Surface Contamination with Two Common Antineoplastic Agents (CF and 5-FU)

Cross-Sectional Study in 24 Flemish Hospital Pharmacies Reveals Low Surface Contamination Rates for Two Widely Used Antineoplastic Agents

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- raise awareness for the value of our profession
- national and international cooperations
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Basic terminology

Cytostatics, Cytotoxic agents, Antitumor agents, Antineoplastic agents...

- Cytostasis: inhibition of cell growth and proliferation
- Cytostatics:
  - agents provoking cytostasis, diverse, very different physicochemical properties
  - divided into categories based on their working principle: alkylating agents, antimetabolites, antimitotics, antitumour antibiotics,....
  - usefull application: cancer treatment
    - interrupting uncontrolled growth and proliferation of cells (=cancer)
    - cancer cells proliferate faster, have more difficulties to repare DNA damage
  - also toxic to healthy cells, cancerous cells are only more susceptible
- Antitumor or Antineoplastic agents:
  - often used as synonyms for cytostatics
  - not completely correct: cancer is always malignant, tumours/neoplasms can be benign, potentially malignant (pre-cancer) or malignant (cancer)

Consequences of occupational exposure to cytostatics

Both long and short term health effects are possible

- Short term:
  - Irritation
  - Allergic reactions
  - ...
- Long term:
  - Carcinogenicity:
    - around ten cytostatics are proven cancerogenic to humans (IARC group 1)
    - ten others probably (2a), ten more possibly cancerogenic (2b) (see table last slide)
  - Genotoxicity:
    - cytogenetic damage
  - Reprotoxicity:
    - longer time to pregnancy, early birth, lower birth weight (Fransman 2006, 2007,...)
    - others reported spontaneous abortion, congenital effects, abnormalities, infertility,...

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How many people are at risk for occupational exposure?

An example from the Netherlands (2006) and some rough estimates

- Fransman (2006): ~13,750 exposed / 16,800,000 total population (0.08%)

Table 3.6 Number of employees, potentially exposed employees, most important tasks, and estimated frequencies and levels of exposure to antineoplastic drugs for each identified sector relative to oncology nurses in hospitals.

Occupation sector	Number of employees	Potentially exposed employees	Most important tasks	Relative exposure frequency	Relative exposure intensity
Home Care	123,900	5,000 – 10,000	Administering, nursing, cleaning	<	>
Nursing homes	200,000	> 1,000	Administering, nursing, cleaning	<	>
Pharmacies	17,500	100 – 200	Preparation	<[a]	=[a]
Laundries	12,200	100 – 200	Sorting laundry	>[b]	=[b]
Waste plant	5,200	20	Loading waste containers	<	<
Pharmaceutical industry	14,900	20 – 40	Producing antineoplastic drugs	<[a]	<[a]
Veterinary medicine	4,100	20 – 100	Preparation, administering	>[c]	>[c]
Universities	56,300	10 - 40	Experiments	<	?[d]

[a]relative to pharmacy technicians in hospitals; [b]relative to oncology nurses only while handling contaminated bed sheets; [c]only for veterinarians that use antineoplastic drugs; [d]no information available on the way of use of antineoplastic drugs at universities.

- Some rough estimates (~8% of all health care professionals):
  - UK (2001): ~53,270 / 58,800,000 (0.09%)
  - France (2002): ~49,000/ 61,400,00 (0.08%)
  - Belgium (2014): ~ 9,400 / 11,200,00 (0.08%)

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How and when might occupational exposure occur?

Mainly throug skin contact within and outside the hospital pharmacies...

- compared to patients: long term, low level exposure to multiple agents
- no safe OEL for genotoxic agents (one molecule might be enough to induce cancer)
- exposure ALARA: many technical measures are applied to avoid inhalation (aerosols, powders, mists,...)
- the skin remains the most important route
- skin exposure might occur during:
  - preparation of drugs,
  - cleaning of the pharmacy,
  - transportation to and administation of drugs in the patient rooms,
  - nursing of patients, contact with contaminated excreta,
  - special procedures (e.g. intraperitoneal chemotherapy),
  - what with homecare, residences for the elderly,...?

