

STABILITY OF PHARMACEUTICALS AND OTHER POLAR ORGANIC COMPOUNDS STORED ON POLAR ORGANIC CHEMICAL INTEGRATIVE SAMPLERS AND SOLID-PHASE EXTRACTION CARTRIDGES

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Abstract—The stability of 24 chemicals, including pharmaceuticals and personal care products, and some agrochemicals on extraction media was evaluated by preloading them onto Oasis hydrophilic lipophilic balanced solid-phase extraction (SPE) cartridges and polar organic chemical integrative samplers (POCIS) followed by storage at -20°C over time. After 20 months, the average loss was 11% on POCIS, with only 2,4-dichlorophenoxyacetic acid, atrazine, chlorpyrifos, and gemfibrozil showing a statistically significant decline compared with initial concentrations. Losses on SPE cartridges were below 19%, with an average loss of 9%. In addition to laboratory spiked samples, multiple POCIS deployed in wastewater-impacted surface waters and SPE extracts of these waters were stored in their original coextracted matrix for nearly two years with minimal observed losses. Errors from typical sampling, handling, and concentration estimates from POCIS sampling rates were typically ± 15 to 30% relative standard deviation, so observed storage losses are minimal for most POCIS applications. While losses during storage on SPE cartridges for 20 months were small but statistically significant for many compounds, addition of labeled internal standards prior to freezing should correct for such losses. Thus, storage of processed water samples for analysis of polar organic pollutants is viable for archival purposes or studies for which samples cannot be analyzed in the short term. Environ. Toxicol. Chem. 2013;32:337–344. © 2012 SETAC

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INTRODUCTION

Determining the presence and concentrations of pharmaceuticals and personal care products (PPCPs) and agrochemicals in surface waters is important for risk assessment of these compounds in aquatic ecosystems [1–3], especially in systems receiving wastewater effluent and agricultural runoff [4,5]. In many cases, the ability to analyze samples retrospectively would be beneficial in quantifying changes in exposure to new and emerging contaminants such as these over time. To some extent, this can be done through the use of instrumental techniques, such as time-of-flight-based mass spectrometry, which collects full spectra continuously for possible reanalysis at a later date (e.g., for chemicals without known standards, such as degradates [6]). However, this approach presumes that the original sample-processing procedures and/or instrumental conditions were sufficient to produce a usable signal for the analytes of interest. This may not necessarily be the case, for example, for highly polar metabolites that may not be well retained during sample concentration and/or coelute with matrix interferences [6].

Archival of raw samples is also very useful when specific analysis methods are not in place at the time of sampling and can be later developed, when there is a lack of knowledge about the contaminants present in the system at the time, or if the number of samples is too high at the time of collection

for immediate analysis. This approach of accessing archived samples is used extensively with, for example, animal tissues and the characterization of persistent organic compound bioaccumulation and temporal trends [7,8]. Indeed, formal sample archival programs such as the Canadian Wildlife Service's Great Lakes herring gull egg monitoring program [9] has yielded new insights into behavior and effects of chemical pollutants, such as brominated flame retardants [10], that were not envisioned at the time of the original sample collection. Likewise, some studies have investigated the effects of long-term storage for pharmaceuticals in human blood [11–13], albeit typically for clinical or biomedical applications, for which concentrations are typically orders of magnitude higher than for trace environmental analysis. Yet, few studies have examined the effects of long-term and archival storage (i.e., more than three months) for polar organic contaminants, such as PPCPs and agrochemicals, for surface waters in a manner analogous to that used for persistent organic pollutants.

A number of approaches to monitoring organic contaminants in surface waters can be employed. The present study focuses on two common techniques: grab sampling and passive sampling. Many monitoring studies employ grab (or discrete) sampling, followed by laboratory-based solid-phase extraction (SPE) and analysis [4,14,15] to provide a snapshot of environmental concentrations at the time of sampling. Grab sampling can be effective for monitoring concentrations of contaminants, but can be time-consuming if sampling is extensive, and may not fully account for temporal variations in concentrations due to changes in flow, specific weather events, or episodic inputs (e.g., sewage lagoon or retention pond releases). Passive sampling approaches—such as semipermeable membrane

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devices, Chemcatcher, and polar organic chemical integrative samplers (POCIS)—can address some of the shortcomings of standard grab sampling, allowing for continuous monitoring of an aquatic system for a desired period of time and providing time-weighted average concentrations for polar organic chemicals [16,17]. The POCIS is a solid sorbent held between two microporous polyethersulfone membranes. Aqueous analytes diffuse to and are sequestered by the sorbent, from which they are extracted in the laboratory and analyzed. Several studies have employed POCIS for the detection and quantification of PPCPs and agrochemicals in aquatic systems [17–23].

For studies that require storage (i.e., archival retrospective analysis or extensive monitoring work where samples need to be stored for an extended period of time before analysis) the stability of the studied compounds during storage is a chief quality-assurance concern. Labile analytes, such as PPCPs and polar pesticides that are frozen and stored directly in their original matrix (e.g., wastewater, surface water), may undergo a number of different chemical, physical, and biological processes between the time of sampling and analysis, the extent of which may depend on the storage time. For example, Chiaia et al. [24] reported on the stability of illicit drugs and their metabolites stored in wastewater at -20°C and observed no statistically significant losses after three weeks. In contrast, Baker and Kasprzyk-Hordern [25] observed a significant decrease in recoveries for a number of illicit drugs and some pharmaceuticals in raw wastewater when using glassware without silanization, attributable to the binding of analytes to silanol functional groups on the glassware. Additionally, they observed a lack of stability of analytes stored in raw wastewater at 2°C , with 34% of compounds studied exhibiting $>15\%$ loss after only 12 h of storage [25]. However, no study to our knowledge has investigated systematically the storage of analytes directly in their aqueous matrix for longer time periods (i.e., months to years) and, specifically, the stability of pharmaceuticals stored in the original matrix for any period of time.

