Research centre for toxic compounds in the environment

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Cytotoxic drugs

adverse effects, risks, monitoring

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CYTO project - Czech Republic

http://www.cytostatika.cz

- 2006-2010, specific research grant 2B06171
  - Hospital pharmacy
  - Pharma company
  - ~ 3 full time persons

Objectives

- ✓ study / evaluate occupational risks of cytostatics in the Czech Republic *(pharmacies)*
- ✓ to evaluate existing measures & suggest possible improvements
- ✓ suggest (reasonable) monitoring procedures

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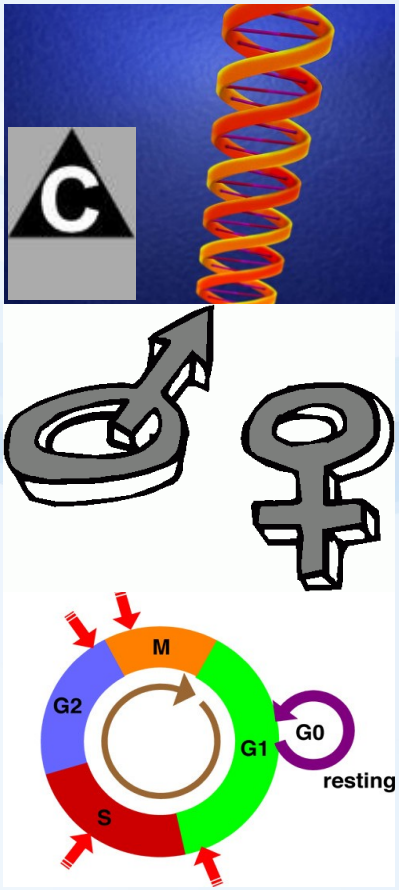
CYTOTOXIC DRUGS - „hazardous drugs“

- **„Hazards“** (will be discussed in detail)
  - Genotoxicity
    (urine mutagenicity, micronuclei)
  - Reproduction toxicity
  - Teratogenicity / developmental toxicity
  - Organ toxicity at low doses
    (hepatotoxicity, immunotoxicity)
  - Carcinogens (13 therapies - IARC class 1)



CYTOTOXIC DRUGS - „hazardous drugs“

- **„Hazards“**
  cytotoxic drugs may cause adverse effects

- **Present situation –** increased occupational risks
  - More patients with malignant tumors
  - More treatments and their combinations, higher doses
  - Drugs with higher efficiency, new procedures

- **Source of the occupational „hazard“ problem**
  - **Primary focus – safety of the patient**
    - QA/QC in preparation, microbiological safety …
  - **Secondary … workers safety (pharmacists etc.)**

Risk Assessment - definitions

- **Hazard**: inherent capacity of a chemical to cause effects
- **Risk**: probability of the effect occurrence