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What are important exposure determinants?

and other properties of the agents as the way in which they are handled

- manipulated quantities of the agents, frequency and duration of the manipulations,
- location and manner of preparation (type of preparation system: (open /) semi-closed (e.g. 1) / closed (e.g. 2), flow cabinet, facility,...),
- physicochemical properties (evaporation rate, dustiness, skin absorption/penetration rates,...),
- PPE and the way in which they are used,
- cleaning procedures, decontamination and desinfeciton of materials and workplaces,
- skills, quality of the manipulations of the (qualified) personnel,
- ...

(1) Chemoprotect® Spike (Codan)

(2) PhaSeal™ (BD)

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What is an acceptable surface contamination?

a pragmatic, conservative solution based on a worst case scenario…

- Cyclophosphamide (CF)
  - highly toxic, persistent
  - easy skin permeable
  - sensitive analytical methods
  - a lot of monitoring data in literature
    - 90% wipe samples < 0.1 ng/cm²
    - 99% wipe samples < 10 ng/cm²
    - no positive urine samples from exposed workers when surface contamination < 0.1 ng/cm²

Reference values surface contamination with cyclophosphamide (CP) in The Netherlands

PJM Sessink. Safety Considerations in Oncology Pharmacy
Special Edition - Fall 2011 pages 3-5 www.ppme.eu

Contamination CP (ng/cm²)	< 0.10	0.10 – 1.0	1.0 – 10	> 10
Actions	Monitoring once a year Evaluate after 4 years	Risk estimate Monitoring within 3 – 6 months Eventually followed by measures		Take measures Check by monitoring

- "Werkgroep toetsingswaarden cytostatica – NVvA, NVVK, NVZA (2009). Meetstrategie en werkinstructie veegproeven cytostatica." (consulted online 25/04/2016, http://goo.gl/5ndMWX)

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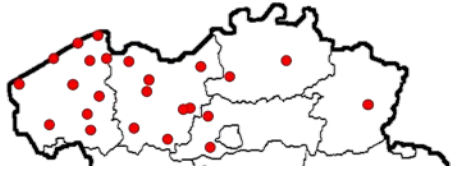
Workplace challenge: what is the situation in Flanders?

What do we monitor, where do we monitor, what do we want to learn?

- What: CF use is decreasing, 5-FU use is used more frequently and in larger quantities: are both relevant and suitable as markers?
- Where: in hospital pharmacies to compare with literature?
  - Janssens, 2004 (masters thesis, study in Flemish pharmacies)
    - Cross sectional study on CF contamination in hospital pharmacies
    - 12 pharmacies, 2 independent measurements per pharmacy (24 in total)
    - Result: 80% detectables
  - Sessink, 2013 (study in US pharmacies): even with a CSTD 38% > 0.1 ng/cm²
  - …
- What is the situation in Flanders?
    - Cross sectional study on CF and 5-FU contamination
    - 24 pharmacies, 6 pseudoreplications per pharmacy (144 in total)
    - Important contextual information is lacking at the moment: which products, quantities, preparation systems, cleaning procedures are used?



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Methods

In Collaboration with AZ Groeninge, Courtray, Belgium

- Chemical/Analytical: internal standards, SOP, LC-MS/MS
  - LOQ CF: 1 ng per wipe (~400 cm^2): ~0,0025 ng/cm^2
  - LOQ 5-FU: 50 ng per wipe (~400 cm^2): ~0,125 ng/cm^2
  - simple, sterile widely available consumables, inert template
- Physical: recovery from typical surface (stainless steel)
  - personal communication with mr. Alvin Heah (ESCO Global): 10% of ESCO BSC with SS316 (more resistant to agressive cleaning) 90% with SS304 (less resistant to agressive cleaning), kindly donated spike sample surfaces

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Methods

Questionnaire + 6 samples (BSC surface, airfoil, floor, bin lids, worksurface)






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Results

Questionnaire: (potential) exposure determinants (1)

- Number of beds (median hospital and total number across all)
  - Median: 269 beds (aacross all 9571 beds)
- CF use
  - Median: 154 g CF used / year (across all 6257 g)
  - Median: 130 CF preparations / year (across all 5904)
  - Median: 0 g CF used / day of measurements (across all 22 g)
  - Median: 0 CF preparations / day of measurements (across all 21)
- 5-FU use
  - Median: 2740 g 5-FU used / year (across all 98805 g)
  - Median: 993 5-FU preparations / year (across all 36322 preparations)
  - Median: 26 g 5-FU used / day of measurements (across all 665 g)
  - Median: 8 5-FU preparations / day of the measurements (across all 225)

