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1 Environmental monitoring by surface sampling for cytotoxics: 2 a review

3

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16

17

18 **Keywords:**cytotoxic drugs, surface sampling, chromatography, hospital.

19

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29 **Abstract**

30 **Object:**Environmental monitoring is usually conducted by surface sampling to detect and quantify the presence
31 of cytotoxic drugs after their reconstitution and administration. This technique reveals the origins of residual
32 contamination and is an important component in order to protect healthcare workers from the potential risk of
33 occupational exposure. The aim of this work is to compare various techniques and results of surface sampling
34 for cytotoxics.

35 **Materials and methods:**For each technique, sample processing methods and their analysis were compared from
36 literature data. Sampling is often performed by the wiping technique. After treatment, various single or multi-
37 compound technical analyses are used, in particular liquid or gas chromatography involving different detection
38 methods: ultraviolet, mass spectrometry, plasma torch, voltammetry. Some methods are validated to ensure
39 reliability.

40 **Results:** Despite published guidelines and the use of isolator technology for the preparation of cytotoxic drugs,
41 workplace contamination persists, leading to chemotherapeutic agents' exposure of healthcare workers. Efforts
42 need to be maintained with particular emphasis on harmonization and on determining alert level for cytotoxic
43 contamination.

44
45 **Introduction**

46
47 In recent decades, cancer survival has improved due to advances in cancer treatment by
48 chemotherapy. Unfortunately, treated patients suffer from significant side effects, because the cytotoxic activity
49 of anticancer drugs also extends to normal cells. Healthcare workers' occupational exposure to cytotoxic drugs
50 has been recognized as a potential health hazard since the 1970s (Ng and Jaffe 1970; Donner 1978). Hospital
51 personnel involved in the preparation or administration of cytotoxic agents is exposed to a wide variety of
52 antineoplastic substances. The precautionary principle requires that exposure should be as low as possible (Turci
53 and Minoia 2006), and minimizing exposure appears to be a real challenge. Numerous published guidelines exist,
54 like the Good Manufacturing Practices in France (ANSM 2007) or those of several other countries (OSHA 1999;
55 Schierl et al. 2009; Randolph 2012; Easty et al. 2015). Several good occupational hygiene practices were also
56 published worldwide, as World Health Organization regional office for European Union countries (WHO Europe
57 2002). Following the US National Institute for Occupational Safety and Health (NIOSH) publication, many
58 healthcare organizations (American Society of Health-System Pharmacists 2006; International Society of

59 Oncology Pharmacy Practitioners 2007; USP <797> 2004; Working Committee on the Safe Handling of
60 Hazardous Drugs 2008) revised their guidelines, policies and procedures in order to enhance safety for care
61 workers (National Institute for Occupational Safety and Health 2004). However, despite compliance with safety
62 directives contamination can occur.

63 Environmental monitoring is essential to assess the risk of contamination in order to take measures to
64 improve working conditions through effective cleaning or protection of cytostatic drugs handlers especially. Even
65 though hospital personnel may be exposed to antineoplastic agents by inhalation or by inadvertent ingestion
66 (hand-to-mouth contamination for example), direct skin contact appears to be the primary path of exposure.

67 To ensure accurate risk assessment, a monitoring strategy is recommended, with the following
68 conditions (Turci et al. 2003): sources of contamination in working areas must be identified. The efficacy of
69 personal protective equipment and biological safety cabinets (BSC) must be verified. Contamination of other
70 areas adjacent to the area of preparation and administration rooms must be monitored and controlled.
71 Information on work activities should be compiled to allow different periods to be compared.

72 Rapid, reliable and validated analytical methods are needed to ensure safe handling of these dangerous
73 drugs by reducing healthcare worker exposure to the lowest possible level. While the literature covers numerous
74 analytical methods of environmental monitoring, few authors in the past carried out a formalized validation on
75 their assay. Most of them were reviewed in 2003 (Turci et al. 2003). Only more recent studies include validation
76 procedures using quality controls (QCs). Several techniques were developed for the detection of a single
77 compound, but assay techniques have since tended towards simultaneous detection of several compounds (multi-
78 compound technology). Since workers are usually exposed to a large number of drugs, studies focused on the
79 most toxic (Group 1 IARC) and the most frequently prescribed drugs.

80 Biological and environmental monitorings are essential to identify the potential paths of exposure and to
81 improve procedures. Moreover, generalization and standardization of environmental monitoring allows
82 the establishment of guidance values, useful tool for occupational safety. Considering the current scientific
83 knowledge limitation on toxicity of chronic exposure to nanomolar quantities of cytotoxic drugs, these guidance
84 values are actually based on comparison of results of environmental monitoring. This risk assessment requires
85 specific standardized sampling techniques and analytical methods. In this review, a critical overview of the main
86 methods of environmental monitoring available in the literature is presented. In addition, the procedures that
87 have been validated as ensuring reliability are highlighted. The results of the largest surveys in hospital
88 departments are also cited with a view to improving both monitoring strategies and working conditions.

