	Chen et al. (2013)

Sulfameter	Agarose	XAD18	4.01[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfamethazine	Agarose	HLB	4.04	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Sulfamethazine	Agarose	HLB	4.04[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Sulfamethazine	Agarose	HLB	4.04[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfamethazine	Agarose	XAD18	4.01	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfamethazine	Agarose	XAD18	4.01[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2014)
Sulfamethazine	Agarose	XAD18	4.01[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfamethazine	Agarose	XAD18	4.01[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015a)
Sulfamethazine	Agarose	XDA-1	2.90	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfamethazine	Polyacrylamide	Sepra ZT	3.19	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfamethoxazole	Agarose	HLB	4.65	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Sulfamethoxazole	Agarose	HLB	4.65[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Sulfamethoxazole	Agarose	HLB	4.65[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Sulfamethoxazole	Agarose	HLB	4.65[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfamethoxazole	Agarose	PCM	4.59	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfamethoxazole	Agarose	XAD18	3.62	(5 mL methanol + 20 min US) x2	Chen et al. (2012)
Sulfamethoxazole	Agarose	XAD18	5.10	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfamethoxazole	Agarose	XAD18	5.10[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2014)
Sulfamethoxazole	Agarose	XAD18	5.10[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfamethoxazole	Agarose	XAD18	5.10[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015a)
Sulfamethoxazole	Agarose	XDA-1	4.72	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfamethoxazole	Polyacrylamide	Sepra ZT	3.23	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfamethoxypyridazine	Agarose	PCM	4.43	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfamonomethoxine	Agarose	XAD18	4.08	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfamonomethoxine	Agarose	XAD18	4.08[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfamonomethoxine	Agarose	XDA-1	4.06	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfanilamide	Agarose	XAD18	6.24	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfanilamide	Agarose	XAD18	6.24[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfapyridine	Agarose	HLB	4.19	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Sulfapyridine	Agarose	HLB	4.19[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)

Sulfapyridine	Agarose	HLB	4.19[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfapyridine	Agarose	PCM	4.75	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfapyridine	Agarose	XAD18	4.75	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfapyridine	Agarose	XAD18	4.75[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfapyridine	Agarose	XDA-1	4.65	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfapyridine	Polyacrylamide	Sepra ZT	3.60	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfaquinoxaline	Agarose	XAD18	3.50	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfaquinoxaline	Agarose	XAD18	3.50[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfathiazole	Agarose	PCM	4.68	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Sulfathiazole	Agarose	XAD18	4.61	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfathiazole	Agarose	XAD18	4.61[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfathiazole	Agarose	XDA-1	3.83	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Sulfisoxazole	Agarose	HLB	3.66	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Sulfisoxazole	Agarose	HLB	3.66[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Sulfisoxazole	Agarose	HLB	3.66[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Sulfisoxazole	Agarose	XAD18	3.79	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Sulfisoxazole	Agarose	XAD18	3.79[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Sulfisoxazole	Polyacrylamide	Sepra ZT	2.00	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Tetracycline	Agarose	XAD18	1.16[c]	4 mL acetonitrile:H_3PO_4 (0.05 M) 50:50 (v/v) + 30 min US	D'Angelo et al. (2018)
Thiamethoxam	Agarose	HLB	4.17	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Thiamethoxam	Agarose	HLB	4.17[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)
Thiamethoxam	Agarose	HLB	4.17[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Thiamethoxam	Polyacrylamide	Sepra ZT	3.45	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Thiamphenicol	Agarose	XDA-1	5.56	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Tonalid	Agarose	Strata-X	2.89	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Tonalid	Agarose	Strata-X	3.72	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2018)
Triclocarban	Agarose	HLB	3.36	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Triclosan	Agarose	HLB	3.63	5 mL acetonitrile + 30 min US	Chen et al. (2017)
Trimethoprim	Agarose	HLB	4.02	(3 mL methanol + 2 min US) x3	Challis et al. (2016)
Trimethoprim	Agarose	HLB	4.02[b]	(3 mL methanol + 2 min US) x3	Challis et al. (2018)

Trimethoprim	Agarose	HLB	4.02[b]	(3 mL methanol + 2 min US) x3	Buzier et al. (2018) – submitted to Chemosphere
Trimethoprim	Agarose	HLB	4.02[b]	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Trimethoprim	Agarose	PCM	2.64	(5 mL methanol:acetic acid 90:10 (v/v) during 24h) x2	Ren et al. (2018)
Trimethoprim	Agarose	XAD18	3.79	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Trimethoprim	Agarose	XAD18	3.79[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2014)
Trimethoprim	Agarose	XAD18	3.79[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
Trimethoprim	Agarose	XAD18	3.79[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015a)
Trimethoprim	Agarose	XDA-1	2.86	(3.5 mL methanol + 20 min US) x2	Xie et al. (2018a)
Trimethoprim	Polyacrylamide	Sepra ZT	3.07	(3 mL methanol + 2 min US) x3	Stroski et al. (2018)
Tris(isobutyl)phosphate	Agarose	Strata-X	2.89	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Tris(n-butyl)phosphate	Agarose	Strata-X	2.89	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Tris(phenyl)phosphate	Agarose	Strata-X	2.89	Freeze-drying, (40mL dichloromethane during 24h) x2	Belles et al. (2017)
Tylosin	Agarose	XAD18	1.09	(5 mL methanol + 20 min US) x2	Chen et al. (2013)
Tylosin	Agarose	XAD18	1.09[a]	(5 mL methanol + 20 min US) x2	Chen et al. (2015b)
β-estradiol	Agarose	HLB	3.58	5 mL acetonitrile + 30 min US	Chen et al. (2018)

Annexe 2. Taux d'échantillonnage des résidus pharmaceutiques (mL/d) disponibles dans la littérature (Chapitre IV.C).

