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**Evaluation of the environmental contamination and exposure risk in medical/non-medical staff after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy**

1

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4

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27

28 Trial registration: **NCT04014426**

29

30 **Abstract:**

31 Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a technique to directly deliver  
32 chemotherapeutic drugs in the abdomen for the treatment of peritoneal metastases.

33 Pressurization improves the treatment efficacy but increases the risk of exposure for the  
34 medical/non-medical staff who can be contaminated by dermal or ocular contact, or inhalation  
35 of aerosols containing the cytotoxic drugs. The aim of this study was to evaluate the risk of  
36 contamination for the medical/non-medical staff (nurses, surgeons, anaesthesiologists and  
37 cleaning personnel; n=13) during PIPAC with oxaliplatin or cisplatin-doxorubicin performed  
38 according to the protocol recommended in France. Blood samples were collected 1 hour before  
39 and immediately after PIPAC, and urine samples 1 hour before, and then 3 hours and the  
40 morning after PIPAC. In the control, non-exposed group (n=7), only one urine and blood  
41 sample were collected. Surface contamination in the operating room was assessed in water- and  
42 Surfianios-impregnated wipe samples. The total elemental platinum in each sample was  
43 quantified by inductively coupled plasma mass spectrometry, using a method adapted to  
44 quantify trace amounts ( $\text{ng.L}^{-1}$ ) in very low volumes (100 $\mu\text{l}$ ). No surface contamination was  
45 detected. Although 25% of urine samples in the exposed group contained platinum, no  
46 statistical difference was observed in urine and plasma samples collected before and after  
47 PIPAC and with the control group samples. These findings suggest that the French PIPAC  
48 protocol does not increase the risk of exposure to platinum in all staff categories involved. This  
49 protocol could be considered in future occupational policies and consensus statements.

50

51 **Keywords:** PIPAC, oxaliplatin, occupational safety, occupational hazard, personal protective  
52 equipment.

53

54

## 55 **Abbreviations**

56 EG: exposed group

57 NEG: non-exposed group

58 PIPAC: pressurized intraperitoneal aerosol chemotherapy

59 PIPAC-CD: pressurized intraperitoneal aerosol chemotherapy with cisplatin-doxorubicin

60 PIPAC-Ox: pressurized intraperitoneal aerosol chemotherapy with oxaliplatin

61 Pt: platinum

62

## 63 **1. Introduction:**

64

65 Life-threatening peritoneal metastases from various cancers respond poorly to intravenous  
66 drugs. Therefore, innovative loco-regional strategies and systemic chemotherapy are currently  
67 combined to improve the prognosis of these patients (Ceelen and Flessner, 2010). For instance,  
68 pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an intraperitoneal drug delivery  
69 method performed in the operating room during laparoscopy (Alyami et al., 2019). Oxaliplatin  
70 (PIPAC-Ox) and the cisplatin and doxorubicin combination (PIPAC-CD) are frequently used  
71 for PIPAC. PIPAC-Ox is mainly proposed to patients with peritoneal metastases of colorectal  
72 origin, but also for other indications (Di Giorgio et al., 2020; Sgarbura et al., 2019). During  
73 PIPAC, microdroplets of the chosen chemotherapeutic drug are delivered by constant flow after  
74 establishment of a stable pressure capnoperitoneum in the purpose of improving their intra-  
75 abdominal distribution and penetration in the peritoneal tissue (Solass et al., 2014). PIPAC

76 efficacy is based on the delivery of the chemotherapeutic drug(s) in the form of pressurized  
77 aerosols during 37 minutes, but this delivery could also increase the risk of exposure to such  
78 cytotoxic drugs and represents an occupational hazards for the involved medical/non-medical  
79 staff (CDC, n.d.). Specifically, inhalation is considered to be the main contamination route  
80 associated with PIPAC, whereas contamination via the dermal and oral routes should be less  
81 common. Therefore, in Germany, very rigorous safety protocols have been put in place with at  
82 least three containment levels (zero flow abdominal pressure, laminar airflow system in the  
83 operating room, and remote controlled administration of the drug) (Solaß et al., 2013). The  
84 French safety protocol also includes a plastic sheet around the patient and a toxic gas aspiration  
85 device under the sheet during the procedure (Cazauran et al., 2018) as the fourth level of  
86 containment. However, a French study suggested that the laminar air flow could be replaced by  
87 any advanced airflow system (Delhorme et al., 2019).

88       Some German groups have already evaluated the occupational exposure risk to platinum  
89 linked to PIPAC with platinum-based drugs (Ametsbichler et al., 2018; Solaß et al., 2013). They  
90 determined air and surface contamination by quantifying platinum concentration in air and wipe  
91 samples, respectively. Operating room air sampling revealed low platinum contamination levels  
92 ( $<9 \text{ pg/m}^3$ ), and surface contamination ranged from 0.01 to 1733  $\text{pg/cm}^2$ , depending on the area  
93 (higher contamination on the injector and trocars) (Ametsbichler et al., 2018). No platinum was  
94 detected in the operating room air at the places where the surgeon and anaesthesiologist work  
95 during PIPAC (Solaß et al., 2013). These data suggest a low exposure risk when PIPAC is  
96 performed following the safety protocol implemented in Germany. Few studies focused on the  
97 biological monitoring of the medical staff. In 2016, Graversen et al. showed the absence of  
98 contamination in two surgeons after two consecutive PIPAC procedures, by quantifying  
99 platinum in blood samples. However, these authors did not describe the method used for  
100 platinum quantification and the limits of detection. Ndaw et al. analysed platinum concentration

101 in urine samples of the medical staff collected at 24h post-PIPAC-CD and from a control group  
102 and did not find any significant difference between groups (Ndaw et al., 2018).

