



PIPAC ESSENTIALS

Occupational Health and Safety Aspects of PIPAC

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Disclosures

- I have no relevant disclosures.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

The off-label or investigational use of Cisplatin, Doxorubicin, Oxaliplatin will be discussed.

Occupational Health Safety: Background



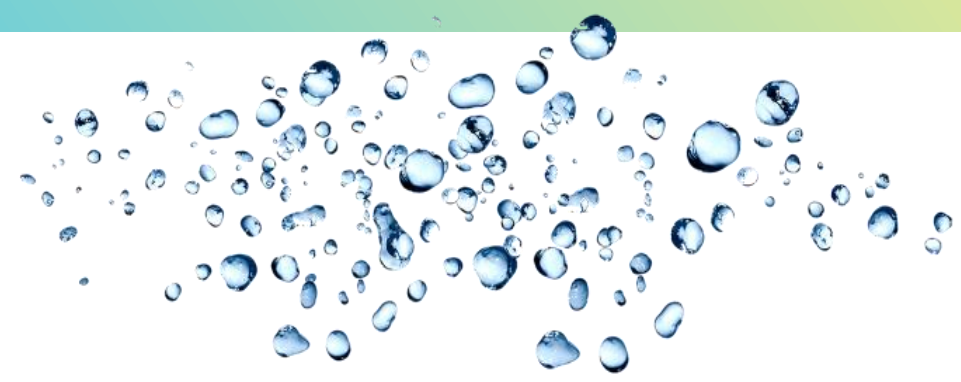
Preventing exposure to chemotherapeutic drugs is an important occupational health issue in pharmacy and oncology

Delivering chemotherapy as an aerosol could pose an increased risk of exposure to healthcare workers

It is the responsibility of the employer to reduce occupational health risk to a minimum

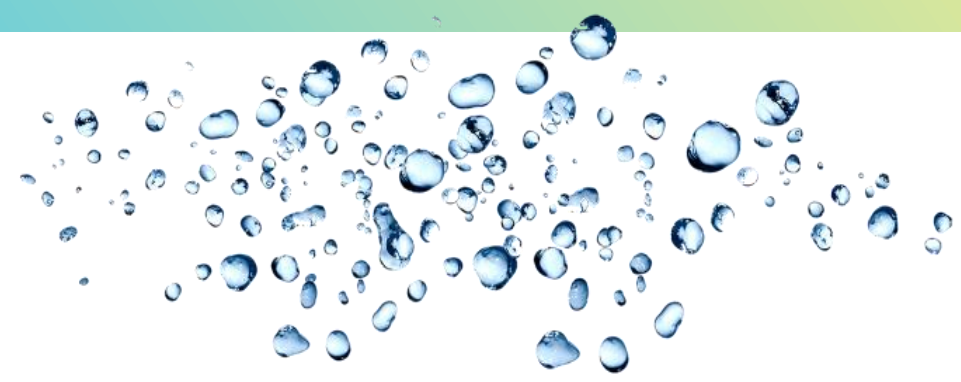


Risk Management Program



1. Risk analysis
 - Substances and amount
 - Identification of potential hazards and possible contamination pathways
2. Design of simulations in the operating room
3. Develop a safety protocol
4. Multi-disciplinary Team training
 - Surgical or gyn oncologists, OR staff, anesthesiologists, and pharmacists
5. Workplace measurements (environmental) under real conditions
6. Mathematical simulations (worst case scenario)
7. Safety monitoring (Critical Incident Reporting System)
 - Feed-back to the manufacturer
8. Biological assessment after 500 & 1500 PIPACs

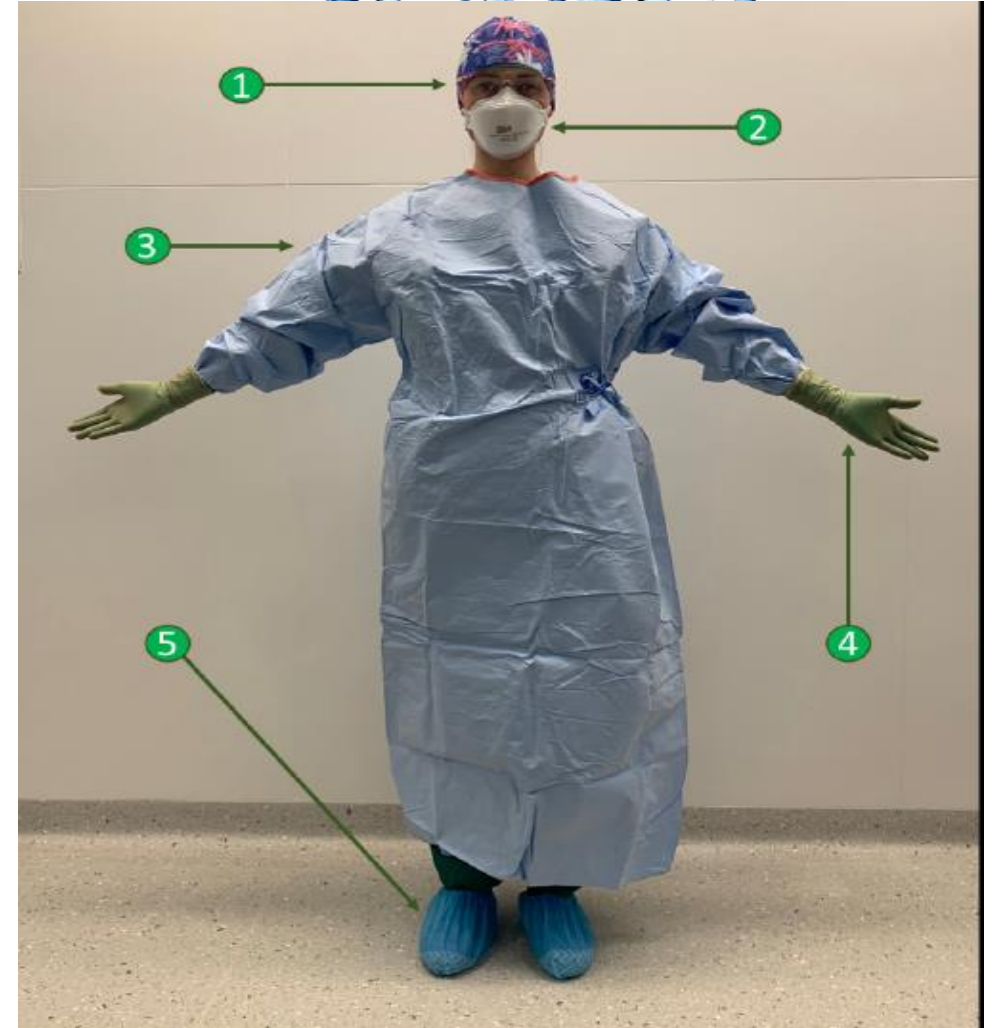
Safety Concept: Risk Analysis



- Drugs
 - cisplatin, doxorubicin, oxaliplatin, nab-Paclitaxel, Mitomycin C, nanoparticles
- Amount
 - one order of magnitude lower than a HIPEC dose
 - 5 – 20 % of the dose
- Contamination pathways
 - liquid: eyes, skin
 - aerosol: inhalation

Recommended PPE During PIPAC Procedure

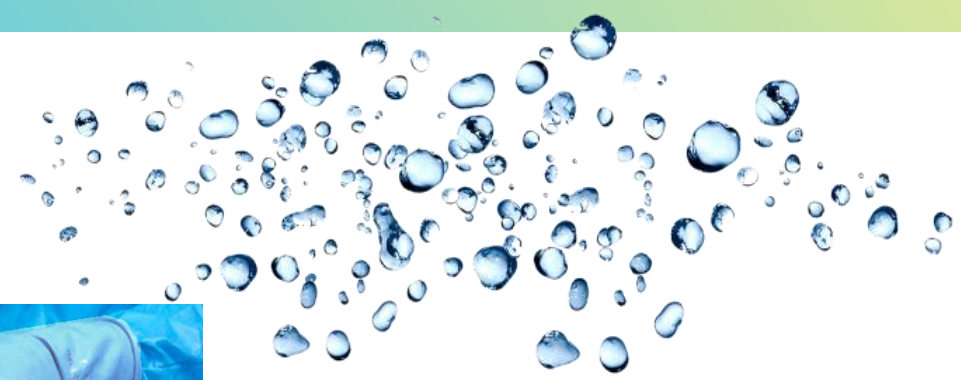
- (1) Eye protection (plastic goggles or face shields)
- (2) FFP mask class 3 or N95 masks
- (3) Reinforced surgical gown
 - AAMI level 4 sterile gowns (Association for the Advancement of Medical Instrumentation)
 - nonoperative personnel may use either the same gowns or chemotherapy-rated (USP-800-compliant) gowns with double nitrile gloves
- (4) Double gloving with an inner pair resistant to chemotherapy
- (5) Plastic overshoes



Safety Concept:

