



Monitoring exposure to antineoplastic drugs in Sweden

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Work Health Authority (WHA)

- First ordinance in 1984
- Current ASF Ordinance 2005:5
 - Protective equipment
 - Gown, double gloves, eye protection
 - Preparation in BSC or similar required
 - Scheduled maintenance of equipment
 - Annual tests of systems
 - Staff with technique
 - Waste and garbage
 - Handling and destruction procedures
 - Written instructions and adequate education





Government and Authority activities

- NIWL closed down 2007-06-30
- WHA
 - 100 MSEK cut in budget for 2008 (about 20%)
 - No planned activities or surveillance
 - No official in charge of the drug exposure issue from May 2008



Routine measurements 2007

- About 200 external wipe samples (both Pharmacy & wards)
 - Cyclophosphamide analysed
 - Level between <LOD - 800 ng/prov
- About 100 wipe samples in Tc-tests
 - More than 90 % positive samples
- No biological samples



Apoteket Sweden

- Owned 100 % by the Government
- 980 pharmacies
- 11 000 employees
- 64 million prescriptions
- Net sale SEK 37 billion
- 32 000 daily day doses (DDD) of antineoplastic drugs



Research in Sweden

- Method development
- Equipment tests
- Arranged working situations
- Real working situations
- Focus on nursing situation in wards



Method development

- Sampling
 - Wipes (from various surfaces)



- Collected material (e.g. cover sheets, gloves)
- Aerosols (on membrane filters)
- Biological samples (e.g. blood, urine)



Wipe or air sampling?

- Air sampling (filters or adsorbents)
 - Aerosols and vapours
- Wipe sampling (wet tissue)
 - Direct spill
 - Deposited aerosols
 - Deposited condensed vapour
 - Adsorbed vapour
 - Contaminated objects
 - Distribution of spill and aerosols



Evaluation

- Tissue
- Wetting solution
- Wipe procedure
- Sample handling



Tissue

- Medical dry tissues (3 brands)
 - Purified water
 - NaOH (0,03 M)
 - HCl (0,03 M)
- Household and medical single packed wet tissues (4 brands)
 - Non-perfumed
 - Water, ethanol, (sorbic acid, preservatives)



Wipe procedure

- Surface material
- Reproducible area
- Tissue folding
- Wipe pattern



Sample handling

- Storage procedure
- Storage time
- Folding for XRF



Validation procedure

- Surfaces spiked with 1 mL CP-solution or Pt-solution
- Left over night to dry
- Wipe sampling next day
- Samples were then handled and stored
- Analysis



Tissues and wetting solutions

- Appropriate material, size with low blank and minimal analytical interferences obtained with one
 - Dry tissue (Hartmann, ScandiCare) and 1 mL NaOH (0.03M)
 - Wet tissue (Apoliva, Apoteket AB) non-perfumed with water, ethanol and sorbic acid



Surface materials

Appropriate recovery, precision and reproducibility on

- Glass
- Laminar bench top
- Plastic carpet
- Stainless steel



Area reproducibility

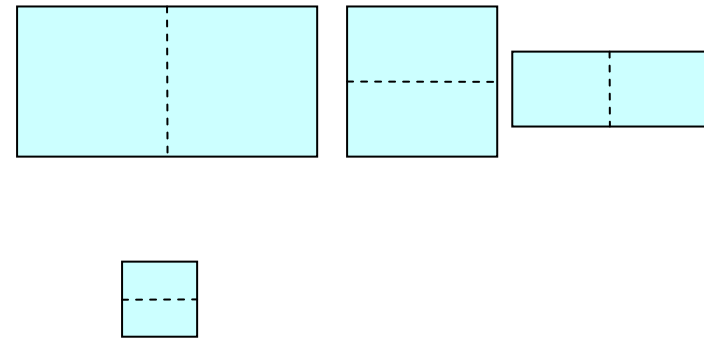
- Plastic frames
 - 10 x 10 cm (100 cm²)
 - 20 x 20 cm (400 cm²)
- Possible cross-over contamination
 - Clean between samples





Tissue folding

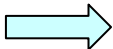
- Best procedure
 - Fold 3 times
 - Do first wipe
 - Fold once more
 - Do second wipe

