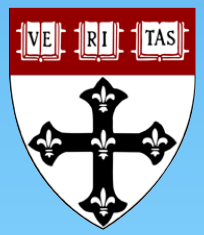
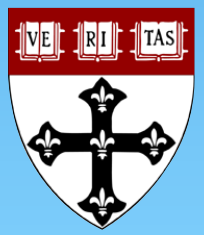
Environmental Monitoring of Cytotoxics in the Oncology Clinic: Implications for Employee Health

Toxicology Conference
Prague



Thursday
June 7, 2012



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Presentation Overview

* Introduction ~
* Basics on Cytotoxics :
* Environmental Assessment Monitoring Study –
* Questions for Occupational Health and Safety ?
* Discussion ;
* Conclusions !
* Future directions …

Introduction ~

- Several anti-neoplastic agents are categorized as carcinogens by the IARC
- Extensive experience on the adverse effects of anti-neoplastic agents dates back in the 60s and 70s with the first studies reported in the medical literature
- Documented adverse health effects
  - Acute symptoms
  - Long term consequences
  - Reproductive toxicity
- Several studies among hospital employees assessing risk of workplace exposure (prior to and after the introduction of Bio-safety cabinets) 80s

Employees at risk

* Physicians
* Nurses
* Pharmacists
* Pharmacy Technicians
* Personnel handling medications (shipping, receiving, storage)
* Cleaning staff
* Maintenance workers
* Operating room personnel
* Waste handlers

Procedures associated with exposure

- Generated
  - Dust
  - Aerosols
- Contaminated surfaces
- Medication packages
  - Storage
  - Preparation
  - Administration
  - Disposal
- Spillage accidents

Exposure routes I

- Skin absorption
  - Handling of medications
  - Handling of patients' clothing, linens etc.
  - Leakage - accidents

- Inhalation (storage, preparation, administration)
  - Dust
    - Storage
    - Transportation of diluted agents
  - Aerosol particles
    - Preparation of needles for IV bolus (air emptying)
    - Handling of drug ampoules
    - Changing of IV bags between doses
    - Ventilation defects (isolation room)

Exposure routes II

* Ingestion (contamination)
  * Food
  * Drinks
  * Smoking
* Injection
  * Needle stick injuries (Bio-safety cabinet / isolation room)

Exposure modifying factors

* Drug handling conditions
  * Bio-safety cabinet / Isolation room
* Volume of drugs processed
* Ventilation systems / negative pressure
* Frequency and duration of administration
* Use of PPEs
  * Opportunities for skin absorption
* Administration techniques
* Drug delivery systems

Categories of Human carcinogens – IARC

* Group – 1 (classified carcinogens)
  * Adequate evidence from human studies
* Group – 2
  * A (Probable carcinogens)
  * B (Possible carcinogens)
* Group – 3 (non classified)
* Group – 4 (most likely not carcinogens)

Group - 1

* Azathioprine (Imuran)
* Busulfan (Myleran)
* Melphalan (Alkeran)
* Tamoxifen citrate (Tamofen)
* Cyclophosphamide (Cytoxan)
* Chlorambucil (Leukeran)
* Combined therapy for lymphomas

Group – 2A

* Cisplatin (Platinol)
* Doxorubicin (Adriamycin)
* Procarbazine (Natulan)
* Methoxsalen (Oxsoralen)
* Lomustine (CeeNU)
* Carmustine (BiCNU)

Group – 2B

* Bleomycin
* Dacarbazine
* Mitomycin
* Streptozocin
* Daunorubicin
* Hormones (Medroxyprogesterone)

Scientific reports in the literature - I

Sessink PJ, Boer KA, Scheefhals AP, Anzion RB, Bos RP.

Occupational exposure to anti-neoplastic agents at several departments in a hospital. Environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. Int Arch Occup Environ Health. 1992;64(2):105-12.

RESULTS: Contamination of the work environment was found not only on the working trays of the hoods and on the floors of the different rooms but also on other objects like tables, the sink unit, cleaned urinals and chamber pots, and drug vials and ampoules used for preparation and packing of drugs. The gloves used during preparation of the drugs and during cleaning of the hoods were always contaminated. The uptake of CP or IF was determined by the analysis of both compounds in urine. CP or IF was detected in the urine of eight pharmacy technicians and nurses. The amounts ranged from less than 0.01 to 0.5 micrograms (median: 0.1 microgram). CP and IF were found not only in the urine of pharmacy technicians and nurses actively handling these compounds (n = 2) but also in the urine of pharmacy technicians and nurses not directly involved in the preparation and administration of these two drugs (n = 6).

- CP and IF were excreted during different periods ranging from 1.40 to 24.15h after the beginning of the working day, suggesting different times of exposure, different exposure routes, and/or inter-individual differences in biotransformation and excretion rate for these compounds.

Scientific reports in the literature - II

Valanis B, Vollmer WM, Labuhn KT, Glass AG.