Table A.2: Pharmaceutical Rs (in mL/d) available in literature and difference between maximum and minimum Rs (Rs_{max} / Rs_{min}) (*n.i.* not indicated).

Compound	T (°C)	Flow velocity	Doping level (µg/L)	Matrix	Rs (mL/d)	Reference	Factor
Atenolol	20	10 cm/s	3	tap water	25	Morin et al. (2013)	7
	5	stirred	2-10	distilled water	87	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	73	Li et al. (2010a)	
	25	stirred	2-10	distilled water	94	Li et al. (2010a)	
	22	0	1	distilled water	37	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	40	MacLeod et al. (2007)	
	20	11 cm/s	10	tap water	107	Bailly et al. (2013)	
	20	29 cm/s	10	tap water	171	Bailly et al. (2013)	
	15	29 cm/s	10	tap water	102	Bailly et al. (2013)	
	25	29 cm/s	10	tap water	129	Bailly et al. (2013)	
	25	16 cm/s	10	tap water	101	Bailly et al. (2013)	
	25	16 cm/s	10	wastewater	92	Bailly et al. (2013)	
	29	3-5 cm/s	*n.i.*	*n.i.*	51	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	33	Bayen et al. (2014)	
Caffeine	5	stirred	2-10	distilled water	96	Li et al. (2010a)	17
	15	stirred	2-10	distilled water	151	Li et al. (2010a)	
	25	stirred	2-10	distilled water	127	Li et al. (2010a)	
	25	45 cm/s	5	distilled water	44	Bartelt-Hunt et al. (2011)	
	25	1300 rpm	5	tap water	35	Magi et al. (2018)	
	5	1300 rpm	5	tap water	33	Magi et al. (2018)	
	25	1300 rpm	5	tap water	102	Magi et al. (2018)	
	5	1300 rpm	5	tap water	141	Magi et al. (2018)	
	29	3-5 cm/s	*n.i.*	*n.i.*	550	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	133	Bayen et al. (2014)	
	29	3-5 cm/s	*n.i.*	water + 30g/L NaCl	44	Bayen et al. (2014)	
Carbamaze-pine	*n.i.*	*n.i.*	Various during time (20-400 ng/L)	*n.i.*	140	Belles et al. (Belles et al. 2014a)	5
	20	10 cm/s	3	tap water	188	Morin et al. (2013)	
	5	stirred	2-10	distilled water	230	Li et al. (2010a)	
	15	stirred	2-10	distilled water	397	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	235	Li et al. (2010a)	
	25	stirred	2-10	distilled water	561	Li et al. (2010a)	
	25	45 cm/s	5	distilled water	288	Bartelt-Hunt et al. (2011)	
	22	0	1	distilled water	112	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	348	MacLeod et al. (2007)	
	21	stirred	0.5	sea water	342	Martinez-Bueno et al. (2009)	
	29	3-5 cm/s	*n.i.*	*n.i.*	600	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	157	Bayen et al. (2014)	
	29	3-5 cm/s	*n.i.*	water + 30g/L NaCl	497	Bayen et al. (2014)	
	22	0	1	distilled water	90	MacLeod et al. (2007)	7

Clarithro-mycin	28	3-12 cm/s	1	distilled water	668	MacLeod et al. (2007)	
Diclofenac	18	2	0.2	tap water	69	Di Carro et al. (2014)	54
	18	2	1	tap water	64	Di Carro et al. (2014)	
	18	5.1	0.2	tap water	55	Di Carro et al. (2014)	
	18	5.1	1	tap water	59	Di Carro et al. (2014)	
	18	10.2	0.2	tap water	65	Di Carro et al. (2014)	
	18	10.2	1	tap water	56	Di Carro et al. (2014)	
	18	15.3	0.2	tap water	53	Di Carro et al. (2014)	
	18	15.3	1	tap water	54	Di Carro et al. (2014)	
	20	10 cm/s	3	tap water	225	Morin et al. (2013)	
	22	0	1	distilled water	92	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	166	MacLeod et al. (2007)	
	25	1300 rpm	5	tap water	117	Magi et al. (2018)	
	5	1300 rpm	5	tap water	133	Magi et al. (2018)	
	25	1300 rpm	5	tap water	8	Magi et al. (2018)	
	5	1300 rpm	5	tap water	13	Magi et al. (2018)	
	29	3-5 cm/s	*n.i.*	*n.i.*	429	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	97	Bayen et al. (2014)	
	29	3-5 cm/s	*n.i.*	water + 30g/L NaCl	383	Bayen et al. (2014)	
Erythromy-cin	25	45 cm/s	5	distilled water	253	Bartel-Hunt	5
	22	0	1	distilled water	183	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	911	MacLeod et al. (2007)	
Fluoxetine	*n.i.*	quiescent	*n.i.*	*n.i.*	27	Alvarez	51
	n.i.	turbulent	*n.i.*	*n.i.*	200	Alvarez	
	n.i.	*n.i.*	Various during time (20-400 ng/L)	*n.i.*	150	Belles et al. (Belles et al. 2014a)	
	5	stirred	2-10	distilled water	484	Li et al. (2010a)	
	15	stirred	2-10	distilled water	694	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	433	Li et al. (2010a)	
	25	stirred	2-10	distilled water	974	Li et al. (2010a)	
	22	0	1	distilled water	223	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	1370	MacLeod et al. (2007)	
Gemfibrozil	*n.i.*	*n.i.*	Various during time (20-400 ng/L)	*n.i.*	270	Belles et al. (Belles et al. 2014a)	4
	5	stirred	2-10	distilled water	257	Li et al. (2010a)	
	15	stirred	2-10	distilled water	306	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	222	Li et al. (2010a)	
	25	stirred	2-10	distilled water	350	Li et al. (2010a)	
	22	0	1	distilled water	112	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	192	MacLeod et al. (2007)	
	29	3-5 cm/s	*n.i.*	*n.i.*	321	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	89	Bayen et al. (2014)	
	29	3-5 cm/s	*n.i.*	water + 30g/L NaCl	356	Bayen et al. (2014)	
Ketoprofen	18	2	0.2	tap water	80	Di Carro et al. (2014)	30
	18	2	1	tap water	64	Di Carro et al. (2014)	
	18	5.1	0.2	tap water	80	Di Carro et al. (2014)	
	18	5.1	1	tap water	72	Di Carro et al. (2014)	
	18	10.2	0.2	tap water	73	Di Carro et al. (2014)	
	18	10.2	1	tap water	41	Di Carro et al. (2014)	
	18	15.3	0.2	tap water	69	Di Carro et al. (2014)	