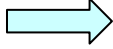


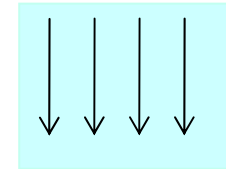
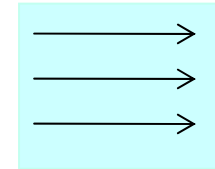


Wipe procedure

- First wipe cross-angular

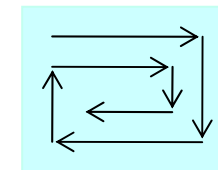
– Left  right

– Up  down



- Second wipe circular

– From edge towards center





Summary validation result

- Appropriate tissue material and wetting solution
- Appropriate wipe procedure
- Sampling on glass, laminar bench top, plastic carpet, stainless steel
- More than 98 % average recovery from all tested surface materials
- Less than 2 % average variation between individual surfaces and surface materials
- Can be stored in normal plastic bags
- Can be stored in room temperature up to 1 week
- Can be stored in freezer more than 3 month
- Can be adequately performed by unskilled person with a simple written instruction
- Suitable for self-control wipe sample kit



Compounds

- Technetium m-99 (^{m99}Tc)
- Platinum (Pt)
- Cyclophosphamide (CP)
- i-Fosfamide (i-F)
- Methotrexate (Mtx)
- Antibiotics



Method development

- $m^{99}\text{Tc}$
 - Tc-method with gamma-ray detector
- Pt
 - AdCSV
 - ICP-MS
 - XRF for on-site monitoring
- CP, i-F, Mtx, Antibiotics
 - HPLC-MS/MS





Tc-method



- Independent test of leakage from preparation systems or techniques
- Radioisotope ^{99m}Tc Technetium (^{99m}Tc), with 6 h half life, is used as tracer substance
- Standardised compounding with vials prepared with ^{99m}Tc



Sampling protocols



- Gloves, bench cover can be collected
- Wipe samples can be collected at and around the work area



Determinations

- The activity in the samples are measured
- Possible leakage is calculated from the activity with correction for the natural decay



Tc-method characteristics

- Leakage down to 1 nL/cm² can be measured
- Do not monitor vapours
- Can monitor aerosols collected on filters
- Measurements can easily be done at hospitals that perform contrast X-ray



Research in Sweden

- Comparison open/closed systems
- Characterization of real working situations
- Contamination of drug vials



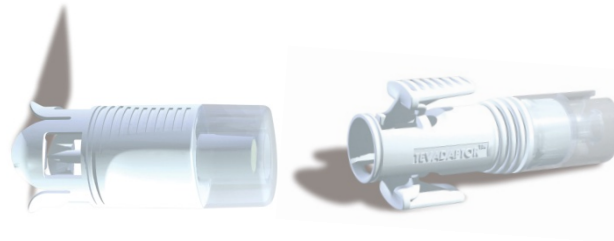
Comparison of preparation systems

- Controlled experiments
 - Same designend work area
 - Same compounding type
- Tc-method
 - Collection of cover sheet and gloves after each compounding
- Different occasions for each system



Tested systems

- Traditional milking technique
- Various spikes with or without filters
- PhaSeal™ preparation system
- Tevadaptor™ system





Results of comparisons

| Technique | Milking | PhaSeal | Tevadaptor |
|------------------------------|-----------------------|-----------------------|-----------------------|
| Max level | 262 μL | 0,085 μL | 0,054 μL |
| Mean level | 56 μL | 0,009 μL | 0,002 μL |
| Lowest level | < 0,001 μL | < 0,001 μL | < 0,001 μL |
| No of samples | 60 | 60 | 75 |
| No of persons | 10 | 10 | 8 |
| Samples > 0.01 μL | 49 | 3 | 2 |
| Persons < 0.01 μL | 0 | 8 | 6 |



Wipe samples in authentic environment, controlled

- Hospital pharmacy, cleaned BSC
- Preparation of one 1000 mg CP infusion bag with filter spike
- Five wipe samples collected inside BSC before and after preparation
- Samples analysed for CP
- No detectable CP before prep
- CP after prep 3.3 – 3.5 $\mu\text{g cm}^{-2}$