103 However, to our knowledge, no study measured the platinum concentration in both blood  
104 and urine samples. Moreover, despite this encouraging preliminary evidence and the rigorous  
105 safety protocol put in place for the medical (Alyami et al., 2020) and non-medical staff (Al  
106 Hosni et al., 2020), the use of PIPAC, and also of other types of intraperitoneal chemotherapy  
107 procedures, such as hyperthermic intraperitoneal chemotherapy, is still considered as an  
108 occupational hazard and requires continuous updating and education (Al Hosni et al., 2020;  
109 Clerc D et al., 2021).

110 The aim of this study was to evaluate the risk of exposure for the operating room  
111 medical/non-medical staff during PIPAC-Ox procedures by measuring and comparing platinum  
112 concentration in blood and urine samples collected from potentially exposed staff members and  
113 from healthy volunteers. Contamination of the operating room surfaces after PIPAC was also  
114 evaluated.

115

## 116 2. **Material and methods:**

117

### 118 2.1. *PIPAC procedure*

119 The PIPAC procedure is performed in a dedicated operating room with an advanced  
120 ventilation system and remote controlled administration according to the French safety protocol  
121 (Cazauran et al., 2018). The standardized surgical technique includes a two-port access with  
122 double-balloon trocars and aerosolization of the chemotherapeutic drug after evaluation of the  
123 metastatic disease, as described elsewhere (Hübner et al., 2017). In PIPAC-Ox, oxaliplatin  
124 ( $92\text{mg}\cdot\text{m}^{-2}$ ) is diluted in 5% glucose solution, and administered with a flow of  $0.6\text{ml}\cdot\text{sec}^{-1}$  and

125 upstream pressure limit of 290 psi (Dumont et al., 2020; Sgarbura et al., 2020). The total  
126 administration time is 37 minutes.

127

## 128 2.2. *Study participants*

129 The study was carried out at the Cancer Institute of Montpellier (ICM), France, in 2018. In  
130 our centre, more than 70 PIPAC procedures are performed annually since its introduction in  
131 2016 (Al Hosni et al., 2020). The operating room staff members who took part in two different  
132 PIPAC-Ox sessions two weeks apart were enrolled in the current study: session 1 (one senior  
133 surgeon, one assistant surgeon, one circulating nurse, one scrub nurse, one nurse anaesthetist,  
134 one anaesthesiologist, and the cleaner), and session 2 (one senior surgeon, one assistant  
135 surgeon, one circulating nurse, one scrub nurse, one nurse anaesthetist, one anaesthesiologist).  
136 With the exception of the anaesthesiologists and of the senior surgeon, all staff members  
137 involved in PIPAC delivery undergo a 2-week non-exposure period before and between PIPAC  
138 sessions. The participation was voluntary and the group was defined as “Exposed group” (EG).

139 Seven healthy volunteers formed the control “Non-Exposed group” (NEG) and were  
140 selected among the ICM researchers and administrative staff who had no identified contact with  
141 platinum-containing cytotoxic drugs.

142 All participants received oral and written information about the study and signed an  
143 informed consent. The study was carried out in accordance with the current version of the  
144 Declaration of Helsinki and approved by a national ethics committee (2017-A01921-52). The  
145 study was registered at ClinicalTrials.gov (NCT04014426).

146

## 147 2.3. *Analysis of biological samples*

148 In the EG group, blood samples were collected in heparinized tubes 1 hour before and  
149 immediately after the PIPAC intervention. Urine samples were collected 1 hour before (T0), 3

150 hours after (T1), and the morning (T2) after the PIPAC procedure. In the NEG group, only one  
151 sample of urine and one sample of plasma were collected. Plasma was separated from blood by  
152 centrifugation at 2000g for 5 minutes. All biological samples were stored at -80°C until  
153 analysis.

154 Several methods using mineralization or direct dilution in acidic or alkaline media were  
155 previously published for platinum quantification in biological samples (Abduljabbar et al.,  
156 2019; Chantada-Vázquez et al., 2019; Gong et al., 2017; Lu et al., 2015). Nevertheless, due to  
157 the very small concentrations ( $\text{ng.L}^{-1}$ ) and small sample volume, these methods could not be  
158 used directly. Therefore, the method was optimized using oxaliplatin-spiked samples. Briefly,  
159 mineralization was optimized in acidic (69%  $\text{HNO}_3/\text{H}_2\text{O}_2$ ) or alkaline (25% tetramethyl  
160 ammonium hydroxide, TMAH) solutions at different ratios, but important matrix effect and  
161 nebulization clogging was observed. A 5- or 10-fold dilution in nitric acid did not improve  
162 platinum recovery as protein precipitation leads to the loss of platinum. Finally, a direct 10-fold  
163 dilution in 0.1% TMAH/0.1% Triton X-100 was retained to minimize the matrix effect, with a  
164 >75% recovery.