Acute Symptoms associated with anti-neoplastic drug handling among nurses. Cancer Nurs. 1993 ;16(4):288-93.

OBJECTIVE: The study investigated the association between occupational exposure to anti-neoplastics and the presence of acute symptoms in a nationwide sample of 2,048 nurses and nurses aids.

RESULTS: Acute symptoms were significantly associated with skin contact while preparing and/or administering anti-neoplastic drugs. No significant association was found with skin contact of patients excreta or with skin contact while cleaning cytotoxic spillages.

- Number of doses handled and extend of protection used were significantly associated with acute symptoms, however, this effect was not independent of skin contact.

Scientific reports in the literature - III

Valanis B, Vollmer WM, Steele P.

Occupational exposure to anti-neoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. J Occup Environ Med. 1999 Aug;41(8):632-8.

RESULTS: A total of 7094 pregnancies of 2976 pharmacy and nursing staff were examined. After age during pregnancy, prior gravidity, maternal smoking during the pregnancy, and occurrence of a spontaneous abortion or stillbirth in a prior pregnancy were controlled for,

- Exposure to anti-neoplastic agents was associated:

Increased risk of spontaneous abortion (OR=1.5; 95% CI 1.2 to 1.8) and

Combined risk of spontaneous abortion and stillbirth (OR= 1.4; 95% CI 1.2 to 1.7) but not stillbirth alone.

Among the wives of exposed men, too few stillbirths occurred to allow analysis. However, for spontaneous abortion and any loss, the patterns of increased risk were similar to those seen for women, although the odds ratios were not statistically significant.

Scientific reports in the literature - IV

Dranitsaris G, Johnston M, Poirier S,Schueller T, Milliken D, Green E, Zanke B.

Are health care providers who work with cancer drugs at an increased risk for toxic events? A systematic review and meta-analysis of the literature. J Oncol Pharm Pract. 2005 Jun;11(2):69-78

RESULTS: The systematic review (1966 – 2004) identified 14 studies evaluating the outcomes of interest, seven of which were suitable for statistical pooling. Due to lack of evidence, we were unable to estimate a pooled OR for the risk of cancer and acute toxic events.

- However,

  No significant association was detected between exposure to cytotoxic drugs and

  Congenital malformations (OR = 1.64; 95% CI: 0.91-2.94) or

  Stillbirths (OR = 1.16; 95% CI: 0.73-1.82).

- In contrast, an association was identified between exposure to chemotherapy and Spontaneous abortions (OR = 1.46; 95% CI: 1.11-1.92).

CONCLUSIONS: The results of this systematic review identified a small incremental risk for spontaneous abortions in female staff working with cytotoxic agents. Health policy decision makers should effectively communicate the magnitude of this risk to their staff and implement cost effective interventions for its reduction or elimination.

Aim of the BOCOC study

* To evaluate the possible environmental contamination of the Bank of Cyprus Oncology Center workplace setting with cytotoxic medications.

Materials and Methods

* Wipe samples were taken from several surfaces at BOCOC and examined for possible contamination with cyclophosphamide, ifosphamide and 5-fluorouracil.
* In addition, gloves were collected and checked for contamination with 5-fluorouracil.
* The Environmental sampling for cytotoxics was performed at all departments of BOCOC
  * Central Pharmacy,
  * Outpatient Pharmacy,
  * Chemotherapy Pharmacy,
  * Day Care,
  * Patient wards,
  * Radiotherapy, and
  * Administration.

Materials and Methods

- On November 14 2011, wipe samples were taken and gloves were collected under the responsibility of a BOCOC team.
- Wipe samples were taken from forty positions and two pairs of gloves were also collected.
- The total surface from each sampling site was measured and the areas were calculated.
- The wipe samples were taken with Cyto Wipe Kits obtained from Exposure Control Sweden AB laboratory.
- The wipe samples were prepared by adding 140 ml of a 0.03 M NaOH solution. For the gloves 120 or 140 ml was used.
- All samples were stored frozen after sampling and during transport until sample preparation and analysis.

Sampling for Environmental Assessment of cytotoxic contamination

Department	Number of samples
Central Pharmacy (shelves, trolley)	3
Outpatient pharmacy	3
Chemotherapy pharmacy (shelves, outside the vial)	3
Day Care Unit (bed, nursing station)	5
Clean room (preparation and aseptic room)	5
Outpatient Nurses station	2
Doctor's office	2
Administration offices	2
Ward A (patient's room, nurses' station)	5
Ward B (patient's room, nurses' station)	5
Cytotoxic waste fridge	1
Waste fridge for cytotoxics	1
Junior Doctor's office	2
WC outpatient	1
Radiotherapy Department	2
Total	42

Materials and Methods

* After extraction, a part of the extract was further cleaned up according to standard procedures.
* Cyclophosphamide and ifosphamide samples were analyzed using a GC-MS method on a corresponding GC-MSMS laboratory system to improve sensitivity and specificity.
* The analysis of 5-fluorouracil was performed on an HPLC system with UV detection.
* The detection limits were 0.1 ng/ml for Cyclophosphamide and Ifosphamide and 5 ng/ml for 5-fluorouracil.
* The contamination per cm^2 was calculated assuming 100% recovery.