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5-FU is used much more frequently (and in higher doses)

Results

Questionnaire: (potential) exposure determinants (2)

- Protection of the preparation
  - 22 / 24 pharmacies use hairnets
  - 19 / 24 pharmacies use chirurgical masks
- Collective measures
  - 22 / 24 BSC in stainless steel
  - 16 / 24 forced ventilation, 19 / 24 exhaust without recycling
  - 7 / 24 cleanrooms
  - 12/24 PhaSeal™ , 8/24 other systems (Equashield®, Tevadaptor®,...), 4/24 Chemoprotect®,
- Personal measures
  - 10 / 24 use latex gloves, 13 nitril, 1 neoprene
  - 6 / 24 use double pairs of gloves
  - 22 / 24 apron, 15 / 24 overshoes, 0 /24 protective glasses

Both closed and semi-closed systems are used, double glove pairs in 25%

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Results

Questionnaire: (potential) exposure determinants (3)

- Cleaning of flacons with cytostatics:
  - 22 / 24 pharmacies clean the flacons before use
    (vials should be regarder as contaminated, sleeving of vials reduces contamination, Connor *et al*., Am J Health-Syst Pharm 2005;62:475-84)
- Cleaning of the BSC:
  - desinfecting product (alcohol, javel, ,...): 21 / 24 daily, 2 / 24 weekly
  - cleaning product (water and detergent,...): 8 / 24 daily, 3 / 24 weekly
  - combination product (cleaning/desinfecting): 10 / 24 daily
- Cleaning of the preparation room
  - desinfecting product (alcohol, javel,...): 5 / 24 daily
  - cleaning product (water and detergent,,...): 10 / 24 daily, 9 / 24 weekly
  - combination product (cleaning/desinfecting): 4 / 24 daily, 2 / 24 weekly

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Less than 50% aware of the ineffectivity of alcohol alone

Results

Measurements: surface contamintions obtained through wipe sampling

- 5-FU: median <0,125 ng/cm² (range: <0,125 – 73,5 ng/cm²)
  - detectables: 20/144 samples – 10/24 pharmacies
  - > 1 ng/cm²: 10/144 samples – 6/24 pharmacies
  - > 10 ng/cm²: 2/144 samples – 2/24 pharmacies
- CF: median <0,0025 ng/cm² (range: <0,0025 – 2,050 ng/cm²)
  - detectables: 25/144 samples – 11/24 pharmacies
  - > 1 ng/cm²: 2/144 samples – 1/24 pharmacies
  - > 10 ng/cm²: 0/144 samples – 0/24 pharmacies
- 8 / 24 pharmacies all CF and 5-FU results <LOQ
- Visualisation using censored boxplots (plotting on a logscale and using ROS to avoid distortions) with BWStat (available for free at http://www.bsoh.be/?q=en/node/123; instead of comparing workers we are comparing pharmacies)

