Journal of Environmental Monitoring

Cite this: *J. Environ. Monit.*, 2011, **13**, 1480

www.rsc.org/jem

PAPER

Utilization of the solid sorbent media in monitoring of airborne cyclophosphamide concentrations and the implications for occupational hygiene

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Received 26th November 2010, Accepted 8th March 2011
DOI: 10.1039/c0em00660b

The main objective of the study was to evaluate the applicability of two solid sorbent media (Anasorb 708 and Strata X), the impinger filled with distilled water and PTFE filters for determination of airborne cyclophosphamide (CP) in the hospital working environment. For this purpose, air contamination of Masaryk Memorial Cancer Institute (Czech Republic) was monitored using the sampling apparatus containing the samplers described above. In addition, the surface contamination was also determined using the wipe sampling technique. During the monitoring, contamination of three different workplaces (storage room, preparation room and outpatient clinic) was studied. Using Strata X solid sorbent tubes, airborne CP was determined in all (n = 5) samples collected at the outpatient clinic over a 5 day monitoring period (concentration range: 0.3–4.3 ng m^{-3}). Other samplers (including PTFE filters) did not collect any detectable amount of CP (the limit of detection, LOD $\leq$ 0.1 ng m^{-3}). Negative results detected at filter samples indicate that CP determined at Strata X samples was most probably of gaseous origin. Surface contamination ranged from <2 to 19, <8 to 418 and 133–15 500 pg cm^{-2} at the storage room, preparation room and outpatient clinic, respectively. The study showed that evaporation of antineoplastic drugs should not be neglected, albeit the concentrations determined in our study are relatively low. Therefore, proper monitoring of airborne contamination should involve simultaneous sampling of both particle-bonded and gaseous phases. In this way, Strata X sorbent tubes seem to be an effective tool for the sampling of gaseous CP in the indoor air.

Introduction

Occupational health risks related to handling antineoplastic drugs (ADs) were discussed in many studies since the 1970s, when serious side-effects of chemotherapy (secondary malignancies) were firstly reported. The scientific interest even increased, when numerous monitoring studies dealing with airborne and surface contamination showed that the presence of ADs in the working environment is common and frequent. Nanograms to micrograms of individual ADs per cubic metre were found in the air in the aerosol form.[1–3] Analyses of wipe samples indicated comparable amounts of ADs per square centimetre on floors, walls, benches, shelves, doors, telephones and other surfaces within pharmacies and administration areas.[3–6] Contamination by ADs was also revealed on protective gloves, cloths and linens, lavatories and sanitary rooms.[6,7] Some studies showed also traces of ADs and/or their metabolites in the urine of exposed healthcare workers.[8–12]

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Environmental impact

Although some experimental studies demonstrated the potential of antineoplastic drugs to evaporate under the common atmospheric conditions, only rare studies focused on the determination of their vapours in the indoor air of the hospital working environment. Our study describes successful application of the Strata X solid sorbent media for the determination of the gaseous cyclophosphamide, which is often analysed as a marker reflecting occupational exposures to hazardous cytotoxic drugs. In the present study, the monitoring of airborne contamination was accompanied by the determination of surface contamination. Thus, our research also contributes to the discussion on the relative importance and risks of inhalation and dermal uptake of the cytotoxic drugs during occupational exposures.

Consequently, several guidelines addressing safe handling with ADs have been prepared by various governmental institutions and international agencies.[13–15]

Great progress in the field of occupational safety was recorded after the implementation of some protective measures like centralization of drug preparation in specialized hospital pharmacies equipped with biological safety cabinets or positive/negative pressure isolators. Thus, the most hazardous activities related to the preparation of ADs were localized to the well-controlled area of the preparation room with special rules for the occupational safety, especially in the term of wearing personal protective equipment. Nevertheless, the overall contribution of these measures to occupational safety and health protection was still not fully clarified. Contrary to original expectations, some studies showed that neither vertical laminar hoods[1,4,12,16–18] nor isolators[3] were able to prevent release of ADs-containing aerosols. The efficiency of the biological safety cabinets to retain the airborne contamination was also compromised when ADs-containing aerosols were shown to pass through the high efficiency particulate air filters in the form of gaseous matter.[4]

