Multicenter study of environmental contamination with cyclophosphamide, ifosfamide and methotrexate in 48 Canadian hospitals

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Introduction

- Oncology workers are occupationally exposed to antineoplastic drugs. This exposition can induce adverse health effects.
- In order to reduce their exposure, contamination on surfaces should be kept as low as possible; no health-based safe exposition limit is known.
- Since 2004, the *National Institute for Occupational Safety and Health* frequently updates a list of drugs that should be considered hazardous, including antineoplastic drugs.
- Previous multicenter studies of environmental contamination were conducted in Quebec (2008-2010, 2012 and 2013) and in Canada (2014).

Objectives

- To monitor environmental contamination with cyclophosphamide, ifosfamide, and methotrexate in oncology pharmacy and patient care areas in Canadian hospitals.
- To describe some factors impact that may limit surface contamination.

Methods

- Descriptive and comparative study.
- 202 directors of pharmacy departments in hospitals with at least 50 acute care beds across 11 Canadian provinces were contacted in February 2015.
- 12 standardized sites were sampled (surface of 600 cm²):
  → 6 sites in pharmacy areas + 6 sites in patient care areas
- Samples were collected between April and June 2015 at the end of a working day or the next morning, before cleaning surfaces.
- Participants filled out a form describing their practice such as outer package removal, exterior vials cleaning, closed-system drug transfer devices use and antineoplastic drug consumption.
- Analysis by the Institut National de Santé Publique du Québec
- Samples were analyzed for the presence of cyclophosphamide, ifosfamide and methotrexate by ultra-performance liquid chromatography tandem mass spectrometry technology.

Table I. Limits of detection and limits of quantification

	Limit of detection (pg/cm²)	Limit of quantification (pg/cm²)
Cyclophosphamide	0.36	1.21
Ifosfamide	0.95	3.17
Methotrexate	0.97	3.25

- Descriptive analyses were done to evaluate surface contamination.
- Subanalyses were performed according to working practices and cyclophosphamide contamination (Kolmogorov-Smirnov test for independent samples).

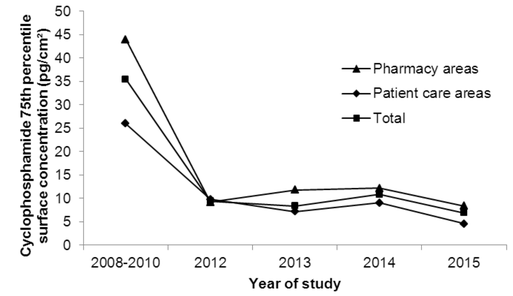
Results

- 48/202 Canadian hospitals participated in the 2015 study (24%)
- **Cyclophosphamide:** 75th percentile value was 6.9 pg/cm²
  Highest concentration was 130 000 pg/cm² (exterior surface of an antineoplastic drug container)
- **Ifosfamide:** 75th percentile value was lower than the limite of detection
  Highest concentration was 440 pg/cm² (arm rest)
- **Methotrexate**: 75th percentile value was lower than the limite of detection
  Highest concentration was 7300 pg/cm² (storage shelf)

Table II. Cyclophosphamide, ifosfamide and methotrexate positive samples in pharmacy and patient care areas in the 2015 study (n=48 centers)

Sample site (n samples)	Positive samples n (%)		
	Cyclophosphamide	Ifosfamide	Methotrexate
Pharmacy areas			
Shipment reception counter (46)	4 (9)	1 (8)	3 (7)
Storage shelf (47)	20 (43)	13 (28)	4 (9)
Front grille inside the hood (48)	30 (63)	8 (17)	13 (27)
Floor in front of the hood (48)	29 (60)	4 (8)	1(2)
Service hatch or counter for post-preparation validation (48)	10 (21)	3 (6)	1(2)
Trays used for drug delivery (45)	6 (13)	2 (4)	3 (7)
Total (282)	**99 (35)**	**31 (11)**	**25 (9)**
Patient care areas			
Storage shelf (43)	9 (21)	2 (5)	2 (5)
Counter used for priming or > validation (45)	12 (27)	1 (2)	1 (2)
Arm rest (42)	26 (62)	6 (14)	2 (5)
Patient room counter (33)	12 (36)	0 (0)	0 (0)
Outpatient clinic counter (39)	10 (26)	1 (3)	1 (3)
Exterior surface of hazardous drugs container (41)	13 (82)	0 (0)	0 (0)
Total (243)	**82(34)**	**10 (4)**	**6 (2)**
Total (525) (pharmacy & patient care areas)	**181 (34)**	**41 (7)**	**31 (6)**

Sampling sites with more than 50% of positive samples are shown.
A sample was considered positive if the value was above the limit of detection.



Cyclophosphamide surface concentration is decreasing over the years, in participating canadian centers.

Figure 1. Cyclophosphamide surface concentration in Canadian multicenter studies

Table III. Comparison of cyclophosphamide surface concentration

Comparisons (n samples)	75th percentile of cyclophosphamide concentration (pg/cm²)
Participation in multicenter studies	*p=0.528*
Participation in 5 studies (n=199)	9.7
Participation in 1-4 studies (n=326)	4.7
Use of closed-system drug transfer devices	*p=0.878*
Use (n=133)	9.5
No use (n=380)	6.1
Removal of outer packaging	*p=0.075*
Removal (n=417)	8.4
No Removal (n=96)	< limit of detection
Cleaning of vials after receipt	*p=0.312*
Cleaning (n=369)	8.5
No cleaning (n=156)	3.4
Antineoplastic drugs consumption	*p<0.0001*
< 5,000 preparations/year (n=211)	< limit of detection
5,000-15,000 preparations/year (n=115)	8.2
> 15,000 preparations/year (n=120)	40.8
Cyclophosphamide consumption	*p<0.0001*
< 500 g/year (n=314)	2.2
500-1,000 g/year (n=113)	10.9
> 1,000 g/year (n=74)	42.3

Centers who used less antineoplastic drugs were the least contaminated

*Kolmogorov-Smirnov for independent samples.
The limit of detection was of 0.36 pg/cm² (19.8 pg/mL) for cyclophosphamide.

Discussion / Conclusions

- Concentration of antineoplastic drugs measured on hospital surfaces in Canada is decreasing.
- Some sites are still frequently contaminated such as hoods and arm rests.
- Regular environmental monitoring is a good practice to maintain contamination as low as reasonably achievable.
- As long as no health-based limit is known, centers should monitor their contamination.

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