Freezing large volumes of environmental water samples can be logistically difficult as well, due to the large space required, the potential binding of compounds to the storage vessel, the fragile nature of certain storage bottles (i.e., glass), and the time required for samples to thaw. In contrast, samples that have been stored via SPE cartridges or POCIS may be more efficient in terms of the space and thawing time required. However, very little is known regarding the long-term stability of PPCPs and agrochemicals once sequestered onto the sorbent phase of SPE cartridges or POCIS and subsequently frozen. No study has published information regarding the long-term storage stability of PPCPs and agrochemicals on POCIS. The data that do exist pertain mostly to the SPE sample storage of illicit drugs, with the exception of a small number of pharmaceuticals and pesticides [25–33]. Ferrer and Barceló [26] found that a group of four pesticides (desethylatrazine, fenamiphos, fenitrothion, and fonofos) were stable on non- C_{18} polymeric SPE cartridges kept at -20°C for one month; however, some losses were noticed when cartridges were kept at 4°C and at room temperature. Other studies show increased stability on SPE cartridges kept between 4 and -20°C , with storage stability times ranging from several weeks for fluoroquinolone antibiotics [33] to two to three months (depending on the original water matrix) for nonionic surfactants and linear alkylbenzene sulfonates [29] to longer than three months for a suite of illicit drugs [25,28]. Considering the expanding use of passive samplers such as POCIS for monitoring not only PPCPs and agrochemicals but also other contaminants, such as perfluorinated compounds

[34], understanding the storage stability of these compounds on POCIS is an important data gap.

The present study investigates the stability of a group of 24 environmentally common PPCPs and agrochemicals stored at -20°C for extended periods of time on Waters Oasis hydrophilic–lipophilic balanced (HLB) sorbent on either SPE cartridges or POCIS. Our objectives were to evaluate whether PPCPs and agrochemicals sorbed to this commonly used sorbent in these common sample collection devices are stable, not only over periods of several months to permit flexibility in monitoring studies, but also over longer periods for archival storage, for use in ongoing monitoring programs, or for retrospective analyses.

MATERIALS AND METHODS

Chemicals

The specific pharmaceuticals and pesticides used in the present study were selected due to their prevalence in the environment [4,35]. Atenolol, chlorpyrifos, diazinon, 2,4-dichlorophenoxy acetic acid (2,4-D), fluoxetine, gemfibrozil, ibuprofen, metoprolol, propranolol, sulfachloropyridazine, sulfadimethoxine, sulfamethazine, sulfamethoxazole, and trimethoprim were from Sigma-Aldrich; atrazine, carbamazepine, clofibric acid, diclofenac, and naproxen were from MP Biochemicals; 17β -estradiol, estrone, and 17α -ethinylestradiol were from EQ Laboratories; ketoprofen was from ICN Biomedicals; and sulfapyridine was from Toronto Research Chemicals. All chemicals were of $>98\%$ purity.

Stable isotope standards (all $>97\%$ isotopic purity) were obtained from various sources: [isopropyl- $^2\text{H}_7$]-atenolol, [ethyl- $^2\text{H}_5$]-atrazine, [rings- $^2\text{H}_{10}$]-carbamazepine, [4-chlorophenyl- $^2\text{H}_4$]-clofibric acid, [diethyl- $^2\text{H}_{10}$]-diazinon, [phenyl- $^2\text{H}_4$]-diclofenac, [2,4,6,16- $^2\text{H}_4$]- 17α -ethinylestradiol, [2,4,16,16- $^2\text{H}_4$]- 17β -estradiol, [2,2-dimethyl- $^2\text{H}_6$]-gemfibrozil, [α -methyl- $^2\text{H}_3$]-ibuprofen, [propionic- $^2\text{H}_4$]-ketoprofen, [isopropyl- $^2\text{H}_7$]-metoprolol, [α -methyl- $^2\text{H}_3$]-naproxen, [ring- $^2\text{H}_7$]-propranolol, and [4-methoxy- $^2\text{H}_3$]-trimethoprim were from C/D/N Isotopes; [diethyl- $^2\text{H}_{10}$]-chlorpyrifos, [dimethyl- $^2\text{H}_6$]-malathion, [2,6-dimethoxy- $^2\text{H}_6$]-sulfadimethoxine, and [benzene- $^2\text{H}_4$]-sulfamethoxazole were from Dr. Ehrenstorfer GmbH; [benzene- $^2\text{H}_4$]-sulfapyridine was from Toronto Research Chemicals; and [ring- $^{13}\text{C}_6$]-2,4-D[2,4,16,16- $^2\text{H}_4$]-estrone, [3-phenyl,3-propyl- $^2\text{H}_6$]-fluoxetine, and [phenyl- $^{13}\text{C}_6$]-sulfamethazine were from Cambridge Isotope Laboratories.