Wipe samples in authentic environment, actual

- Wipe samples collected in drug preparation facilities in hospitals (not only pharmacies) during everyday work. No special arrangements
- Four different hospitals
- CP and Pt analysed in wipe samples



Results from everyday drug preparation work

| Place | Range | | | | | N |
|-------|------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-----------------------------------|----|
| | CP wipes (pg cm ⁻³) | IF wipes (pg cm ⁻³) | Pt wipes (µg cm ⁻³) | CP urine (ng L ⁻¹) | IF urine (ng L ⁻¹) | |
| A | 0.6 – 7500 | 1.3 – 420 | | < 10 | < 30 | 30 |
| B | | | < 1 – 8 | | | 10 |
| C | 2.2 – 870 | 0.3 – 740 | | | | 15 |
| D | 4 – 4950 | | < 0.2 | | | 6 |

A – Hosp pharm, drug prep room, BSC, pharmacist

B – Ward, drug prep room with sluice, BSC, pharmacist

C – Hosp pharm, drug prep room with sluice, BSC, pharmacist

D – Ward, open drug preparation room, nurse



Surface contamination

- 14 wards (5 hosp), 5 wards and 9 outpatient wards
- 100% CP, 33% i-F
- One sampling occasion each
- Wipe samples on floor, work areas and other surfaces



Results

- Measurable CP on 59% of surfaces
- Measurable i-F on 36% of surfaces
- All floor surfaces contaminated
(median 3 pg/cm²; highest 250 pg/cm²)
- High levels in patient lavatories
(5 pg/cm² - 10 ng/cm²)
- Low levels on work areas
($<$ LOD – 2 pg/cm²)
- Detected on door and other handles
($<$ LOD – 15 pg/cm²)



Distribution of spill

- Two different facilities
- Wipe samples collected on benches or floor at increasing distance for the BSC
- Pt or CP analysed in wipe samples



Wipe samples showing gradient distribution

| Sampling place | Distance (m) | Pt ($\mu\text{g cm}^{-2}$) | CP (ng cm^{-1}) |
|--|--------------|------------------------------|----------------------------|
| Working area, inside BSC | 0 | 7.6 | 22 |
| Floor under BSC | 0.5 | | 1.82 |
| Floor, under BSC | 0,7 | 1.8 | |
| Bench-top, left of BSC | 1,5 | 0.6 | 0.32 |
| Bench-top, right of BSC | 2 | 0.5 | 0.12 |
| Bench-top, other side of the drug room | 4 | 0.2 | |
| Top of wall cupboard | 5 | | 0.05 |
| Floor, corridor outside of the drug room | 7 | < 0.1 | < 0.01 |