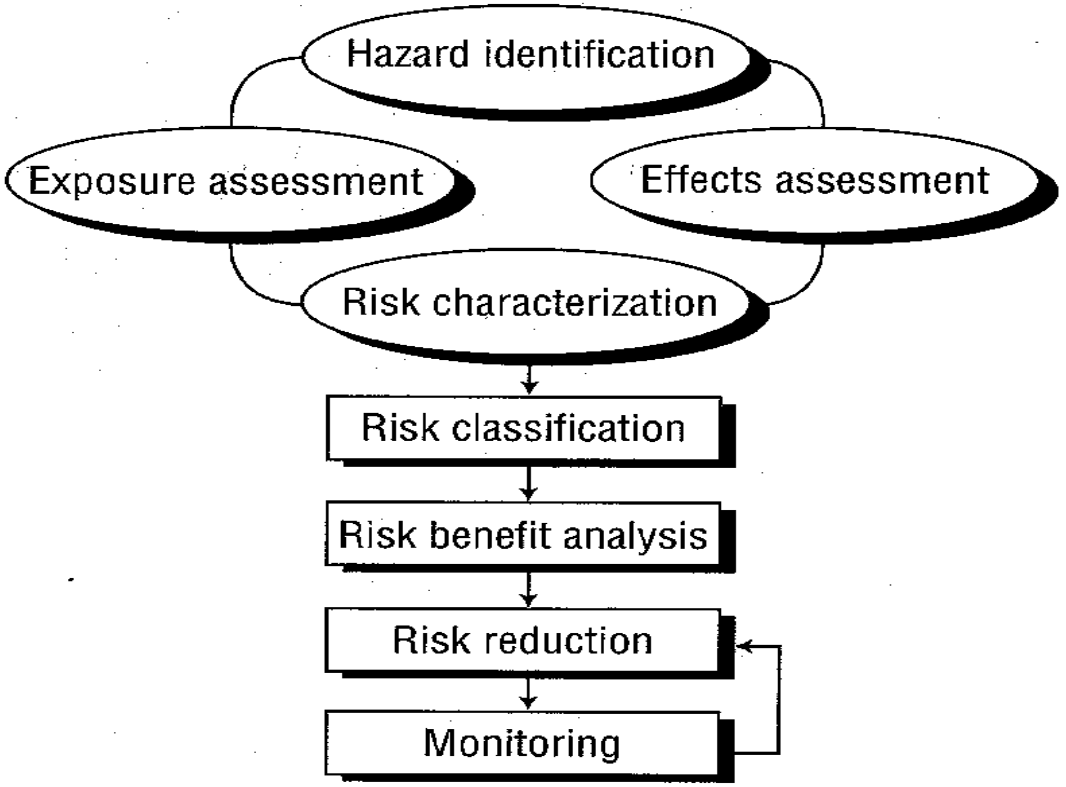


Figure 1.3. Steps in the risk management process.

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Examples – HAZARD vs. RISK

RISK **Exposure to *HAZARD***

Table 1.5. Annual mortality rate associated with certain occurrences and activities in the Netherlands [23]

Activity/occurrence	Annual mortality rate	
Drowning as a result of dike collapse	10^{-7}	1 in 10 million
Bee sting	$2x10^{-7}$	1 in 5 million
Struck by lightning	$5x10^{-7}$	1 in 2 million
Flying	$1.23x10^{-6}$	1 in 814,000
Walking	$1.85x10^{-5}$	1 in 54,000
Cycling	$3.85x10^{-5}$	1 in 26,000
Driving a car	$1.75x10^{-4}$	1 in 5,700
Riding a motorbike	$2x10^{-4}$	1 in 1,000
Smoking cigarettes (1 packet a day)	$5x10^{-3}$	1 in 200

Risk Assessment step 1: Hazard identification

- Goal: identification of the adverse effects which a substance has the inherent capacity to cause
- Method: gathering and evaluating data on the types of health effects or disease that may be produced by a chemical and exposure conditions under which damage, injury or disease will be produced

- Hazard of cytotoxic drugs – **2 scenarios**
  - Therapeutic doses (patients)
  - Occupational exposures (workers)

Hazard - carcinogenicity

IARC - INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
www.iarc.fr

Group 1 (Carcinogenic to humans)	Group 2A (Probably carcinogenic)
Arsenic trioxide	Azacitidine
Azothioprin	BCNU
Chlorambucil	CCNU
Chlomaphazine	Chlorozolocin
Cyclophosphamide	Cisplatin
Myleran	Doxorubicin HCL
Melphalan	N-Ethyl-N-Nitrosourea
Semustine	Etopside
Tamoxifen	Mechlorethamine HCL
Thiotepa	N-Methyl-nitrosourea
Treosulfan	Procarbazine HCL
Mustargen-Oncovin-Procarbazine-Pednisone (MOPP)	Teniposide
Etopside-Cisplatin-Bleomycin (ECB)	

Hazards – effects observed at **THERAPEUTIC** doses

REPRODUCTION RELATED EFFECTS

- Reproduction toxicity
- Developmental toxicity (embryotoxicity, teratogenicity)

Other organs-specific toxicity

- Hepatotoxicity, Renal toxicity, Cardiotoxicity …
- Growing tissues (cell replication) – Dermal, Hair, GIT, Haemopoesis (Immunotox.)