Methanol of liquid chromatographic (LC) grade (Fisher Scientific), formic acid (Fisher Scientific), ammonium acetate (Sigma Aldrich), and $18\text{ M}\Omega\text{-cm}$ Milli-Q water (Millipore) were employed for making mobile phase for LC/mass spectrometric (MS) analysis as well as for analytical standards, and sorbent processing.

Study design

A laboratory-based study was carried out to investigate the stability of polar organic contaminants stored at -20°C on POCIS and SPE cartridges. The basic approach was to spike a number of POCIS and SPE samples with the compounds of interest at a predetermined concentration and to store them in the freezer for varying periods of time ranging from weeks to years. In each case, one triplicate set of POCIS and SPE samples was extracted and analyzed immediately after being spiked, representing the time-zero storage point. All other storage time samples were compared to the time-zero concentrations and assessed for any losses. In addition to laboratory samples, POCIS and SPE samples from a natural river system were

stored for up to nearly two years to assess the effects of storage stability in environmental matrices.

POCIS production and extraction

Oasis HLB sorbent material was obtained from Environmental Sampling Technologies. Four grams of sorbent was weighed into an aluminum dish, and 600 μ l of the 24 compound mixture (5 mg/L) in methanol was added to the phase for a nominal concentration of 750 ng/g sorbent. Following the 600- μ l amendment, a second addition of a small volume of methanol to the 4 g of spiked sorbent was done to ensure that the spike material was evenly mixed throughout the sorbent. The phase was dried in the dark at room temperature to allow the methanol to evaporate and then placed overnight in a desiccator in the dark. Each POCIS ($n = 18$) sample was made with 200 ± 2 mg of the spiked sorbent, placed between two polyethersulfone membranes, and secured between two stainless steel disks screwed together. The POCIS samples were wrapped in aluminum foil (preheated at 450°C) and then stored at -20°C until extraction. These were extracted and analyzed at six different storage time points: 0, 31, 51, 112, 186, and 609 d. Given representative POCIS chemical sampling rates of 0.05 to 0.5 L/d and a deployment period of 20 d, our nominal concentration would represent a time-weighted average aqueous concentration of 75 to 750 ng/L, which is typical of many such chemicals in wastewater effluents. Indeed, the nominal concentration is similar to that observed for POCIS deployed in impacted systems [23].

Prior to extraction, POCIS ($n = 3$) were taken out of the freezer and placed in Milli-Q water for at least 15 min to wet the Oasis HLB phase. Wetting the Oasis HLB phase simplifies the extraction procedure by avoiding the fine, powdery nature of the Oasis HLB sorbent, which can be very vulnerable to air currents when dry. A large funnel, cleanup column, and round-bottomed flask were precleaned with methanol, and approximately 3 g of anhydrous sodium sulfate (Sigma) predried at 450°C was added to the column. Each POCIS sampler was opened above the funnel, and the sorbent was washed into the column using 25 to 35 ml of methanol, followed by addition of 50 ng of each internal standard to the solution from a single mixture. The methanolic extract was gravity-drained into a round-bottomed flask, rotary evaporated at 47 to 52°C to approximately 5 ml, and dried under a slow stream of high-purity nitrogen at 40°C. Samples were reconstituted in 1 ml of methanol and kept at 4°C for no longer than one week until analysis. At the time of analysis, samples were again evaporated to dryness with nitrogen and reconstituted in 20:80 methanol:water (v/v) and analyzed. For each time point, one POCIS laboratory blank containing only the internal standard was also extracted as described above and analyzed.

Environmental POCIS

To assess the potential effect of environmental matrices on analyte stability, six unspiked POCIS were deployed at the same site and time, in separate cages (three/cage), in Dead Horse Creek in southern Manitoba, Canada (Carlson et al., unpublished manuscript), stored at -20°C , and extracted in sets of three at two different time periods 356 d apart (8.5 and 20 months from sampling). Masses (nanograms per gram sorbent) of each chemical observed in the creek were determined, to avoid complications from variability in sampling rates reported in the literature [16]. Samples were extracted as described above.

SPE production and extraction

Oasis HLB cartridges (3 cc/60 mg; Waters) were used to simulate the storage of extracted grab samples on SPE cartridges, which were loaded with the same mixture of 24 organic compounds used for spiking POCIS. Multiple amber bottles containing 100 ml of Milli-Q water were spiked with the compound mixture at 1 $\mu\text{g/L}$ or with both compound and internal standard mixtures at concentrations of 1 and 0.5 $\mu\text{g/L}$, respectively. These concentrations are typical of the target chemicals in wastewaters [6]. The 576-d SPE storage sample was spiked with internal standard poststorage, as opposed to prestorage as for the other five storage sets, to assess absolute losses incurred during long-term storage versus total losses due to storage, extraction, and instrumental analysis. Each SPE cartridge was preconditioned with 2 ml of methanol followed by 2 ml of water, with analytes then introduced onto the cartridge at <3 ml/min. Cartridges were then fully dried under vacuum, individually wrapped in aluminum foil, and stored at -20°C for 0, 13, 31, 73, 126, and 576 d.

Prior to extraction, SPE cartridges were allowed to thaw for at least 15 min. Cartridges were eluted with 3 ml of methanol at 0.5 ml/min. Extracts were evaporated under a steady stream of nitrogen at 40°C, reconstituted in 1 ml methanol, and refrigerated at 4°C for up to one week until analysis. At that time, samples were again evaporated to dryness with nitrogen, reconstituted in 20:80 methanol:water, and analyzed. For each set of frozen SPE samples extracted, one laboratory blank sample containing only internal standards was also extracted as described above and analyzed.