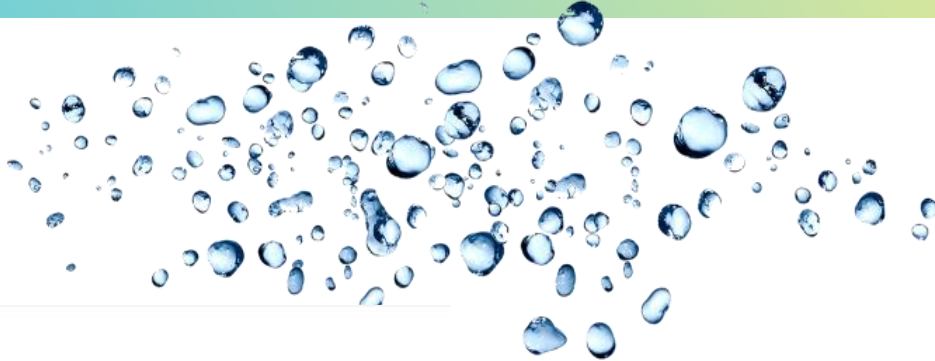
Protection Against Liquids

- Cutaneous exposure
 - Transdermal exposure is the main risk
 - Protective clothes
 - Chemotherapy double pairs gloves (néoprène, latex, nitrile)
- Ocular injury
 - Protective glasses



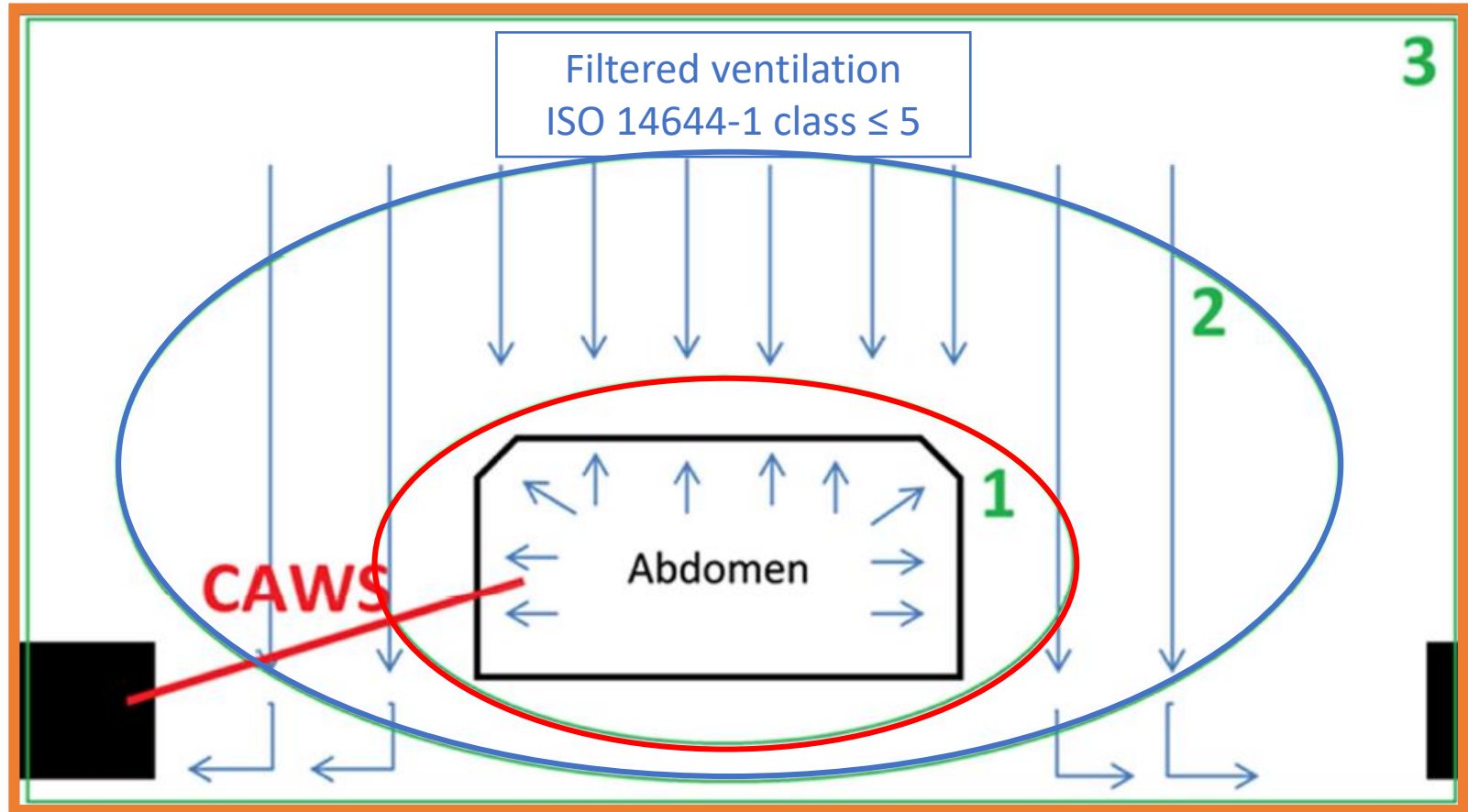
-Ref : <http://www.gerpac.eu/risque-d-exposition-chimique-et-permeabilite-des-gants>

