EXPOSURE CONTROL
monitoring and consultancy

Antineoplastic Drug Monitoring

Dr. Paul J.M. Sessink PhD

Exposure Control B.V.
The Netherlands

www.exposurecontrol.nl

Dr. Paul J.M. Sessink PhD

- 1980-1988 Chemistry
- 1988-1993 PhD study / Thesis

  “Monitoring of occupational exposure to antineoplastic drugs”
- 1995 Exposure Control B.V.

  Consultancy for monitoring of occupational exposure to antineoplastic drugs

  (sampling – analysis – advise)
- 1996 PhD Medical Sciences

Antineoplastic Drug Monitoring

- Introduction
  - Toxicity (genotoxic carcinogens)
  - Safety guidelines and personal protection
  - Directive EU carcinogenic compounds
- Monitoring
  - Environmental and biological monitoring
  - Cyto Wipe Kits and Cyto Urine Kit
- Environmental contamination (results from several studies)
  - Preparation: gloves, BSC, surface contamination
- Urine analysis
- Cancer risk
- Benchmarking model for environmental contamination
- Health based surface contamination limits
- Conclusions

Toxicity of antineoplastic drugs

Acute effects

- Irritation (skin, eyes)
- Alopecia
- Nausea
- Vomiting
- Diarrhea
- Organs (liver, kidney, bladder, lung)
- Bone marrow suppression

Delayed effects

- Reproductive effects
  - Spontaneous abortions
  - Malformations off-spring
  - Low birth weight
  - Prolonged time to pregnancy
- Menstrual dysfunction
- Mutagenicity
- Carcinogenicity
  - Genotoxic/Non-genotoxic
  - IARC classification

Genotoxic carcinogens

Mechanism of action

→ Absence no-adverse-effect level supposed:

one molecule is able to induce cancer !

→ Exposure has to be avoided
→ Workers need to be protected
→ Safety guidelines and protective measures
→ Monitoring of the workers

Council Directive European Union Carcinogenic Compounds

28 June 1990

STRATEGY (decreasing priority)

1) replacement by a less toxic compound

   If not possible →

2) reduce sources of exposure

   If not possible →

3) ventilation

   If not possible →

4) personal protection

Council Directive European Union Carcinogenic Compounds

28 June 1990

STRATEGY FOR ANTINEOPLASTIC DRUGS

1) replacement by a less toxic compound

→ Impossible

2) reduce sources of exposure

→ Closed systems

3) ventilation

→ Clean rooms with BSCs

4) personal protection

→ Gloves, gowns, masks, special clothes, …

Environmental and Biological Monitoring

Environmental Monitoring

- Measures the presence/release of the drug in the environment
- No information about uptake of the drug in the body of the worker
- No information about health-risk for the worker

Biological Monitoring

- Assessment of uptake of the drug in the body of the worker
- Estimation of health-risk for the worker

Monitoring antineoplastic drugs
Exposure Control B.V.

Environmental Monitoring

• Cyclophosphamide	0.1 ng/ml sample
• Ifosphamide	0.1 ng/ml sample
• 5-Fluorouracil	20 ng/ml sample
• Methotrexate	5 ng/ml sample
• Platin compounds (cis-platin & carbo-platin)	0.2 ng/ml sample
• Etoposide	50 ng/ml sample
• Mitomycine C	100 ng/ml sample

Analysis:
HPLC, GC-MSMS, Voltammetry

Monitoring antineoplastic drugs
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Biological Monitoring (urine)

• Cyclophosphamide	+/- 0.1 ng/ml sample
• Ifosphamide	+/- 0.1 ng/ml sample
• 5-Fluorouracil (a-fluoro-ß-alanine)	20 ng/ml sample

Analysis:
GC-MSMS

Cyto Wipe Kits – 4 types

- 6 x 2 = 12 tissues
- 6 droppers with 17 ml solution
- 6 containers, labels and plastic mini bags
- 6 pair of gloves
- registration form
- label address lab Exposure Control B.V.
- waterproof pen
- instruction of use

Cyto Urine Kit

This urine kit contains the materials to take 10 urine samples (24 hour period)

- 10 vacuette urine tubes and labels
- 1 urine transfer device
- measuring cup
- registration form
- label address lab of Exposure Control B.V.
- instructions of use
- waterproof pen

Sources of contamination and potential exposure

- External vial contamination
- Spillage during preparation and administration (handling technique)
- BSC/isolator
- Patient (urine, sweat, vomit, blood, faeces)
- Waste
- Laundry and clothing patient

Glove contamination during preparation of antineoplastic drugs

Pair of gloves	Drug	N(pos)	Range (µg/pair)
17	Cyclophosphamide	8	1.5 – 9.6
	5-Fluorouracil	11	21 – 620
	Methotrexate	2	220 – 1900
10	Cyclophosphamide	1	37
	5-Fluorouracil	10	16 – 1040
	Methotrexate	4	19 – 156

Conclusion: most gloves contaminated during preparation

Contamination BSC

Day	Before preparation	After preparation	After alcohol cleaning
1	+	+	+
2	+++	++	+
3	+	-	-
4	-	-	+