US Food & Drug Administration (FDA) – Drug hazard during pregnancy

United States FDA Pharmaceutical Pregnancy Categories	
Pregnancy Category A	Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Pregnancy Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
Pregnancy Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

US FDA

45 drugs – „D“

5 drugs „X“

Drug	Pregnancy Category	Drug	Pregnancy Category
Arsenic trioxide	D	Imatinib mesylate	D
Azathioprine	D	Interferon alfa-2b	X
Bleomycin	D	Irinotecan HCL	D
Capecitabine	D	Leflunomide	X
Carboplatin	D	Lomustine	D
Carmustine	D	Mechlorethamine HCL	D
Chlorambucil	D	Melphalan	D
Cisplatin	D	Mercaptopurine	D
Cladribine	D	Methotrexate	X
Cyclophosphamide	D	Mitoxantrone HCL	D
Cytarabine	D	Oxaliplatin	D
Dactinomycin	D	Paclitaxel	D
Daunorubicin HCL	D	Pipobroman	D
Docetaxel	D	Procarbazine	D
Doxorubicin HCL	D	Tamoxilin	D
Epirubicin	D	Temozolomide	D
Etopside	D	Teniposide	D
Floxuridine	D	Thalidomide	X
Fludarabine	D	Thioguanine	D
Fluorouracil	D	Thiotepa	D
Gemcitabine	D	Topotecan	D
Hydroxyurea	D	Tositumomab	X
Ibritumomab tiuxetan	D	Vinblastine sulfate	D
Idarubicin	D	Vincristine sulfate	D
Ifosfamide	D	Vinorelbine tertrate	D

Effects at lower doses ? (occupational exposure)

Some studies indicate „risks“

- K. Falck et al.: Mutagenicity in urine of nurses handling cytostatic drugs. Lancet, 1979;1:1250-1251
- R.W. Anderson et al. Risk of handling injectable antineoplastic agents. Am J Hosp Pharm 1982;39:1881-1887 *(mutagens in urine)*
- Barbara G. Valanis et al.: Association of antineoplastic drug handling with **acute adverse effects** in pharmacy personnel. Am J Hosp Pharm 1993;50:455-462 *(hair loss, headache, irritations, miscarriage)*
- Saurel-Cubizolles et al. Ectopic Pregnancy and Occupational Exposure to Antineoplasic Drugs. The Lancet, Vol.341:May 8, 1993. 11691171. … (*cytostatics - 10% increased risk of 95% CI = (1.02 – 56.2), P=0.02)*
- Skov et al.: Risk for physicians handling antineoplastic drugs. Lancet 1990;336: 1446 *(leukemia risk – 2.85, 95% CI = (0,51– 16,02))*

Some studies don’t…

Valanis et al. Occupational Exposure to Antineoplastic Agents: Self-Reported Miscarriages and Stillbirth Among Nurses and Pharmacists. J of Occup & Environ Med 41(8):638,1999 *(no significant effect of cytostatics)*