Safety Concept: Inhalation Protection



Triple protection system

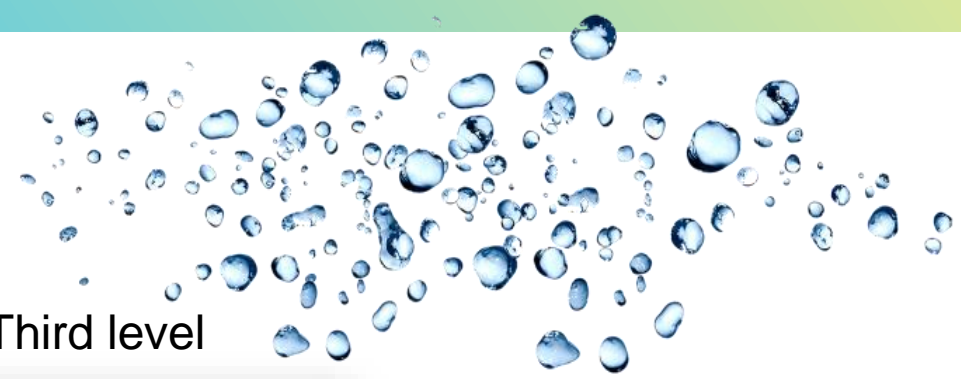
Operating room



Remote chemo initiation
All Staff outside the OR

CAWS = Closed Aerosol Waste System

PIPAC: Inhalative Risk: Triple Protection System



First level



Second level



Third level



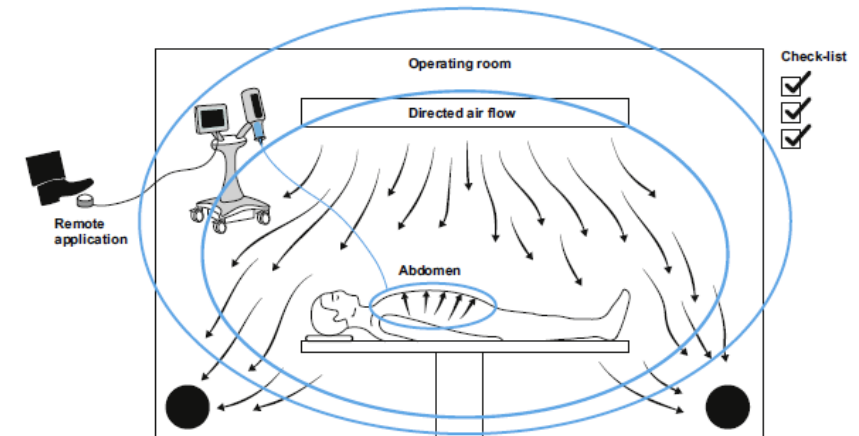
Closed abdomen

OR ventilation/ HEPA filter

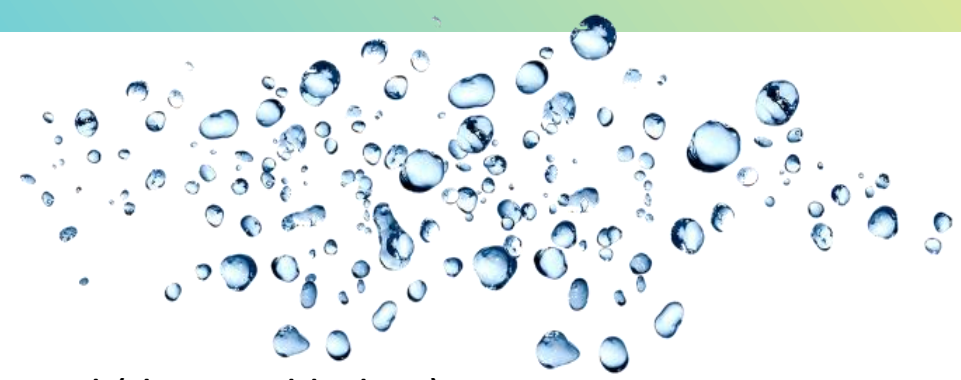
Remote control

Protection Through the OR Ventilation System

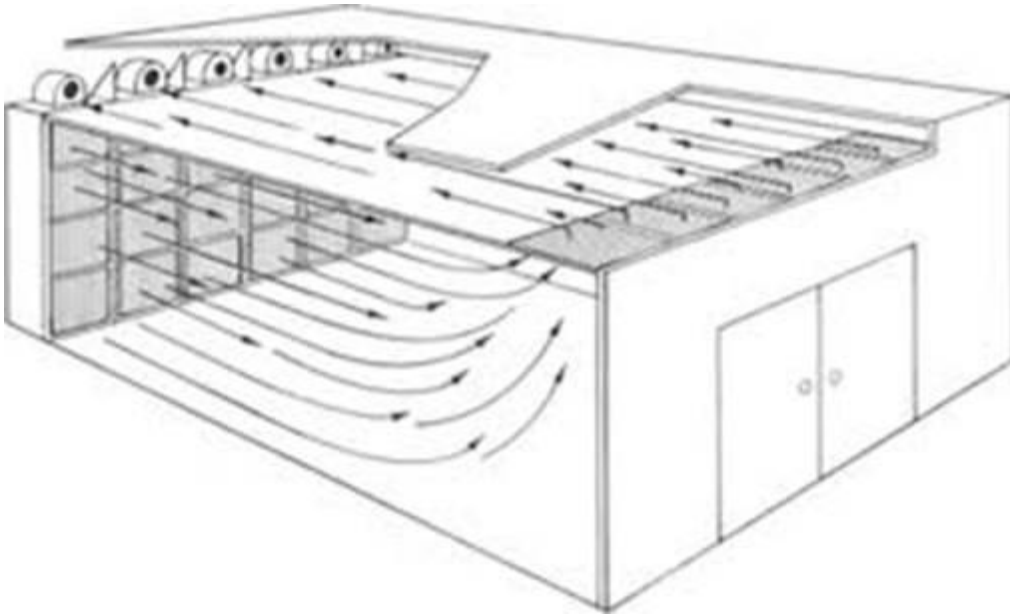
- Europe: laminar airflow system requirement to achieve occupational safety.
- U.S.: most ORs in the United States use advanced filtration systems ; not fitted with laminar flow
- The ISSPP recommendation
 - advanced filtering system **ISO14644-1 class ≤ 5 criteria** (ISO=International Organization for Standardization) for adequate safety.
- In the absence of a laminar flow or advanced filtration system, a protection curtain over the patient and a controlled aerosol waste system have demonstrated occupational safety.



Laminar Flow



OR laminar flow ventilation comes in two types, horizontal and vertical (depicted below).



you should be able to confirm the presence of vertical laminar flow by checking the placement of the room's air supply vents. With vertical laminar flow, there will be a bank of vents in the ceiling directly over the table

Table of ISO 14644-1 air quality standards (2015)

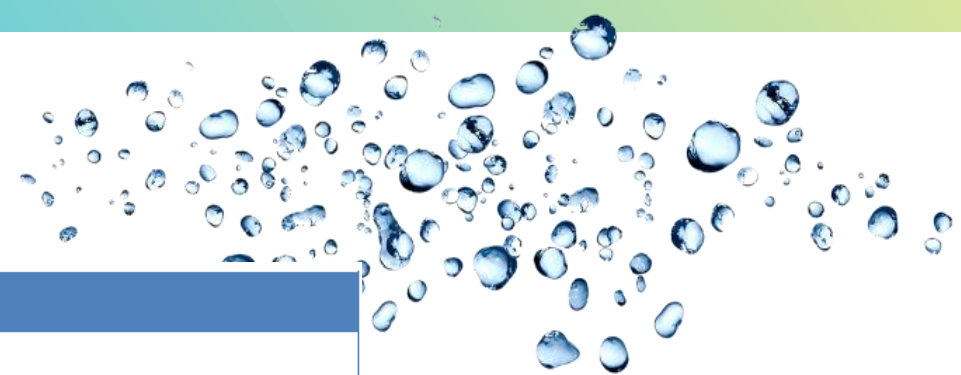


Table 1 Selected airborne particulate cleanliness classes						
ISO 14644-1:2015 Classification Number (N)	Maximum concentration limits (particles/m ³)					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO Class 1	10					
ISO Class 2	100	24	10			
ISO Class 3	1 000	237	102	35		
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	298
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

Filtered ventilation
ISO 14644-1 class ≤ 5

- The ISO 14644-1 standards are clean room standards that are used for pharmaceutical cleanrooms in the United States but not operating rooms.
- The California building code only dictates what filter and ventilation configurations must be used in hospital operating rooms. The ISO standards are not even referenced.

Check with your Safety Department
+/- Infection control

Particle counter to determine what classification your OR has



Air Contamination: Alternative Safety System

- When no advanced ventilation system is available in the OR
- Patient is completely covered with a single plastic sheet
- This sheet is perforated, an ostomy bag adapted
- The ostomy bag is connected to a mobile HEPA filtering device
- System validated by national safety instance (INRS) in France

Passeron J et al, Ref Santé Travail (INRS), 2016; 147:29-39
Ndaw et al, Toxicol Lett 2018

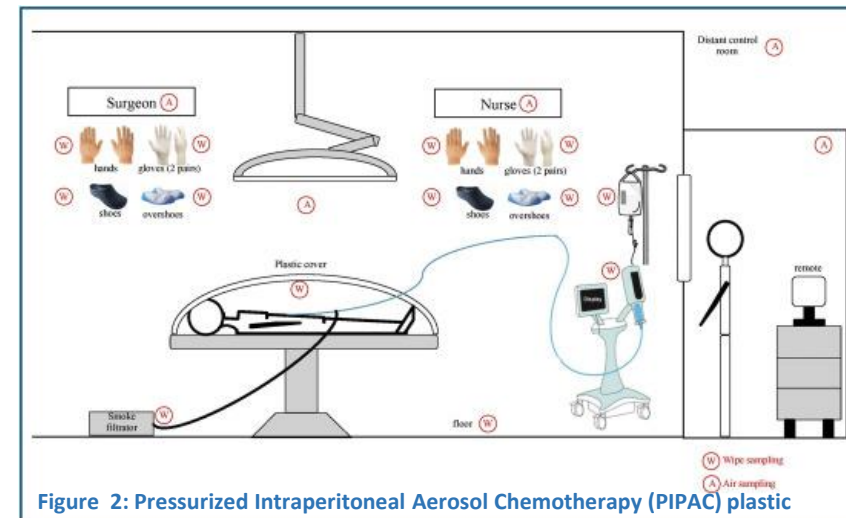


Figure 2: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) plastic sheet protection

Plastic sheet containment to prevent chemotherapy leakage in the operating theater (Delhorme et al, 2019).



Air Contamination: Alternative Safety System

- No surface contamination
- 25% of urine samples contained platinum
- no statistical difference was Observed before and after PIPAC
- French PIPAC protocol does not increase the risk of exposure to platinum in all staff categories involved

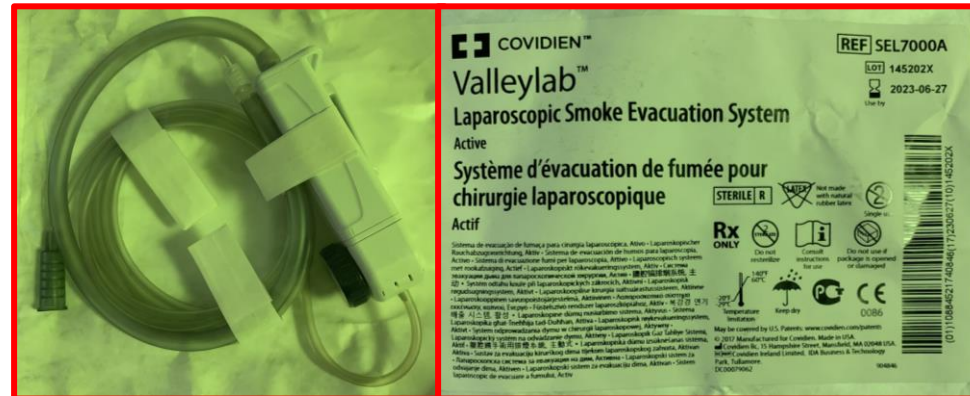
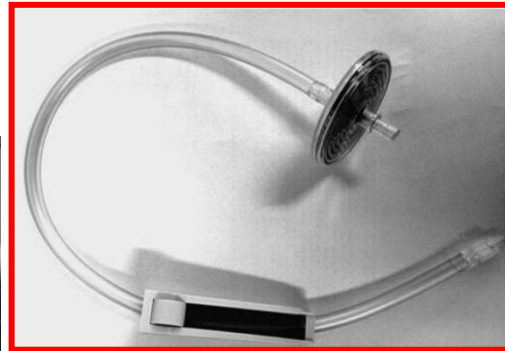
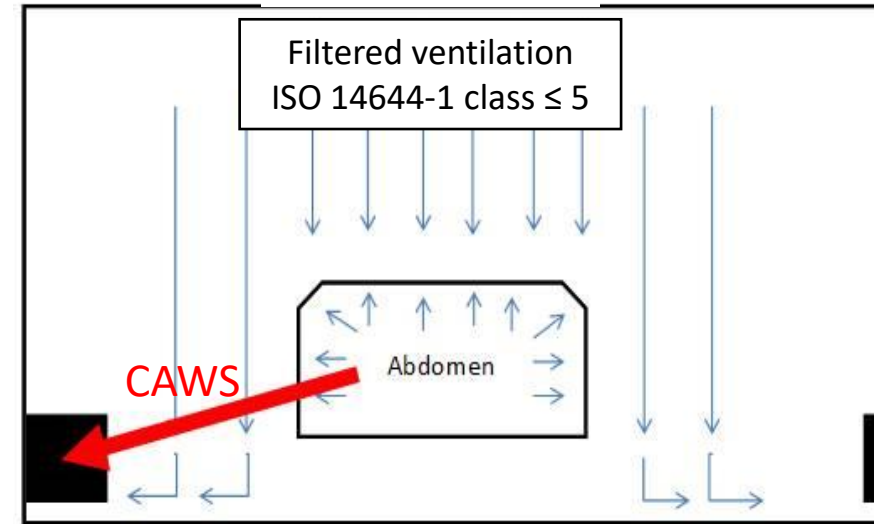