165 Thus, a 100 $\mu\text{L}$  aliquot of each plasma and urine sample was 10-fold diluted in 0.1%  
166 TMAH/0.1% Triton X-100 (Sigma Aldrich, St Quentin Falavier, France). Tantalum  
167 (PlasmaCAL, SCP Science, Courtaboeuf, France) was added at a concentration of 1  $\text{ng.L}^{-1}$  as  
168 internal standard. After stirring, samples were centrifuged at 11000rpm, 4°C for 15 min, and  
169 analysed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Matrix-dependent  
170 calibration curves were obtained by spiking known concentrations of pure oxaliplatin in the  
171 control urine or plasma samples to study the matrix effect. Then, the limit of detection (LOD)  
172 and of quantification (LOQ) were estimated as 3 and 10 times, respectively, the standard  
173 deviation of the intercept divided by the calibration curve slope.

174



175 2.4. *Analysis of samples from contaminated surfaces and determination of the Limits of*  
176 *quantification (LOQ).*

177 2.4.1 *Standardization and LOQ determination:*

178 An oxaliplatin standard solution (platinum concentration ranging from 70 fg.cm<sup>-2</sup> to 250  
179 ng.cm<sup>-2</sup>), water, or the surface disinfectant Surfanios (blanks) were deposited onto 4 cm<sup>2</sup> glass  
180 surfaces and allowed to dry under moderate heating (50°C). After complete dryness, each  
181 surface was rubbed with a 2.25 cm<sup>2</sup> multi-layered wipe wetted with 150 µl of water or  
182 Surfanios. Wipes were then mineralized by addition of 400 µl pure nitric acid and 150 µl of  
183 hydrogen peroxide (Sigma Aldrich, St Louis Missouri, United States) at 75°C for 3 hours, and  
184 centrifuged at 15000 g for 15min. Platinum in the supernatant was then quantified by ICP-MS  
185 after addition of 1µg.L<sup>-1</sup> indium as internal standard (SCP Science, Courtaboeuf, France). The  
186 LOQ after recovery was determined as the lowest concentration that can be measured with an  
187 accuracy within 30% of the nominal value deposited onto the test surface.

188 2.4.2 *Operating room surface contamination:*

189 Six potentially contaminated surfaces were identified on the basis of previous publications  
190 and the operating room staff's experience: anaesthesia monitoring screen, surgical lamp,  
191 laparoscopy tower, surgical gas aspirator, surgical gas aspiration filter, and laparoscopic  
192 monitor (Fig. 1). To evaluate their contamination, surfaces (area=9 cm<sup>2</sup>) were rubbed twice  
193 with water- or Surfanios-impregnated multi-layered wipes in both directions by the same  
194 experienced person who collected the wipe samples also for the standardization experiment.  
195 Wipes were handled as described in 2.4.1 and platinum quantified by ICP-MS.

196

197 2.5. *Analytical quantification*

198 Diluted serum and urine samples were analysed using an Agilent 7700x quadrupole ICP-  
199 MS (Agilent Technologies, Tokyo, Japan) equipped with a Scott spray chamber (cooled at 2°C),

200 a MicroMist nebulizer ( $400\mu\text{L}\cdot\text{min}^{-1}$ ), X-Lenses and nickel cones. Plasma power was set to  
201 1550W. Platinum determination was performed by quantifying three major isotopes ( $^{194}\text{Pt}$ ,  
202  $^{195}\text{Pt}$ ,  $^{196}\text{Pt}$ ) with an integration time of 999msec per isotope. Quantification was performed by  
203 internal calibration with tantalum-181 (integration time 100ms).

204 After acid digestion, wipes were analysed by high resolution ICP-MS using an Element XR  
205 (ThermoScientific, Bremen, Germany) equipped with a Scott spray chamber (cooled at  $2^{\circ}\text{C}$ ), a  
206 MicroMist nebulizer ( $200\mu\text{L}\cdot\text{min}^{-1}$ ) and nickel cones. To improve sensitivity, the instrument  
207 operating conditions were plasma power of 1200W and low resolution ( $m/\Delta m$  400). Internal  
208 calibration was performed for platinum quantification using indium as internal standard.  $^{194}\text{Pt}$ ,  
209  $^{195}\text{Pt}$  and  $^{115}\text{In}$  were monitored (50 sample/peak, mass window 20%, sample time 5 sec for  $^{194}\text{Pt}$   
210 and  $^{195}\text{Pt}$  and 10 msec for  $^{115}\text{In}$ ). Platinum concentrations were determined using the  $^{194}\text{Pt}$  and  
211  $^{195}\text{Pt}$  values, but only the  $^{195}\text{Pt}$  concentration was reported, if not otherwise mentioned. All  
212 standard solutions were from SCP Science (Courtaboeuf, France).

213

## 214 *2.6. Statistical analysis*

215 The descriptive analysis was performed using median and range for continuous parameters,  
216 frequency and percentage for categorical variables. The comparative analysis was based on  
217 non-parametric tests (Mann Whitney, Wilcoxon) and was performed with STATA 16 (Stata  
218 Corporation, College Station, Tx, USA). A p-value  $<0.05$  was considered significant.

219

## 220 **3. Results**

221

### 222 *3.1. Platinum concentration in biological samples*

223 The instrument LOD and LOQ of platinum were estimated at 0.3 ng.L<sup>-1</sup> and 0.9 ng.L<sup>-1</sup>  
224 respectively. This corresponded to 5 and 16 ng.L<sup>-1</sup>, respectively, in plasma, and to 3 and 9 ng.L<sup>-1</sup>  
225 <sup>1</sup>, respectively, in urine, by taking into account the matrix effect and dilution factor.