	18	15.3	1	tap water	47	Di Carro et al. (2014)	
	n.i.	*n.i.*	Various during time (20-400 ng/L)	*n.i.*	160	Belles et al. (Belles et al. 2014a)	
	20	10 cm/s	3	tap water	118	Morin et al. (2013)	
	22	0	1	distilled water	83	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	135	MacLeod et al. (2007)	
	20	11 cm/s	10	tap water	128	Bailly et al. (2013)	
	20	29 cm/s	10	tap water	234	Bailly et al. (2013)	
	15	29 cm/s	10	tap water	144	Bailly et al. (2013)	
	25	29 cm/s	10	tap water	243	Bailly et al. (2013)	
	25	16 cm/s	10	tap water	206	Bailly et al. (2013)	
	25	16 cm/s	10	wastewater	149	Bailly et al. (2013)	
	25	1300 rpm	5	tap water	87	Magi et al. (2018)	
	5	1300 rpm	5	tap water	68	Magi et al. (2018)	
	25	1300 rpm	5	tap water	31	Magi et al. (2018)	
	5	1300 rpm	5	tap water	8	Magi et al. (2018)	
Metoprolol	20	10 cm/s	3	tap water	195	Morin et al. (2013)	200
	15	stirred	2-10	distilled water	309	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	156	Li et al. (2010a)	
	25	stirred	2-10	distilled water	465	Li et al. (2010a)	
	22	0	1	distilled water	97	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	599	MacLeod et al. (2007)	
	6-18	stirred	*n.i.*	wastewater	3	Harman et al. (2011b)	
Nadolol	20	10 cm/s	3	tap water	114	Morin et al. (2013)	4
	5	stirred	2-10	distilled water	118	Li et al. (2010a)	
	15	stirred	2-10	distilled water	178	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	309	Li et al. (2010a)	
	25	stirred	2-10	distilled water	447	Li et al. (2010a)	
Omeprazole	*n.i.*	quiescent	*n.i.*	*n.i.*	16	Alvarez et al. (2007)	154
	n.i.	turbulent	*n.i.*	*n.i.*	68	Alvarez et al. (2007)	
	28	3-12 cm/s	2	distilled water	2460	MacLeod et al. (2007)	
Paroxetine	5	stirred	2-10	distilled water	905	Li et al. (2010a)	7
	15	stirred	2-10	distilled water	942	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	605	Li et al. (2010a)	
	25	stirred	2-10	distilled water	987	Li et al. (2010a)	
	28	3-12 cm/s	3	distilled water	883	MacLeod et al. (2007)	
	29	3-5 cm/s	*n.i.*	*n.i.*	1632	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	219	Bayen et al. (2014)	
Prednisolo-ne	20	11 cm/s	10	tap water	156	Bailly et al. (2013)	2
	20	29 cm/s	10	tap water	208	Bailly et al. (2013)	
	15	29 cm/s	10	tap water	151	Bailly et al. (2013)	
	25	29 cm/s	10	tap water	232	Bailly et al. (2013)	
	25	16 cm/s	10	tap water	195	Bailly et al. (2013)	
	25	16 cm/s	10	wastewater	120	Bailly et al. (2013)	
Propranolol	20	10 cm/s	3	tap water	165	Morin et al. (2013)	9
	5	stirred	2-10	distilled water	484	Li et al. (2010a)	
	15	stirred	2-10	distilled water	646	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	271	Li et al. (2010a)	
	25	stirred	2-10	distilled water	917	Li et al. (2010a)	
	22	0	1	distilled water	147	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	980	MacLeod et al. (2007)	
	29	3-5 cm/s	*n.i.*	*n.i.*	1266	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	172	Bayen et al. (2014)	