Larroque et al Toxicology and Applied Pharmacology 2021

Closed Aerosol Wasting System (CAWS)

- Safe removal of the toxic aerosol at the end of the PIPAC procedure
- Critical phase of the procedure

Operating room



OR

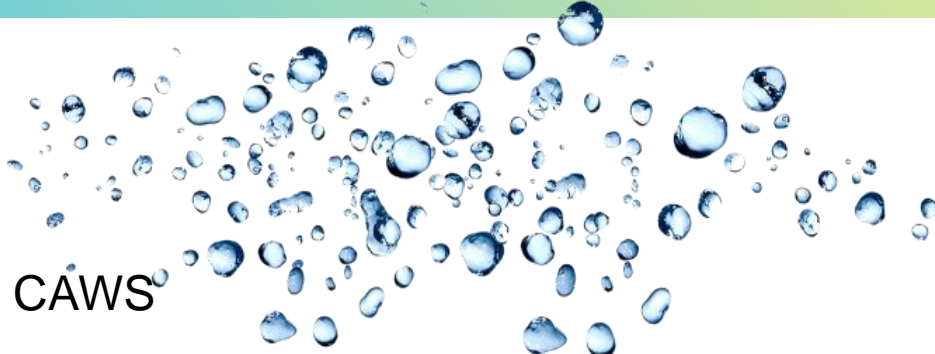


Safety: Workplace Measurements

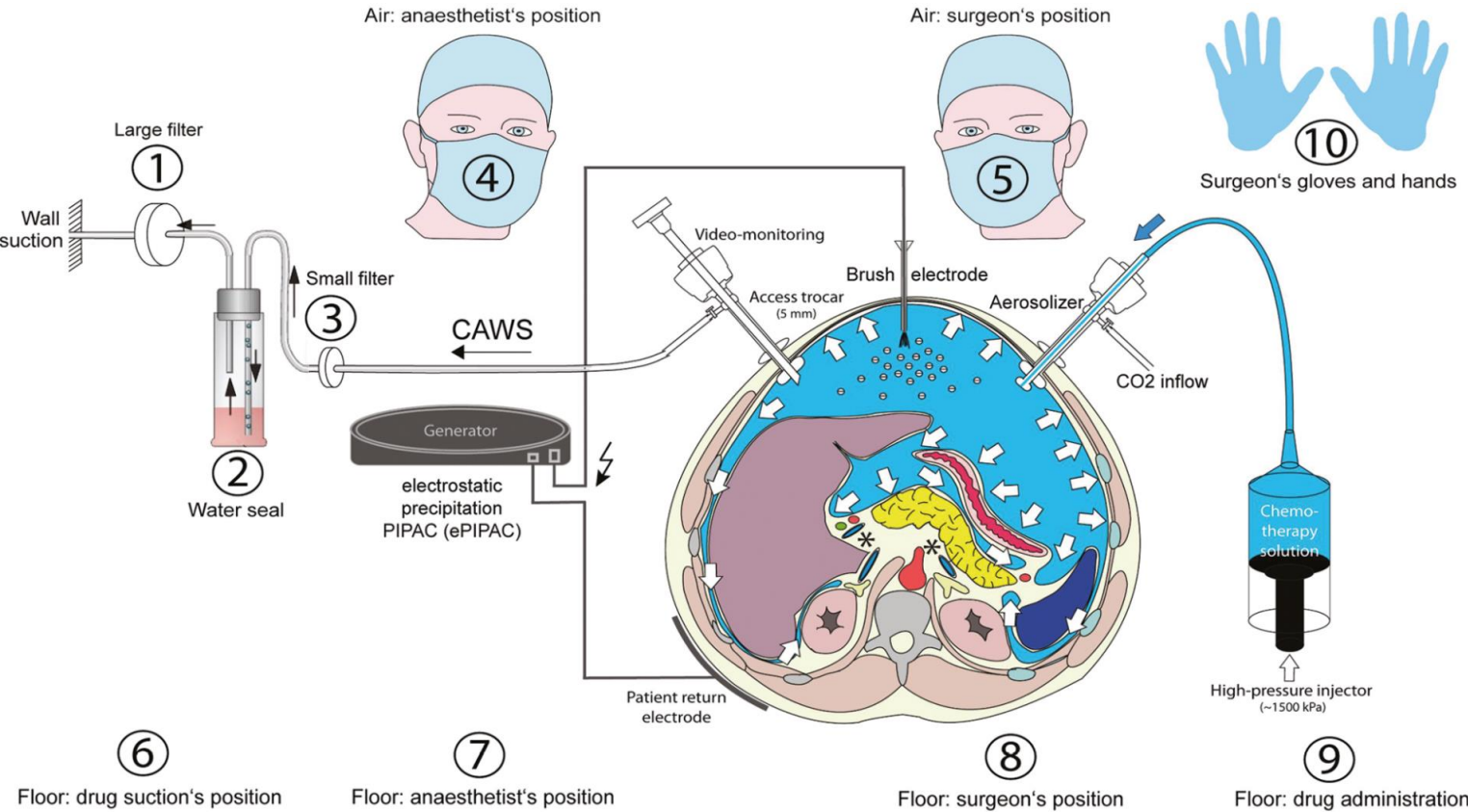


- Analysis of serum from provider volunteers shows no measurable levels of platinum after more than 1000 procedures
- Several studies have demonstrated the **absence of platinum** contamination in samples at several time points during PIPAC from:
 - Air
 - Floor
 - surgeon glove and hand
 - circuit filters
 - fluid from water seal collection chambers
- One study reported detection of **very low platinum levels** on
 - outer gloves of surgeons (but not the inner)
 - Trocars
 - angio-injector
 - *may account for institutional variability*

Platin Concentration at the Exit of CAWS ?