Originally, vaporization of ADs was neglected for a long time and concentrations of airborne aerosols were exclusively studied (studies investigated airborne CP contamination in the past along with used sampling media and measured CP concentrations are summarised in Table 1). More recently during the late 1990s, it was shown that ADs can evaporate to some extent. Connor *et al.* studied evaporation of some ADs indirectly by the determination of mutagenicity of the vapour phase above the drug solutions.[19] According to the study conducted by Kiffmeyer *et al.*, the vapour pressure of frequently used ADs can reach up to several mPa and the equilibrium concentrations can reach up to several mg m^{-3} (see Table 2). Depending on the density and size of the particles, vaporisation can be expected in seconds to several minutes.[4]

With respect to the results of the recent vaporisation studies, proper monitoring of airborne ADs should involve determination of vapours in addition to ADs-containing aerosols. However, there is only scarce information and limited literature on methods for monitoring of gaseous ADs. In one study, the presence of gaseous cyclophosphamide (CP) in the preparation room was successfully detected using the cryo-trap as a sampling device.[4] This sampler is based on active ducting of the air through the container cooled by the mixture of acetone and dry ice, where all vapours are frozen out and trapped. However, the drawbacks of the cryo-trap method are high demands on special technical equipment and the price. Alternatively to the cryo-trap, some authors considered solid sorbent media as suitable tools for sampling ADs and suggested some of the first sampling protocols. Thus, extraction and retention efficiency of methacrylic acid polymer (Anasorb 708 tubes) and styrene divinylbenzene polymer (Bond Elute LMS columns) for several “marker” ADs were studied.[20,21] However, monitoring studies that would verify suitability and reliability of these materials have not been conducted.

The main objective of this study was to evaluate the suitability of four different air sampling techniques for determination of airborne CP concentrations as markers of indoor air contamination by ADs. Results of five-days monitoring performed at three different hospital workplaces (storage, preparation and administration area) are presented. The sampling equipment consisted of (i) the cassette Teflon filter for aerosol collection, (ii) Anasorb and (iii) Strata-X solid sorbent tubes for vapours sampling and (iv) the impinger filled with distilled water for non-selective collection of airborne contamination (particle and gaseous matter). All the techniques used active pumping of air through the sampling media. Furthermore, surface contamination within the same working areas was studied and the relevance of both types of contamination is discussed.

Experimental

Chemicals

Cyclophosphamide monohydrate (purity 99.5%) was purchased from Sigma-Aldrich Chemie (Steinheim, Germany) and $^{2}H_{4}$-labelled cyclophosphamide (CP-D4; purity 97%) was obtained from Niomech (Bielefeld, Germany). Methanol (HPLC gradient grade 99.9%), acetonitrile (HPLC gradient grade 99.9%), acetic acid (p.a. eluent additive for LC-MS) and ammonium acetate (p.a. for HPLC 99%) were all from Sigma-Aldrich Chemie (Steinheim, Germany). Water was purified in a Milli-Q Water Purifier (Millipore, Billerica, MA, USA).

Description of workplaces

Ambient contamination was monitored in two workplaces of the hospital pharmacy (storage area and preparation room) and in the outpatient clinic. Basic characterisation of the workplaces (including the mean amounts of CP handled during the sampling days and annually) is presented in Table 3. All workplaces were cleaned by routine sanitation processes each day. Sampling of surface contamination was provided before the cleaning.