80% of all samples <LOQ:
in general low contamination

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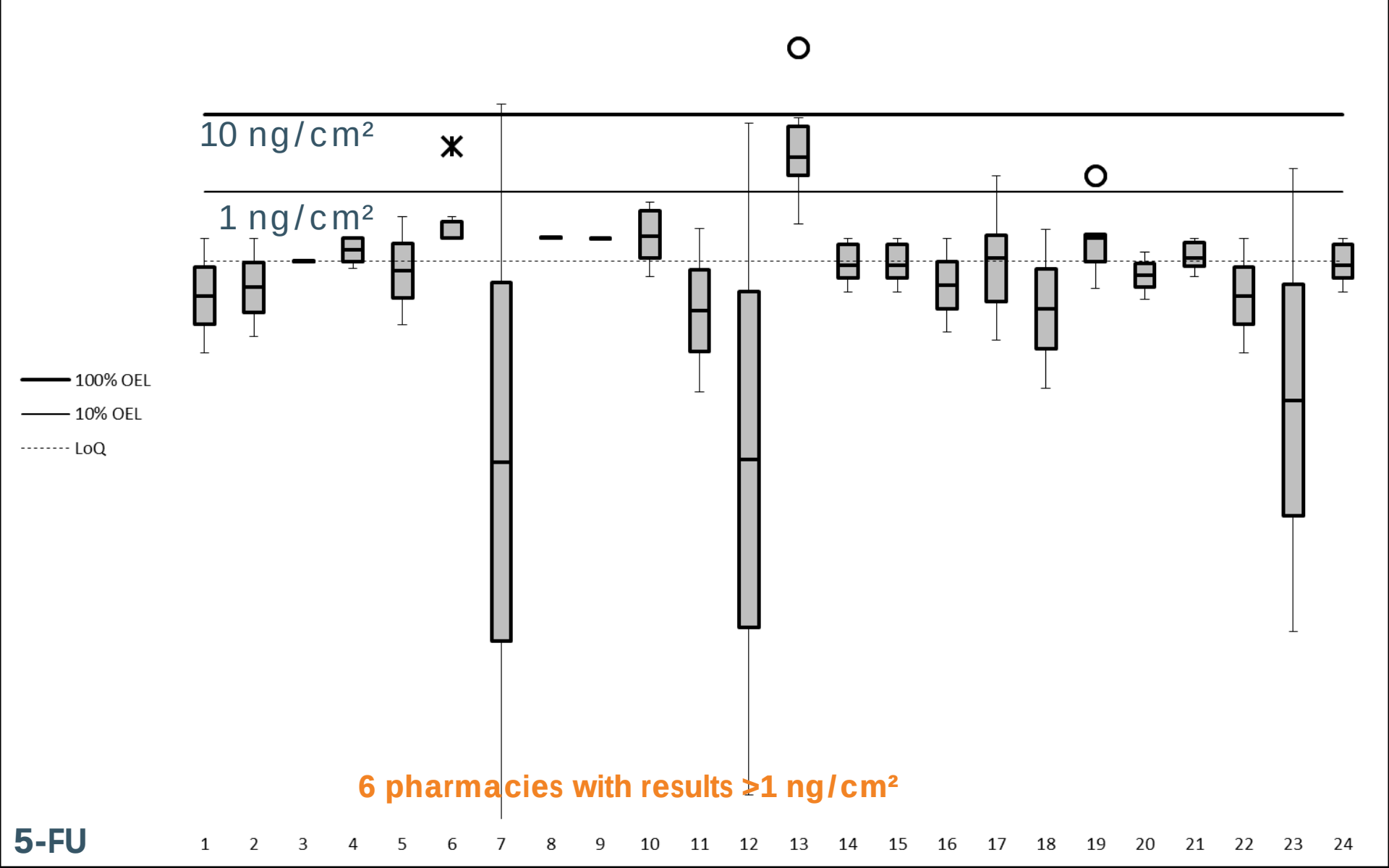
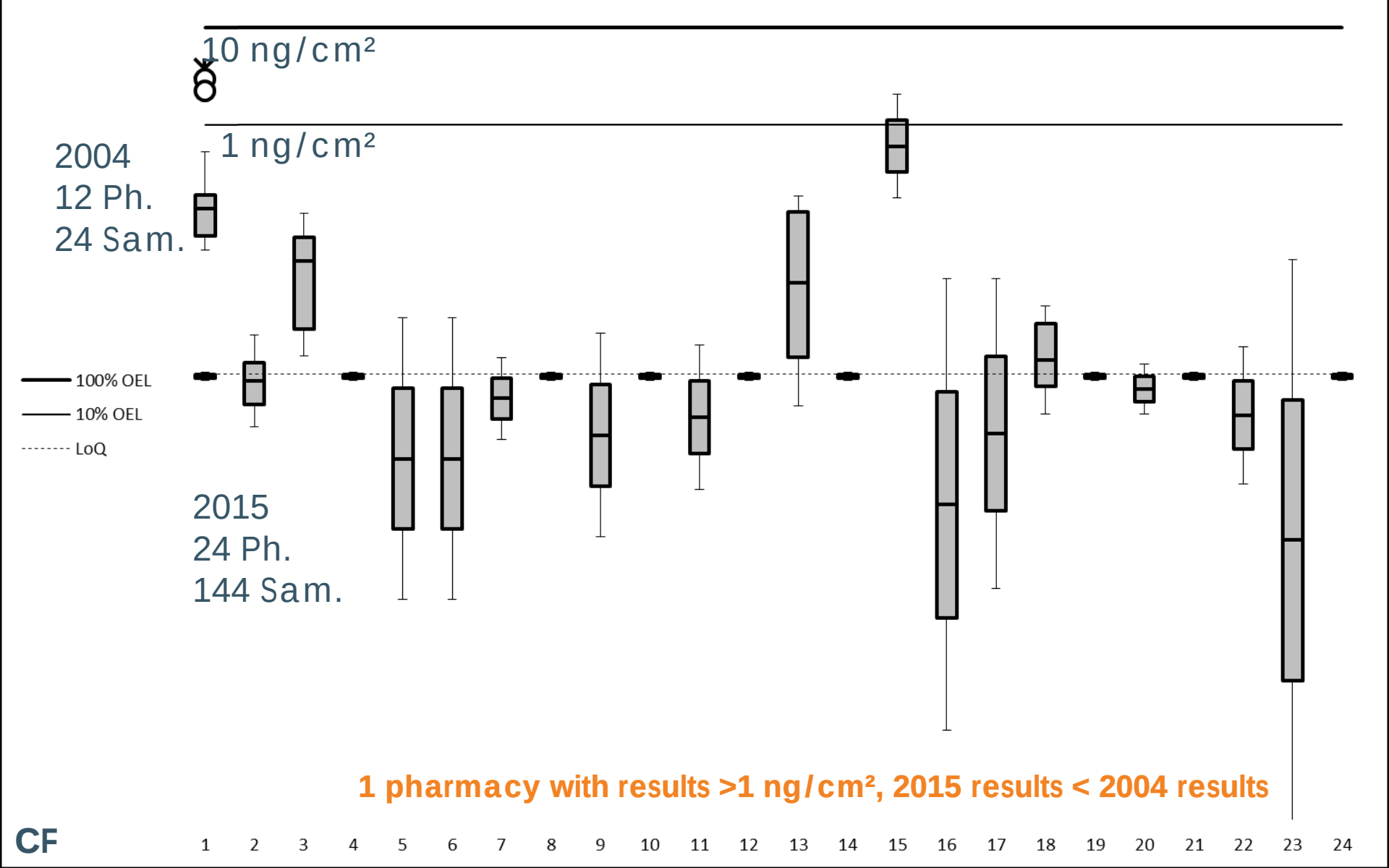