Environmental SPE

As with environmental POCIS, six SPE cartridges were loaded with water samples taken from Dead Horse Creek (Carlson et al., unpublished manuscript), stored at -20°C , and extracted as described above in sets of three, 350 d apart, 10 and 22 months after sampling.

Instrumental analysis

Analyte concentrations were quantified by LC/MS/MS with an Agilent 6410B equipped with an electrospray ionization source (Agilent Technologies) and a 1200 Series Agilent UHPLC binary pump using three separate methods with different mobile phases, gradient elutions, and source parameters depending on the compound (Supplemental Data, Tables S1 and S2). The analytical column used was an Agilent Zorbax C₁₈ column (50 mm $\times$ 2.1 mm $\times$ 1.8 μm particle size) with a Phenomenex SecurityGuard C₁₈ guard cartridge (4 $\times$ 3.0 mm ID). Calibrations were performed using standards over a concentration range of 10 to 500 $\mu\text{g/L}$ with internal standard concentrations of 50 $\mu\text{g/L}$. Extraction efficiencies from POCIS and SPE extracts ranged from 90 to 110% when corrected with internal standards based on spike-and-recovery experiments (data not shown). Relative standard deviations (RSDs) were typically $<8\%$ for triplicates from SPE and $<15\%$ for triplicates from POCIS.

Statistical analysis

Prism software (v. 5.01; GraphPad Software) was used for statistical analysis. A one-way analysis of variance followed by Tukey's and Dunnett's post hoc analyses was conducted on data for all spiked POCIS and SPE samples. Student's t test was used to compare the two storage times for the environmental POCIS and SPE samples. A confidence level of 95% was set for all tests.

($p < 0.05$). All errors are expressed as standard deviations unless otherwise noted.

RESULTS AND DISCUSSION

Variations in measured concentrations of laboratory-spiked materials were higher in POCIS (Table 1) versus SPE cartridges (Table 2), with RSD values for POCIS generally below 20% and a mean of 8%. Concentrations for SPE samples had a mean RSD of 3%, with a maximum value of 13%. The variability in the environmental POCIS and SPE samples is consistent with what was observed for the laboratory samples, which had average RSD values of 19 and 4%, respectively. Variability was higher for POCIS deployed in Dead Horse Creek, while SPE variability was correspondingly lower (Table 3).

These data suggest that the production, extraction, and analysis procedures for both POCIS and SPE samples are reasonably reproducible and accurate to the degree expected for these respective techniques, based on spike-and-recovery experiments (data not shown). A larger experimental error associated with POCIS versus SPE samples is expected and likely a result of the extraction procedures involved in the use of POCIS. These involve a greater number of sample transfers, a greater amount of glassware, and a longer process of evaporation and heating.

For a majority of the compounds studied, there was no evidence of temporal trends over time, as small losses (10–15%) at the longest storage time compared to time-zero concentrations were not statistically significant in many cases. Loss behavior of individual compounds stored on laboratory POCIS and SPE cartridges was generally consistent. Differences in losses between POCIS and SPE samples for individual compounds were not greater than 12%, with the exception of

two compounds: fluoxetine showed a loss of 16% on SPE cartridges after the longest storage time compared to no corresponding loss after 20 months on POCIS, and sulfamethoxazole losses on POCIS (32% loss) were almost fivefold those of SPE samples (7% loss). The mechanistic processes affecting observed losses are unclear at present.

Laboratory-spiked POCIS

Compound-specific losses ranged from 0 to 32% on POCIS (Table 1) at the longest storage time (609 d), with five out of the 24 compounds showing a concentration decrease greater than 15%. Only two of these were statistically significant: 2,4-D and gemfibrozil. In total, four compounds exhibited losses statistically different from their initial concentrations, the other two being atrazine (13%) and chlorpyrifos (9%). The observed loss of 2,4-D was not significant (<15%) after 186 d but was significantly lower (20%) by 609 d, indicating that long-term storage (>186 d) of 2,4-D may result in significant losses. Atrazine showed statistically significant losses after both 186 d (16%) and 609 d (13%). After six months of storage on POCIS, the average loss for all compounds was 9%, compared with 11% after 20 months, and only one compound (atrazine) showed a statistically relevant loss. For nonarchival storage purposes, for which six months is a more likely maximum storage period, incurred losses were minimal and are likely acceptable for most POCIS applications.

The above observations notwithstanding, losses for all 24 compounds at -20°C on POCIS were generally smaller than the errors associated with using POCIS for environmental measurement of these compounds and in extrapolation to time-weighted average concentrations. The production, extraction, and analysis of POCIS are likely the main factors contributing to

Table 1. Average concentrations of compound on laboratory-spiked polar organic chemical integrative samplers (POCIS) at each storage time and the respective loss after 609 d storage