No platin detected downstream the filters of the CAWS



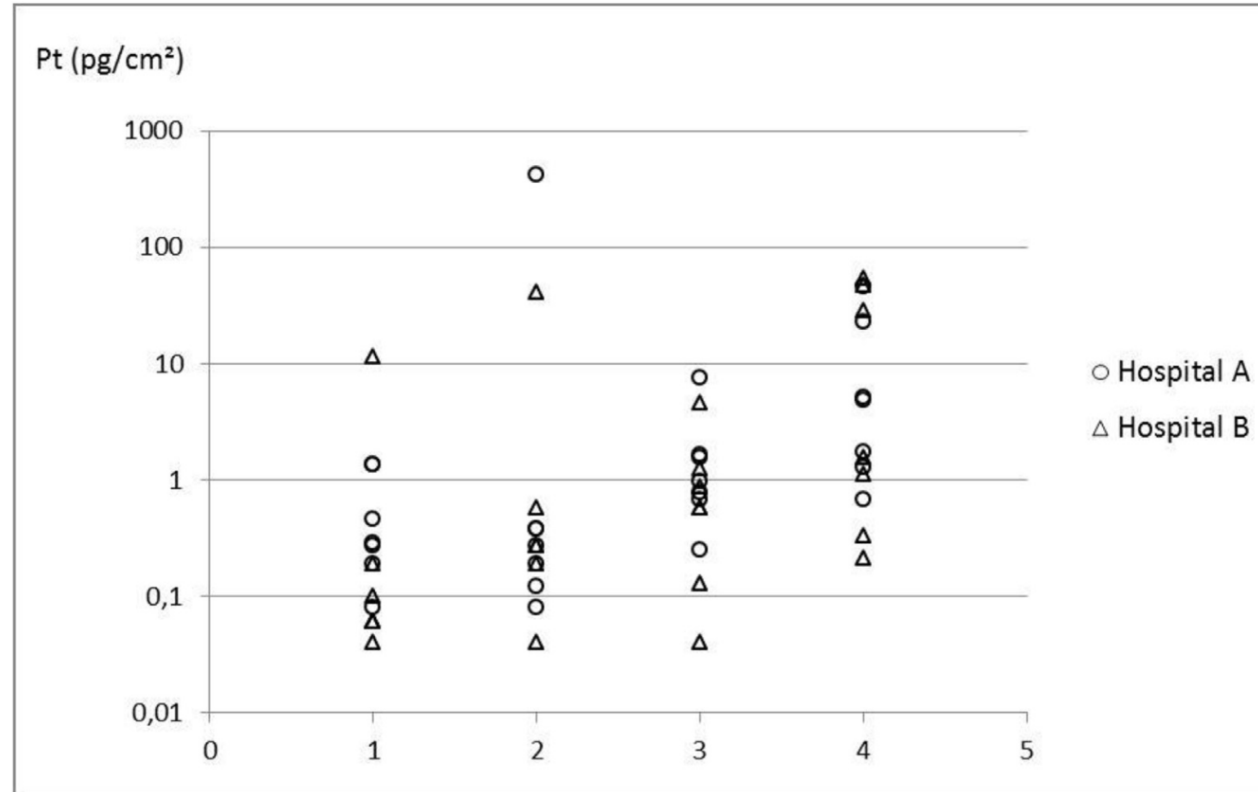
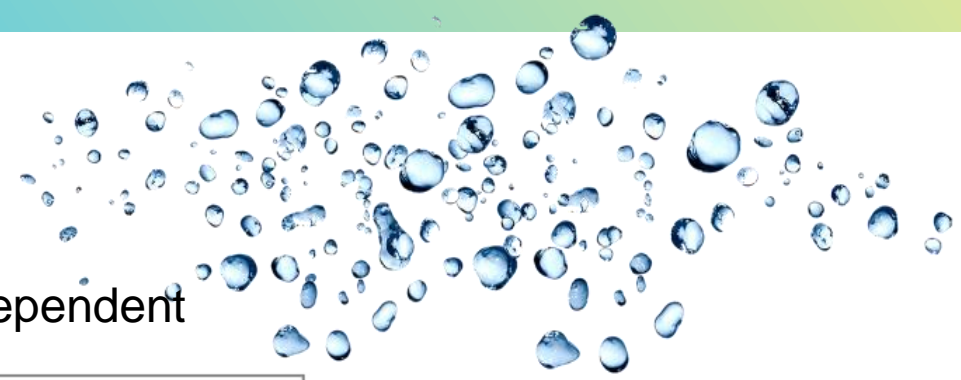
PIPAC	Description	Total PT, extraction volume HCl, mL	PT, ng/mL HCl	PT, ng
1	Smoke evacuation filter ^a	30	ND	< 15
1	Infant-pediatric electrostatic filter HME ^b	20	ND	< 10
1	Liquid from water seal drainage	45	ND	< 23
2	Smoke evacuation filter ^a	30	ND	< 15
2	Infant-pediatric electrostatic filter HME ^b	20	ND	< 10
2	Liquid from water seal drainage	43	ND	< 22

ND, not detected (<0.5 ng/mL HCl). ^aMTP GmbH, Neuhausen Ob Eck, Germany. ^bMedtronic, Brussels, Belgium.

- absence of platinum contamination in samples from air, floor, surgeon glove and hand, circuit filters, and fluid from water seal collection chambers at several time points during PIPAC.

Platin Contamination of Gloves ?

Gloves are contaminated at the end of PIPAC; contamination is surgeon-dependent



1=Loading (A:n=7, B:n=7), 2=Removing (A: n=7, B:n=6), 3= Cleaning (A: n=7, B:n=7), 4= Surgery (A:n=7, B:n=7)

Ametbischler et al Eur J Surg Oncol 2018

Platin Contamination of Instruments ?

Only reusable surgical instrument in contact with chemotherapy :
Laparoscopic camera (Hopkins optics)



Instruments and devices	Contact with chemotherapy	Single-use	Multiple use
Trocars	X	X	
Veress Needle	-	X	
Biopsy forceps	-		X
Endoscopic scissors	-		X
Capnomed ® device including high-pressure line	X	X	
Close aerosol waste system (CAWS) including microparticles filters	X	X	
CO ₂ tubing	-	X	
Op-drapes	X	X	
Videoscopic camera	X		X
Chemotherapy syringe	X	X	

Sample	Drug	Camera ID	Time point	Total HCl (ml)	(PT) (ng/ml HCl)	(PT) (ng)	CisPT equivalents (ng)
1	Cisplatin 12.0 mg	1	Post	157	ND		
2	Cisplatin 12.0 mg	2	Post	157	ND		
3	Cisplatin 14.0 mg	3	Post	157	ND		
4	Cisplatin 13.0 mg	4	Post	157	ND		
5	Cisplatin 13.0 mg	1	Post	157	ND		
6	Cisplatin 12.5 mg	2	Post	157	ND		
7	Cisplatin 14.0 mg	3	Post	157	ND		
8	Cisplatin 14.5 mg	4	Post	157	ND		
9	Cisplatin 14.0 mg	4	Pre	157	0.71	111	171
10	Cisplatin 13.0 mg	3	Pre	157	ND		
11	Cisplatin 11.0 mg	2	Pre	157	ND		
12	No cisplatin	--	Blank		ND		
13	No cisplatin	--	Blank		ND		

Note: ND: Not Detected (PT<0.50 ng/MI HCl); *CisPT equivalents=PT/0.65; Pre=before Sterilization; Post=after sterilization; Blank=negative control.

Demtröder et al,
RRJPPS 2016

Platin Contamination of Surfaces ?

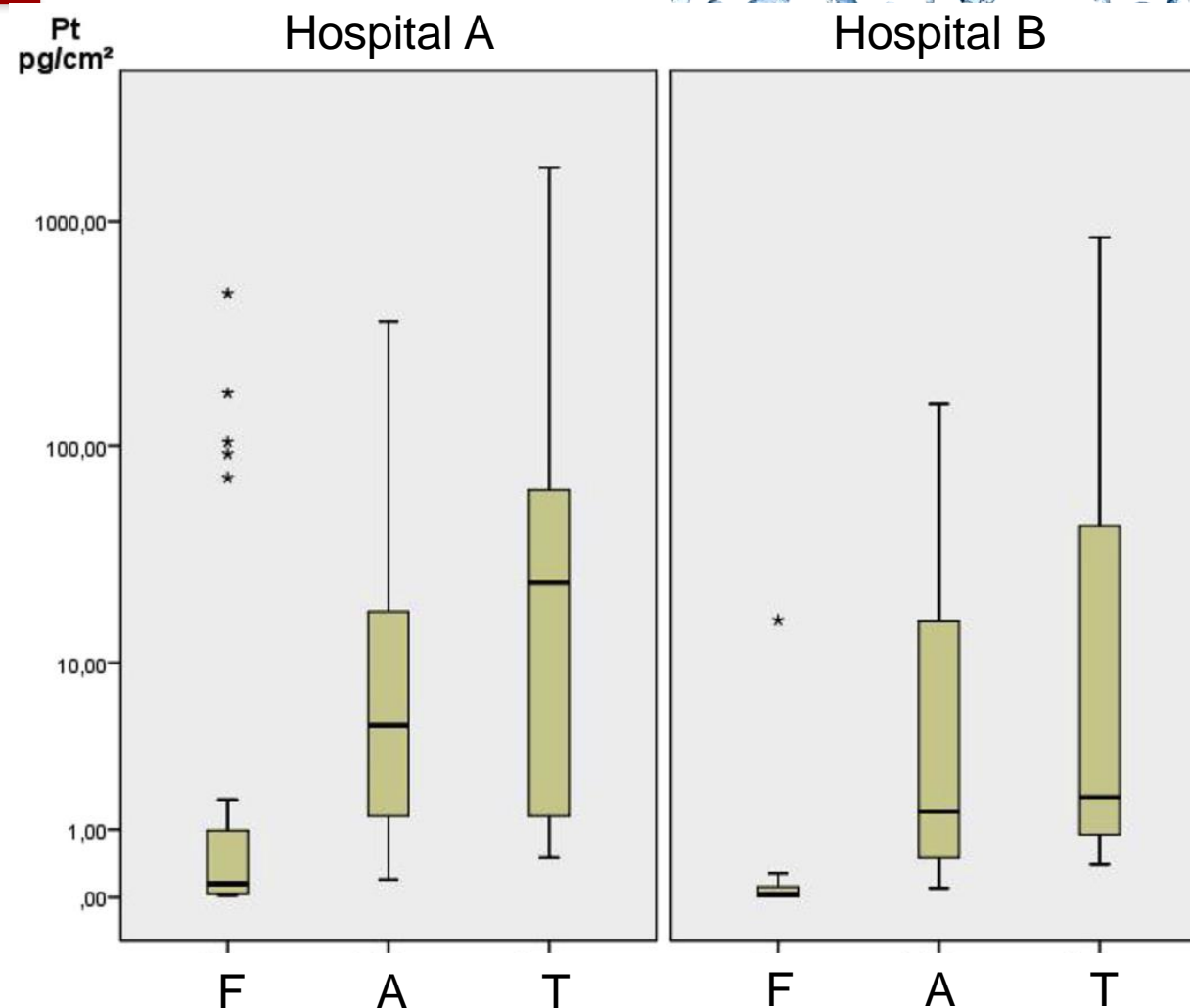
Surfaces (F = Floor, A = Angioinjector, T = Trocars) can be contaminated after PIPAC

The floor was not contaminated

Contaminations were found on the angioinjector syringe head and trocars.