Roxithro-mycin	22	0	1	distilled water	134	MacLeod et al. (2007)	5
	28	3-12 cm/s	1	distilled water	723	MacLeod et al. (2007)	
Sotalol	20	10 cm/s	3	tap water	36	Morin et al. (2013)	5
	5	stirred	2-10	distilled water	76	Li et al. (2010a)	
	15	stirred	2-10	distilled water	172	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	99	Li et al. (2010a)	
	25	stirred	2-10	distilled water	151	Li et al. (2010a)	
	29	3-5 cm/s	*n.i.*	*n.i.*	156	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	59	Bayen et al. (2014)	
Sulfametho-xazole	20	10 cm/s	3	tap water	30	Morin et al. (2013)	12
	5	stirred	2-10	distilled water	291	Li et al. (2010a)	
	15	stirred	2-10	distilled water	348	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	202	Li et al. (2010a)	
	25	stirred	2-10	distilled water	339	Li et al. (2010a)	
	25	45 cm/s	5	distilled water	118	Bartelt-Hunt et al. (2011)	
	20	11 cm/s	10	tap water	92	Bailly et al. (2013)	
	20	29 cm/s	10	tap water	113	Bailly et al. (2013)	
	15	29 cm/s	10	tap water	93	Bailly et al. (2013)	
	25	29 cm/s	10	tap water	85	Bailly et al. (2013)	
	25	16 cm/s	10	tap water	94	Bailly et al. (2013)	
	25	16 cm/s	10	wastewater	80	Bailly et al. (2013)	
	29	3-5 cm/s	*n.i.*	*n.i.*	153	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	50	Bayen et al. (2014)	
	29	3-5 cm/s	*n.i.*	water + 30g/L NaCl	135	Bayen et al. (2014)	
Trimetho-prim	20	10 cm/s	3	tap water	162	Morin et al. (2013)	5
	5	stirred	2-10	distilled water	213	Li et al. (2010a)	
	15	stirred	2-10	distilled water	411	Li et al. (2010a)	
	25	quiescent	2-10	distilled water	215	Li et al. (2010a)	
	25	stirred	2-10	distilled water	436	Li et al. (2010a)	
	22	0	1	distilled water	90	MacLeod et al. (2007)	
	28	3-12 cm/s	1	distilled water	360	MacLeod et al. (2007)	
	29	3-5 cm/s	*n.i.*	*n.i.*	441	Bayen et al. (2014)	
	29	quiescent	*n.i.*	*n.i.*	85	Bayen et al. (2014)	
	29	3-5 cm/s	*n.i.*	water + 30g/L NaCl	346	Bayen et al. (2014)	

Annexe 3. Courbe de la concentration dans l'échantillonneur passif POCIS divisé par la concentration dans l'eau en fonction du temps (Chapitre IV.C).

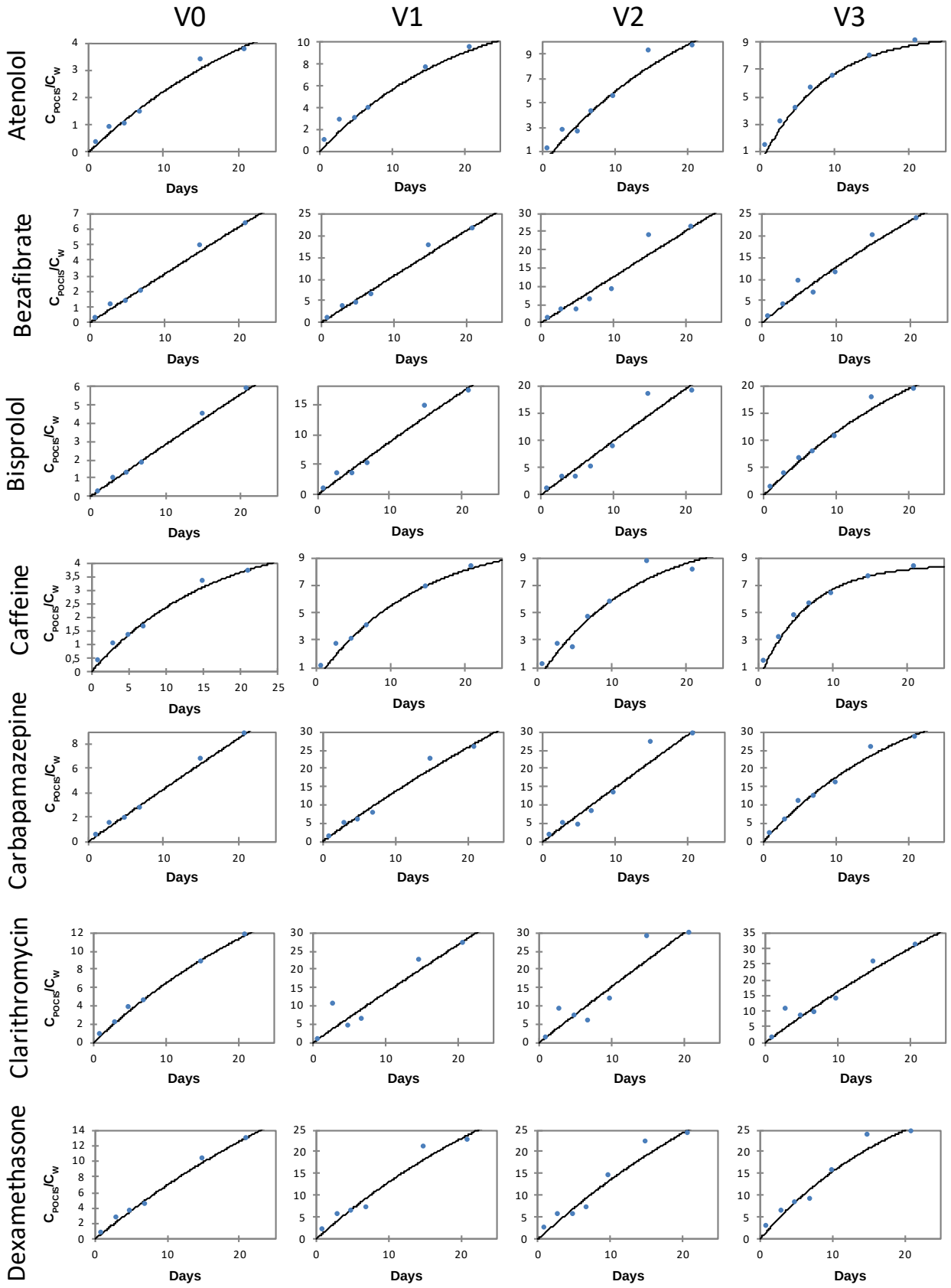

Figure A.1: C_{POCIS}/C_w versus deployment time (days).