Hospital pharmacy. The preparation of ADs is centralized to the hospital pharmacy, which performs most of the hazardous operation procedures related to ADs. The reception of ADs is carried out on the reception desk reserved for hazardous drugs. During the reception, ADs are unpacked and the primary packaging (vial) is labelled with the RFID (Radio Frequency Identification) chip for identifying the drug in our internal drug logistic system. Storing of ADs takes place in a room vented by the air conditioning system. Drug preparation is carried out in a special clean room equipped with two negative pressure isolators (Envair CDC-D 2GD and Envair CDC-F 2G2D (Envair Limited, Haslingden, EN)) ducting the exhaust air outside the building. Drug preparation is performed using a traditional “syringe/needle” mode of operation. Prepared drugs are enclosed (and sealed) in plastic foil before they are taken out from the preparation room. The atmosphere of the preparation room is isolated from the outer working environment by the high-pressure barrier maintained in the adjacent transit rooms.

Outpatient clinic. The outpatient clinic consists of one treatment room, one (smaller) duty room (used for ADs reception, packaging integrity control and unpacking) and two toilets for treated patients. The total capacity of this department is twenty patients at a time (corresponding to app. 120 patients per day). Administration of CP is performed using an intravenous infusion set and the infusion rate is controlled with an infusion pump. Connection of the IV sets to IV bags is exclusively performed by

Table 1 Review of sampling methods and airborne concentrations of cyclophosphamide published in the literature

Reference	Form	Sampling media	Type of sampler	LOD/ ng m^{-3}	No. of samples Total	Positive	Range of conc./ ng m^{-3}	BSC and other protective measures	Comments
deWerk Neal *et al.*, 1983 (33)	Aerosol	PTFE fil. (47 mm, 0.5 µm)	Stationary	Not specified	320 h	80 h	370	No ventilation hood, preparation performed at the oncology ward	Prolonged sampling time was applied (40 h)
Sessink *et al.*, 1992 (16)	Aerosol	Glass fibre fil. (150 mm, 1.6 µm)	Stationary	Not specified	2*	0	≤2	Vertical laminar airflow hood	*Number of samples collected, when the drug was handled
Sessink *et al.*, 1994 (1)	Aerosol	PTFE fil. (50 mm, 1.0 µm)	Stationary	3–30	17 days	1 day	200	Vertical laminar airflow hood	
		PTFE fil. (37 mm, 1.2 µm)	Personal	40–500	17 days	4	1000–10 100		
Sessink *et al.*, 1997 (18)	Aerosol	PTFE fil. (37 mm, 1.2 µm)	Personal	20–150	28*	2	60–2000	Vertical laminar airflow hood	*Number of samples collected, when the drug was handled
Minoia *et al.*, 1998 (12)	Aerosol	Borosilicate fibre fil. (20 mm)	Personal	2	24	1	240	Vertical laminar airflow hood	
Kromhout *et al.*, 2000 (5)	Aerosol	Not specified	Stationary	0.5–1.6	66	11	0.5–1.7		Study conducted in outpatient and nursing clinics
Kiffmeyer *et al.*, 2002 (4)	Aerosol	Borosilicate fibre fil. (Millipore, AP20, 47 mm)	Stationary	≤1.1	20	6	1.1–65	Vertical laminar airflow hood	
	Vapours	Cryotrap (−78 °C)	Stationary	≤1.1	15	7	45–13 000		
Hedmer *et al.*, 2004 (21)	Aerosol	PVDF fil.	Stationary	0.4–0.5	4	0	0	Vertical laminar airflow hood, spikes for drug preparation	
	Vapours	Bond Elut LMS	Stationary	0.3	4	0	0		
Mason *et al.*, 2005 (3)	Aerosol	GFA fil.	Stationary	0.8–1.0	8	1	4.8	Positive and negative pressure isolators	
		GFA fil. in IOM heads	Personal	0.8–1.0	22	<5	≤57		

Table 2 Vapour pressures and equilibration concentrations of widely used antineoplastic drugs at 20 °C

	Vapour pressure/ mPa	Equilibration conc./mg m^{-3}	Reference
Carmustine	19.0	1.70	4
Cisplatin	1.8	0.22	4
Cyclophosphamide	3.3	0.36	4
Dacarbazine	3.7	0.27	[a]
Doxorubicin	3.0	0.67	[a]
Etoposide	2.6	0.63	4
Fluorouracil	1.4	0.08	4
Paclitaxel	22.5	7.89	[a]

[a] Unpublished data provided by the Institute of Energy and Environmental Technology (Duisburg, Germany). Measurements performed according to standardised methodology.[4]

the pharmacy technicians in the isolators immediately after the admixing activities. Reuse of the IV sets is forbidden.