This contamination is dependent on a careful manipulation of chemotherapy during the procedure

- Role of training
- Importance of cleaning



Platin Contamination of Air ?

No traces of platin detected in the air
at the working positions of:

- surgeon
- anesthesiologist

(lowest detection threshold 3.1 pg/m³)

Solass et al Ann Surg Oncol 2013

Oyais et al Zbl Chir 2014

Graversen et al, Pleura Peritoneum 2016

Willaert et al, Pleura Peritoneum 2017

Ametbischler et al, Eur J Surg Oncol 2018

Ndaw et al, Toxicol Letters 2018

Delorme et al J Visc Surg 2019

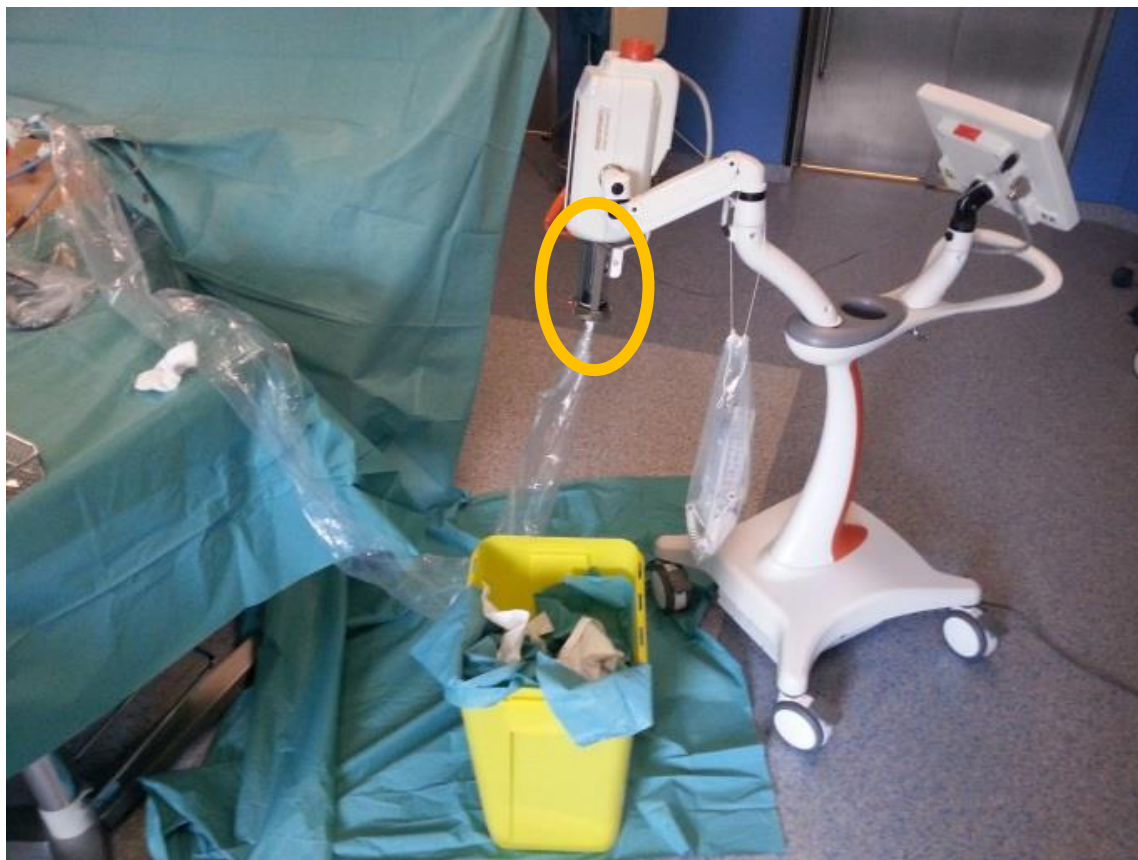
Jansen et al Chirurg 2019

Larroque et al Toxicology and Applied Pharmacology 2021



Safety: Surface Contamination

Platin traces detected on the head of the angio-injector



Consequences :

- wear gloves working properly,
- cleaning protocol and team training

Safety protocol at City of Hope

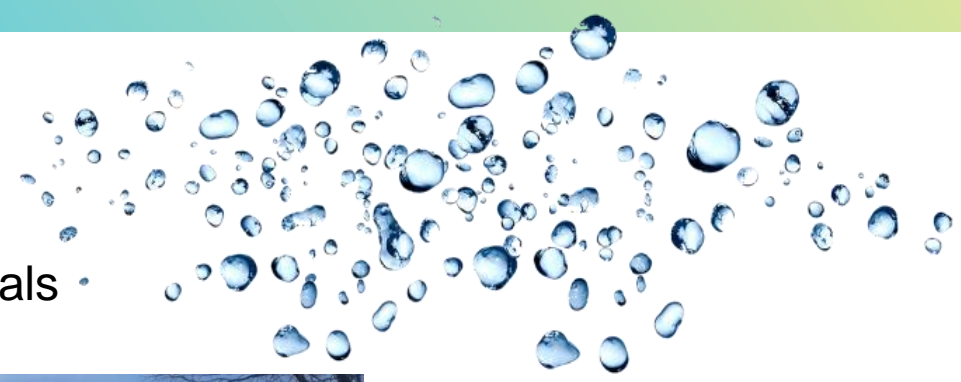


- In the event of a chemotherapy leak, a hazardous spill kit should be readily available, and a dedicated waste chain for removal should be established.
- Personal protective equipment (PPE) should be considered for these scenarios.
- Specific PPE recommendations adequate for handling chemotherapy have been published by the Oncology Nursing Society (ONS), the American Society of HealthSystem Pharmacists (ASHP), the Occupational Safety and Health Administration (OSHA), and the National Institute of Occupational Safety and Health (NIOSH).
- AAMI level 4 sterile gowns with double gloves. All remaining nonoperative personnel use either the same gowns or chemotherapy-rated (USP-800-compliant) gowns with double nitrile gloves.
- All team members use either eye protection or a face shield and either an N95 mask or a fully powered air-purifying respirator (PAPR).



Safety: Need for a Dedicated Waste Chain

Need for a dedicated waste chain for hazardous substances and materials

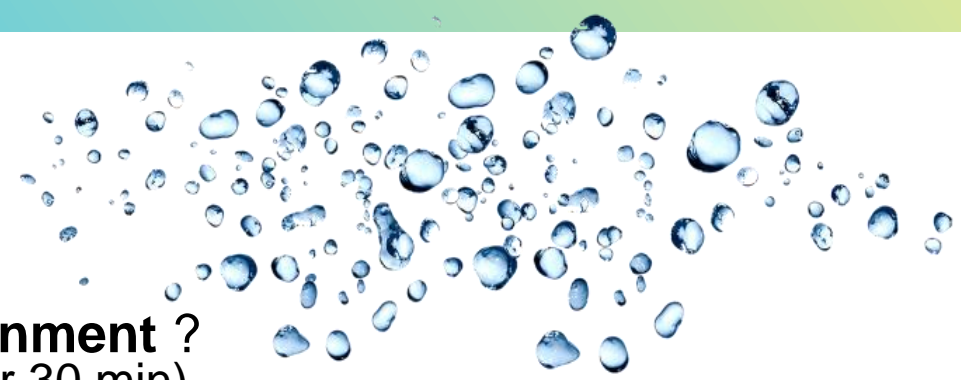


Special bins (tight, definitive closing, special labeling)
Waste management involves several steps going well beyond the
surgical department / OR

Air Contamination: Simulation of Worst Case Scenario

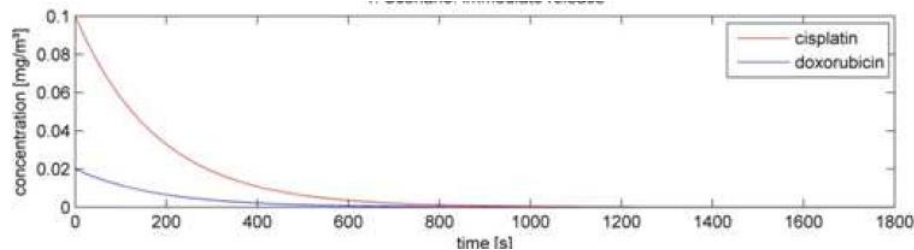
In-silico simulations:

What happens when complete aerosol released in the environment ?
Platin concentration in the air (over 30 min)



Immediate release scenario

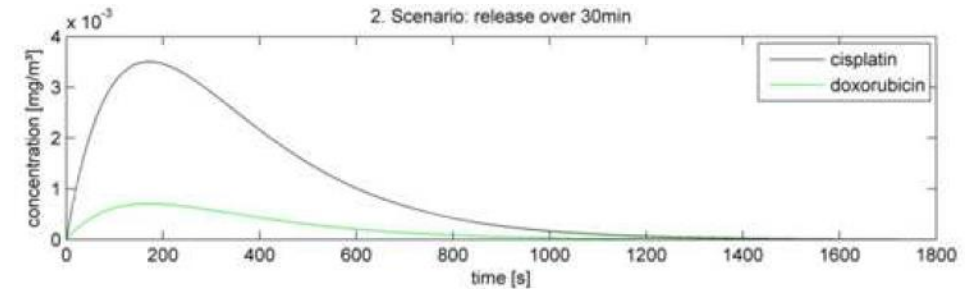
$$c_1(t) = c(t_0) * e^{-\alpha * t} \text{ with } c(t_0) = \frac{m_{start}}{V_{OR}}$$



> 50x

Slow release scenario

$$c_2(t) = c(t_0) * (1 - e^{-b*t}) * e^{-\alpha * t} \text{ with } c(t_0) = \frac{m_{start}}{V_{OR}}$$



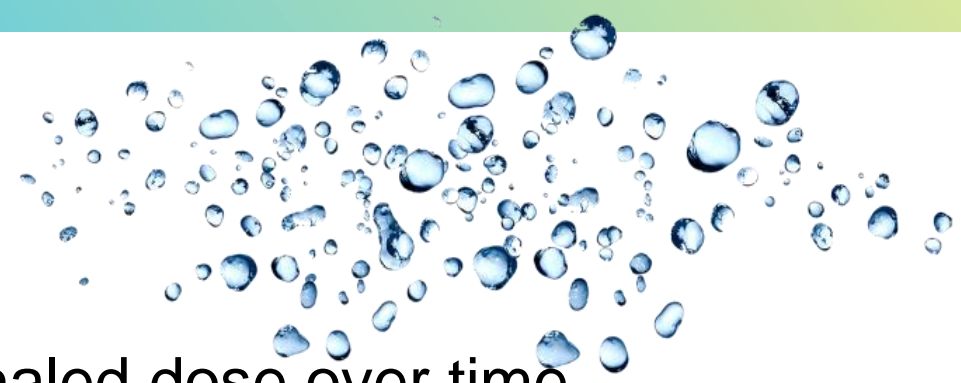
Reymond L et al, Nova Publishers 2016

$ci(t)$ = concentration over time, $t0$ = concentration at time 0, m_{start} = administered chemotherapy dose, V_{OR} = volume of the operating room, α = air exchange rate

Mathematical simulations of either a slow continuous aerosol leak over time or an immediate complete leak at the beginning of PIPAC have demonstrated a time-dependent decrease in the air concentration level of platinum with a maximal inhaled dose 1:100,000 to 1:1,000,000 of a usual systemic dose during 30 min

Air Contamination:

Simulation of Worst Case Scenario



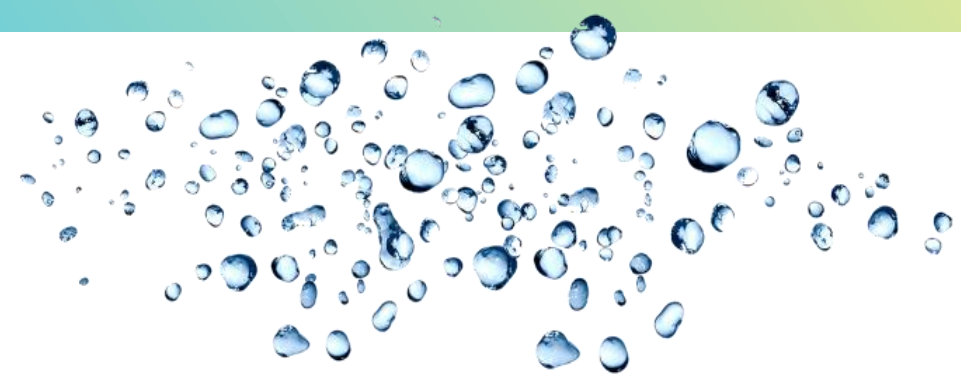
In-silico simulations: integration of the inhaled dose over time

Chemotherapeutics	Inhaled dose over a period of 30 minutes	
	Immediate release	Slow continuous release
Cisplatin (15 mg)	$1,49 \cdot 10^{-3}$ mg	$1,36 \cdot 10^{-4}$ mg
Doxorubicin (3mg)	$2,99 \cdot 10^{-4}$ mg	$2,72 \cdot 10^{-5}$ mg

Inhaled dose after 30 min is very low =
Between 1:100'000 and 1:1'000'000 of a standard systemic chemotherapy dose

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Are There Any Traces of Chemotherapy in the Blood ?



- Direct measurement of Platin in the blood
 - 2 surgeons after 50 PIPAC ¹
 - No measurable level of these substances in any of the persons at risk
- Direct measurement of Platin and Doxorubicin in the blood
 - 2014: 4 surgeons, 1 nurse after 500 PIPAC
 - 2017: 14 surgeons, gynecologists and nurses after 1500 PIPAC ^{2,3}
 - No measurable level of these substances in any of the persons at risk
- Direct measurement of Platin in urine
 - 5 PIPAC, 5 HIPEC, 5 controls: no statistical difference ⁴
- Direct measurement of platin before and after PIPAC in urine and blood
 - No different

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¹ Graversen et al Pleura Peritoneum 2016

^{2,3} Marien Hospital Herne, Germany, data on file, Giger-Pabst et al J Gastroint Surg 2018

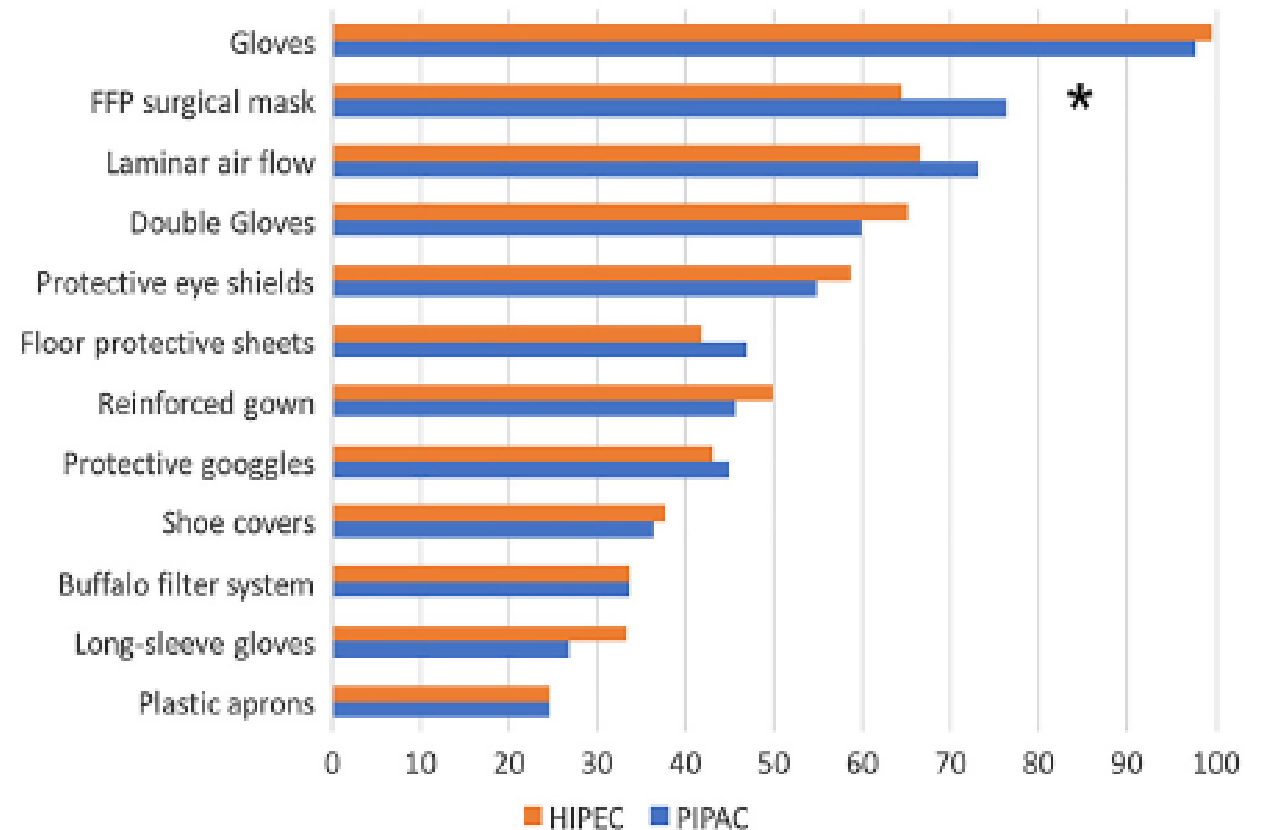
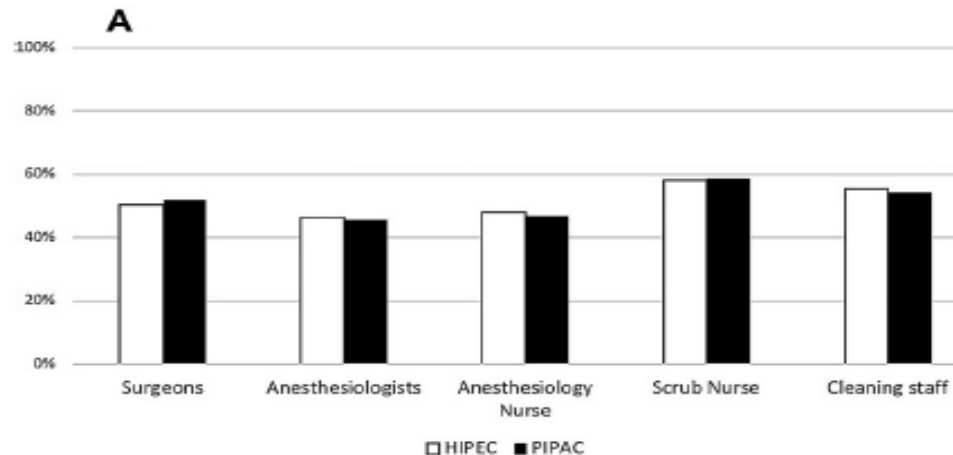
⁴ Ndaw et al Toxicol Letters 2018