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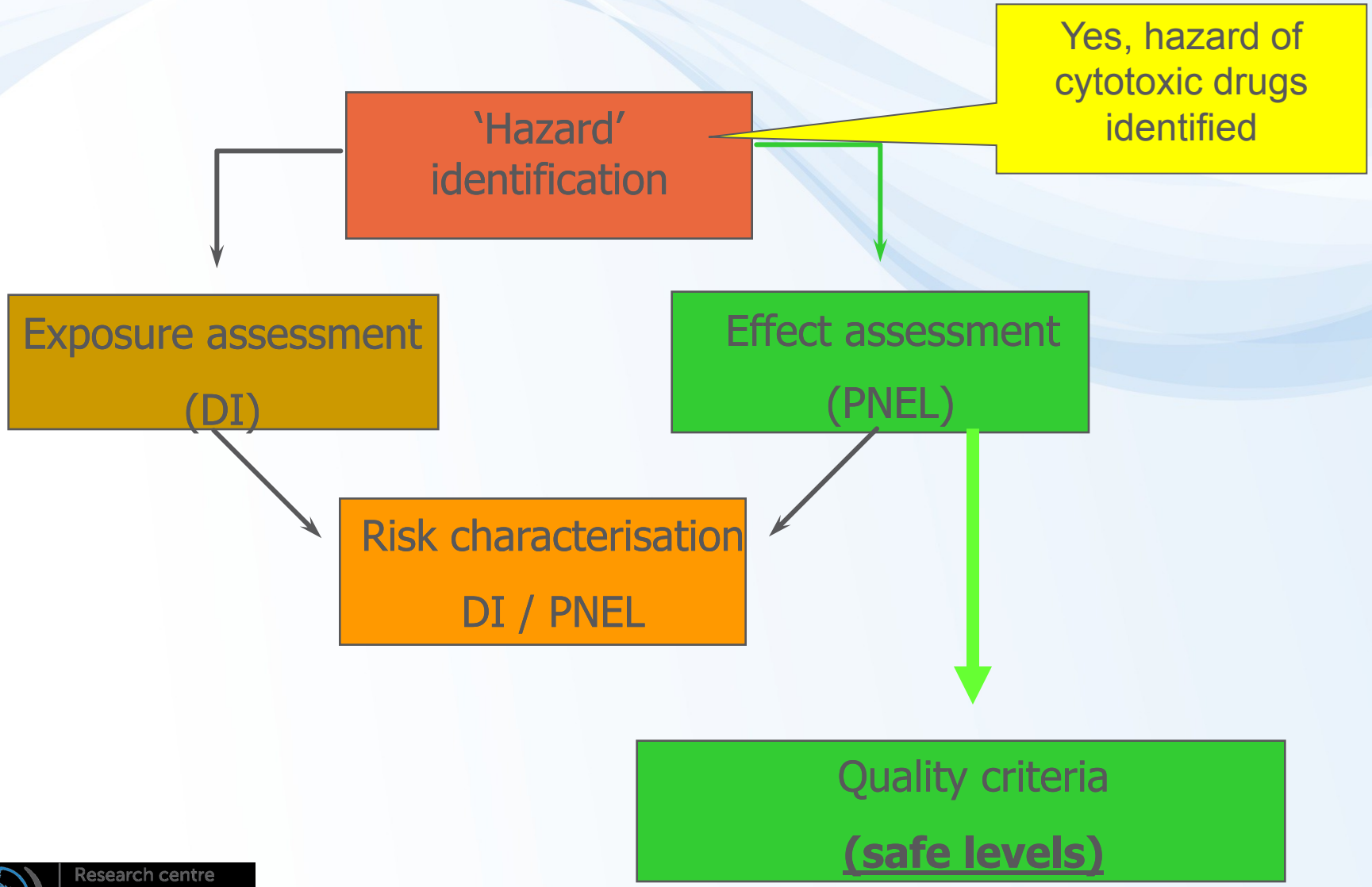
Risk assessment – principal steps



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EXPOSURE assessment

- Purpose: assessment or prediction of the exposure dose (concentration) of a chemical

- **Methods**
  - monitoring and/or prediction (models)
  - accounting for release, pathways and rates of movement of the substance, its transformation and degradation

- **Result:**
  - Predicted Exposure Concentration - PEC
  - Human: Daily Intake - DI (dose …)

EFFECT assessment

- Purpose: assessment of **concentrations (doses) that may cause toxic effects**

- **Method:**
  - Toxicological studies
  - Epidemiological studies

- **Result:**
  - Humans:
    Tolerable Daily Intake – TDI
    Predicted No Effect Level - PNEL
  - Predicted No Effect Concentration - PNEC

Effect assessment
Toxicological studies

Dose-Response relationship

Assessment of LD50
& „safe“ values (LOEC, NOEC)