Sampling and work-up procedures of air samples

The stationary sampling apparatus consisted of push cart, 4 personal pumps XR5000 (SKC Ltd., Eighty Four, PA, USA) and four different sampling devices. During the sampling, the equipment was situated in close vicinity (1–2 metres) to the site, where ADs were intensively handled (working table, isolator and application chair in the storage room, the preparation room and the outpatient clinic, respectively). Each sample was collected for 8 hours and the monitoring study was performed in five consecutive days (five samples of each type were collected). Details of sampling and work-up procedures depended on the sampling material.

Solid sorbent samples. For gaseous CP sampling, Anasorb 708 tubes (methacrylic acid polymer; sorbent mass: 100 mg per tube; surface area: 140 m^2 g^{-1}; obtained from SKC Ltd., Eighty Four, PA, USA) and Strata X columns (modified styrene polymer; sorbent mass: 30 mg; surface area: 800 m^2 g^{-1}; obtained from Phenomenex Inc., Torrance, CA, USA) were utilized. A flow rate of 0.25 l min^{-1} per each tube was applied according to the manufacturer recommendations. To enhance the sensitivity limited by the low flow rate, five tubes of each solid sorbent were used in parallel utilizing an air manifold system (Supelco, Bellefonte, PA, USA) for the connection of the tubes to the pump. After the sampling, tube openings were sealed with tube caps or Parafilm and stored at a temperature of −20 °C until analyses (max. two weeks). Each solid sorbent tube was extracted/eluted with 1 ml acetonitrile/methanol (1 : 1). Extracts of parallel samples were pooled together and evaporated in SpeedVac concentrator to dryness. Dried samples were reconstituted in acetate buffer (20 mM, pH = 4) containing CP-4D (25 ng ml^{-1}) and analysed.

PTFE filter samples. For airborne aerosol sampling, PTFE cassette filters (porosity = 1.0 μm, diameter = 47 mm) obtained from SKC Ltd. (Eighty Four, PA, USA) were utilized. A flow rate of 2 l min^{-1} was applied. After the sampling, the filter sample was enclosed into the polypropylene dish and stored at a temperature of −20 °C until analyses (max. two weeks). Each filter sample was extracted with 5 ml acetonitrile/methanol (1 : 1). Extracts were evaporated in SpeedVac concentrator to dryness. Dried samples were reconstituted in acetate buffer (20 mM, pH = 4) containing CP-4D (25 ng ml^{-1}) and analysed.

Impinger samples. Impinger samples were collected by glass impinger filled with 100 ml redistilled water. A flow rate of 1 l min^{-1} was applied. After the sampling, 50 ml of impinger sample was enclosed into the polypropylene dish and stored at a temperature of −20 °C until analyses (max. two weeks). Frozen impinger samples were lyophilized to dryness and reconstituted in 5 ml acetonitrile/methanol (1 : 1). Organic solutions were evaporated in SpeedVac concentrator to dryness. Dried samples were reconstituted in acetate buffer (20 mM, pH = 4) containing CP-4D (25 ng ml^{-1}) and analysed.