Cyto Wipe KIT

Estimated Cost

Table 2: Estimated cost of the Environmental Assessment			
Item	Cost	Number	Total
Sample kits	€ 31	7	€ 217
Sample Analyses	€ 78	42	€ 3,276
Postage	Estimated		€ 250
Total			€ 3,960

Sampling process . . .

Central pharmacy

Trolley

Central pharmacy

Department	Description Surface	Area Surface (cm^2)	Total Volume NaOH (ml)	[CP] (ng/ml NaOH)	CP (ng)	CP (ng/cm^2)
Central Pharmacy	Front bench	2500	157	0.84	132	0.05

Chemotherapy pharmacy

Floor

Pharmacy elevator

Day Care

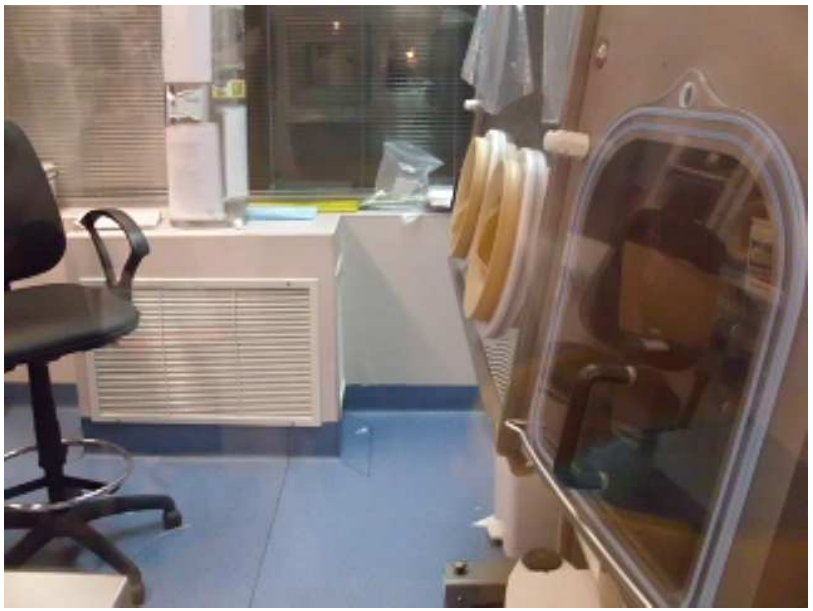
Chemotherapy transfer box

Day Care

Room A – Nursing desk

Bio-safety cabinet / Aseptic room

Department	Description Surface	Area Surface (cm^2)	Total Volume NaOH (ml)	[CP] (ng/ml NaOH)	CP (ng)	CP (ng/cm^2)
Day Care	Pair disposable gloves from checker clean room		120			
Day Care	Aseptic Unit – bench in preparation room	2500	157			
Day Care	Prepared 50 ml syringe CP		143	ND		
Day Care	Inside transfer hatch from prep room to isolator	2500	157	ND		
Day Care	Floor under foot rest isolator	2500	157			
Day Care	Work space inside isolator	2500	157	161.15	25301	10.12



Work space inside the isolator

Cytotoxic waste fridge

Ward A

Nursing station A

Prepared IV Infusion bag

Department	Description Surface	Area Surface (cm^2)	Total Volume NaOH (ml)	[5FU] (ng/ml NaOH)	5FU (ng)
Ward A	Prepared 1000 ml infusion bag 5FU		145	21.60	3132

Ward A – Inpatient Room

Floor of patient's room

Patient's bed

Area Surface (cm^2)	Total Volume NaOH (ml)	[IF] (ng/ml NaOH)	IF (ng)	IF (ng/cm^2)
2500	157	4.15	652	0.26

Ward B – Inpatient Room

Patient's toilet cap

Patient's toilet floor

Ward B

Drug preparation area B

Ward B

Infusion pump with stand

Patient Wards – Staff kitchen Table

Patient Wards - Junior doctor’s desk

Patient Wards – Room Waste bin

Radiotherapy - CT scan

Summary Results

- The results show contamination with cyclophosphamide on the work space inside the isolator and on the office phone of an outpatient medical office as well as on the front of the bench in the Central Pharmacy.
- Ifosphamide was only detected on the floor of a patient's room at Ward A.
- Contamination with 5-fluorouracil was not found in the environment.
- Instead, an IV infusion bag prepared in the isolator was contaminated with 5-fluorouracil.
- Except for the work space inside the isolator and the bag, the levels of contamination are very low.
- The two pair of used gloves were not contaminated with 5-fluororuracil.