89 **Cytotoxic drugs covered by environmental sampling**

90
91 Cytotoxic chemotherapeutic agents can be divided into several classes (OSHA 1999; Turci et al. 2003).

92 Alkylating agents forming covalent bonds with DNA and RNA and leading to the formation of adducts.
93 They include nitrogen mustards (such as cyclophosphamide (CP), and ifosfamide (IF)), derivatives of platinum
94 (such as cisplatin (Pt)) and nitrosoureas (such as the carmustine).

95 Antimetabolites are nucleotide structural analogs and are incorporated into cellular components,
96 inhibiting nucleic acids synthesis and leading to cell death. They include antifolates (such as methotrexate
97 (MTX)), pyrimidine analogues (such as cytarabine (Cyt), gemcitabine (Gem) and 5-fluorouracil (5FU)) and
98 purine analogs (such as fludarabine).

99 Topoisomerase inhibitors are designed to be inserted between the pairs of bases of DNA and to disrupt
100 the synthesis and / or function of nucleic acids. Topoisomerase I inhibitors are derived from camptothecins (such
101 as topotecan (Top) and irinotecan (Iri)) and topoisomerase II inhibitors contain anthracyclines (such as
102 doxorubicin (Dox) and epirubicin (Epi)) and epipodophyllotoxin derivatives (such as etoposide (Eto)).

103 Finally, anti-proliferative agents disrupting mitotic spindle include taxanes (such as paclitaxel (Pac) and
104 docetaxel (Doc)) and vinca-alkaloids (such as vincristine (VCR)).

105 Several cytostatic drugs are classified as carcinogenic to humans (Group 1) by the International Agency
106 for Research on Cancer (IARC) (International Agency for Research on Cancer 2016). This classification (Table
107 1) is based on epidemiological studies showing the development of secondary tumors in cancer patients treated
108 with these drugs and primary tumors in patients treated with medications for other purposes. Several cytotoxic
109 drugs are classified by IARC in group 2A and 2B (probably and possibly carcinogenic to humans, respectively).
110 Antimetabolites and mitotic spindle agents are not classifiable as carcinogenic to humans (Group 3).
111 Nevertheless, they remain mutagenic and teratogenic.

112 **Table 1:** Classification of anticancer drugs according to IARC monographs

Cytotoxic chemotherapeutic agents	Groups	Group definition
CP, etoposide	Group 1	Carcinogenic to humans
Pt, Dox, daunorubicine	Group 2A	Probably carcinogenic to humans
Bleomycin, dacarbazine	Group 2B	Possibly carcinogenic to humans
IF, 5FU, MTX, vincristine, vinblastine	Group 3	Not classifiable as carcinogenic to humans
Pac, Doc, Top, Iri, Epi, Cyt, Gem	--	Actually not classified in IARC monographs

113 CP: cyclophosphamide; Pt: cisplatin; Dox: doxorubicin; IF: ifosfamide; 5FU: 5-fluorouracil; MTX: methotrexate; Pac: paclitaxel; Doc:
114 docetaxel; Top: topotecan; Iri: irinotecan; Epi: epirubicin; Cyt: cytarabine; Gem: gemcitabine.

115 A wide variety of these drugs were analyzed for environmental monitoring (National Institute for
116 Occupational Safety and Health 2014), primarily cyclophosphamide (CP), ifosfamide (IF), methotrexate (MTX),
117 5-fluorouracil (5FU), cisplatin (Pt), paclitaxel (Pac), vinca alkaloids and anthracyclines. These substances are
118 among the most frequently used and the most important from a toxicological point of view. In addition, they are
119 commercially available as analytical standard products.

120 Any choice of marker cytotoxic drugs should be based on a thorough knowledge of hospital activities
121 and specialties. For example, hospitals carrying out the Heated Intraperitoneal Perioperative Chemotherapy
122 Procedure (HIPEC) should evaluate environmental contamination for platinum derivatives (Konate et al. 2011).

123

124 **Environmental sampling dosing methods**

125

126 The range of drugs monitored depends on currently available analytical techniques. High performance
127 liquid chromatography – tandem mass spectrometry (LC/MS/MS) can be used to monitor a wide variety of drugs
128 *via* previously described multi-compound techniques. Inductively coupled plasma mass spectrometry (ICP-MS)
129 or voltammetry can be used for environmental monitoring of platinum salts. High performance liquid
130 chromatography – UV detection (LC-UV) imposes a choice of marker cytotoxic drugs, such as CP (Siderov et
131 al. 2010) or 5FU (Tkaczuk et al. 2010; Lee et al. 2007). Gas chromatography – mass spectrometry (GC/MS) was
132 also used for the environmental monitoring of CP, IF and 5FU (Sessink et al. 1992; Castiglia et al. 2008; Kosjek
133 et al. 2013).

134

135 **Wipe sampling method and extraction**

136

137 In several investigations, wipe sampling was performed on different surfaces and objects. This was the most
138 common practice to monitor residual contamination in reconstitution and care areas, administrative units,
139 equipment, and to test the effectiveness of decontamination techniques (Sottani et al. 2007). A variety of
140 materials, of sampling areas, of types of solution and volumes of desorption solution were addressed. Major wipe
141 sampling and extraction methods are detailed in Table 2.