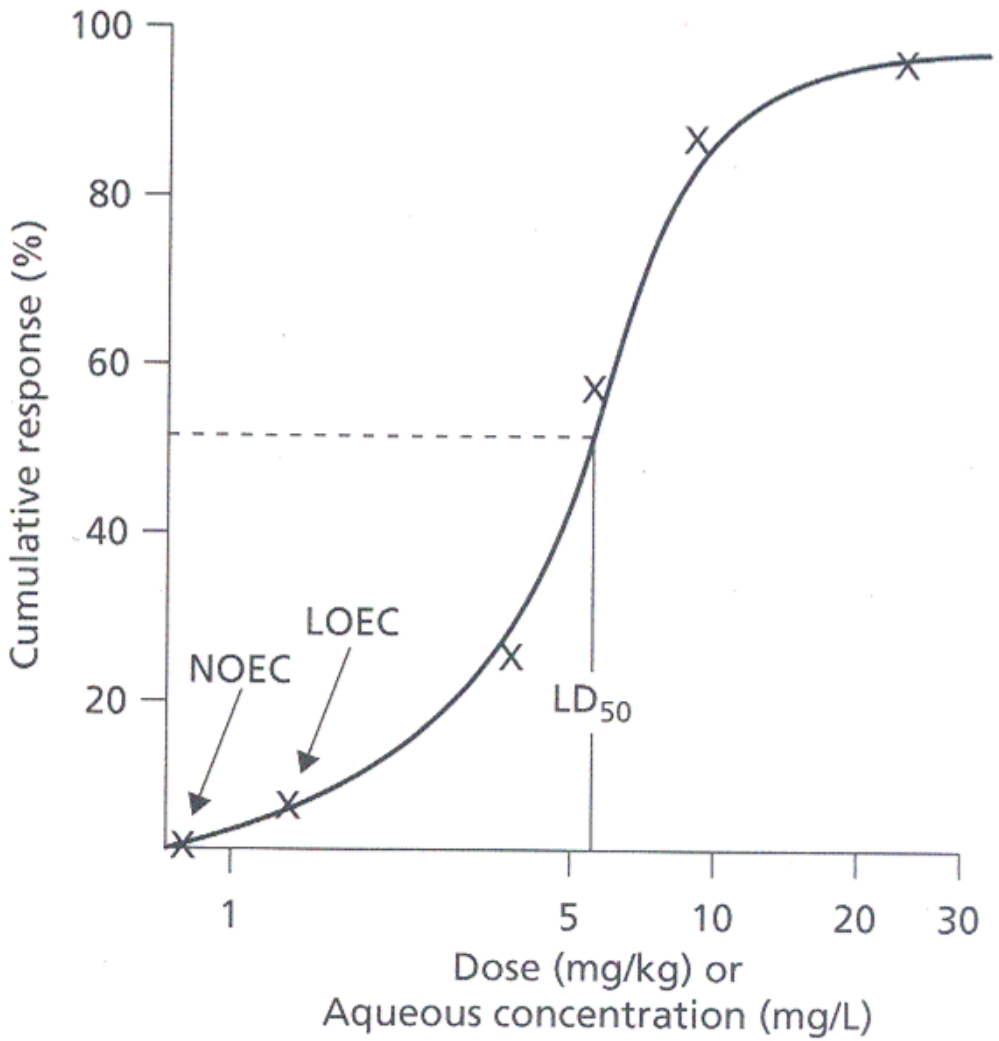


Fig. 6.2 Cumulative dose–response curve. In a lethality experiment the response is the cumulative percentage of animal mortalities with the actual data points indicated as crosses. Lowest observable effect concentration (LOEC) and no observable effect concentration (NOEC) are indicated.

EFFECT assessment – carcinogens … a special case

- **No threshold for carcinogens exists (no safe value can be established)**
  - Each dose (single molecule) is considered effective / genotoxic
  - Doses only **increase probability** of the cancer development