Table 1: Cyclophosphamide (CP), ifosphamide (IF) and 5-fluorouracil (5FU)

Sample Code	Department	Description Surface	Area Surface (cm^2)	Total Volume NaOH (ml)	[CP] (ng/ml NaOH)	CP (ng)	CP (ng/cm^2)	[IF] (ng/ml NaOH)	IF (ng)	IF (ng/cm^2)	[5FU] (ng/ml NaOH)	5FU (ng)
1	Central Pharmacy	Front bench	2500	157	0.84	132	0.05					
2	Central Pharmacy	Trolley	1936	157	ND							
3	Central Pharmacy	Floor	2500	157							ND	
4	Outpatient Pharmacy	Pharmacy elevator 1st shelve	2500	157	ND							
5	Outpatient Pharmacy	Working bench	2500	157	ND							
6	Chemotherapy Pharmacy	Telephone	125	143	ND							
7	Chemotherapy Pharmacy	Outside vial		143				ND				
8	Chemotherapy Pharmacy	Shelve inside cabinet	1950	157	ND							
9	Chemotherapy Pharmacy	Floor	2500	157							ND	
10	Day Care	Staff kitchen – top of fridge next to microwave	1100	157	ND							
11	Day Care	Exit doors to waste bins	900	152	ND							
12	Day Care	Reception floor next to information booklets	2500	157	ND							
13	Day Care	Room A nursing desk	2500	157							ND	
14	Day Care	Chemo transfer box	945	157							ND	
15	Day Care	Infusion pump 012	900	155	ND							
16	Day Care	Room B, couch arm chair, right hand corner A	850	150	ND							

Table 1: Cyclophosphamide (CP), ifosphamide (IF) and 5-fluorouracil (5FU)

Sample Code	Department	Description Surface	Area Surface (cm^2)	Total Volume NaOH (ml)	[CP] (ng/ml NaOH)	CP (ng)	CP (ng/cm^2)	[IF] (ng/ml NaOH)	IF (ng)	IF (ng/cm^2)	[5FU] (ng/ml NaOH)	5FU (ng)
17	Day Care	Couch junior doctor's office	2500	157							ND	
18	Day Care	Pair disposable gloves from checker clean room		120							ND	
19	Day Care	Aseptic Unit – bench in preparation room	2500	157							ND	
20	Day Care	Prepared 50 ml syringe CP		143	ND							
21	Ward A	Prepared 1000 ml infusion bag 5FU		145							21.60	3132
22	Day Care	Inside transfer hatch from prep room to isolator	2500	157	ND							
23	Day Care	Floor under foot rest isolator	2500	157							ND	
24	Day Care	Work space inside isolator	2500	157	161.15	25301	10.12					
25	Day Care	Outpatient main reception desk end nearest corridor	2500	157							ND	
26	Day Care	Outpatient consultation office phone room 324	125	143	0.41	59	0.47					
27	Day Care	Blue chemotherapy tray after washing	806	157	ND							
28	Ward A	Nursing station A	1500	157							ND	
29	Ward A	Drug preparation area A	2500	157				ND				
30	Ward B	Drug preparation area B	2500	157							ND	

Table 1: Cyclophosphamide (CP), ifosphamide (IF) and 5-fluorouracil (5FU)

Sample Code	Department	Description Surface	Area Surface (cm^2)	Total Volume NaOH (ml)	[CP] (ng/ml NaOH)	CP (ng)	CP (ng/cm^2)	[IF] (ng/ml NaOH)	IF (ng)	IF (ng/cm^2)	[5FU] (ng/ml NaOH)	5FU (ng)
31	Ward A	Bed patient 's room (29)	120	150							ND	
32	Ward A	Floor patient's room (29)	2500	157				4.15	652	0.26		
33	Ward B	Infusion pump with stand 085	2500	157							ND	
34	Ward B	Floor patient's toilet (43)	2500	157							ND	
35	Ward B	Cap patient's toilet (43)	900	148							ND	
36	Ward	Desk junior doctor's office	2500	157							ND	
37	Ward	Waste bin room 44	1849	157							ND	
38	Ward A	Pair of gloves after administration 5FU		140							ND	
39	Ward	Table staff kitchen	2500	157							ND	
40	Administration	Front reception	2500	157	ND							
41	Administration	Fridge chemotherapy waste	1600	157	ND							
42	Radiotherapy	CT scan	2500	157	ND							

Questions ?

Discussion ;

Conclusions !

Future directions . . .

* What do we do next ?
* How do we interpret these results ?
* Should we be doing something differently ?

* How do our results compare with the international experience based on the scientific literature ?

Scientific Literature - Environmental Assessment for Cytotoxics

Table 1: Environmental assessment of Cyclophospamide in different hospitals

Variable *	BOCOC 2011	Japan - Nagoya University Hospital 2010	Swedish Hospital Pharmacy 2005	Netherlands Four Hospital Departments 1992	Six British Columbian Hospital Pharmacies 2011
Mean (ng/ml)	3.55 (0.26) (5)	1.79 (16)	-	-	-
Lower	0.05 (0.05)	0.01	0.60	0.10	0.06
Higher	10.12 (0.47)	7.18	2.33	4500	8.53
Absolute higher value	25301 (132)	23706	2100	8300	426
Percentage	12%	94%	100%	-	61%

* **What is the association between environmental contamination with cytotoxic drugs and employees' occupational exposure ?**

Uptake of antineoplastic agents in pharmacy personnel. Part II: study of work-related risk factors

Int. Arc. Occup Env. Healt; 2003 Feb;76(1):11-6. Epub 2002 Oct 9.