10 ng/cm²
1 ng/cm²
100% OEL
10% OEL
LoQ
6 pharmacies with results ≥1 ng/cm²
5-FU
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24


10 ng/cm²
1 ng/cm²
2004
12 Ph.
24 Sam.
100% OEL
10% OEL
LoQ
2015
24 Ph.
144 Sam.
1 pharmacy with results >1 ng/cm², 2015 results < 2004 results
CF
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Discussion

- 24 pharmacies from 20 / 64 hospitals groups: ~1/3 of the population
- 80% <LOQ in 2015 vs 80% >LOQ in 2004:
  - our results show a decrease in surface contamination with CF
- impaired statistical analysis
  - large variation in determinants across pharmacies: not possible at this time to compare relative importance of those determinants
  - 6 pseudoreplications per pharmacy (same sampling moment), consider 24 samples in stead of 144
  - highly censored dataset: how would you calculate e.g. a mean value?
- CF contamination differences between preparation systems non-significant, but consistent with literature (semi closed > closed)

	<LOQ	>LOQ	Totaal
Phaseal	61	11	72
Other	41	7	48
Codan	17	7	24
Total	119	25	144

	<LOQ	>LOQ
Phaseal	84,7%	15,3%
Other	85,4%	14,6%
Codan	70,8%	29,2%
Total	82,6%	17,4%

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Lessons learned

- 2015: general low surface contaminations with CF and 5-FU,
- Overall consumption and manipulation frequencies of 5-FU substantially exceed those of CF,
- CF and 5-FU are both usefull markers to assess surface contamination,
- CSTD not fully implemented everywhere, still room for improvement,
- Focus of cleaning procedures too much on microbiological decontamination (often alcohol alone): water and neutral detergents are recommended for chemical decontamination prior to alcohol spraying, alcohol alone is ineffective!
- Practical outcomes (in Dutch): Provikmo Infodocument Cytostatica , individual pharmacy reports delivered 12/2015, follow-up planned.
- HS professionals working in hospitals: do not forget the pharmacy!