Sampling and work-up procedure of wipe samples

The entire object surface (telephone, front side of infusion pump) or the area of 30 × 30 cm (table desk, floor, store shelf, *etc.*) was wiped by nonwoven swab Mesoft (7.5 × 7.5 cm; Mölnlycke Health Care AB, Göteborg, Sweden) moistened with 0.75 ml acetate buffer (20 mM, pH = 4). All wipe samples were collected with a standardised sampling procedure (three repeated wipes varying in the direction by one swab folded in half after each wipe). After sampling, the swab was placed in polypropylene syringe (60 ml; Terumo Europe N.V., Leuven, Belgium) and stored at −20 °C until the work-up procedure. Wipe samples were extracted with 25 ml acetate buffer (20 mM, pH = 4) in ultrasound bath for 30 min. After the extraction, samples were centrifuged for 10 min at 20 × 10^3 × *g*. Aliquots of 1 ml were transferred into the autosampler vials and 10 μl of the internal standard (methanol solution of CP-4D, c = 2.5 μg ml^{-1}) was added to each.

Table 3 Characterisation of the workplaces investigated

Workplace	Activity concerning ADs	Time of handling ADs	Number of workers	Mean amount of CP handled/g: Sampling day	Mean amount of CP handled/g: Annually
Storage area	Unpacking, labelling, storage	8 a.m. to 3 p.m.	2–5	5.0	1500
Preparation room	Preparation (reconstitution, dilution, transfer)	8 a.m. to 3 p.m.	2–4	5.0	1500
Outpatient clinic	Administration	8 a.m. to 5 p.m.	3–5	4.9	1400

Liquid chromatography/mass spectrometry

The samples were analysed by the LC-MS/MS system Agilent 1200 coupled to 6410 Triple-Quad MS (Agilent, USA) with electrospray (ESI) interface operating in negative ion mode. Separation was achieved on Zorbax SB-C18 column (2.1 × 30 mm, 3.5 μm; Agilent Technologies Inc., Wilmington, DE, USA) at 30 °C with a flow rate of 0.3 ml min^{-1}. The separation was performed under the gradient elution (linear gradient 10–25% B for 0–6 min, then ramped from 25% to 80% B in a period of 6–7 min and kept at 80% B for other 3 min, before the next injection the column was equilibrated at 10% B for further 5 min; mobile phases—A: acetate buffer (5 mM, pH = 4) and B: acetonitrile). The mass spectrometer was operated in a multiple reaction monitoring mode (MRM) with a collision energy of 22 eV. The capillary voltage and the fragmentation energy were 2000 V and 130 V, respectively. The CP transition *m/z* 261.1 to 140.0 and the CP-4D (internal standard) transition *m/z* 265.1 to 144.0 were monitored for 250 ms dwell time. Quantitative analyses were performed in MRM mode with the IS technique (analyte peak area/IS peak area ratio *vs.* concentration (RT 6.1 min)) by comparison with the corresponding calibration curve. The limit of detection of LC-MS/MS was less than 0.1 μg l^{-1} using a 10 μl injection volume (1 pg/injection).

Quality assurance

After the methods were introduced to the laboratory, basic tests evaluating the work-up and sampling procedures were performed. The monitoring study followed this partial validation. The results of monitoring are presented as raw data without any adjustments to recovery. Indeed, the recovery and its variability determined during the characterisation of the methods describe the accuracy and precision of the methods, respectively.

Characterisation of the air sampling methods. Each sampling material was characterised by evaluation of the extraction and retention efficiency. Extraction efficiency indicates the percentage of the analyte recovered from the sample spiked with the known amount of the analyte. Retention efficiency is the percentage of the analyte retained on the spiked sampler after a predetermined volume of air was drawn through the sampler (under the condition of the sampling (20 °C, 40% humidity)). Both tests were performed using three replicate samplers spiked with 50 ng of the analyte.