* OBJECTIVES: This study aimed to find working conditions related to internal exposure of substances handled in centralised cytostatic drug preparation units in hospitals.
* METHOD: In a longitudinal study over 3 years, 87 pharmacy technicians and pharmacists of 14 different hospitals in Germany provided 24-h urine samples separately up to three times (three sampling cycles: cycles 1-3) at the end of a working week. Cyclophosphamide and ifosfamide, doxo-, dauno- epi-, and idarubicin, and platinum deriving from cis- and carboplatin were determined in urine samples by gas chromatography/mass spectrometry, liquid chromatography (HPLC) and voltammetry. The following working conditions were assessed by questionnaire: working tasks, different ways that the workbenches were run, cleaning conditions, waste disposal, number of preparations, amount of substances handled, and use of gloves (material, thickness and changing interval). 13 pharmacies used laminar air flow (LAF). 1 with isolation system.
* RESULTS: Two-thirds of the subjects showed at least one positive result with regard to all three cycles (56 of initially 87 subjects – 64%). Employees who only pass material that is needed for processing are affected, just as are those who only prepare administrations and those alternating in both functions (25% vs. 24.1% vs. 50.6%, respectively). The storage of waste in containers that could be opened to add waste tends to increase the risk of internal exposure of ifosfamide and cyclophosphamide (odds ratios (95% confidence interval): 0.08 (0.013-0.5) and 0.19 (0.03-1.12), respectively). The amount handled and number of preparations of cyclophosphamide for "manufacturers" were associated with internal exposure of cyclophosphamide (28.04 (1.75-448.74) and 1.22 (1.03-1.44), respectively). The total number of preparations handled by assistants seemed to increase the risk of intake of any of the substances under study [1.04 (1.00-1.08)].
* CONCLUSION: Since employees who pass materials are affected in the same way as those who prepare administrations, both have to be included in reviewing protective measures. Further studies must be carried out to verify the generated hypotheses of factors related to internal exposure found in this study.

Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to CP.

J Oncol Pharm Pract; 2011 Mar;17(1):14-9. Epub 2010 Feb 23.

* In Japan, concerns exist regarding the dangers inherent when handling cytotoxic drugs, particularly drugs such as 5-FU, Thiotepa, Cytarabine, Tegaful, and Sizofiran which are contained in ampoules or vials, since nurses and medical doctors have been preparing these cytotoxic drugs in the open spaces of wards in the absence of appropriate garments and personal protective equipment. In addition, the administration tubes for these dangerous drugs have been exchanged at the patients' bedside, typically in rooms shared by several patients. To gain insight into the severity of the occupational hazards posed by these practices, we conducted a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide (CP).
* SETTING: At Nagoya University Hospital, Nagoya, Japan, in February 2006, two departments, A and B, were monitored with surface-wipe, and urine samples were analyzed using the Sessink method (exposure control, The Netherlands). Department A had a preparation room with biological safety cabinet (BSC) where the pharmacists prepare cytotoxic drugs. Department B did not have a BSC.
* RESULTS: Many areas of the treatment rooms were contaminated with CP. CP was detected on tables and telephone stands where cytotoxic drugs were not used as well as tables used to prepare cytotoxic drugs. Significant differences in CP concentrations were detected from the urine of two of the three nurses who cared for the same patients without gloves. The nurses rotated and inherited the patient who had the highest risk of contamination. CP was detected only once from the urine of the medical doctor who prepared CP. He was not wearing any PPE other than gloves. All of the pharmacists wearing PPE were free from contamination of CP.
* DISCUSSION: Regardless of the use of BSC, wards were contaminated with CP. The contamination may not occur due to the sealing used in CP containers and administration tubes when discarding them. CP was detected only once in the urine of a medical doctor who prepared CP by warming it. The cause may be inhalation of CP gas from the injector. The contamination of the nurses may be from dermal absorption because absorption continued even after the shift ended and the nurses left the facility. CP was not detected in pharmacists who followed the guidelines for preparation of CP. All of the medical staff should follow the guidelines when they handle CP.

Association between occupational exposure levels of antineoplastic drugs and work environment in five hospitals in Japan.

J Oncol Pharm Pract; 2011 Mar;17(1):29-38. Epub 2010 Aug 10.