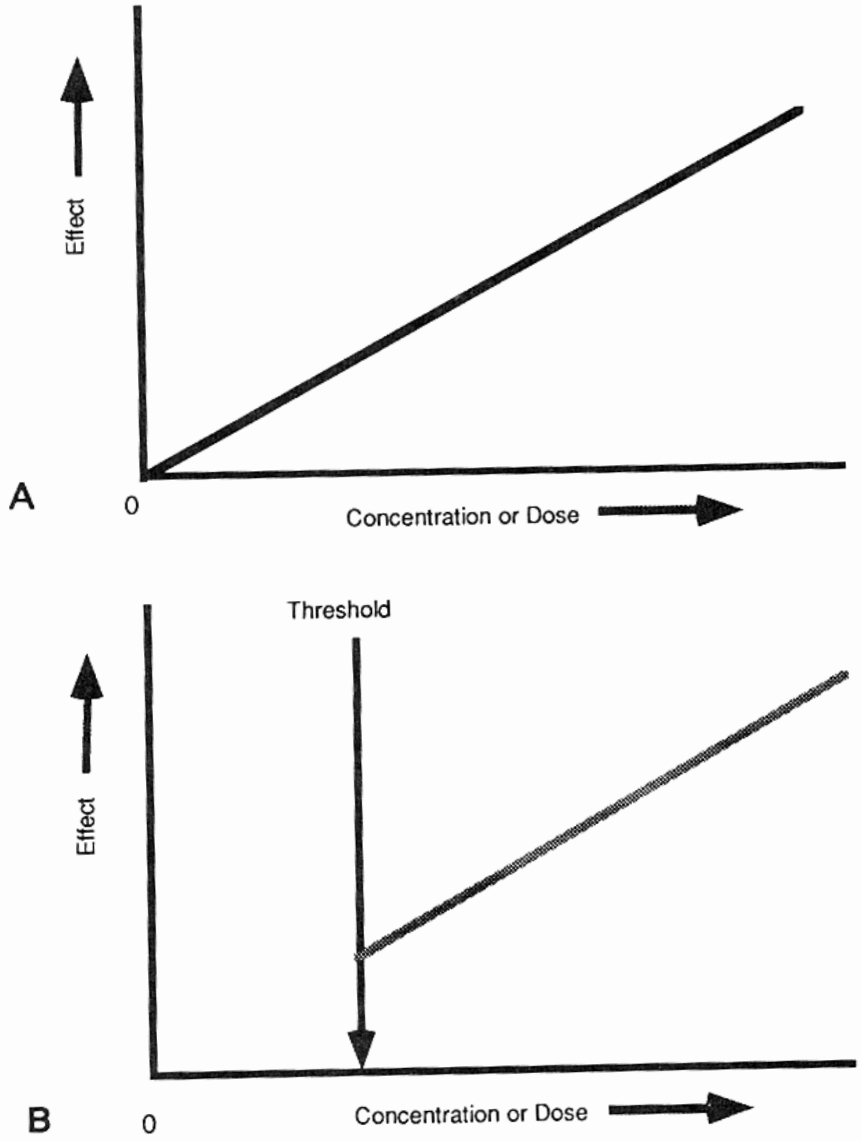
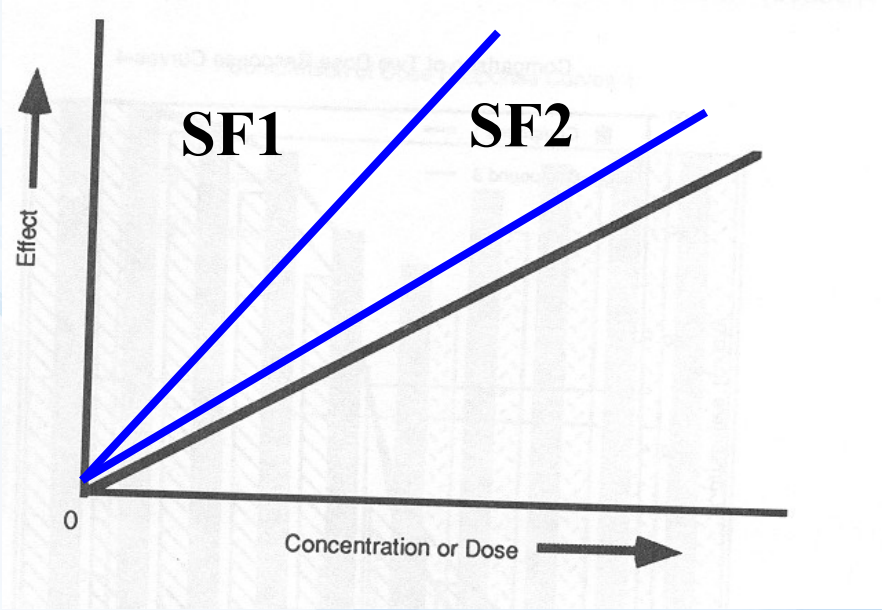


Figure 3.8 Threshold concentration. There are two prevailing ideas on the toxicity of compounds at low concentrations. Often it is presumed that a compound has a toxic effect as long as any amount of the compound is available to the organism (A). Only at zero concentration will the effect disappear. The other prevailing idea is that a threshold dose exists below which the compound is present but no effects can be discerned (B). There is a great deal of debate about which model is accurate.