226 In the EG, 37 urine samples were collected from 13 medical/non-medical staff members  
227 implicated in the two PIPAC procedures (Table 1). Before PIPAC (T0), platinum concentration  
228 was below the LOQ in 9/13 urine samples (69%), and could not be detected (<LOD) in 7/13  
229 samples (54%). Only 4/13 samples (31%) contained platinum (from 9.8 to 42 ng.L<sup>-1</sup>). After  
230 PIPAC, platinum concentration in urine samples was below the LOQ in 18/24 samples (75%)  
231 (18/24) and remained undetectable in 10/24 samples (42%). Platinum could be quantified in  
232 6/24 urine samples (25%) and the concentration ranged from 12.5 to 367 ng.L<sup>-1</sup>. The two  
233 anaesthesiologists' and the senior surgeon's urine samples at T0 were positive (4 and 11). One  
234 surgeon, one assistant surgeon, one circulating nurse and one scrub nurse had positive urine  
235 samples at T2. In all plasma samples, platinum concentration was below the LOQ (7/25; 28%)  
236 or the LOD (18/25; 72%) before and also after PIPAC.

237 There was no statistical difference in platinum concentration in urine and plasma samples  
238 collected before and after PIPAC (p=0.2).

239 In the NEG (n=7), all plasma samples were below the LOQ, and platinum could not be  
240 detected (<LOD) in 6/7 samples (86%). Conversely, in two urine samples, platinum  
241 concentration was slightly above the LOQ and in two slightly below the LOD. There **was** no  
242 statistical difference in the platinum concentrations in the EG and NEG urine and plasma  
243 samples (p=0.2).

244

### 245 **3.2. Surface contamination**

246 Water- and Surfanios-impregnated wipes with known concentrations of oxaliplatin (from  
247 70 fg.cm<sup>-2</sup> to 250 ng.cm<sup>-2</sup>) were used to determine the platinum recovery yield that was higher

248 with water-impregnated wipes (Fig. 2). The LOQ with water-impregnated wipes was 2.5 pg.cm<sup>-2</sup>.  
249 <sup>2</sup>.

250 Platinum concentration was below this LOQ in all wipe samples from the six tested  
251 surfaces.

252

#### 253 **4. Discussion:**

254 The current study shows that exposure to oxaliplatin during PIPAC-Ox performed  
255 following the current French safety protocol is non-existent for all the involved medical/non-  
256 medical staff members. This is the first study to extensively investigate PIPAC-Ox occupational  
257 exposure risk by analysing both environmental and biological samples.

258 PIPAC-Ox was initially used for colorectal cancer peritoneal metastases (Demtröder et  
259 al., 2016), and was then enlarged to other types of gastrointestinal cancers (Di Giorgio et al.,  
260 2020; Sgarbura et al., 2019). Although there is no report on the exact number of healthcare  
261 centres performing PIPAC-Ox worldwide, the recently published PIPAC survey identified 62  
262 centres that carried out at least 5972 procedures in 20 countries, and 74% of all respondents  
263 confirmed the use of oxaliplatin (Sgarbura et al., 2020). However, **studies** on PIPAC-Ox-linked  
264 surface and biological contamination are scarce (Graversen et al., 2016) and based on limited  
265 data. The findings of the current study confirm that PIPAC-Ox use in the operating room  
266 following specific protection regulations (i.e. the French safety protocol) does not increase the  
267 risk of exposure to platinum compared with controls. Moreover, platinum concentration in all  
268 environmental samples was below the LOQ, although previous studies identified the injector  
269 surface as a safety hazard (Ametsbichler et al., 2018; Ndaw et al., 2018).

270 The results of the present study are based on the analysis of two different biological  
271 samples (urine and blood) and environmental samples. Moreover, before the analysis of  
272 environmental samples, the recovery yield was evaluated by ICP-MS quantification of the

273 platinum concentration in water- or Surfanios-impregnated wipes that were used to clean  
274 surfaces with a known oxaliplatin concentration. In previous studies, only the extraction  
275 (mineralization, liquid extraction) and/or quantification methods were evaluated (Ndaw et al.,  
276 2018). A better sensitivity was obtained with water-impregnated wipes. Platinum  
277 concentrations of the operating room samples after PIPAC were all below the LOQ. As we  
278 assumed a recover yield above 70% from the surface to the test tube, we considered that the  
279 operating room was not contaminated after the PIPAC procedure.

280 Human exposure to platins in intraperitoneal drug delivery is usually carried out through  
281 blood and/or urine samples based on the known pharmacokinetic properties of oxaliplatin  
282 (Graham et al, 2000; Ceelen and Flessner, 2010; Villa et al, 2015; Ndaw et al, 2018). Our  
283 analytical method gave LOD and LOQ for urine and blood samples that are within the  
284 previously published ranges. Urinary platinum concentration is commonly used to evaluate  
285 contamination by platinum salts because platinum is rapidly cleared from the plasma, and  
286 urinary excretion is considered the predominant route of elimination (Graham et al., 2000). As  
287 previous studies used 24h urine samples (Konate et al., 2011) or pre-shift and post-shift urine  
288 samples (Ndaw et al., 2018), we cannot directly compare our results (1 hour before, 3 hours  
289 after, and the morning after the PIPAC procedure). We chose this sampling schedule on the  
290 basis of pharmacokinetic data obtained after intravenous injection of oxaliplatin that showed a  
291 concentration decreases by 50% at 6h post-injection (Graham et al., 2000). After PIPAC, 25%  
292 of urine samples in the EG were positive. However, the urine samples of the anaesthesiologists  
293 and of the senior surgeon were positive already at T0. These staff members did not have a 2-  
294 week non-exposure period before and between PIPAC procedures. That is not the case for the  
295 scrub nurse of the second procedure where urine sample was also positive at T0 without any  
296 identified exposure. The other positive samples at T2 were from the surgeon, assistant surgeon,  
297 circulating nurse, and scrub nurse implicated in the second PIPAC session. However, these