* PURPOSE: The aim of the present study was to evaluate the measurement of contamination by antineoplastic drugs for safer handling of such drugs by medical workers. We investigated the relationship between the contamination level of antineoplastic drugs and the conditions of their handling.
* METHODS: Air samples and wipe samples were collected from equipment in the preparation rooms of five hospitals (hospitals A-E). These samples were subjected to measurement of the amounts of cyclophosphamide (CPA), fluorouracil (5FU), gemcitabine (GEM), and platinum-containing drugs (Pt). Twenty-four-hour urine samples were collected from the pharmacists who handled or audited, the antineoplastic drugs were analyzed for CPA and Pt.
* RESULTS: Pt was detected from air samples inside BSC in hospital B. Antineoplastic drugs were detected from wipe samples of the BSC in hospitals A, B, D, and E and of other equipment in the preparation rooms in hospitals A, B, C, and D. Cyclophosphamide and 5FU were detected from wipe samples of the air-conditioner filter in hospital A, and CPA was detected from that in hospital D. Cyclophosphamide was detected from urine samples of workers in hospitals B, D, and E.
* CONCLUSION: The contamination level of antineoplastic drugs was suggested to be related with the amount of drugs handled, cleaning methods of the equipment, and the skill level of the technique of maintaining negative pressure inside a vial. In order to reduce the contamination and exposure to antineoplastic drugs in the hospital work environment very close to zero, comprehensive safety precautions, including adequate mixing and cleaning methods was required in addition to BSC and closed system device.

* **What is the etiological basis between current exposure levels to cytotoxic drugs and adverse health outcomes ?**

Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide.

Int Arch Occup Environ Health 1995;67(5):317-23.

* In the present study a cancer risk assessment of occupational exposure to cyclophosphamide (CP), a genotoxic carcinogenic antineoplastic agent, was carried out following two approaches based on (1) data from an animal study and (2) data on primary and secondary tumors in CP-treated patients. Data on the urinary excretion of CP in health care workers were used to estimate the uptake of CP, which ranged from 3.6 to 18 micrograms/day. Based on data from an animal study, cancer risks were calculated for a health care worker with a body weight of 70 kg and a working period of 40 years, 200 days a year (linear extrapolation). The life-time risks (70 years) of urinary bladder cancer in men and leukemias in men and women were found to be nearly the same and ranged from 95 to 600 per million. Based on the patient studies, cancer risks were calculated by multiplication of the 10-year cumulative incidence per gram of CP in patients by the estimated mean total uptake in health care workers over 10 years, 200 days a year. The risk of leukemias in women over 10 years ranged from 17 to 100 per million using the secondary tumor data (linear extrapolation). Comparable results were obtained for the risk of urinary bladder tumors and leukemias in men and women when primary tumor data were used. Thus, on an annual basis, cancer risks obtained from both the animal and the patient study were nearly the same and ranged from about 1.4 to 10 per million. In The Netherlands it is proposed that, for workers, a cancer risk per compound of one extra cancer case per million a year should be striven for ("target risk") and that no risk higher than 100 per million a year ("prohibitory risk") should be tolerated. From the animal and the patient study it appears that the target risk is exceeded but that the risk is still below the prohibitory risk.
* 1 microgram = 1000 nanograms (3600 ng – 18000 ng) (2.6 ng – 19.8 ng) 0.0055

* **Are the current levels of cytotoxic contamination dangerous for hospital employees ?**