Characterisation of the wipe sampling method. The wiping tissue was characterised by evaluation of the recovery of the work-up procedure (extraction) and the recovery of the whole method (including the sampling procedure). Extraction recovery was assessed in three replicates at three different levels (16, 160 and 1600 ng CP per sample modelling the surface contamination corresponding to 18, 180 and 1800 pg cm^{-2}). In order to test the recovery of the whole method (including the sampling procedure), model surfaces (stainless steel, 30 × 30 cm) were spiked in one replicate at three levels described above (surface coated by 0.5 ml of CP solution in methanol). The surfaces were processed after the solvent evaporated.

Results and discussion

Pre-monitoring characterisation of the methods

Laboratory characterisation of the air sampling methods showed good extraction and retention efficiency at all sampling media. The recovery of the work-up procedure (extraction efficiency) ranged from 84 to 104% depending on the sampling media (see Table 4). The retention test showed that the air sampling media retained ≥90% of the extractable amount of the analyte after the sampling period (8 h). The precision calculated as the observed coefficient of variation (CV%, 100 × SD/mean) ranged from 2 to 16. The expected limit of detection (LOD, signal-to-noise ratio ≥ 3) was ≤0.1 ng m^{-3} for all air sampling methods (assuming that the sampling efficiency is 100%).

The extraction recovery rate of the wipe sampling method ranged from 90 to 98% depending on the contamination level (see Table 5). The accuracy of peak integration was slightly affected by the increased baseline noise observed at realistic wipe samples. Thus, the recovery of the entire method (including the sampling procedure) ranged from 96 to 116%. The coefficient of variation ranged from 3 to 7% and the limit of detection was 2 pg cm^{-2} (at most surfaces with the sampling area 900 cm^2).

Utilization of the air sampling media in the monitoring study

Despite the good retention efficiency determined in the pre-monitoring study, detectable airborne CP levels were determined only with Strata X solid sorbent tubes. Using the Strata X tubes, airborne CP was detected in the outpatient clinic in concentrations ranging from 0.3 to 4.3 ng m^{-3}. These concentrations are at least 6-times higher than the limit of detection (0.05 ng m^{-3}). In our study, we have used 5 parallel tubes to increase the sensitivity, but good efficiency of the Strata X indicates that the use of parallel sampling could be avoided, which is highly recommended according to the fact that parallel sampling is a potential source of additional analytical errors. Alternatively, other sampling settings are also possible to use in the purpose of

Table 4 Cyclophosphamide recovery (%) from air-sampling media determined by the extraction and retention tests

	Extraction test		Retention test	
	Mean	SD	Mean	SD
PTFE filter	104	2	94	3
Anasorb 708	99	7	94	7
Strata X	88	3	91	2
Impinger	84	13	80	16

Table 5 Cyclophosphamide recovery (%) of the wipe sampling method (the work-up procedure and the entire method including the sampling procedure)

	Extraction		Entire method
Contamination level/pg cm^{-2}	Mean	SD	Mean
18	90	6	116
180	90	3	100
1800	98	3	96

enhancing the analytical sensitivity (*e.g.* larger tubes with more sorbent material and/or higher air flow). These adjustments would however require a more efficient air pump because of higher backpressure expected.

Strata X is a polymeric sorbent based on styrene divinylbenzene similar to that, which was previously characterised by Hedmer *et al.*[21] These authors used Bond Elute LMS (30 mg, 1 ml) tubes for sampling of gaseous CP. The suitability of this material was verified by the determination of the extraction and retention efficiency and also by the sampling of CP evaporated from spiked Teflon-wool wads under various temperatures.[21] The study contained also measurements of the airborne CP in the hospital pharmacy but no positive results were recorded. However, this negative result could be explained by the relatively low working load reported (the number of preparations performed at the sampling day) and the protective measures used during the drug preparation procedures (spikes for solution transfer from vials to syringes, BSC with exhaust ducted outside the building). We originally planned to use the Bond Elut LMS columns in our study but due to their limited availability on the market we decided to use another polymeric sorbent based on styrene divinylbenzene (Strata X). The dimension of the tubes was chosen according to Hedmer *et al.*[21]

Strata X sorbent (as well as Bond Elut LMS) was primarily designed for traditional solid phase extraction of liquid samples. However, several previous studies indicated that SPE sorbents can also be used for sampling of vapours. For example C18 and C8 sorbents were used for trimethylamine[22] and organophosphate esters,[23] respectively. Modern sorbents with polymer based structure (*e.g.* Strata X, Bond Elut LMS, *etc.*) seem to be even more suitable for sampling of vapours than traditional SPE sorbents based on the particles with bonded monomolecular organic layers, since their retention capacity does not depend on the activation of the stationary phase by conditioning process.