298 results (platinum ranging from 10.5 to 367 ng.L<sup>-1</sup>) are in the same range but cannot be directly  
299 compared with the maximum concentration of 136 ng.L<sup>-1</sup> detected in 24h urine collected after  
300 PIPAC (Ndaw et al., 2018), or the 1300 ng.L<sup>-1</sup> in post-shift urine samples from nurses or  
301 pharmacy technicians (Turci et al., 2002). Furthermore, no statistical difference was observed  
302 for urine samples collected before and after PIPAC and between EG and NEG samples, strongly  
303 suggesting that the level of contamination in urine is not significant.

304 As oxaliplatin binds to plasma proteins (Casini and Reedijk, 2012; Chalret du Rieu et  
305 al., 2014; Turci et al., 2002), we analysed also blood samples collected before and after PIPAC.  
306 Several methods using mineralization or direct dilution in acidic or alkaline media were  
307 previously described (Abduljabbar et al., 2019; Chantada-Vázquez et al., 2019; Gong et al.,  
308 2017; Lu et al., 2015). Nevertheless, due to the very small concentrations of platinum (ng.L<sup>-1</sup>)  
309 and the small sample volume, these methods could not be used directly. Therefore, we  
310 optimized them using oxaliplatin-spiked samples and we chose a direct 10-fold dilution in 0.1%  
311 TMAH/0.1% Triton X100 to minimize the matrix effect compared with mineralization in HNO<sub>3</sub>  
312 or TMAH alone. Indeed, the combination of TMAH, which improves protein solubilization by  
313 cutting protein disulphide bridges, and Triton X-100, which improves cell lysing, protein and  
314 fat solubilization, allowed us to efficiently recover platinum from plasma and urine. For all  
315 plasma samples, the platinum concentration never exceeded the LOQ, without any significant  
316 difference between pre- and pots-PIPAC values and with the NEG. These results indicate the  
317 effectiveness of the implemented PIPAC safety protocol.

318 It would be now important to review all the available evidence concerning PIPAC safety  
319 for the involved medical/non-medical staff to define international guidelines. These  
320 recommendations could then be considered as the expert opinion to be taken into account by  
321 regulatory bodies to define a homogenous safety protocol for PIPAC procedures worldwide.

322 The limitations of the study include the low number of tested PIPAC procedures (n=2)  
323 and the fact that the included staff members have been repeatedly exposed to oxaliplatin.  
324 Moreover, the number of samples collected from each participant was limited in time (before,  
325 after and the morning after PIPAC). The current findings cannot be extended to ePIPAC that  
326 has administration times shorter than 30 minutes (Taibi et al., 2020) because in this case the  
327 operating room staff return in the room earlier after the remote administration, and this might  
328 modify the risk of exposure.

329 In conclusion, PIPAC-Ox performed following the French safety protocol does not seem  
330 to increase the risk of platinum exposure for the involved medical/non-medical staff. Therefore,  
331 this safety protocol could be considered in future occupational policies and consensus  
332 statements.

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#### 341 **References**

- 342 Abduljabbar, T.N., Sharp, B.L., Reid, H.J., Barzegar-Befroeid, N., Peto, T., Lengyel, I., 2019.  
343 Determination of Zn, Cu and Fe in human patients' serum using micro-sampling ICP-  
344 MS and sample dilution. *Talanta* 204, 663–669.  
345 <https://doi.org/10.1016/j.talanta.2019.05.098>  
346 Al Hosni, M., Rouget, C., Cusumano, C., GarciaLozcano, E., Popescu, H., Carrere, S.,  
347 Quénet, F., Sgarbura, O., 2020. Non-medical caregivers and the use of intraperitoneal  
348 chemotherapy in the operating theatre: A survey on the perception of safety. *Journal of*  
349 *Visceral Surgery*. <https://doi.org/10.1016/j.jvisc Surg.2020.02.005>

350 Alyami, M., Hübner, M., Grass, F., Bakrin, N., Villeneuve, L., Laplace, N., Passot, G.,  
351 Glehen, O., Kepenekian, V., 2019. Pressurised intraperitoneal aerosol chemotherapy:  
352 rationale, evidence, and potential indications. *The Lancet Oncology* 20, e368–e377.  
353 [https://doi.org/10.1016/S1470-2045\(19\)30318-3](https://doi.org/10.1016/S1470-2045(19)30318-3)

354 Alyami, M., Sgarbura, O., Khomyakov, V., Horvath, P., Vizzielli, G., So, J., Torrent, J.,  
355 Delgadillo, X., Martin, D., Ceelen, W., Reymond, M., Pocard, M., Hübner, M., 2020.  
356 Standardizing training for Pressurized Intraperitoneal Aerosol Chemotherapy.  
357 *European Journal of Surgical Oncology*. <https://doi.org/10.1016/j.ejso.2020.05.007>

358 Ametsbichler, P., Böhländt, A., Nowak, D., Schierl, R., 2018. Occupational exposure to  
359 cisplatin/oxaliplatin during Pressurized Intraperitoneal Aerosol Chemotherapy  
360 (PIPAC)? *European Journal of Surgical Oncology* 44, 1793–1799.  
361 <https://doi.org/10.1016/j.ejso.2018.05.020>