142 Cytotoxic exposure should be as low as possible. Environmental samples often need to be concentrated
143 to increase sensitivity, in particular when samples are analyzed by LC-UV. In contrast, the sensitivity of
144 LC/MS/MS means that preconcentration is not always necessary (Sabatini et al. 2005).

145 Sample concentration should be performed by solid phase extraction (SPE) or liquid-liquid extraction
 146 (LLE). SPE is often described as faster than LLE, but also more expensive and it does not always allow to
 147 increase the Limit of Detection (LOD) and the Lowest Limit of Quantitation (LLQ) (Juhascik and Fenkins
 148 2009).

149 Several methods of environmental sample extraction were described and compared (Table 2).

150

151 **Table 2:** Sampling and extraction techniques for cytotoxic drugs environmental monitoring.

Drug quantified (Reference)	Sampling technique	Extraction technique	Extraction yields
Pac (Sottani et al. 2000)	Cotton / methanol	LLE (water pH 7.0/ethyl acetate)	> 90%
5FU (Gilles et al. 2009)	Filter paper (Whatman [®])	LLE (water/ethylacetate/isopropanol)	71%
5FU (Micoli et al. 2001)	Cotton / acetate buffer (pH 4.7)	SPE Isolute [®] ENV+ columns (200 mg/6 mL)	Mean = 94.1%
5FU (Kosjek et al. 2013)	100 mL water samples	SPE Isolute [®] ENV+ columns (500 mg/6 mL)	Wastewater = 53 ± 28% Surface water = 93 ± 2%
MTX (Turci et al. 2000)	Cotton	SPE Isolute [®] C18 (500 mg/10 mL)	Mean = 78.4%
CP (Hedmer et al. 2004)	Nonwoven swab /NaOH 0.03M	LLE (water/ethyl acetate)	> 78%
Pt (Brouwers et al. 2007)	Kimtech [®] Science precision wipes / water	Ultrasonic desorption (1% HCl) and filtration	50.4% to 81.4%
5FU, CP, MTX (Sabatini et al. 2005)	Kleenex [®] / ammonium acetate solution (pH 6.9)	none	5FU MTX: ≈ 78% CP: 100%
5FU, IF, CP (Castiglia et al. 2008)	TNT gauzes / NaOH 0.03M	Ultrasonicdesorption, diatomaceousearth (elutiondiethylether)	SPE NR
CP, IF, Pac, Gem (Sottani et al. 2007)	Ashless filter paper (Whatman [®]) / water	OASIS [®] HLB cartridges (200 mg/ 6 mL) SPE	Gem: 62-81% Pac: 55-81% CP, IF: 63-81%
CP, Cyt, Dox, Epi, Eto, Gem, IF, Iri, MTX, VCR (Nussbaumer et al. 2010)	Blotting paper (Whatman [®])	Ultrasonic desorption (water/formic acid)	From 20% (VCR) to 89% (Cyt) on stainless steel surfaces.
CP, Cyt, Dox, Epi, Eto, Gem, IF, Iri, MTX, VCR (Nussbaumer et al. 2012)	Filter paper (Whatman [®])	Ultrasonic desorption (water/ACN/formic acid) and centrifugation	From 45% (Eto) to 86% (CP) on stainless steel surfaces

152 CP: cyclophosphamide; Pt: cisplatin; Dox: doxorubicin; IF: ifosfamide; 5FU: 5-fluorouracil; MTX: methotrexate; Pac: paclitaxel; Doc:
 153 docetaxel; Top: topotecan; Iri: irinotecan; Epi: epirubicin; Cyt: cytarabine; Gem: gemcitabine; VCR: vincristine; SPE: solid phase extraction;
 154 LLE: liquid-liquid extraction.

155

156 When analyzed by LC-UV, 5FU always needs to be concentrated by LLE or SPE. 5FU is very difficult to extract
 157 byreverse phase (RP)SPE because it is an extremely polar weak acid (Kosjek et al. 2013).5FU extraction yields

158 were evaluated for several SPE columns, with highly varying recovery results, from 0.2% to more than
159 90%. Isolute[®] ENV+ SPE appears to be the most suitable column, (Micoli et al. 2001; Kosjek et al.
160 2013) providing effective extraction regardless of both 5FU concentration and applied volume (Micoli et al.
161 2001).

162 LC-UV sensitivity appears to be inadequate for environmental monitoring of CP without
163 preconcentration. A sufficiently sensitive method, for example with SPE as in biological sample
164 treatment (Baumann and Freiss 2001), needs to be developed. Currently, samples can be analyzed with either
165 LC/MS/MS or Gas chromatography - mass spectrometry (GC/MS). Six different types of wipe tissue were
166 evaluated for their recovery potential: Easi-Tex Master[®] Plus, Care Facial[®] tissues, nonwoven swabs, sterile
167 compresses, Kimcare[®] medical wipes and Swedish filter papers (Hedmer et al. 2004). Nonwoven swabs had the
168 best and the highest CP absorption capacity. Size of sampling area was also evaluated (100 or 400 cm²) and a
169 large sample area was generally preferable.