The second sorbent evaluated in the study was Anasorb 708. This sorbent was included in the study based on the results of Larson *et al.*[20] This author published the study focused on characterisation of some sampling materials with the aim to identify the sampling media appropriate for gaseous ADs analyses. Based on their investigation of the extraction and retention efficiency, the Anasorb 708 appeared to be the most suitable material.[20] Nevertheless, despite the good extraction and retention efficiency of Anasorb 708 (see also Table 4), this sorbent did not collect any detectable amount of CP in our monitoring study. According to Hedmer *et al.*, CP binds to glass surfaces[21] and therefore Anasorb 708 tubes with the glass tubing material may be less suitable than other devices. However, no such binding of CP to glass was observed during our pre-monitoring study, and in our opinion, low sampling efficiency of the Anasorb 708 is attributed to relatively small specific surface of the sorbent.

This study investigated also the applicability of two other sampling media: an air impinger filled with the distilled water and the Teflon filter. However, any of the samples collected by these media did not reveal a detectable amount of CP. Based on these results, we can assume that (i) no aerosols containing CP were present in the sampling air and (ii) an impinger filled with distilled water is not an efficient tool for sampling of gaseous CP (despite the fact that CP is a polar substance with relatively high hydrophilicity and water solubility). Taken together, except Strata X solid sorbent no other materials revealed positive results although the extraction and retention potentials of the materials tested during the material characterisation were well comparable (see Table 4). Thus, it seems that neither extraction nor retention efficiency is the appropriate marker of sampling potential in real conditions.

For the near future it may be expected that SPE membranes, whose structure combines fibres with sorbent particles, will be used for sampling airborne contaminants because they enable simultaneous sampling of aerosols and vapours.[24]

Distribution and levels of CP in the working environment

Results of the monitoring study are summarised in Table 6. Measurable CP amounts were detected in all Strata X samples (n = 5) collected in the outpatient clinic (concentration range: 0.3–4.3 ng m^{-3}). Negative results of the filter samples indicate that CP determined in the Strata X samples was predominantly of gaseous origin. The coincidence of the determination of relatively high surface contamination (see Table 6) and gaseous CP at this workplace is interesting and it can indicate that surface contamination is an important source of the vapours in the working environment. The absence of CP-containing aerosols could be explained either by the absence of the source of this contamination or by rapid evaporation of aerosolised particles to

Table 6 Surface and airborne contamination of the working areas studied

	Storage area			Preparation room			Outpatient clinic		
	Pd[a]	Median	Range	Pd[a]	Median	Range	Pd[a]	Median	Range
Surface contamination/pg cm^{-2}									
Table	2/5	<2	<2 to 19	5/5	58	45–418	5/5	175	133–273
Floor	1/5	<2	<2 to 2	5/5	73	57–207	5/5	5311	2032–15 476
Phone	0/5	<8	<8	3/5	56	<8 to 404	5/5	293	234–821
Shelf	0/5	<2	<2						
Refrigerator				5/5	267	159–399			
IV pump							5/5	866	836–6341
Floor at the toilet							5/5	1274	188–1830
Air contamination/ng m^{-3}									
Vapours[b]	0/5	<0.05	<0.05	0/5	<0.05	<0.05	5/5	0.68	0.26–4.29
Aerosols[c]	0/5	<0.05	<0.05	0/5	<0.05	<0.05	0/5	<0.05	<0.05