362 Casini, A., Reedijk, J., 2012. Interactions of anticancer Pt compounds with proteins: an  
363 overlooked topic in medicinal inorganic chemistry? *Chemical Science* 3, 3135.  
364 <https://doi.org/10.1039/c2sc20627g>

365 Cazauran, J.-B., Alyami, M., Lasseur, A., Gybels, I., Glehen, O., Bakrin, N., 2018.  
366 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Procedure for Non-  
367 resectable Peritoneal Carcinomatosis (with Video). *Journal of Gastrointestinal Surgery*  
368 22, 374–375. <https://doi.org/10.1007/s11605-017-3565-0>

369 CDC, n.d. NIOSH [WWW Document]. URL <https://www.cdc.gov/niosh/>

370 Ceelen, W.P., Flessner, M.F., 2010. Intraperitoneal therapy for peritoneal tumors: biophysics  
371 and clinical evidence. *Nature Reviews Clinical Oncology* 7, 108–115.  
372 <https://doi.org/10.1038/nrclinonc.2009.217>

373 Chalret du Rieu, Q., White-Koning, M., Picaud, L., Lochon, I., Marsili, S., Gladiëff, L.,  
374 Chatelut, E., Ferron, G., 2014. Population pharmacokinetics of peritoneal, plasma  
375 ultrafiltrated and protein-bound oxaliplatin concentrations in patients with  
376 disseminated peritoneal cancer after intraperitoneal hyperthermic chemoperfusion of  
377 oxaliplatin following cytoreductive surgery: *Cancer Chemotherapy and Pharmacology*  
378 74, 571–582. <https://doi.org/10.1007/s00280-014-2525-6>

379 Chantada-Vázquez, M.P., Herbello-Hermelo, P., Bermejo-Barrera, P., Moreda-Piñeiro, A.,  
380 2019. Discrete sampling based-flow injection as an introduction system in ICP-MS for  
381 the direct analysis of low volume human serum samples. *Talanta*.  
382 <https://doi.org/10.1016/j.talanta.2019.02.050>

383 Clerc, D., Hübner, M., Ashwin, K.R., Somashekhar, S.P., Rau, B., Ceelen, W., Willaert, W.,  
384 Bakrin, N., Laplace, N., Al Hosni, M., Garcia Lozano, E.L., Blaj, S., Piso, P., Di Giorgio,  
385 A., Vizzelli, G., Brigand, C., Delhorme, J.B., Klipfel, A., Archid, R., Nadiradze, G.,  
386 Reymond, M.A., Sgarbura, O. Current practice and perceptions of safety protocols for  
387 the use of intraperitoneal chemotherapy in the operating room: results of the IP-OR  
388 international survey. *Pleura and Peritoneum*. vol. 6, no. 1, 2021, pp. 39-45.  
389 <https://doi.org/10.1515/pp-2020-0148>

390 Delhorme, J.B., Klipfel, A., D'Antonio, F., Greget, M.C., Diemunsch, P., Rohr, S., Romain,  
391 B., Brigand, C., 2019. Occupational safety of pressurized intraperitoneal aerosol  
392 chemotherapy (PIPAC) in an operating room without laminar airflow. *Journal of*  
393 *Visceral Surgery*. <https://doi.org/10.1016/j.jvisc Surg.2019.06.010>

394 Demtröder, C., Solass, W., Zieren, J., Strumberg, D., Giger-Pabst, U., Reymond, M.A., 2016.  
395 Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal  
396 peritoneal metastasis. *ColorectalDisease*. <https://doi.org/10.1111/codi.13130>

397 Di Giorgio, A., Sgarbura, O., Rotolo, S., Schena, C.A., Bagalà, C., Inzani, F., Russo, A.,  
398 Chiantera, V., Pacelli, F., 2020. Pressurized intraperitoneal aerosol chemotherapy with  
399 cisplatin and doxorubicin or oxaliplatin for peritoneal metastasis from pancreatic



400 adenocarcinoma and cholangiocarcinoma. *Therapeutic Advances in Medical*  
401 *Oncology*. <https://doi.org/10.1177/1758835920940887>

402 Dumont, F., Passot, C., Raoul, J.-L., Kepenekian, V., Lelièvre, B., Boisdron-Celle, M., Hiret,  
403 S., Senellart, H., Pein, F., Blanc-Lapierre, A., Raimbourg, J., Thibaudeau, E., Glehen,  
404 O., 2020. A phase I dose-escalation study of oxaliplatin delivered via a laparoscopic  
405 approach using pressurised intraperitoneal aerosol chemotherapy for advanced  
406 peritoneal metastases of gastrointestinal tract cancers. *European Journal of Cancer*  
407 140, 37–44. <https://doi.org/10.1016/j.ejca.2020.09.010>

408 Gong, Z.S., Jiang, X.H., Sun, C.Q., Tian, Y.P., Guo, G.H., Zhang, Y.Z., Zhao, X.H., Wang,  
409 Y., 2017. Determination of 21 elements in human serum using ICP-MS with  
410 collision/reaction cell. *International Journal of Mass Spectrometry*.  
411 <https://doi.org/10.1016/j.ijms.2017.10.001>