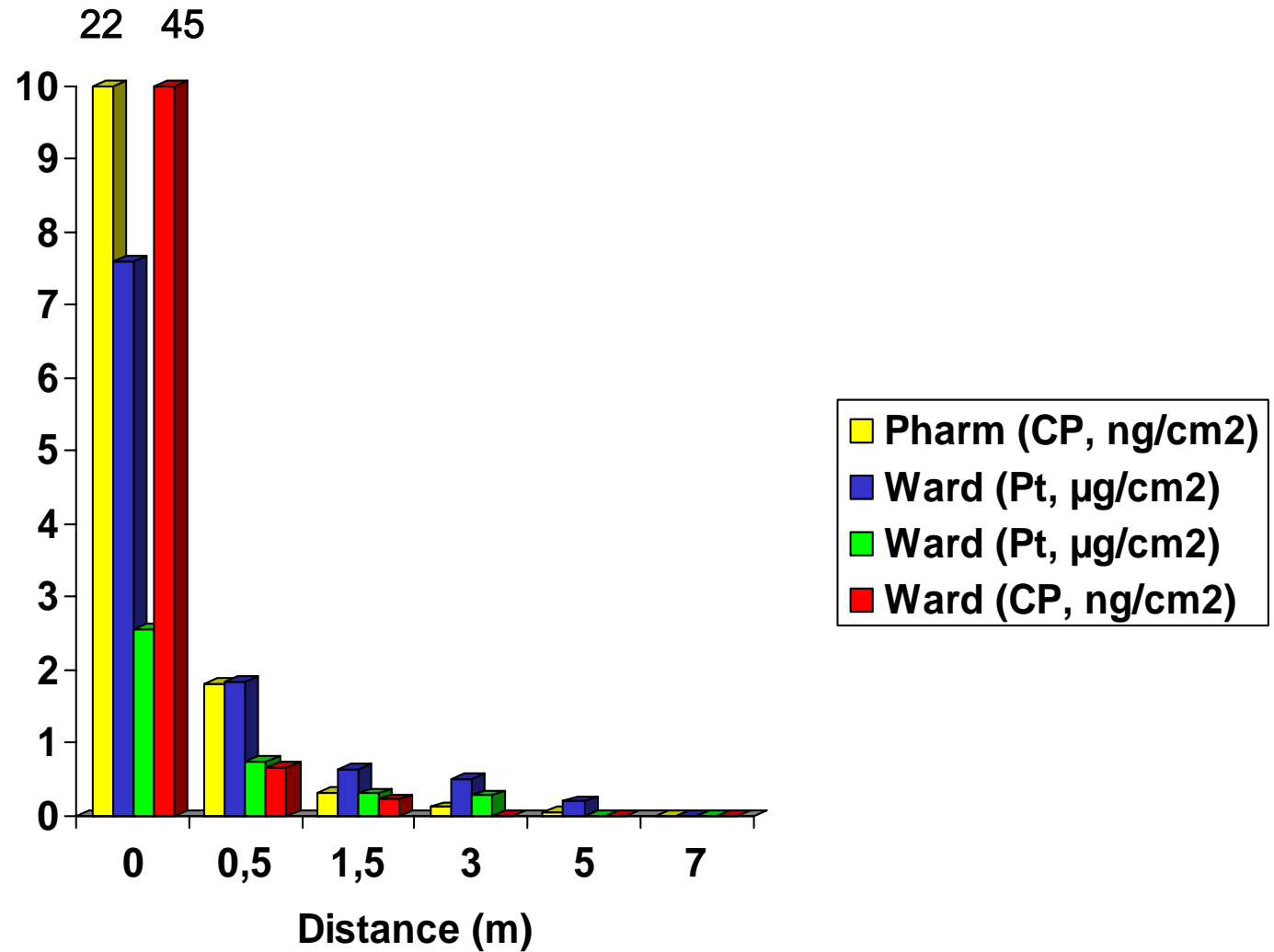


Spatial distribution

- Four drug preparation facilities
 - one pharmacy, three wards
- Wipe samples at various distances
 - inside preparation box
 - in prep room 0.5, 1.5, 3, 5 m from box
 - in corridor outside of prep room 7 m from box



Result of distribution study





Contaminated drug packages

- Cisplatin
 - vials from three manufacturers
 - 10 random vials from newly opened packages
- CP
 - Sendoxan (Baxter),
 - Vials, 200 and 100 mg powder (10 vials each)
 - Tablet blister packs 10 x 50 mg (2 packs)
 - Outer packages (cardboard boxes to above)
- Wipe samples were collected from vials, blister packs and cardboard boxes



Contamination of drug packages, cont.

| Value (ng/sample) | CisPt vials | CP blister | CP vials | CP outer box |
|-------------------|-------------|------------|-----------|--------------|
| Mean | 8.3 | 0.6 | 16 | 0.75 |
| Range | < 1–35 | <0.04–7.4 | <0.04–130 | 0.2–7.1 |
| No samples | 10 | 2 | 10 | 12 |
| | | | | |



Wipe samples on-site

- Cisplatin preparation
- Wipe samples
 - collected BSC, benches beside BSC, on the floor away from BSC, corridor
 - analysed on-site using portable-XRF
 - Results obtained directly





Preventive measures

- Centralized preparation
- BSC with separate ventilation
- Use of spikes or "Closed" systems
- Cleaning routines
- Waste handling
- Education \Rightarrow test \Rightarrow certification
- Independent tests of handling systems



Conclusions

- Wipe sampling is
 - a simple and quick sampling method for screening
 - suitable for monitoring distribution and deposition of drug aerosols
- Drug emission occur during preparation and administration
- Closed handling systems reduce the emission



Thank you for your attention



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