Drugs analyzed: cyclophosphamide - 5-fluorouracil - methotrexate

+ one drug detected

++ two drugs detected

+++ three drugs detected

- no drugs detected

Conclusion: contamination and ineffective cleaning procedure

Surface contamination with cyclophosphamide in preparation areas (ng/cm^2)

**Connor et al., Am J Health-Syst Pharm 1999; 56:1427-32*

Description surface	Canada*	USA*	Belgium	Sweden	Germany	Netherlands
Table top cyto preparation/BSC	0.01-2.63	0.05-40.13	0.13-6.61	4.74-15.32	14.02-14.22	0.01-1.16
Floor under BSC	0.05-0.32	0.03-2.40	0.05-0.55	1.79	0.05	0.01-0.03
Floor central preparation room	0.11-0.16	0.01-2.36	0.15-0.31	1.24	1.77	0.01-0.02
Table top not for cyto preparation				0.02	0.03-0.19	0.01-0.36
Floor entrance preparation room				0.52	0.16	0.01-0.02
Floor entrance preparation room/corridor		0.01-0.13	0.14-0.19	0.09		0.01

Contamination with cyclophosphamide (ng/cm^2) in a clean room 1997-2004 (NL)

Spot	1997 (n=4)	2002 (n=4)	2004 (n=8)	2004 (n=3)
Surface LAF left	ND - 0.10	ND - 0.01	ND	
Airfoil LAF left	0.02 - 0.08	ND	ND	
Floor LAF left	ND – 0.01	ND - 0.01	ND – 0.01	ND
Surface LAF right	0.05 – 1.16	ND - 0.64	0.10 – 1.15	ND
Airfoil LAF right	1.52 – 7.71	ND - 0.22	ND - 0.03	ND
Floor LAF right	ND - 0.01	ND	ND - 0.01	ND
Table	ND - 0.02	ND	ND - 0.01	ND

ND: Not Detected

Conclusion: Reduction of contamination in time

Surface contamination with cyclophosphamide in preparation areas reduced with PhaSeal

**Sessink et al., submitted to Am J Health-Syst Pharm*

22 US Hospital Pharmacies 2001-2005	Cyclophosphamide (ng/cm^2)				
Surface	N	Min-Max		**Median**	
		Standard techniques	PhaSeal	**Standard techniques**	**PhaSeal**
BSC surface	30	< 0.01-17.19	< 0.01-5.41	**0.13**	**0.02**
BSC airfoil	26	< 0.02-158.00	0.01-17.15	**3.86**	**0.20**
Floor in front BSC	29	< 0.01-34.76	< 0.01-16.33	**0.14**	**0.01**
Counter	29	< 0.01-122.27	< 0.01-0.90	**0.03**	**0.03**
				P < 0.0001	

Cyclophosphamide (CP) in urine of technicians preparing cytotoxic drugs 1986-2002 (NL)

Year	Number of technicians	Collection period (days)	Mean amount CP in urine (µg/day)	Range CP (µg/day)
1986	20	4	0.39	0 - 2.5
1992	2	2	0	0
1992	18	1 – 2	0.05	0 - 0.5
1994	9	1 – 2	1.36	0 - 10.05
1995	**8**	**8 – 16**	**0.18**	**0.01 - 0.53**
1996	9	5	0.16	0 - 0.51
1997	4	2	0.013	0 - 0.04
1999	7	1 – 2	0	0
2002	4	2	0.003	0 - 0.014

Additional cancer risk exposure to cyclophosphamide

- **Technicians**
  - 0.18 µg CP in urine/day
  - 1.4-10 extra cancer cases a million workers a year
- **Nurses**
  - 0.80 µg CP in urine/day
  - 10-50 extra cancer cases a million workers a year

- **Prohibitory risk level**
  - 100 extra cancer cases a million workers a year
- **Strive risk level**
  - 1 extra cancer case a million workers a year

Conclusion

strive risk level not achieved →

too high exposure levels

Benchmarking model for environmental contamination

- Comparison of contamination with comparable reference studies
  - Per country
  - Preparation or administration
  - Per drug
  - Contamination level ng/cm^2 (low – medium – high)
  - Spread (no spread – some spread – totally spread)
- Ranking (high – medium – low)
- Long-term result: contamination will be reduced

Health based (cancer) surface contamination limits for cyclophosphamide in hospitals

	Strive risk level			Prohibitory risk level
Urine CP (µg/24 hr)	< 0.02	0.02 – 0.2	0.2 - 2	> 2
Contamination CP (ng/cm^2)	< 0.1	0.1 – 1	1.0 – 10	> 10
Action	No	Yes At short notice	Yes Immediately	Yes Stop working
Monitoring	Now and then	Yes	Yes	Yes

Conclusions

- Antineoplastic drugs are spread in the environment during preparation, administration, patient care and waste handling
- Healthcare workers are exposed to antineoplastic drugs
  - Current preparation and administration techniques need to be improved
- The main exposure routes are:
  - Dermal uptake → contact with contaminated surfaces
  - Inhalation → particles (vapors?)
- Depending on the level of exposure:

  → additional cancer risk for hospital workers handling antineoplastic drugs

  → reproductive effects unknown (more sensitive?)
- Development of health based surface contamination limits is recommended for monitoring
- Till then, a bench marking model is a good alternative to reduce environmental contamination