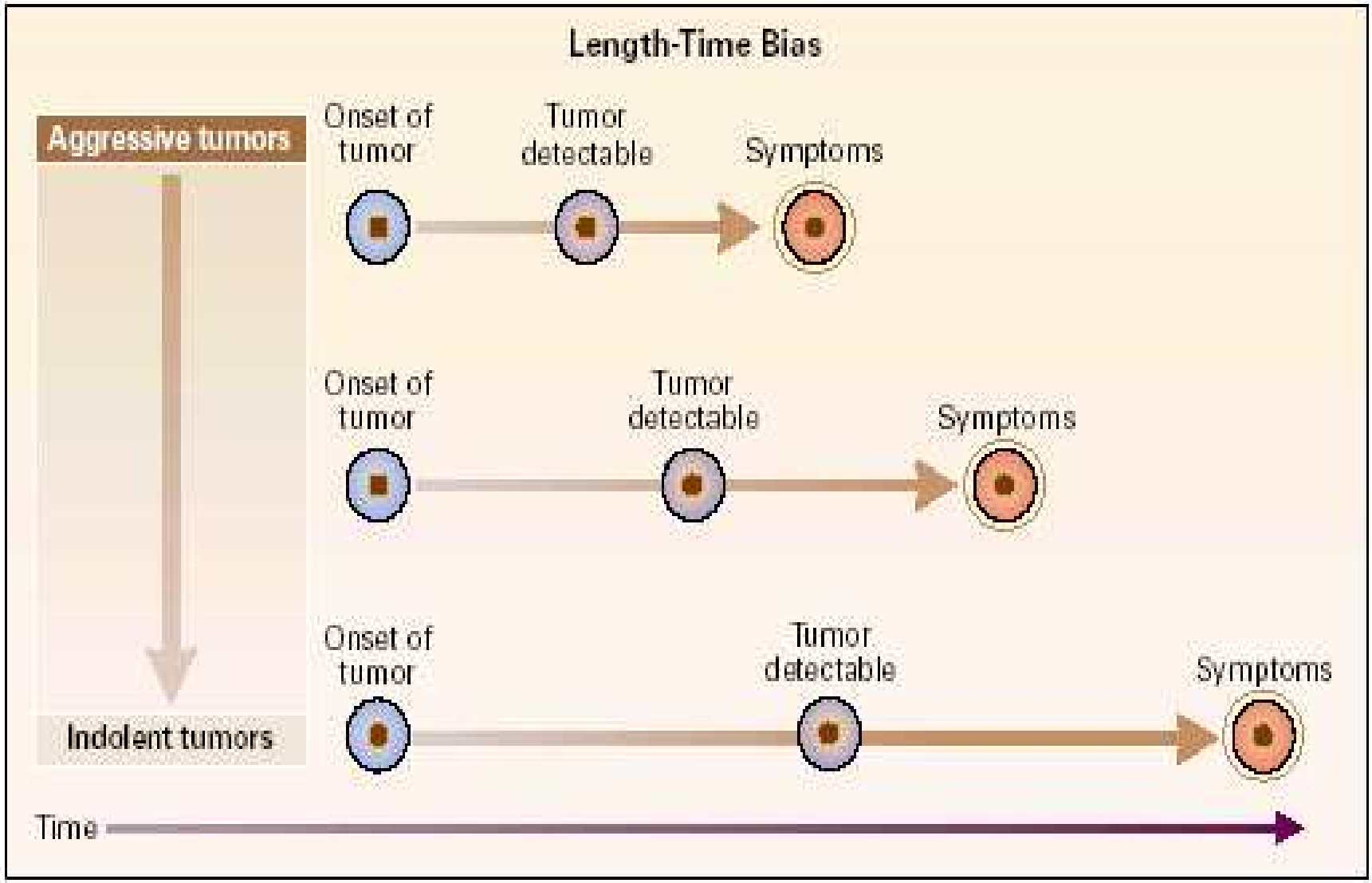


Figure 2. Length-Time Bias.

The probability of detecting disease is related to the growth rate of the tumor. Aggressive, rapidly growing tumors have a short potential screening period (the interval between possible detection and the occurrence of symptoms). Thus, unless the screening test is repeated frequently, patients with aggressive tumors are more likely to present with symptoms. More slowly growing tumors have a longer potential screening period and are more likely to be detected when they are asymptomatic. As a result, a higher proportion of indolent tumors is found in the screened group, causing an apparent improvement in survival.

How could we quantify the risk to Healthcare Workers ?

* Sister chromatid exchanges (SCE)
* Micronuclei (MN)
* DNA damage (Comet assay)
* Chromosomal Aberrations (CA)

Evaluation of genotoxic effects induced by exposure to antineoplastic drugs in lymphocytes and exfoliated buccal cells of oncology nurses and pharmacy employees.

Mutat Res; 2005 Nov 10;587(1-2):45-51. Epub 2005 Oct 3.

* The continuous introduction of new antineoplastic drugs and their use as complex mixture emphasize the need to carry out correct health risk assessment. The aim of this study was to evaluate genotoxic effects of antineoplastic drugs in nurses (n=25) and pharmacy technicians (n=5) employed in an oncology hospital. The nurses administered antineoplastic drugs in the day-care hospital (n=12) and in the wards (n=13), and pharmacy technicians prepared the drugs in the central pharmacy. We performed the micronucleus (MN) test with lymphocytes and exfoliated buccal cells and conducted traditional analysis of chromosomal aberrations (CA). Thirty healthy subjects were selected as controls. Monitoring of surface contamination with cyclophosphamide, 5-fluorouracil, ifosfamide, cytarabine, and gemcitabine showed the presence of detectable levels only for cyclophosphamide, 5-fluorouracil and ifosfamide. In addition, we measured the 5-fluorouracil metabolite alpha-F-betaalanine in the urine of all subjects and found significant concentrations only in 3 out of 25 nurses. The micronucleus assay with lymphocytes did not show significant differences between exposed and control groups, while the same test with exfoliated buccal cells found higher values in nurses administering antineoplastic drugs than in pharmacy employees. In the CA analysis, we detected in exposed groups a significant increase (about 2.5-fold) of structural CA, particularly breaks (up to 5.0-fold). Our results confirm the genotoxic effect of antineoplastic drugs in circulating blood lymphocytes. Moreover, in exfoliated buccal cells the data show more consistent genetic damage induced during administration of the antineoplastic drugs than during their preparation. The data also stress the use of this non-invasive sampling, to assess occupational exposure to mixture of chemicals at low doses.

The genotoxic risk of hospital, pharmacy and medical personnel occupationally exposed to cytostatic drugs--evaluation by the micronucleus assay.