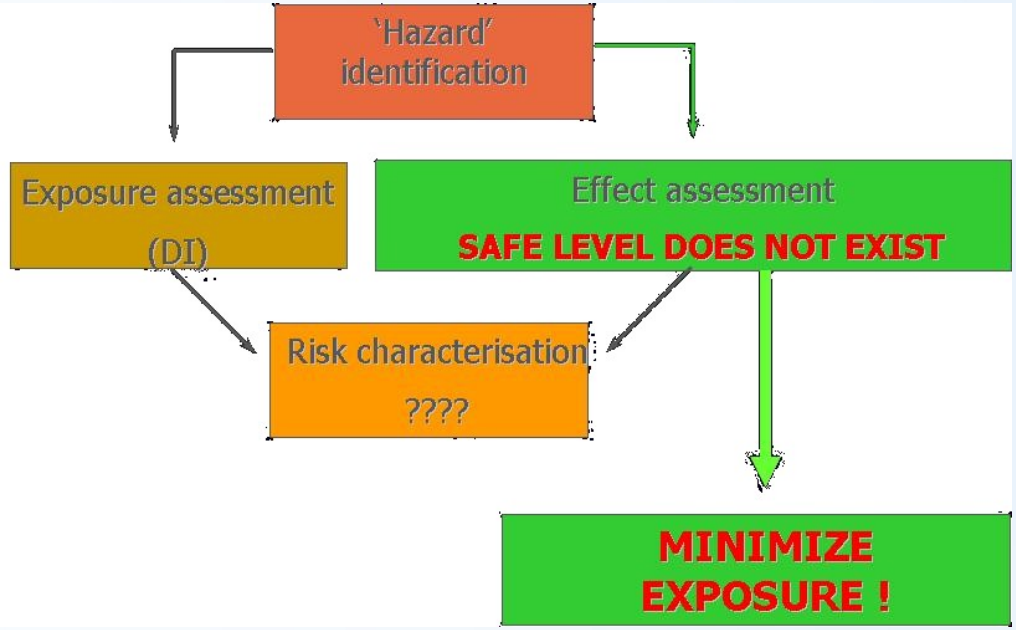
Mutagens
Carcinogens

Other
(general)
toxicants

Effect characterization for carcinogens



- Derivation of the slope factor (SF)
  - SF [mg . kg b.w. $^{-1}$. day^{-1}]
  - Higher SF
    -> more effective carcinogen



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Risk **CHARACTERIZATION**

- Purpose: **integration** of the three previous steps
  - Hazard ID
  - PNEC and PNEL
  - PEC and TDI

- **Method – calculation for traditional chemicals:**
  - Human: DI (Intake) / PNEL (Safe level) = Margin of Safety= MOS