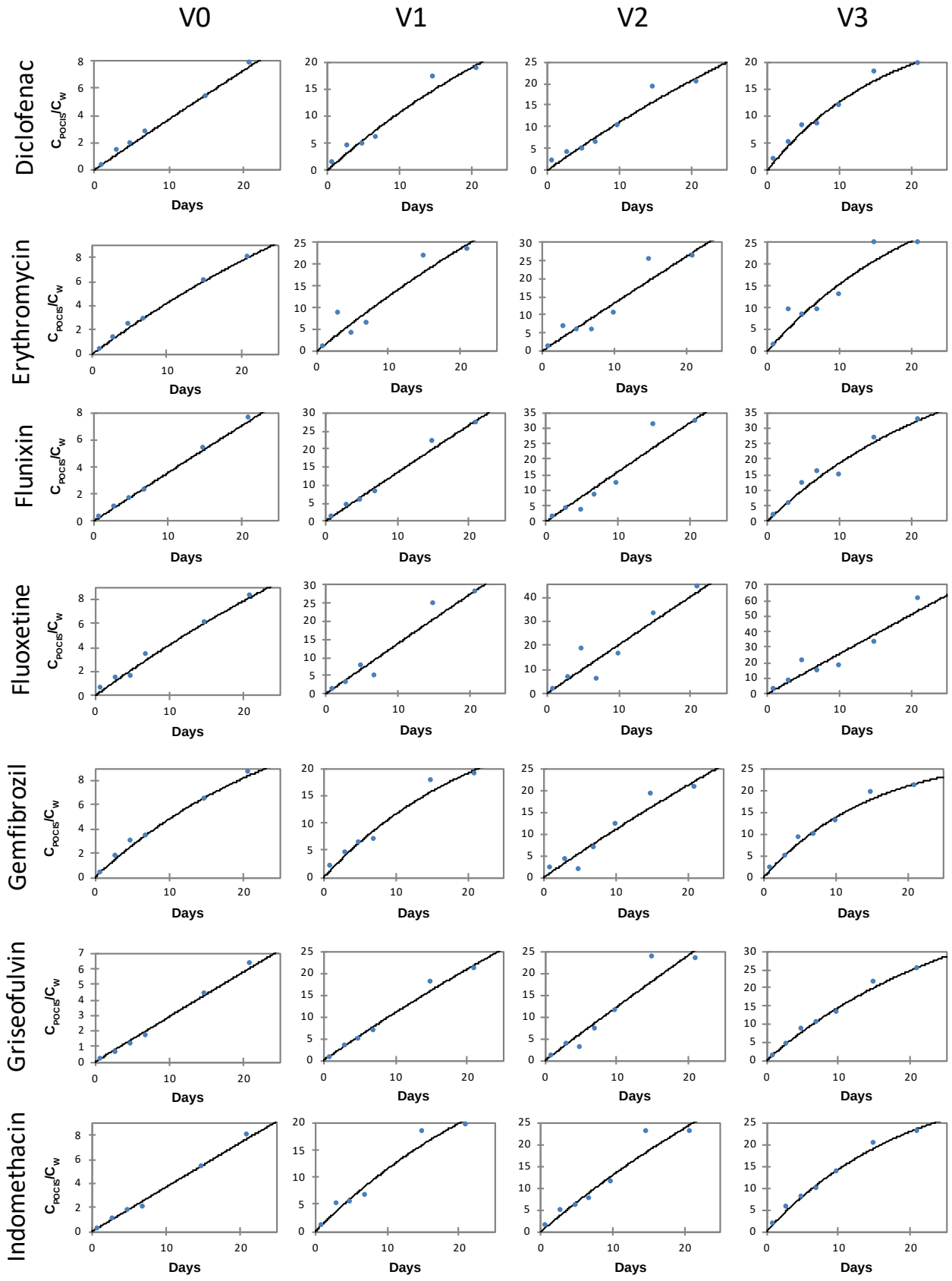

Figure A.1: Continued.