Compound (CAS)	POCIS concentration (ng/g) ^a						Loss ^b
	0 d	31 d	51 d	112 d	186 d	609 d	
2,4-Dichlorophenoxy acetic acid (94-75-7)	740 ± 25	810 ± 76	779 ± 69	732 ± 51	636 ± 39	589 ± 52*	20%
Atenolol (29122-68-7)	647 ± 17	730 ± 35	691 ± 68	783 ± 51*	594 ± 47	609 ± 28	6%
Atrazine (1912-24-9)	774 ± 11	786 ± 30	779 ± 58	821 ± 37	651 ± 21*	675 ± 59*	13%
Carbamazepine (298-46-4)	745 ± 23	784 ± 62	771 ± 57	812 ± 19	774 ± 43	709 ± 81	5%
Chlorpyrifos (2921-88-2)	695 ± 48	681 ± 67	767 ± 118	733 ± 120	689 ± 64	634 ± 102*	9%
Clofibric acid (882-09-7)	837 ± 27	768 ± 78	766 ± 92	714 ± 21	728 ± 32	692 ± 30	17%
Diazinon (333-41-5)	746 ± 25	867 ± 68	840 ± 11	820 ± 95	722 ± 47	751 ± 55	-1%
Diclofenac (15307-86-5)	647 ± 14	693 ± 45	673 ± 46	683 ± 54	622 ± 38	585 ± 57	10%
17 α -Ethinylestradiol (57-63-6)	738 ± 35	787 ± 97	762 ± 93	660 ± 29	696 ± 34	641 ± 42	13%
Estradiol (50-28-2)	735 ± 53	810 ± 23	794 ± 119	675 ± 47	632 ± 35	674 ± 60	8%
Estrone (53-16-7)	777 ± 84	843 ± 55	834 ± 77	706 ± 55	653 ± 63	729 ± 56	6%
Fluoxetine (54910-89-3)	718 ± 43	745 ± 129	758 ± 108	708 ± 24	675 ± 117	755 ± 49	-5%
Gemfibrozil (25812-30-0)	833 ± 52	843 ± 57	848 ± 81	791 ± 48	736 ± 67	690 ± 34*	17%
Ibuprofen (15687-27-1)	750 ± 62	796 ± 66	770 ± 69	878 ± 54	706 ± 158	657 ± 29	12%
Ketoprofen (22071-15-4)	677 ± 31	737 ± 66	723 ± 73	702 ± 59	696 ± 48	614 ± 27	9%
Metoprolol (51384-51-1)	783 ± 38	834 ± 56	817 ± 94	812 ± 41	718 ± 17	707 ± 50	10%
Naproxen (22204-53-1)	885 ± 27	907 ± 38	867 ± 59	1,060 ± 103*	796 ± 71	783 ± 59	12%
Propranolol (525-66-6)	690 ± 53	752 ± 80	691 ± 55	736 ± 83	578 ± 47	597 ± 52	13%
Sulfachloropyridazine (80-32-0)	692 ± 27	664 ± 82	675 ± 62	699 ± 55	580 ± 18	649 ± 107	6%
Sulfadimethoxine (122-11-2)	746 ± 21	804 ± 91	761 ± 55	693 ± 52	713 ± 37	629 ± 44	16%
Sulfamethazine (57-68-1)	701 ± 35	755 ± 88	726 ± 58	662 ± 21	652 ± 39	621 ± 58	11%
Sulfamethoxazole (723-46-6)	927 ± 259	793 ± 87	551 ± 247*	671 ± 21	705 ± 21	630 ± 98	32%
Sulfapyridine (144-83-2)	721 ± 79	681 ± 58	661 ± 34	735 ± 18	774 ± 56	663 ± 77	8%
Trimethoprim (738-70-5)	673 ± 23	723 ± 42	711 ± 72	705 ± 50	653 ± 48	586 ± 41	13%

^a Errors are standard deviation, $n = 3$ each except $n = 2$ for diazinon on day 31.

^b Concentration at longest time point relative to the day-zero concentration.

* Statistically significant difference from the day-zero concentration according to a one-way analysis of variance and Dunnett's post hoc test ($p < 0.05$).

Table 2. Average concentrations of compound on laboratory-spiked Oasis hydrophilic-lipophilic balanced solid-phase extraction (SPE) cartridges at each storage time and the respective loss after 576 d storage