170 SPE should be avoided for Pac because the vehicle formulation (Cremophor EL[®]) can affect the
171 effectiveness of the extraction technique. Instead of SPE, LLE with ethyl acetate can be used (Sottani et al.
172 2007). For MTX, however, SPE is necessary with LC-UV analysis and with LC/MS/MS for smaller areas, such as
173 gloves. LLE is not recommended because of the low aqueous solubility of MTX (Turci et al. 2000).

174 For platinum environmental monitoring (Brouwers et al. 2007), wipe materials (Kimtech[®] wipes,
175 Whatman[®] filters and Klinion[®] gauzes) were evaluated for platinum contamination and for their ability to release
176 platinum from stainless steel surfaces. Wipe solvents (water, 1% HCl, 80% ethanol) and desorption solvents (1%
177 HNO₃, 5% HNO₃, 1% HCl) were also evaluated. Best experimental conditions were reported (Entry 7).

178 More generally, the variability of cytotoxic drugs' recovery (Gem, Pac, CP and IF) has been
179 demonstrated to be more than 20% according to surface type (for example, stainless steel hood work tray,
180 linoleum flooring, laminated bench top) (Sottani et al. 2007).

181 Recently developed multi-compound methods allow quantification by LC/MS/MS of a set of 10
182 cytotoxic drugs simultaneously. Initially, this elegant method involved wipe sampling with blotting paper
183 (Whatman 903[®]) followed by ultrasonic desorption from the paper with water/formic acid (0.1%) (Nussbaumer et
184 al. 2010). The major limitation of this method was the wide variation in percentage recovered among the 10
185 cytotoxic drugs, from 18±12% (VCR) to 94±10% (Cyt). High standard deviations were also reported, for
186 example 34±18% for Iri. Several modifications were consequently realized to improve this technique and
187 extraction procedure (Nussbaumer et al. 2012). First, 20% acetonitrile (ACN) was added to the desorption

188 solution, thereby increasing the hydrophobic substances recovery, and a centrifugation step was added. Then,
189 several filter papers (Whatman[®], Ahlstrom[®], Texwipe[®]) were compared, and the Whatman[®] filter paper was best
190 for environmental monitoring. Finally, recoveries were assessed on a wide variety of surfaces (stainless steel,
191 polypropylene, polystyrol, glass, latex, computer mouse, paperboard) for each cytotoxic, enabling to determine a
192 correction factor per compound and per surface.

193

194 LLQs and LODs of environmental analysis

195

196 GC/MS, LC-UV or LC/MS/MS are the most frequently analytical techniques used for cytotoxic analysis (Sottani
197 et al. 2007). LLQ is often defined as the lowest concentration level with between-day relative error and precision
198 less than or equal to 20% and LOD is the concentration giving signal intensity at least equal to three times the
199 background value (Micoli et al. 2001). LLQ and LOD of several techniques are presented in Table 3. Moreover,
200 these methods were validated with determination of linearity and accuracy in most of the cases.

201 There is not yet any standardization of units of measurement for LOD and LLQ determination. Authors
202 use ng/mL (sample concentration) or ng/cm² (surface of the area sampled), or ng (per sample). Where possible,
203 the units described by authors were harmonized here, in order to facilitate comparison. We believe that
204 expressing LOD, LLQ and surface contamination results in ng/cm² should be standardized, facilitating
205 comparison of results from different studies, this unit of measurement is also more readily comprehensible to
206 clinicians.

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217 **Table 3:** LLQs and LODs of analytical techniques for environmental monitoring