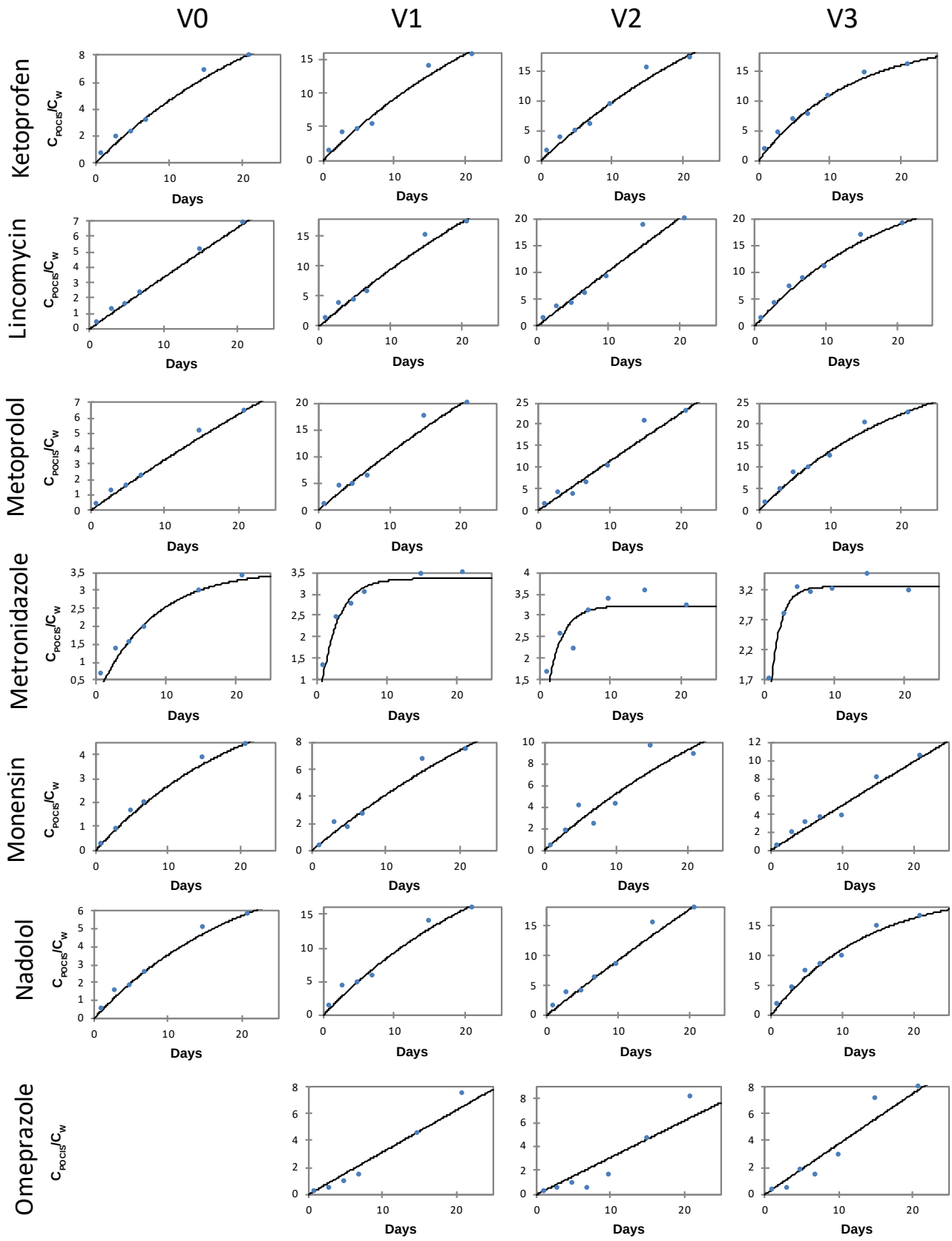

Figure A.1: Continued.

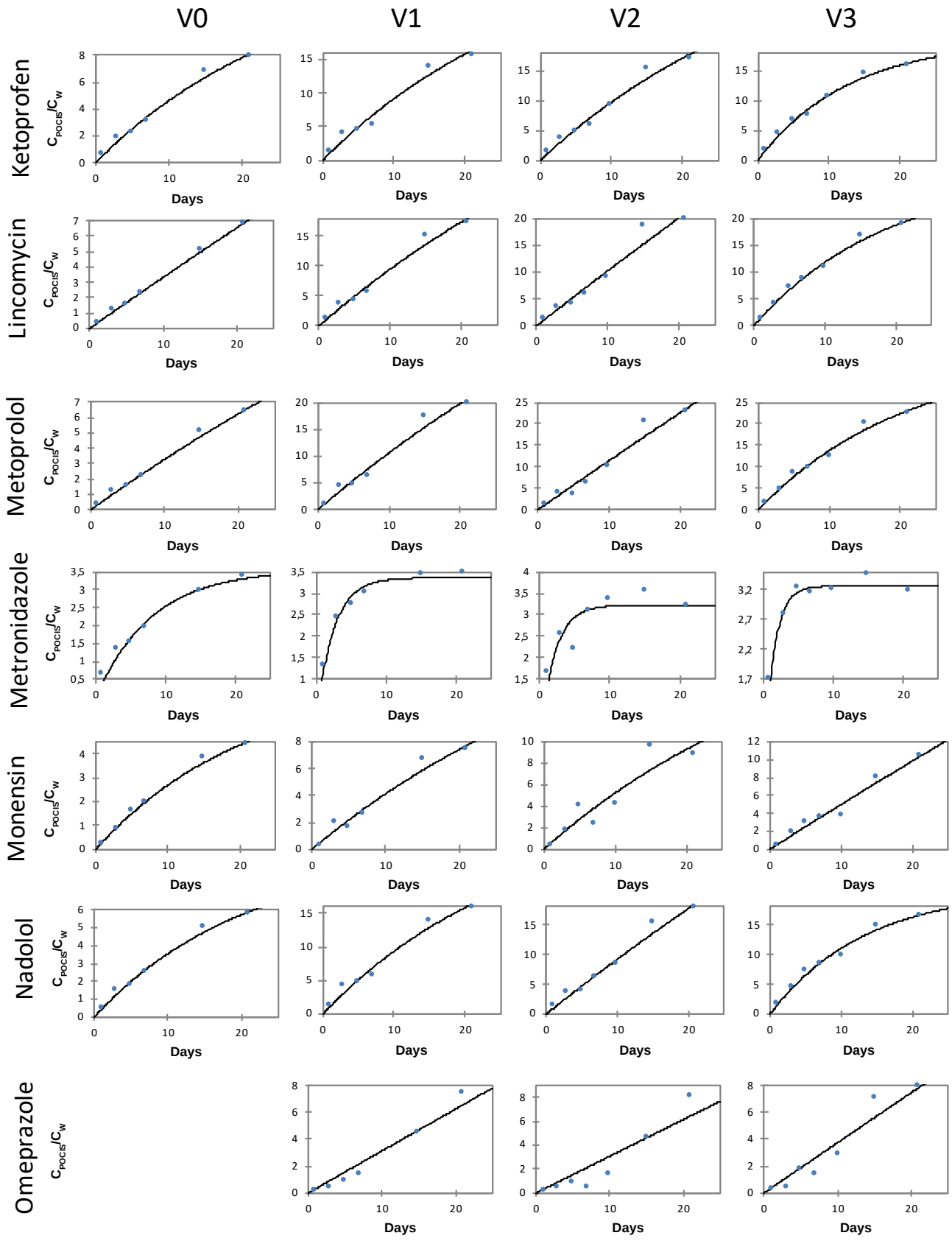

Figure A.1: Continued.