⁵ Larroque et al Toxicology and Applied Pharmacology 2021

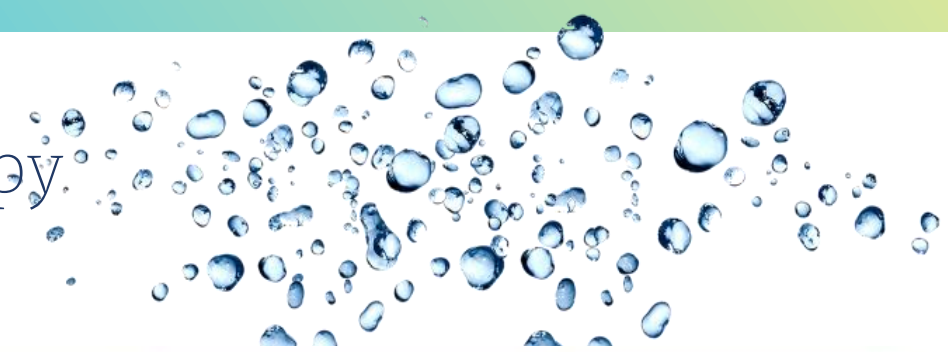
Systematic Use of Protective Measures





HIPEC vs PIPAC protective measures

- Most of the protective measure was not respected by all the team members
- Participation in dedicated training on protective measures during HIPEC and PIPAC was reported for 42.6 and 50.5%

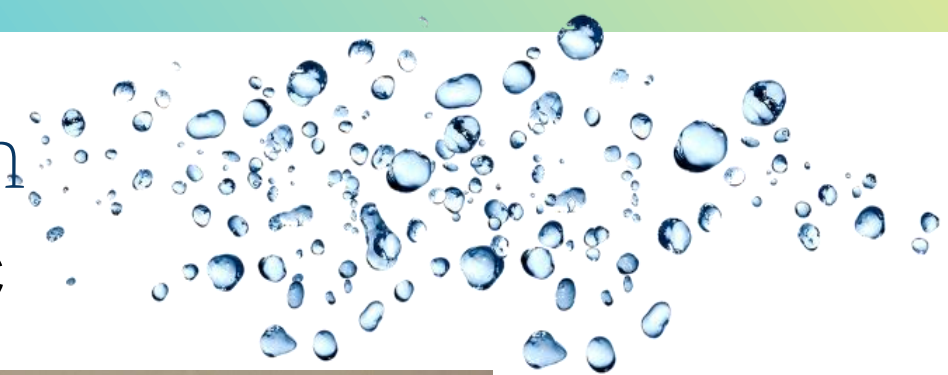


Consensus Statement on Safety Measures for Pressurized Intraperitoneal Aerosol Chemotherapy



	Surgeons 	Scurb Nurses 	Anesthesiology team 	Cleaning Staff 
Prior information related to biohazards of administration of CA	97.9 %	95.7 %	91.5 %	87.2 %
Prior training on safety measures	95.7 %	93.6 %	89.4 %	78.7 %
Prior information on emergency measures	97.9 %	95.7 %	95.7 %	83 %
Prior information on waste management and cleaning procedures	95.7 %	95.7 %	72.3 %	93.6 %

Reports (CIRS) on Liquid Contamination



5.11.2011 until 4.2.2016: 965 consecutive PIPAC/PITAC



2014

Contamination with fluids:

- Two intraoperative incidents
- 2x disconnection of the high-pressure line between the injector and the device



Consequence



2017

Device modified:

- Sterile
- Sealed together with high-pressure line
- Only a single safety connection

Is it Allowed to Reuse the Aerosolizing Device ?

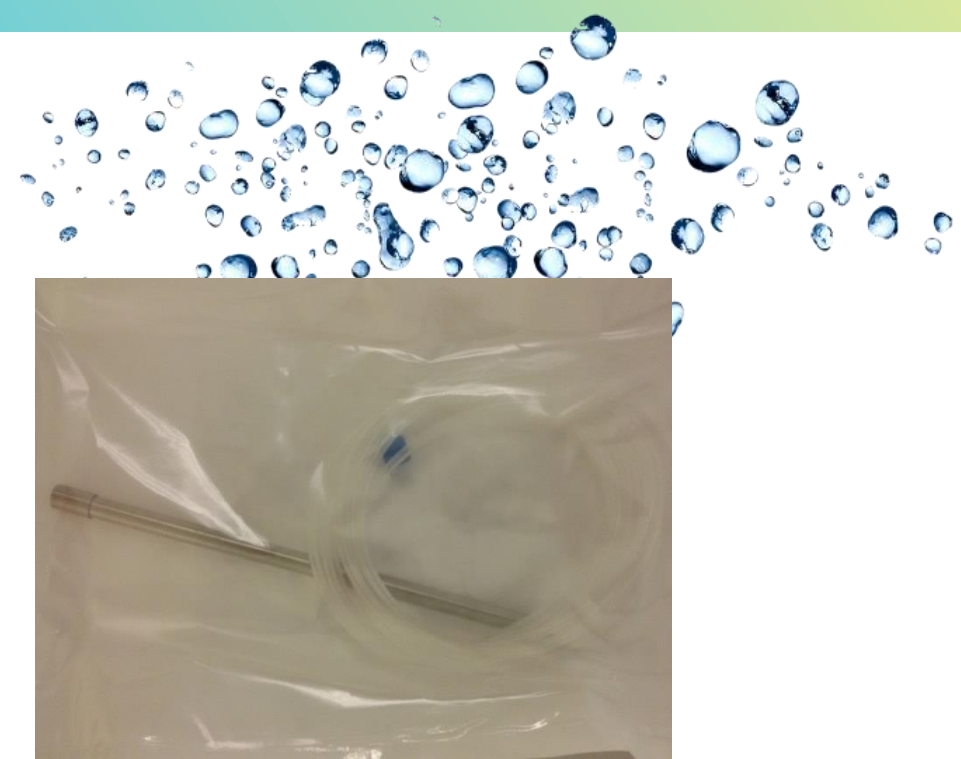
Capnopen ® device is certified as a single-use device

Sterilisation of instruments used to apply chemotherapy or radioisotopes is not allowed in Europe/ Germany (Krinko, RKI, 2012)

Fatigue of the material caused by repeated use might cause leakage: risk of blowing



Consequence



2018

Device modified:

- Modification of the connection
- Incorporation of thermolabile components



Occupational Health Safety: Take Home



PIPAC is a safe procedure

- Risk of exposure of OR personnel to toxic aerosols is very low.
- The angioinjector, the **laparoscopic camera** and the **gloves** might show traces of platinum.
- Little risk of exposure to platinum drugs during PIPAC
 - **ensure that adequate safety/protection measures are implemented**
 - cleaning standards for PIPAC workplaces must be implemented
- Apply safety protocols ! **Use of checklists is mandatory !**
- Train the personal on a regular basis !
- Regular safety monitoring is useful after program start