Mutat Res; 2001 Oct 18;497(1-2):101-9.

* The aim of this study was to evaluate the genotoxicity of cytostatic drugs in hospital and pharmacy employees (n=100), occupationally exposed. The micronucleus assay was used to study lymphocytes in 247 peripheral blood samples. Samples were collected at "baseline level" without any cytostatic drugs exposure before recruiting or after at least 3 weeks without cytostatic drugs contact and at three times (cycle 1-3) post-exposure. Samples from 60 office employees served as controls. Furthermore, our results were compared to urinary analyses of cytostatic drugs (oxazaphosporines, anthracyclines, platinum) which were collected in parallel to the cytogenetic investigation. Statistical analyses were performed under consideration of age, gender and X-ray exposure. The frequency of micronuclei was significantly related to the age of the subjects (r(Spearman)=0.16; P<0.05). However, there were no significant differences in micronucleus rates between controls and exposed hospital workers. Similarly, micronucleus rates were not significantly different at the various sampling time points and there was no correlation between duration of employment and micronucleus rates. Furthermore, no correlation between current biomonitoring data of exposure (urine tests) and micronuclei frequency was found. Therefore, significantly increased genotoxic damage of the lymphocytes investigated in this study could not be demonstrated.

* **What can we do to improve the current situation ?**

Exposure to hazardous drugs in healthcare: an issue that will not go away. J Oncol Pharm Pract; 2011 Mar;17(1):9-13.

- Comprehensive safety precautions
  - Cleaned vials and packages
  - Cleaning practices in the BSC and elsewhere
  - Personal protective equipment
- Adequate preparation techniques (negative pressure)
- Biological safety cabinet use
- Continuing education programs for Employees
- Closed-system drug transfer devices (CSDTD)

Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device.

J Oncol Pharm Pract; 2011 Mar;17(1):39-48. Epub 2010 Feb 15.

* **PURPOSE: Surface contamination with the antineoplastic drugs cyclophosphamide, ifosfamide, and 5-fluorouracil was compared in 22 US hospital pharmacies following preparation with standard drug preparation techniques or the PhaSeal® closed-system drug transfer device (CSTD).**
* **METHODS: Wipe samples were taken from biological safety cabinet (BSC) surfaces, BSC airfoils, floors in front of BSCs, and counters and analyzed for contamination with cyclophosphamide, ifosfamide, and 5-fluorouracil. Contamination was reassessed several months after the implementation of the CSTD. Surface contamination (ng/cm(2)) was compared between the two techniques and evaluated with the Signed Rank Test.**
* **RESULTS: Using the CSTD compared to the standard preparation techniques, a significant reduction in levels of contamination was observed for all drugs (cyclophosphamide: $p < 0.0001$; ifosfamide: $p < 0.001$; 5-fluorouracil: $p < 0.01$). Median values for surface contamination with cyclophosphamide, ifosfamide, and 5-fluorouracil were reduced by 95%, 90%, and 65%, respectively.**
* **CONCLUSIONS: Use of the CSTD significantly reduces surface contamination when preparing cyclophosphamide, ifosfamide, and 5-fluorouracil as compared to standard drug preparation techniques.**

Conclusions !

* The environmental assessment of the Bank of Cyprus Oncology Center indicates limited cytotoxic contamination of the workplace most likely associated with preparation and administration of cytotoxic drugs.

* Contamination during the preparation procedure is supported by the detection of cytotoxics in the BSC and on the prepared IV infusion bag. Contamination during drug delivery is supported by the occasional positive findings in Ward A.

Conclusions !

- Prepared bags may further spread contamination into the workplace environment.
- Current observations stress the importance of using state-of-the-art techniques to perform each and every procedure associated with cytotoxics handling in the hospital environment:
  - Storage and transfer,
  - reconstitution,
  - administration,
  - disposal, and
  - cleaning.

Conclusions !

* The use of Personal Protective Equipment at all steps and by all employees involved in the process cannot be highlighted enough.
  * Administrative personnel
  * Employees working in the Hospital storage facilities,
  * Pharmacy personnel,
  * Pharmacy technicians,
  * Nurses,
  * Physicians,
  * Cleaning staff.

Conclusions !

* The results of the environmental assessment for cytotoxics at the Bank of Cyprus Oncology Center were similar and perhaps even better compared to findings from other hospitals around the world.

* Assumed risk potentially associated with the levels of cytotoxics detected, is thought to be minimal for employees at the BOCOC, if exists at all.

Future directions . . .

* Should we repeat environmental assessment ?
* Is biological monitoring of BOCOC employees warranted ?

Future directions . . .

* Next steps:
  * Enhanced employee education program,
  * Further evaluation of preparation and reconstitution processes,
  * Re-evaluation of written policies and procedures,
  * Improved cleaning practices,
  * Optimization of use of the closed-system drug transfer devices.
* Repeated environmental assessment of the workplace and/or biological monitoring of employees in due course may be warranted.


Thank you