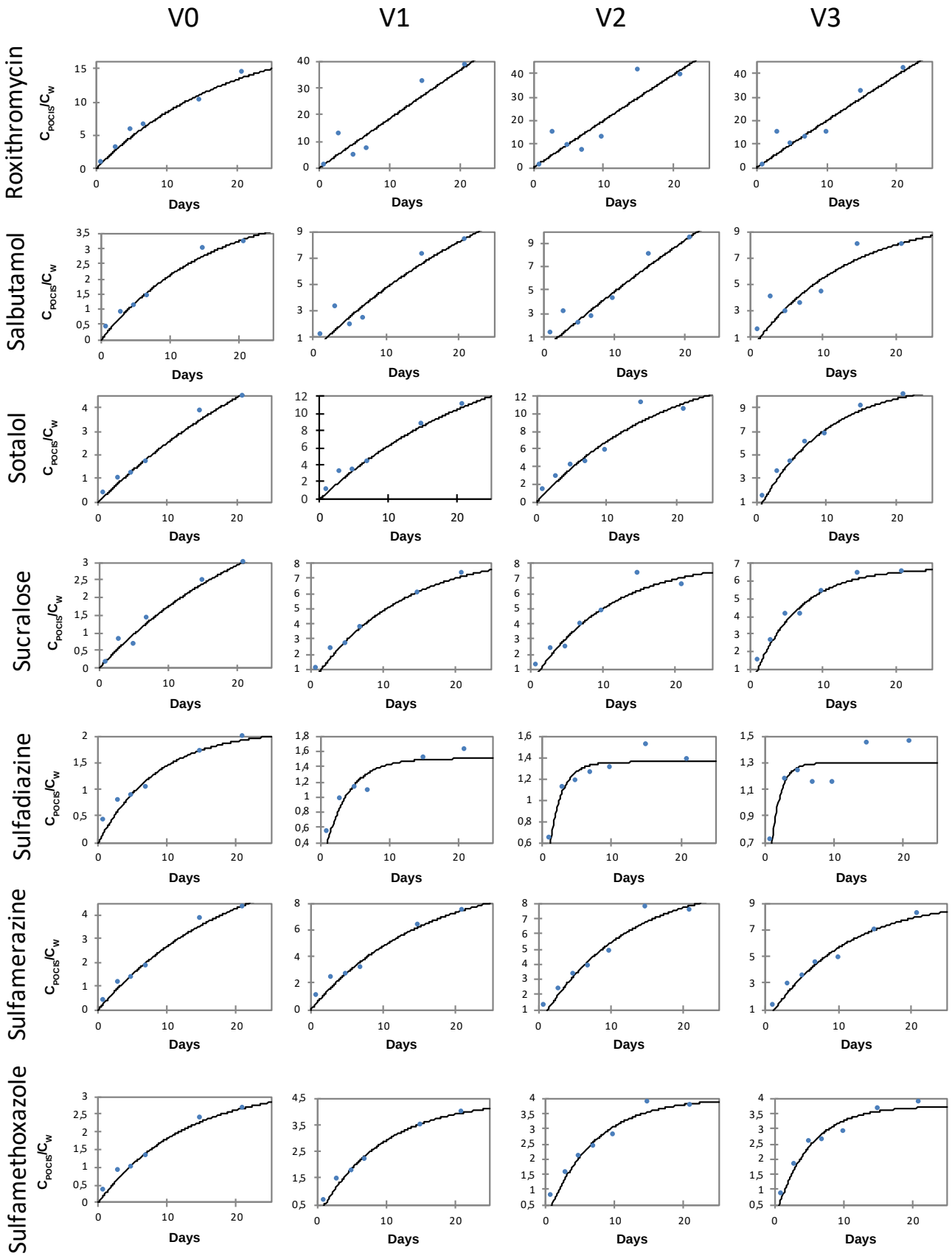

Figure A.1: Continued.