Reference	Analytes	Technique	LOD (ng/mL)	LLQ (ng/mL)	LOD (ng/cm ²)	LLQ (ng/cm ²)	LOD (ng/sample)	LLQ (ng/sample)
Huizing et al. 1995 ^p	Pac ⁿ	LC-UV		SPE: 10 LLE: 250				
Sotani et al. 2007	Pac	LC/MS/MS						10
Sessink et al. 1992 ^o	MTX	LC-UV	60		0.4 - 1		3 - 6	
Turci et al. 2000	MTX	LC-UV						150
Turci et al. 2000	MTX	LC/MS/MS						5
Micoli et al. 2001	5FU	LC-UV					50	150
Gilles et al. 2009	5FU	LC-UV	5	15				
Sessink et al. 1992 ^o	5FU	LC-UV	7		0.04 - 0.1		0.3 - 0.7	
Kosjek et al. 2013	5FU	GC/MS/MS	0.16-0.48 10 ⁻³	0.54-1.6 10 ⁻³				
Hedmer et al. 2004	CP	LC/MS/MS			0.05 10 ⁻³		0.02	
McDevitt et al. 1993 ^o	CP	LC-UV			3-25			
Sessink et al. 1992 ^o	CP	GC/MS	0.1		0.01-0.02		0.06 - 0.1	
Minoia et al. 1998 ^p	CP, IF	LC/MS/MS			0.01		20	
Castiglia et al. 2008	3 ^{a,b,d}	GC/MS/MS ^{a,d} LC-UV ^b			0.12, ^a 0.6, ^d 4.4 ^b	0.2, ^a 1, ^d 7.4 ^b		
Sabatini et al. 2005	3 ^{a,b,c}	µLC/MS/MS	1.1 ^{a,c} 33.3 ^b		0.01 ^{a,c} 0.33 ^b			
Sottani et al. 2007	4 ^{a,d,e,f}	LC/MS/MS			0.125 ^{e,f} 0.0625 ^{a,d}	0.25 ^{e,f} 1.25 ^{a,d}	12.5 ^{e,f} 6.25 ^{a,d}	25 ^{e,f} 12.5 ^{a,d}
Connor et al. 2010	5 ^{a,b,d,e,g}	LC/MS/MS			0.13, ^g 0.1 ^{a,d} 0.07, ^e 0.06 ^b			
Nussbaumer et al. 2010	10 ^{a,c,d,f,g,h,i,j,k,l}	LC/MS/MS	≤0.5	0.25 - 2				
Nussbaumer et al. 2012	10 ^{a,c,d,f,g,h,i,j,k,l}	LC/MS/MS				0.1		10
Kiffmeyer et al. 2013	8 ^{a,b,c,d,e,f,l,m}	LC/MS/MS	0.07 - 0.35	0.1 - 1		(3.7 ^{a,c,d,l} , 7.3 ^f , 11 ^b , 18 ^e , 37 ^m) 10 ⁻³		3.3 ^{a,c,d,l} 6.6-9.9 ^{b,f} 17-33 ^{e,m}
Schmaus et al. 2002	Platinum	Voltammetry			10 ⁻⁵		5 10 ⁻³	
Ensslin et al. 1994 ^o	Platinum ⁿ	Voltammetry	1.8 10 ⁻³					
Brouwers et al. 2007	Platinum	ICP-MS		0.5 10 ⁻³		0.05 10 ⁻³		5 10 ⁻³

218 ^aCP, ^b5FU, ^cMTX, ^dIF, ^ePac, ^fGem, ^gCyt, ^hVCR, ⁱDox, ^jEpi, ^kIri, ^lEto, ^mDocⁿ analysis on biological samples^oMethod validation was not
219 described in this reference ^pMethod validation done on biological samples.

220 CP: cyclophosphamide; Dox: doxorubicin; IF: ifosfamide; 5FU: 5-fluorouracil; MTX: methotrexate; Pac: paclitaxel; Doc: docetaxel; Top:
221 topotecan; Iri: irinotecan; Epi: epirubicin; Cyt: cytarabine; Gem: gemcitabine; VCR: vincristine

222

223 When compared with LC/MS/MS, LC-UV analytical techniques for environmental monitoring suffer
224 from a lack of sensitivity, but also from a lower specificity. In particular for environmental samples, because of
225 the presence of many agents on the working surface, LC/MS/MS remains the gold standard.

226 Laboratories equipped with an LC/MS/MS should use multi-compound methods for environmental
227 monitoring (Nussbaumer et al. 2000; Nussbaumer et al. 2002; Connor et al. 2010; Kiffmeyer et al. 2013). If the
228 investment appears too high, mono-compound analyses by LC-UV can be alternately worked out. As these
229 methods are time-consuming and the LLQs are higher, the cytotoxic assessed must be chosen carefully. GC/MS
230 and GC/MS/MS were mainly described for the monitoring of CP and IF (Sessink et al. 1992; Castiglia et al.
231 2008), involving a derivatization step using fluorinated anhydrides. GC/MS/MS can also be used for 5FU
232 monitoring, after a derivatization step by silylation with MTBSTFA (N-methyl-N-[tert-
233 butyldimethylsilyl]trifluoroacetamide), described as the better reagent for 5FU (Kosjek et al. 2013). Currently,
234 there are no standards for environmental exposure to cytotoxics. USP <797> recently stated that more than
235 1 ng/cm² of CP was found to cause human uptake. MEWIP, a large-scale investigation, led to a cytotoxic-
236 independent target value of 0.1 ng/cm², based on the 90th percentile of the results (Kiffmeyer et al. 2013).