412 Graham, M.A., Lockwood, G.F., Greenslade, D., Brienza, S., Bayssas, M., Gamelin, E., 2000.  
413 Clinical pharmacokinetics of oxaliplatin: A critical review. *Clinical Cancer Research*.  
414 Graversen, M., Pedersen, P.B., Mortensen, M.B., 2016. Environmental safety during the  
415 administration of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). *Pleura*  
416 *and Peritoneum* 1. <https://doi.org/10.1515/pp-2016-0019>

417 Hübner, M., Grass, F., Teixeira-Farinha, H., Pache, B., Mathevet, P., Demartines, N., 2017.  
418 Pressurized IntraPeritoneal Aerosol Chemotherapy – Practical aspects. *European*  
419 *Journal of Surgical Oncology (EJSO)* 43, 1102–1109.  
420 <https://doi.org/10.1016/j.ejso.2017.03.019>

421 Konate, A., Poupon, J., Villa, A., Garnier, R., Hasni-Pichard, H., Mezzaroba, D., Fernandez,  
422 G., Pocard, M., 2011. Evaluation of environmental contamination by platinum and  
423 exposure risks for healthcare workers during a heated intraperitoneal perioperative  
424 chemotherapy (HIPEC) procedure. *Journal of Surgical Oncology* 103, 6–9.  
425 <https://doi.org/10.1002/jso.21740>

426 Lu, Y., Kippler, M., Harari, F., Grandér, M., Palm, B., Nordqvist, H., Vahter, M., 2015.  
427 Alkali dilution of blood samples for high throughput ICP-MS analysis—comparison  
428 with acid digestion. *Clinical Biochemistry* 48, 140–147.  
429 <https://doi.org/10.1016/j.clinbiochem.2014.12.003>

430 Ndaw, S., Hanser, O., Kenepkian, V., Vidal, M., Melczer, M., Remy, A., Robert, A., Bakrin,  
431 N., 2018. Occupational exposure to platinum drugs during intraperitoneal  
432 chemotherapy. *Biomonitoring and surface contamination*. *Toxicology Letters* 298,  
433 171–176. <https://doi.org/10.1016/j.toxlet.2018.05.031>

434 Sgarbura, O., Hubner, M., Alyami, M., Eveno, C., Gagnière, J., Pache, B., Pocard, M.,  
435 Glehen, O., Quénet, F., 2019. Oxaliplatin use in pressurized intraperitoneal aerosole  
436 chemotherapy(PIPAC) is safe and well tolerated: a multicenter study. *European*  
437 *Journal of Surgical Oncology* 45, e60. <https://doi.org/10.1016/j.ejso.2018.10.226>

438 Sgarbura, O., Villeneuve, L., Alyami, M., Bakrin, N., Torrent, J.J., Eveno, C., Hübner, M.,  
439 PIPAC study group, I., Ceelen, W., 2020. Current practice of pressurized  
440 intraperitoneal aerosol chemotherapy (PIPAC) : still standardized or on the verge of  
441 diversification? *EUROPEAN JOURNAL OF SURGICAL ONCOLOGY*.  
442 <https://doi.org/10.1016/j.ejso.2020.08.020>

443 Solaß, W., Giger-Pabst, U., Zieren, J., Reymond, M.A., 2013. Pressurized IntraPeritoneal  
444 Aerosol Chemotherapy (PIPAC): Occupational Health and Safety Aspects. *Ann Surg*  
445 *Oncol* 20, 3504–3511. <https://doi.org/10.1245/s10434-013-3039-x>

446 Solass, W., Kerb, R., Mürdter, T., Giger-Pabst, U., Strumberg, D., Tempfer, C., Zieren, J.,  
447 Schwab, M., Reymond, M.A., 2014. Intraperitoneal Chemotherapy of Peritoneal  
448 Carcinomatosis Using Pressurized Aerosol as an Alternative to Liquid Solution: First

449 Evidence for Efficacy. *Annals of Surgical Oncology* 21, 553–559.  
450 <https://doi.org/10.1245/s10434-013-3213-1>  
451 Taibi, A., Teixeira Farinha, H., Durand Fontanier, S., Sayedalamin, Z., Hübner, M., Sgarbura,  
452 O., 2020. Pressurized Intraperitoneal Aerosol Chemotherapy Enhanced by  
453 Electrostatic Precipitation (ePIPAC) for Patients with Peritoneal Metastases. *Ann*  
454 *SurgOncol.* <https://doi.org/10.1245/s10434-020-09332-6>  
455 Turci, R., Sottani, C., Ronchi, A., Minoia, C., 2002. Biological monitoring of hospital  
456 personnel occupationally exposed to antineoplastic agents. *ToxicolLett* 134, 57–64.  
457 [https://doi.org/10.1016/s0378-4274\(02\)00163-7](https://doi.org/10.1016/s0378-4274(02)00163-7)  
458 Villa, A.F., El Balkhi, S., Aboura, R., Sageot, H., Hasni-Pichard, H., Pocard, M., Elias, D.,  
459 Joly, N., Payen, D., Blot, F., Poupon, J., Garnier, R. Evaluation of oxaliplatin exposure  
460 of healthcare workers during heated intraperitoneal perioperative chemotherapy  
461 (HIPEC). *nd Health.* 2015;53(1):28-37. doi: 10.2486/indhealth.2014-0025.  
462