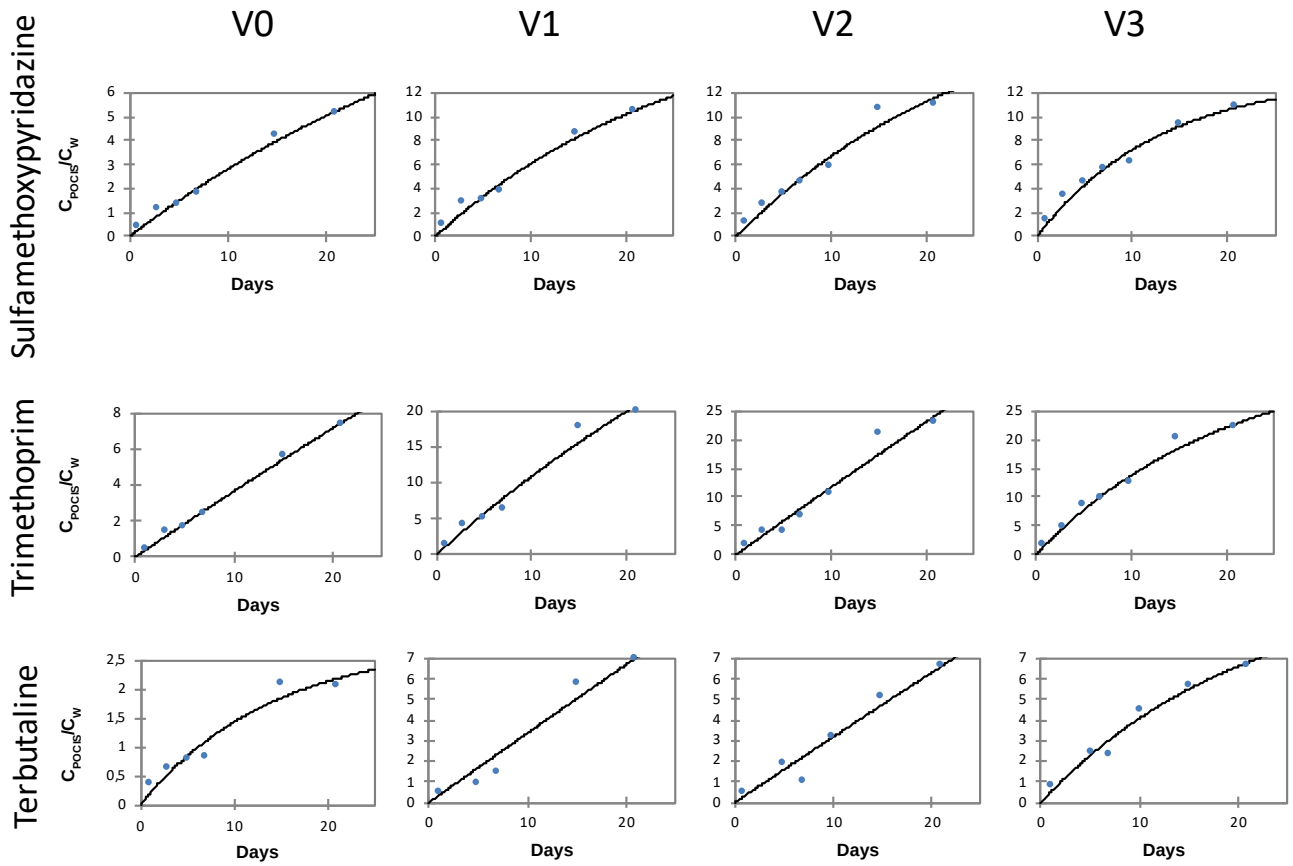

Figure A.1: Continued.

Adaptation du DGT et fiabilisation du POCIS pour le suivi de pesticides et de résidus de médicaments dans les eaux de surface

Les techniques d'échantillonnage passif comme le POCIS (« Polar Organic Chemical Integrative Sampler ») ou le o-DGT (« Diffusive Gradient in Thin films » pour composés organiques) permettent d'obtenir une bonne représentativité de la contamination des eaux de surface par les micropolluants organiques. Cependant, ces dispositifs sont soumis à des conditions environnementales qui engendrent des biais sur la quantification des analytes cibles. Une meilleure connaissance des données issues de l'échantillonnage passif a donc été essentielle afin de les utiliser sur deux têtes de bassin versant. Pour cela un dispositif innovant, utilisant la technique DGT, a été développé et testé sur 4 pesticides ioniques. La robustesse du o-DGT étudiée sur une plage de pH allant de 3 à 8 et de force ionique allant de 0,01 à 1 mol.L^{-1}, lui permette d'être utilisé dans la plupart des eaux naturelles. Des déploiements en milieu naturel et dans une rivière artificielle, en même temps que le déploiement de POCIS, a permis de comparer les performances de ces 2 échantillonneurs. Le POCIS, avec des limites de quantification plus basses, était l'échantillonneur le plus adapté au suivi de contamination des têtes de bassin versant, cependant il a été nécessaire de l'améliorer pour fiabiliser les concentrations de micropolluants mesurées.. Une libération de polyéthylène glycol issu des membranes utilisées pour la fabrication de POCIS provoquant des effets de matrice a été supprimé grâce à deux bains successifs d'1h d'un mélange 50:50 méthanol:eau suivi d'un bain de rinçage à l'eau. De même, une quantification des molécules cibles est obtenue grâce à des taux d'échantillonnage (Rs) déterminés dans conditions proches de celle de l'environnement. Les Rs de 44 molécules pharmaceutiques ont été déterminés grâce à une rivière artificielle. Après cette étape de fiabilisation, le POCIS a été appliqué à deux têtes de bassin versant avec des suivis de 1 et 3 ans sur, respectivement, l'Aixette et l'Auvézère. Des prélèvements ponctuels ont également été réalisés et ont pu mettre en évidence des pics de pollution de pesticides (> 2,3 µg.L^{-1}). Ces suivis « semi-continus » ont permis de mettre en évidence et de caractériser l'existence d'une pollution des têtes de bassin versant par les pesticides et les résidus pharmaceutiques.

Mots-clés : POCIS, o-DGT, pesticides, résidus pharmaceutiques, tête de bassin versant

Adaptation of DGT and reliability of POCIS for pesticides and pharmaceuticals monitoring in surface waters

Passive samplers, such as POCIS (Polar Organic Chemical Integrative Sampler) or o-DGT (Diffusive Gradient in Thin films for organic compounds), allow to estimate surface water contamination by organic micropollutants. However, these devices are influenced by environmental conditions and quantification error can occur. A better knowledge of passive sampling data was therefore essential before the samplers' application on headwater streams. An innovative sampler, using DGT technique, has been developed and tested on 4 ionic pesticides. The sampler is robust in a pH range from 3 to 8 and an ionic strength range from 0,01 to 1 mol.L^{-1}, which allows to use it in the most of natural waters. Field deployments of POCIS alongside o-DGT in natural waters and in an artificial river made it possible to compare their performances. POCIS with lower limits of quantification was the most suitable sampler for monitoring organic compounds in headwater stream. A release of polyethylene glycol from membranes used in POCIS causing matrix effects was removed by two successive baths of 1h of a 50:50 mix of methanol:water followed by a rinsing bath of water. Quantification is achieved through sampling rates (Rs) estimated under revelant conditions. Rs of 44 pharmaceuticals were estimated in an artificial river. After these steps, POCIS was applied in two headwater streams for 1 and 3 years on Aixette and Auvézère, respectively. Grab samples were also collected and pollution peaks of pesticides were detected (> 2,3 µg.L^{-1}). These "semi-continuous" monitorings highlighted a pollution of headwater streams by pesticides and pharmaceuticals.

Keywords: POCIS, o-DGT, pesticides, pharmaceuticals, headwater stream