237 CP, MTX and 5FU were the main cytotoxic drugs chosen for environmental monitoring from the 1990s
238 by LC-UV (Sessink et al. 1992), and currently by LC/MS/MS. MTX went from an LOD of 0.4 ng/cm² to an LLQ
239 of 3.7 10⁻³ ng/cm², 5FU from an LOD of 0.04 ng/cm² to an LLQ of 11 10⁻³ ng/cm², and CP from an LOD of 3
240 ng/cm² to an LLQ of 3.7 10⁻³ ng/cm² (Sessink et al. 1992; Kiffmeyer et al. 2013). In the absence of any consensus,
241 but when compared with the USP values for CP and the MEWIP project target values, the LODs of the methods
242 using LC-UV for MTX and CP do not appear to be sufficient for environmental monitoring. However, the LOD
243 of 5FU evaluated by LC-UV (from 0.04 ng/cm² to 0.1 ng/cm²) may be low enough for effective monitoring. The
244 assessment of Pa environmental monitoring with LC/MS/MS methods alone was assessed (Sottani et al. 2007;
245 Sottani et al. 2000; Connor et al. 2010; Kiffmeyer et al. 2013), led to LLQs ranging from 18.10⁻³ to 125.10⁻³
246 ng/cm², depending on the protocol. Nevertheless, it should be possible to develop LC-UV Pac monitoring using
247 protocols described for biological samples, even though the detection limit will be higher (Huizing et al. 1995).
248 Platinum derivative environmental monitoring with both ICP-MS and voltammetry was assessed, with similar
249 LODs and LLQs (Brouwers et al. 2007; Schmaus et al. 2002; Ensslin et al. 1994). As voltammetry appears to be
250 less expensive than ICP-MS, it should be the preferred platinum environmental monitoring method.

251 Besides these traditional analytical techniques, the current development of a 5FU monitor, able to detect
 252 cytotoxic surface contamination in near real time, appears very promising, with LODs ranging from 0.1 to 0.25
 253 ng/cm² (Smith et al. 2015).

254

255 **Applications and discussion**

256

257 Several procedures for cytotoxic drug environmental evaluation were applied in preparation and
 258 administration units. Results for selected cytotoxics are summarized in Table 4.

259

260 **Table 4:** Environmental monitoring of selected cytotoxics in preparation and administration units.

Reference	Place monitored	number of sample	Positive samples	Results
Cytotoxic: 5FU				
Micoli et al. 2001	4 preparation/ administration units	61	49%	Inside hood = 715 ng/cm ² Floor in front of the hood = 12 - 1461 ng/cm ² Top of hood = 80 - 2110 ng/cm ² Internal surface of gloves = 70 - 3770 ng (preparation) 120 - 3290 ng (administration)
Connor et al. 2010	3 hospitals (7 pharmacies, 10 nursing/patient areas)	143	26%	Pharmacies, mean values = 0.13-0.53 ng/cm ² Nursing/patient areas, mean values = < 0.06-35.44 ng/cm ²
Schierl et al. 2009	102 pharmacies	1237	74.4%	10 sampling sites. 90 th percentile = 0.251 ng/cm ² 75 th percentile = 0.029 ng/cm ²
Kiffmeyer et al. 2013	130 pharmacies	1269	31%	3 sampling sites: Floor, work top and refrigerator door. 90 th percentile = 0.117 ng/cm ² 75 th percentile = 0.016 ng/cm ² Highest values = Work top, 24 ng/cm ²
Cytotoxic: CP				
Connor et al. 2010	3 hospitals (7 pharmacies, 10 nursing/patient areas)	143	43%	Pharmacies, mean values = 0.47-16.00 ng/cm ² Nursing/patient areas, mean values = 0.01-0.12 ng/cm ²
Bussières et al. 2012	25 hospitals	259	52%: 50% in pharmacies, 54% in patient care areas	Highest values = Exterior surface of hazardous drug container, 28 ng/cm ² Median = 0.0035 ng/cm ²
Hedmer et al. 2012	6 hospitals (17 outpatient)	447	80%: 95% on floors, 65% on work areas	Highest values = Floors in the patient lavatories, median = 1.1 ng/cm ²

	wards/wards)		53% on handles	90 th percentile values calculated for different surfaces, ranging from 4.2 ng/cm ² (floors in the patient lavatory) to 6.10 ⁻⁵ ng/cm ² (handles of transport box). Median = 0.0033 ng/cm ²
Kiffmeyer et al. 2013	130 pharmacies	1269	37%	3 sampling sites: Floor, work top and refrigerator door. 90 th percentile = 0.048 ng/cm ² 75 th percentile = 0.007 ng/cm ²
Cytotoxic: IF				
Connor et al. 2010	3 hospitals (7 pharmacies, 10 nursing/patient areas)	143	24%	Pharmacies, mean values = 0.08-0.65 ng/cm ² Nursing/patient areas, mean values = 0.01-0.85 ng/cm ²
Bussières et al. 2012	25 hospitals	259	20%: 25% in pharmacies and 14% in patient care areas	Highest values = Floor in front of the hood, 8.6 ng/cm ² Median < 0.0012 ng/cm ²
Hedmer et al. 2012	6 hospitals (17 outpatient wards/wards)	447	73%: 91% on floors, 59% on work areas 35% on handles	Highest values = Floors in the patient lavatories, median = 0.26 ng/cm ² 90 th percentile values calculated for different surfaces, ranging from 4.2 ng/cm ² (floors in the patient lavatory) to 3.10 ⁻⁴ ng/cm ² (door handles of patient lavatory). Median = 0.0042 ng/cm ²
Kiffmeyer et al. 2013	130 pharmacies	1269	21%	3 sampling sites: Floor, work top and refrigerator door. 90 th percentile = 0.014 ng/cm ²
Cytotoxic: MTX				
Bussières et al. 2012	25 hospitals	259	3% : 4% in pharmacies and 1% in patient care areas	Highest values = Front grille inside the hood, 0.58 ng/cm ² Median < 0.006 ng/cm ²
Kiffmeyer et al. 2013	130 hospital or community pharmacies	1269	3%	3 sampling sites: Floor, work top and refrigerator door. 90 th percentile < 3.7 10 ⁻³ ng/cm ² Highest values = Work top, 35 ng/cm ²
Cytotoxic: Gem				
Kiffmeyer et al. 2013	130 hospital or community pharmacies	1269	32%	3 sampling sites: Floor, work top and refrigerator door. 90 th percentile = 0.034 ng/cm ² 75 th percentile = 0.007 ng/cm ² Highest values = Refrigerator door, 1888 ng/cm ² Work top, 190 ng/cm ² and floor 105ng/cm ²
Cytotoxic: Pt				
Schierl et al. 2009	102hospital or	1008	99.2%	10 sampling sites.