[a] Number of positive samples/total number of samples. [b] Determined with Strata X solid sorbent tubes. [c] Determined with PTFE cassette filters.

the gaseous form shortly after their introduction to the atmosphere, which can be expected at fine aerosol particles with a diameter around 1 μm.[4]

At the hospital pharmacy (preparation room and storage area) no airborne contamination was found, most probably due to the well maintained ventilation system and generally low surface contamination (compared to the outpatient clinic, see Table 6). Furthermore, according to the legislation in the Czech Republic, the preparation of ADs has to be performed only in the negative pressure isolators connected to the air exhaust system ducting the contaminated air outside the hospital, which further limits the contamination inside. However, when air from the preparation box (biological safety cabinet, BSC) is released back to the room, high ADs concentrations may be expected inside the preparation room as indicated by Kiffmeyer *et al.*, who found up to 13 μg m^{-3} in the air exhausted from the BSC and up to 4 μg m^{-3} in the area near the front BSC openings.[4]

In comparison with previous investigators, our airborne contamination levels seem to be rather low (see Table 6). Considering the range of airborne CP concentration determined in the study and the breathing rate of 10 m^3 per 8 hour workday,[25,26] the worker's daily inhalation intake could reach up to 43 ng. This amount seems to be relatively low compared to surface contamination detected. The same amount of CP was often found at various surfaces, *e.g.* phone receiver at the outpatient clinic (median concentration 293 pg cm^{-2}, surface area 125 cm^2). Taking into account that many ADs (including CP) meet the criteria for chemicals with the relevant dermal absorption (log K_{ow} between −1 and 5, molecular weight < 500),[27] the results of our monitoring study support the opinion that the dermal contact with contaminated surfaces is potentially an important exposure route.[1,5,8,28]

In general, relatively high surface contamination was detected at the outpatient clinic and preparation room. At these workplaces concentration ranged from <8 to 418 and 133–15 500 pg cm^{-2}, respectively. In comparison with the studies published previously, contamination levels of our hospital are about one order of magnitude lower than the levels reported by Minoia *et al.*[12] and within the same ranges as those found by Connor *et al.* and Mason *et al.*[3,29] Lower contamination was reported by Schmaus *et al.*, Fransman *et al.* and Hedmer *et al.*[30–32]

The most contaminated surfaces were the display of the infusion pump (concentration range: 0.8–6.3 ng cm^{-2}) and the floor under the infusion stand (2.0–15.5 ng cm^{-2}) indicating that administration activities are currently the most hazardous processes. Especially disconnection of the infusion set from the intravenous port at the end of the ADs application may lead to accidental spillage of the ADs. Other hazardous activities may include for example connection and disconnection of the infusion set to/from the infusion bag to allow repeated usage of the set. However, such practices are not allowed in our outpatient clinic and consequently they are not likely to contribute to the contamination. Further sources of contamination may be the infusion bags externally contaminated by traces of ADs or the patient toilets contaminated by patient excreta containing unmetabolised ADs.

Conclusions

Our study documents good effectiveness of the Strata X solid sorbent in sampling CP from the gaseous phase in contrast to other studied sampling devices—Anasorb 708 tubes and an impinger filled by distilled water. Despite the evidence about evaporation of ADs (see Table 2), gaseous CP was detected only at the outpatient clinic, where no ventilation system was in operation and relatively high surface contamination was recorded. Although the airborne concentrations measured are not expected to cause an unacceptable health risk to exposed workers, additional safety measures for reduction of the surface contamination are recommended at areas with the frequent contamination such as the outpatient clinic in our study.

Acknowledgements

Authors acknowledge financial support from the CYTO project granted by the Ministry of Education C.R. (No. NPVII 2B06171). The Infrastructure of the Research Centre for Toxic Compounds in the Environment at Masaryk University is supported by the CETOCOEN project (no. CZ.1.05/2.1.00/01.0001) from the European Regional Development Fund.

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