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Download abstract: https://goo.gl/ADcksF
Download presentation: https://goo.gl/VwgC86

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Cytostatics classified by IARC (listed 12/12/2015)

adapted from table 1, “Dossier Cytostatica”, www.arbokennisnet.nl

Group 1: carcinogenic to humans	Group 2a: probably carcinogenic to humans	Group 2b: possibly carcinogenic to humans	Group 3: not classifiable as to its carcinogenicity to humans
Azathioprine [446-86-6] (Vol. 100A; 2012), Chlornaphazine) [494-03-1] (Vol. 100A; 2012), Busulfan [55-98-1] (Vol. 100A; 2012), Chlorambucil [305-03-3] (Vol. 100A; 2012), Methyl-CCNU (Semustine) [13909-09-6] (Vol. 100A; 2012), Cyclophosphamide [50-18-0] (Vol. 100A; 2012), Etoposide [33419-42-0] (Vol. 100A; 2012) and Etoposide [33419-42-0] in combination with cisplatin and bleomycin (Vol. 100A; 2012), Melphalan [148-82-3] (Vol. 100A; 2012), MOPP [113803-47-7] (Vol. 100A; 2012), Tamoxifen [10540-29-1] (Vol. 100A; 2012), Thiotepa [52-24-4] (Vol. 100A; 2012), Treosulfan [299-75-2] (Vol. 100A; 2012)	Adriamycin [23214-92-8] (Vol. 10;1975, Suppl. 7; 1987), Azacitidine [320-67-2] (Vol. 50; 1990), Bischloroethyl nitrosourea (BCNU) [154-93-8] (Vol. 26; 1981, Suppl. 7; 1987) 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) [13010-47-4] (Vol. 26; 1981, Suppl. 7; 1987), Chlorozotocin [54749-90-5] (Vol. 50; 1990), Cisplatin [15663-27-1] (Vol. 26; 1981, Suppl. 7; 1987), N-Ethyl-N-nitrosourea [759-73-9] (Vol. 17, 1978, Suppl. 7; 1987), N-Methyl-N-nitrosourea [684-93-5] (Vol. 17, 1978, Suppl. 7; 1987), Nitrogen mustard [51-75-2] (Vol. 9; 1975, Suppl. 7; 1987), Procarbazine hydrochloride [366-70-1] (Vol. 26; 1981, Suppl. 7; 1987), Teniposide [29767-20-2] (Vol. 76; 2000)	Amsacrine [51264-14-3] (Vol. 76; 2000), Aziridine [151-56-4] (Vol. 71; 1999), Bleomycins [11056-06-7] (Vol. 26; 1981, Suppl. 7; 1987), Dacarbazine [4342-03-4] (Vol. 26; 1981, Suppl. 7; 1987), Daunomycin [20830-81-3] (Vol. 10; 1975, Suppl. 7; 1987), Merphalan [531-76-0] (Vol. 9; 1975, Suppl. 7; 1987), Mitomycin C [50-07-7] (Vol. 10;1975, Suppl. 7; 1987), Mitoxantrone [65271-80-9] (Vol. 76; 2000), Streptozotocin [18883-66-4] (Vol. 17, 1978, Suppl. 7; 1987), Trichlormethine (Trimustine hydrochloride) [817-09-4] (Vol. 50; 1990)	5-Fluorouracil [51-21-8] (Vol. 26; 1981, Suppl. 7; 1987), Isophosphamide [3778-73-2] (Vol. 26; 1981, Suppl. 7; 1987) 6-Mercaptopurine [50-44-2] (Vol. 26; 1981, Suppl. 7; 1987) Methotrexate [59-05-2] (Vol. 26; 1981, Suppl. 7; 1987), Prednimustine [29069-24-7] (Vol. 50: 1990), Prednisone [53-03-2] (Vol. 26; 1981, Suppl. 7; 1987), Vinblastine sulfate [143-67-9] (Vol. 26; 1981, Suppl. 7; 1987), Vincristine sulfate [2068-78-2] (Vol. 26; 1981, Suppl. 7; 1987)

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