261 CP: cyclophosphamide; IF: ifosfamide; 5FU: 5-fluorouracil; MTX: methotrexate; Gem: gemcitabine; Pt: cisplatin

262

263 Several studies (Connor et al. 2005; Favier et al. 2003; Fleury-Souverain et al. 2014; Gilbar et al. 2005;
264 Naito et al. 2012; Nygren et al. 2002) described surface contamination of marketed cytotoxic drug vials, with a
265 possibility of cross-contamination by cytotoxic drugs. No Food and Drug Administration (FDA) requirements
266 exist regarding cleanliness of bottle external surfaces. However, contamination may be reduced by using a
267 decontamination device (Touzain et al. 2008) and protective sleeves (Schierl et al. 2010) during manufacturing.
268 Furthermore, cytotoxic drug contamination of marketed vials could be evaluated and taken into account in the
269 hospital tender procedure.

270 A clear improvement in protection for workers handling cytotoxics has been made in recent years.
271 Where simple laminar flow hoods (Mason et al. 2005) were used in the past, today, they often have been
272 replaced by pressure isolators. In units where isolators are used, while contaminants were often found inside
273 isolators, only a few traces were found outside (Kopp et al. 2013; Crauste-Manciet et al. 2005). Isolators'
274 effectiveness mainly depends on operators' work practices, and contamination from the pass-through could be
275 reduced by surface decontamination. Several studies also demonstrated the efficacy of closed-system drug
276 transfer device (CSTDs) (Wick et al. 2003; Connor et al. 2002), which can reduce contamination by 95%
277 (Sessink et al. 2011). Robot assisted preparations were also developed to reduce residual contamination from
278 70% under classic preparation conditions to 15% with the Apoteca[®] chemo system (Schierl et al. 2016).
279 Similarly, the CytoCare[®] chemotherapy compounding robot allowed preparation of CP with low environmental
280 contamination levels and no measurable exposure of technicians (Sessink et al. 2015).

281 However, despite subsequent recommendations and solutions to environmental monitoring,
282 contamination cannot currently be totally eliminated and occupational exposures can occur. Adverse effects on
283 workers handling cytotoxic agents were described such as hair loss, rash (Valanis et al. 1993; Krstey et al. 2003)
284 and delayed effects on reproduction (Stücker et al. 1993; Valanis et al. 1999; Fransman et al. 2007). Some
285 antineoplastic drugs are genotoxic (Rombaldi et al. 2009; Cavallo et al. 2005) and are known to cause or
286 suspected of causing cancerous pathologies (Connor 2006; International Agency for Research on Cancer 2016).
287 Therefore, several environmental monitoring studies involved biological assessment of cytotoxic excretion in
288 healthcare-professionals (Turci et al. 2003; Pethran et al. 2003; Schreiber et al. 2003; Sottani et al. 2010).
289 Analysis of chromosomal effects on the DNA of workers exposed to cytotoxic drugs by fluorescent in situ

290 hybridization (FISH) was conducted, seeking the "signature" lesions found in patients with myelodysplastic
291 syndrome (MDS) or acute myeloid leukemia (AML) (McDiarmid et al. 2014). A dose-related increase
292 was detected, showing that significant biological exposure to genotoxic drugs occurs in oncology workplaces.

293 Environmental monitoring of cytotoxic drugs should follow two main principles. In order to analyze the
294 exposure of healthcare workers and the safety of the "preparation to administration" process, it is necessary to
295 realize a wide variety of sampling points, including surfaces and objects. On the other hand, to evaluate the
296 impact of monitoring on contamination level, the number of sampling points should be standardized.