Compound (CAS)	SPE concentration ($\mu\text{g/L}$) ^a						Loss ^b
	0 d	13 d	31 d	73 d	126 d	576 d	
2,4-Dichlorophenoxy acetic acid (94-75-7)	1.09 $\pm$ 0.01	1.03 $\pm$ 0.03	0.99 $\pm$ 0.04*	1.02 $\pm$ 0.03	0.99 $\pm$ 0.03*	0.94 $\pm$ 0.03*	13%
Atenolol (29122-68-7)	1.00 $\pm$ 0.01	1.03 $\pm$ 0.03	1.04 $\pm$ 0.03	1.02 $\pm$ 0.01	0.98 $\pm$ 0.01	0.90 $\pm$ 0.03*	10%
Atrazine (1912-24-9)	1.02 $\pm$ 0.02	1.05 $\pm$ 0.05	1.00 $\pm$ 0.01	1.04 $\pm$ 0.01	1.02 $\pm$ 0.02	0.92 $\pm$ 0.01*	10%
Carbamazepine (298-46-4)	1.04 $\pm$ 0.01	1.05 $\pm$ 0.03	1.05 $\pm$ 0.02	1.10 $\pm$ 0.03	0.98 $\pm$ 0.01	0.99 $\pm$ 0.04	5%
Chlorpyrifos (2921-88-2)	0.86 $\pm$ 0.04	0.93 $\pm$ 0.02*	0.87 $\pm$ 0.04	0.92 $\pm$ 0.02	0.96 $\pm$ 0.03*	0.77 $\pm$ 0.02*	11%
Clofibric acid (882-09-7)	1.04 $\pm$ 0.02	1.10 $\pm$ 0.04*	1.05 $\pm$ 0.03	1.02 $\pm$ 0.01	1.02 $\pm$ 0.02	0.93 $\pm$ 0.03*	10%
Diazinon (333-41-5)	0.98 $\pm$ 0.01	1.01 $\pm$ 0.06	1.00 $\pm$ 0.02	1.03 $\pm$ 0.02	1.00 $\pm$ 0.03	0.93 $\pm$ 0.04	5%
Diclofenac (15307-86-5)	1.13 $\pm$ 0.02	1.14 $\pm$ 0.02	1.03 $\pm$ 0.03	1.08 $\pm$ 0.05	1.07 $\pm$ 0.02	1.01 $\pm$ 0.08*	11%
17 α -Ethinylestradiol (57-63-6)	1.01 $\pm$ 0.05	0.90 $\pm$ 0.07	0.92 $\pm$ 0.01	1.10 $\pm$ 0.09	0.98 $\pm$ 0.05	0.86 $\pm$ 0.05*	15%
Estradiol (50-28-2)	1.09 $\pm$ 0.07	0.99 $\pm$ 0.09	1.03 $\pm$ 0.02	1.04 $\pm$ 0.06	1.00 $\pm$ 0.01	0.94 $\pm$ 0.01*	14%
Estrone (53-16-7)	1.05 $\pm$ 0.02	1.03 $\pm$ 0.05	0.99 $\pm$ 0.03	1.00 $\pm$ 0.07	1.00 $\pm$ 0.04	0.91 $\pm$ 0.01*	13%
Fluoxetine (54910-89-3)	1.09 $\pm$ 0.06	1.19 $\pm$ 0.09	1.05 $\pm$ 0.04	1.01 $\pm$ 0.03	1.02 $\pm$ 0.04	0.92 $\pm$ 0.04*	16%
Gemfibrozil (25812-30-0)	1.11 $\pm$ 0.03	1.00 $\pm$ 0.02*	1.02 $\pm$ 0.04*	1.05 $\pm$ 0.02	1.02 $\pm$ 0.01*	0.97 $\pm$ 0.04*	13%
Ibuprofen (15687-27-1)	1.03 $\pm$ 0.04	1.04 $\pm$ 0.04	1.03 $\pm$ 0.04	0.93 $\pm$ 0.03	0.95 $\pm$ 0.02	1.04 $\pm$ 0.08	-1%
Ketoprofen (22071-15-4)	1.05 $\pm$ 0.01	1.12 $\pm$ 0.01	0.99 $\pm$ 0.01	0.97 $\pm$ 0.07	0.98 $\pm$ 0.02	0.96 $\pm$ 0.08	9%
Metoprolol (51384-51-1)	1.05 $\pm$ 0.03	1.05 $\pm$ 0.03	1.06 $\pm$ 0.01	1.02 $\pm$ 0.02	0.97* $\pm$ 0.01	1.05 $\pm$ 0.04	0%
Naproxen (22204-53-1)	1.09 $\pm$ 0.05	1.07 $\pm$ 0.04	1.01 $\pm$ 0.03	1.01 $\pm$ 0.02	1.01 $\pm$ 0.03	1.04 $\pm$ 0.13	5%
Propranolol (525-66-6)	1.06 $\pm$ 0.02	1.12 $\pm$ 0.05	1.02 $\pm$ 0.03	1.03 $\pm$ 0.01	1.04 $\pm$ 0.04	1.00 $\pm$ 0.03	6%
Sulfachloropyridazine (80-32-0)	1.02 $\pm$ 0.01	1.12 $\pm$ 0.04*	1.03 $\pm$ 0.03	0.99 $\pm$ 0.02	1.00 $\pm$ 0.02	0.92 $\pm$ 0.01*	9%
Sulfadimethoxine (122-11-2)	1.05 $\pm$ 0.01	1.00 $\pm$ 0.04	1.01 $\pm$ 0.02	1.04 $\pm$ 0.04	1.02 $\pm$ 0.01	0.86 $\pm$ 0.01*	18%
Sulfamethazine (57-68-1)	1.05 $\pm$ 0.01	1.04 $\pm$ 0.03	1.03 $\pm$ 0.03	1.02 $\pm$ 0.03	1.05 $\pm$ 0.02	0.95 $\pm$ 0.01*	10%
Sulfamethoxazole (723-46-6)	1.02 $\pm$ 0.02	0.99 $\pm$ 0.05	0.96 $\pm$ 0.03	1.06 $\pm$ 0.03	0.98 $\pm$ 0.04	0.95 $\pm$ 0.05	7%
Sulfapyridine (144-83-2)	1.00 $\pm$ 0.09	1.04 $\pm$ 0.04	1.00 $\pm$ 0.02	1.02 $\pm$ 0.05	0.97 $\pm$ 0.03	0.98 $\pm$ 0.01	2%
Trimethoprim (738-70-5)	1.05 $\pm$ 0.01	1.06 $\pm$ 0.03	1.03 $\pm$ 0.04	1.02 $\pm$ 0.02	0.98 $\pm$ 0.04	0.94 $\pm$ 0.02*	10%

^aErrors are standard deviation, n = 3 for all data points.^bConcentration at the longest time point relative to the day-zero concentration.*Statistically significant difference from the day-zero concentration according to a one-way analysis of variance and Dunnett's post hoc test ($p < 0.05$).

intrinsic variability in POCIS. Differing amounts of the Oasis HLB phase used in each POCIS as well as the distribution of the phase on the inside of the membranes (i.e., the standard 200 mg of sorbent in a commercially available POCIS does not necessarily coat the exposure surface evenly) may affect variability among POCIS. The extraction process, generally involving a cleanup column followed by rotary and nitrogen evaporation, and instrumental matrix effects all contribute to intervariability among POCIS.