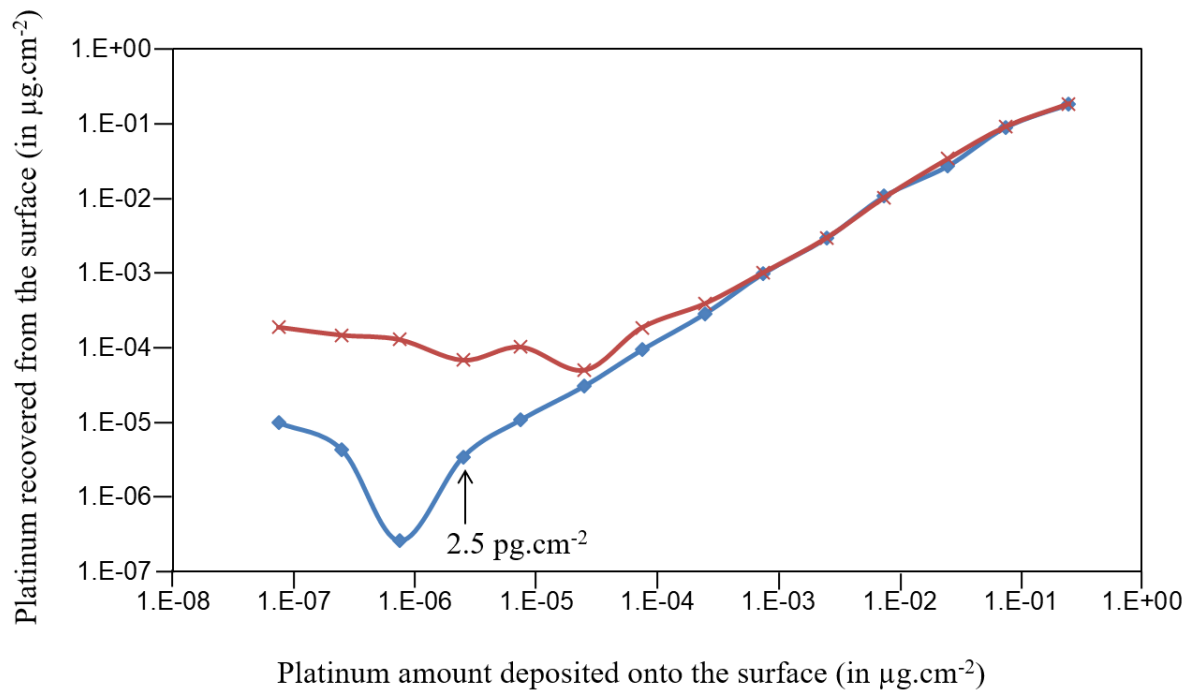
463 Larroque et al Figure 1  
464



465

466

467 **Figure 1:** Sampling areas in the operating room: monitoring screen (1), surgical lamp (2),  
468 laparoscopy tower (3), surgical-gas aspirating device console (4), surgical gas aspiration filter  
469 (5), and laparoscopic monitor (6).  
470



473  
474 **Figure 2:** Determination of the platinum recovered from water- (■) or Surfanios- (x)  
475 impregnated wipes used to wipe test surfaces contaminated with known platinum  
476 concentrations ranging from 100 fg.cm<sup>-2</sup> to 1 µg.cm<sup>-2</sup>.

	Participant	Pt concentration in urine (ng.L <sup>-1</sup> )			Pt Concentration in plasma (ng.L <sup>-1</sup> )	
		T0	T1	T2	T0	T1
<b>Exposed group</b>	1	< LOD	< LOQ	< LOQ	< LOD	< LOQ
	2	< LOQ	< LOQ	< LOQ	< LOD	< LOD
	3	< LOD	< LOD	< LOD	< LOQ	< LOD
	4	10	< LOQ	< LOD	< LOD	< LOD
	5	< LOD	< LOQ	< LOD	< LOD	< LOD
	6	< LOD	< LOD	< LOD	< LOD	< LOD
	7	< LOQ	< LOD		< LOQ	
	8	< LOD	< LOQ	367	< LOD	< LOD
	9	42	< LOD	113	< LOD	< LOD
	10	< LOD	< LOD	13.9	< LOD	< LOQ
	11	< LOD	12.5	< LOD	< LOD	< LOQ
	12	13.8	19.2	< LOQ	< LOD	< LOQ
	13	9.8		49.6	< LOD	< LOQ
<b>Non exposed group</b>	14	< LOQ			< LOD	
	15	< LOD			< LOD	
	16	< LOQ			< LOD	
	17	< LOD			< LOQ	
	18	< LOQ			< LOD	
	19	9.7			< LOD	
	20	11			< LOD	

482  
 483 **Table 1.** Elemental platinum concentration (ng.L<sup>-1</sup>) in plasma and in urine of participants  
 484 from the exposed and non-exposed groups. LOD (urine)= 3 ng.L<sup>-1</sup> ; LOQ (urine) = 9 ng.L<sup>-1</sup> ;  
 485 LOD (plasma)= 5 ng.L<sup>-1</sup> ; LOQ (plasma)= 16 ng.L<sup>-1</sup>. In the Exposed group: participants 1 to 7  
 486 were involved in the first PIPAC session, and participants 8 to 13 in the second, as follows: 1  
 487 (senior surgeon), 2 (assistant surgeon), 3 (circulating nurse), 4 (anaesthesiologist), 5 (nurse  
 488 anaesthetist), 6 (scrub nurse), 7 (cleaner), 8 (assistant surgeon), 9 (senior surgeon), 10  
 489 (circulating nurse), 11 (nurse anaesthetist), 12 (anaesthesiologist), and 13 (scrub nurse).  
 490  
 491