297 Larger studies described contamination occurring in hospitals and/or in community pharmacies (Schierl
298 et al. 2006; Kiffmeyer et al. 2013), but environmental monitoring can also be performed in care areas (Connor et
299 al. 2010) or at every step of the cytotoxic drug circuit. For example, secondary exposure of family members to
300 cytotoxic drugs *via* excreta of the treated cancer patient was recently described for CP. Levels of 0.03-7.34
301 ng/cm² were found in patients' home, and cytotoxic drugs were also found in urine samples of family members
302 (Yuki et al. 2013; Yuki et al. 2015). Exposure to cytotoxic drugs outside the hospital environment could also
303 concern the pharmaceutical industry, universities, pharmacies, veterinary practices, laundry facilities and waste
304 treatment (Meijster et al. 2006). For example, patients' bed sheets appeared to be contaminated with detectable
305 levels of cytotoxics (0.13-30.6 ng/cm²) before the washing procedure in an industrial laundry facility (Fransman
306 et al. 2007).

307 Several studies demonstrated the value of regular environmental monitoring. The MEWIP Project
308 aimed to collect information about the mechanisms and the release/propagation pathways of cytotoxic
309 drugs (Kiffmeyer et al. 2013). To study the impact of monitoring, 130 pharmacies were randomized into two
310 groups. Environmental monitoring in group A was regular throughout the study period, but occurred only at the
311 beginning and at the end of the project in group B. Using a validated multicomponent technique (Tuerk et al.
312 2011), eight cytotoxics were quantified, a sample being considered positive if at least one of the drugs was
313 detected. Contamination levels were constantly decreasing in group A pharmacies, where, after the first report of
314 results, cleaning protocols, gloves, equipment modifications and more intensive training of cytotoxic drugs'
315 handlers were implemented. Thus, it appears that repeated monitoring has a greater effect on level of
316 contamination than a single campaign. Another multicenter study was performed after publication of a prevention
317 guide recommending annual monitoring and the development of an environmental monitoring
318 program (Bussièrès et al. 2012). Every hospital included had at least one sample with a positive result for at least

319 one cytotoxic (CP, IF or MTX). Once again, periodic monitoring of surface contamination was shown to ensure
320 updating of practices for better worker protection.

321 Current knowledge is too limited to set a no-health-effect level for cytotoxic drug exposure (Schierl et
322 al. 2009), and a zero level of exposure is not likely to be achievable in workplaces (Kiffmeyer et al.
323 2013). However, as analytical techniques evolve, LLQs decrease and the number of positive samples increases,
324 even though mean contamination levels have been reduced. In 2009 (Schierl et al. 2009) and 2013 (Kiffmeyer et al.
325 2013), two large studies established from more than 1,200 wipe samplings and more than 100 hospitals or
326 community pharmacies, a mean level of contamination by 5FU and other cytotoxic drugs. For 5FU, although the
327 number of positive samples varied from 31% (LLQ 5FU = 11 pg/cm²) to 74.4% (LLQ 5FU = 0.75 pg/cm²), the
328 75th and 90th percentile from these studies were similar (90th percentile = 0.117 and 0.251 ng/cm², 75th percentile
329 = 0.016 and 0.029 ng/cm²). The first study suggested technical guidance values based on the 50th (5.10⁻³ ng/cm²)
330 and the 75th percentile (0.03 ng/cm²) (Schierl et al. 2009). The second study recommended less strict technical
331 guidance values, based on the 90th percentile (0.1 ng/cm²). This guidance value is the same for all 8 cytotoxic
332 drugs tested in the study. This recommendation is based on two factors: the urgent need to improve the situation
333 in workplaces with high levels of contamination, and the possibility that the 75th percentile of most substances
334 will fall below the LLQ. Furthermore, this technical guidance value of 0.1 ng/cm², applied to CP, is tenfold
335 lower than the USP <797> value (a content higher than 1 ng/cm² of CP was found to cause human uptake). These
336 guidance values were established for pharmacies, as there are fewer studies conducted in hospital wards. From
337 our knowledge, only one large study (Hedmer et al. 2012) conducted in 17 workplaces from 6 hospitals allowed
338 the authors to determine guidance values for hospital wards for CP and IF. In this study, the authors emphasized
339 on the heterogeneity of contamination among the different categories of tested surfaces. The suggested guidance
340 values were established from the 90th percentile, for each sort of surface.

341 **Conclusion**

342
343 The reliability of detection techniques is constantly improving. Multi-compound analyses allow fast and
344 economical environmental monitoring. However, the constant decrease in detection limits inevitably leads to
345 an increase in positive samples. Without toxicological studies establishing a correlation between exposure values
346 and health impact on healthcare workers, “as low as reasonably achievable” levels remain the gold standard.

347 The studies reviewed here underline the need to keep striving to better protect workers, at the same
348 time revealing several working procedure problems. Environmental monitoring is a useful tool not only for local

349 contamination evaluation, but also to evaluate technologies involved in the cytotoxic drug circuit. Recommended
350 dosing techniques should be used routinely in every place where cytotoxic exposure is suspected. Good practice
351 recommendations need to include environmental monitoring from the industrial process to the patient's home,
352 with a special focus on hospital pharmacies and care areas. Real awareness has emerged in several countries
353 regarding the overall management of cytotoxics, but international or at least national recommendations for
354 environmental contamination monitoring are needed.

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