On top of this intrinsic variability, likely the most important parameter influencing the variability in POCIS measurements is the uncertainty in sampling rates resulting from both a lack of performance reference compounds and environmental factors that can significantly affect sampling rates. For example, Bartelt-Hunt et al. [20] applied their laboratory-determined POCIS uptake rates of a group of steroid hormones and pesticides to previous reports (nanograms per POCIS) of the same compounds [36] to estimate aqueous concentrations. The two studies report contaminant concentrations of 17 β -estradiol, estrone, estriol, atrazine, and deethylatrazine with RSD values ranging from 10 to >100%. Jacquet et al. [37] used POCIS for monitoring beta-blockers and hormones in wastewater-treatment-plant effluents and receiving surface waters and reported nanogram POCIS concentrations with RSD values ranging from 4 to 88%.

Furthermore, two reviews [16,38] highlighted the need for compound-specific sampling rates, used to calculate time-weighted average concentrations, as a major issue contributing to the large errors associated with POCIS measurements. Sampling rates represent the amount of water clearing the sampler per unit time for a given analyte. They are specific to each compound and dependent on water flow, temperature, pH, organic carbon content, and biofouling [16,21,38]. In addition,

in situ laboratory calibrations used to determine POCIS sampling rates do not necessarily simulate all conditions in the field. Additionally, natural surface water systems are in a constant state of flux, including over the sampling period. Sampling rates are weakly dependent on water flow and temperature [21]. These two parameters can change significantly through time and across sampling sites. Thus, using a single, static value for the sampling rate of a compound may contribute significantly to the variability observed in measured POCIS concentrations.

Temporal fluctuations in water chemistry parameters will also accentuate errors associated with laboratory sampling rates determined under one set of conditions. For example, POCIS in different river and wastewater systems in France showed variability in beta-blocker sampling rates by as much as a factor of 5 [37]. Similar variations in sampling rates have been seen for some PPCPs with variations in flow rates [21] as well as pH and organic matter content [39]. Sampling rates for individual compounds often vary by a factor of 2 or more between studies, even when done under similar laboratory conditions. The POCIS sampling rates (liters per day) for sulfamethoxazole in flowing waters at 22 to 25°C were found to be 0.339 [21] and 0.118 [20]. Similarly, sampling rates for carbamazepine were 0.561 [21] and 0.288 [20].

These large variations in sampling rates produce corresponding variability in measured POCIS-derived concentrations, and thus losses incurred during long-term storage will not exceed the errors associated in estimates of aqueous concentrations using POCIS as a passive sampling technique. The use of performance reference compounds either to back-stop laboratory-determined sampling rates or for in situ field calibrations can alleviate the influence of these environmental factors. However, this approach requires the selection of a suitable performance reference compound, as well as determining its elimination

Table 3. Average concentrations of target analytes in Dead Horse Creek, Manitoba, Canada, on polar organic chemical integrative samplers (POCIS) deployed June 22 to July 13, 2010, and in water-grab samples collected July 6, 2010, and extracted onto Oasis hydrophilic–lipophilic balanced solid-phase extraction (SPE) cartridges: POCIS and SPE samples were subsequently stored at -20°C and processed for analysis on the dates listed, which were 356 and 350 d apart, respectively^a

Compound (CAS)	POCIS concentration (ng/g sorbent)		SPE concentration (ng/L)	
	March 25, 2011 (255 d)	March 15, 2012 (611 d)	May 9, 2011 (307 d)	April 23, 2012 (657 d)
2,4-Dichlorophenoxy acetic acid (94-75-7)	538 $\pm$ 143	495 $\pm$ 117	nd	nd
Atenolol (29122-68-7)	33.3 $\pm$ 1.0	36.9 $\pm$ 12.9	10.3 $\pm$ 0.1	10.2 $\pm$ 0.4
Atrazine (1912-24-9)	127 $\pm$ 20	125 $\pm$ 10	5.8 $\pm$ 0.3	6.5 $\pm$ 0.4
Carbamazepine (298-46-4)	2,130 $\pm$ 105	1,830 $\pm$ 160	67.2 $\pm$ 4.3	66.8 $\pm$ 1.5
Gemfibrozil (25812-30-0)	794 $\pm$ 114	819 $\pm$ 118	nd	nd
Metoprolol (51384-51-1)	159 $\pm$ 22	124 $\pm$ 7	8.6 $\pm$ 0.2	7.9 $\pm$ 0.6
Sulfamethazine (57-68-1)	6.9 $\pm$ 1.3	5.2 $\pm$ 1.0	nd	nd
Sulfamethoxazole (723-46-6)	138 $\pm$ 52	114 $\pm$ 24	nd	nd
Trimethoprim (738-70-5)	228 $\pm$ 42	167 $\pm$ 74	9.6 $\pm$ 0.3	9.6 $\pm$ 0.5

^a Errors are standard deviation, $n = 3$ for all data points.

nd = not detected.

rate off of the POCIS, both of which are nontrivial [16]. More research is required to validate the use of performance reference compounds in POCIS. Regardless, the data presented in the present study as well as the existing literature would suggest that worst-case losses of 10 to 30% due to storage over the course of 20 months are insignificant when considering the accuracy that can be expected when using POCIS as an environmental monitoring tool.

Environmental POCIS

The POCIS deployed in Dead Horse Creek represent the storage of actual environmental samples with original coextracted matrices. As a result, the analytes were necessarily limited to their occurrence in the study system (Table 3): 2,4-D, atenolol, atrazine, carbamazepine, gemfibrozil, metoprolol, sulfamethazine, sulfamethoxazole, and trimethoprim. The average loss for all nine compounds after nearly two years of storage compared with concentrations after one year of storage was 13%, with a maximum loss of 27% for trimethoprim (Table 3). None was statistically significant. As discussed above, losses in the range of 15 to 30% are in many cases smaller than the variability in using POCIS for the determination of aqueous concentrations. Therefore, the long-term storage stability of these compounds in their original environmental matrices is feasible.

Out of the nine compounds detected in Dead Horse Creek, losses for five (2,4-D, 8%; atenolol, 0%; atrazine, 2%; gemfibrozil, 0%; and sulfamethoxazole, 17%) stored for nearly two years along with coextracted environmental matrix were less than the corresponding loss for the same compounds after 609 d in the laboratory POCIS. The other four compounds—carbamazepine (14%), metoprolol (22%), sulfamethazine (25%), and trimethoprim (27%)—showed greater losses stored on environmental POCIS compared to laboratory POCIS. Metoprolol, sulfamethazine, and trimethoprim all showed losses between 10 and 13% after 609 d on laboratory POCIS (Table 1), which may suggest that storage on POCIS beyond two years may result in significant losses for these three compounds. However, these observations for the environmental POCIS may also result from the variability that may exist between two POCIS samplers deployed in parallel at a sampling site [16]. This could arise from differences in how the sampling cage is orientated in the water or possibly differential biofouling between POCIS samplers.

Laboratory-spiked SPE

Storage at -20°C on SPE cartridges (Table 2) generally exhibited smaller losses compared to POCIS. In general, there was less than 20% loss for all compounds across the board after 576 d of storage. Although the average loss observed for all compounds on SPE cartridges was $<10\%$, a larger number of these compounds resulted in statistically significant losses, due to smaller measurement variation associated with SPE. Of the 24 compounds analyzed, 15 exhibited a statistically significant loss over the duration of the storage. Fourteen of those 15 had losses between 9 and 16% after 576 d of storage, while losses of sulfadimethoxine were 18% of the initial concentration after 576 d of storage (Table 2). Gemfibrozil showed significant losses compared to day 0 concentrations after 13 d of storage but had a total loss of only 13% after 576 d.

Extraction of environmental water samples using SPE allows for the option of spiking the samples with internal standards prior to storage. In this way, any losses incurred during the storage process will be accounted for, if isotope dilution is used. Caution must be taken if labeled internal standards are susceptible to hydrogen–deuterium exchange, which would obviously bias results. Opening and resealing POCIS (a process necessary for spiking internal standards) after sampling but prior to storage is nontrivial and prone to error and large losses of sorbent; thus, using isotope dilution to account for losses during storage of POCIS is logistically not feasible at this time.

The present study was designed to present both SPE sample storage methods, internal standard addition pre- and poststorage. All stored SPE samples from day 0 to day 126 had internal standard added before the storage process. Thus, any losses over the course of the experiment were counted. The 576 d–stored SPE samples were spiked with internal standard after storage and, thus, represent the absolute losses observed over the course of the study. Absolute losses of $<20\%$ for all compounds on SPE after 576 d of storage are within the realm of variability encountered with analysis of samples in environmental matrices [4,28]; however, spiking isotope dilution standards prior to storage is still recommended.

Environmental SPE

As with the environmental POCIS, multiple grab samples were taken at the same time at the same site on Dead Horse Creek and extracted by SPE. Two sets of SPE cartridges were

stored, with internal standard added prior to storage as above. One set was extracted and analyzed after approximately one year of storage and the second set another year later (Table 3). Five compounds were detected: atenolol, atrazine, carbamazepine, metoprolol, and trimethoprim. A maximum loss of 8% was found for metoprolol after two years of storage compared with after one year of storage. This observation suggests that the addition of isotopic/labeled standards to SPE cartridges prior to storage is an effective technique allowing for long-term sample storage (two years) while avoiding significant losses.

CONCLUSION

Twenty-four pharmaceutical and pesticide pollutants were relatively stable on SPE cartridges and POCIS frozen at -20°C for up to 20 months. Losses incurred during POCIS storage for both laboratory-spiked and environmentally exposed samplers, containing coextracted matrix, were smaller than the variability associated with the typical use and application of POCIS. Thus, storage losses are likely insignificant for most studies employing POCIS as an environmental monitoring tool. The storage of SPE samples resulted in a larger number of compounds showing statistically significant losses over the storage period. Although these losses were generally lower than those on POCIS because of the smaller variability in the SPE procedure, they were statistically significant. Adding labeled internal standard to SPE cartridges after sampling but prior to storage can account for losses incurred during the storage process. This technique was tested on real environmental samples and was effective in accounting for any losses during storage.

In summary, the two common sampling devices/techniques studied in the present study can be used to store polar organic contaminants easily and conveniently. Such storage is applicable to archival studies or monitoring studies that incur a large volume of samples over a short period of time and are limited by the analysis throughput.

SUPPLEMENTAL DATA

Tables S1 and S2. (37 KB PDF).

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