    (or Hazard Index …)
  - Environment: PEC/PNEC ratio = risk quotients = RCR

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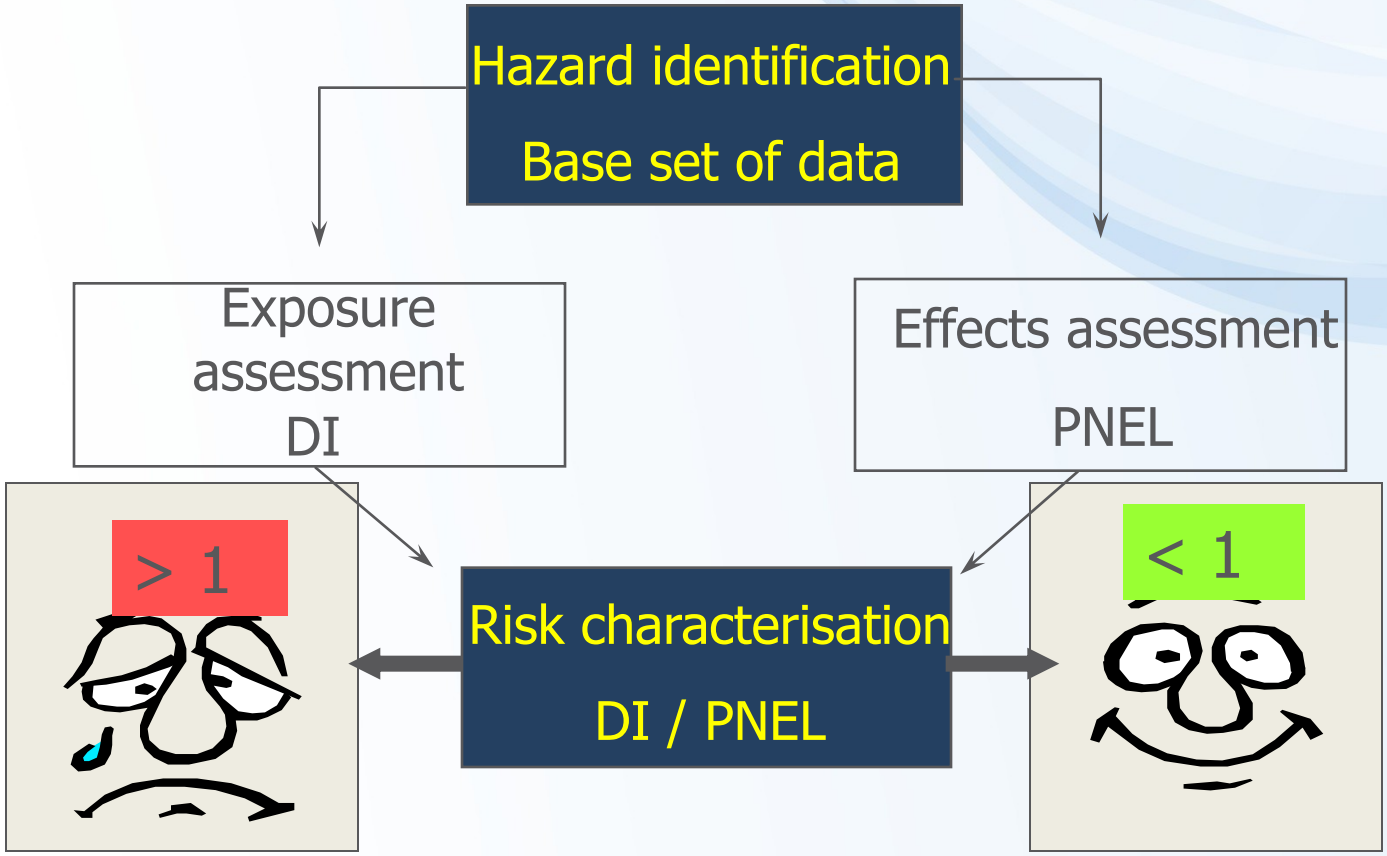
Risk **CHARACTERIZATION**



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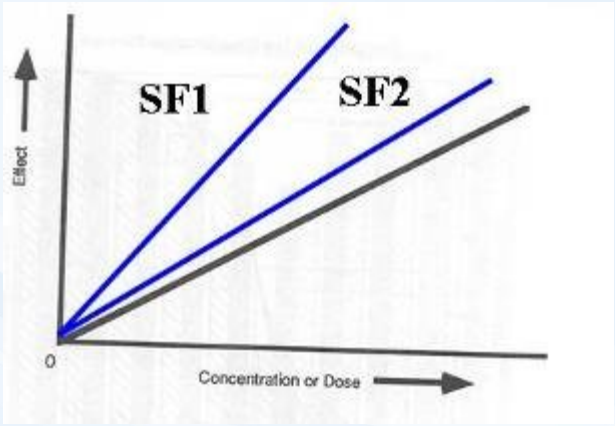
RISK CALCULATION for carcinogens



- **Slope factor (SF)**
  - SF - mg . kg b.w. $^{-1}$. day^{-1}
  - Higher SF -> more effective carcinogen

- **RISK = SF x CDI** = probability (e.g. $2x10^{-5}$)
  - *CDI - chronic daily intake (averaged 70years)*
- Result = „extra cancer incidences“

- *Question: what risk of cancer is „acceptable“ ?*

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Risk **MANAGEMENT**

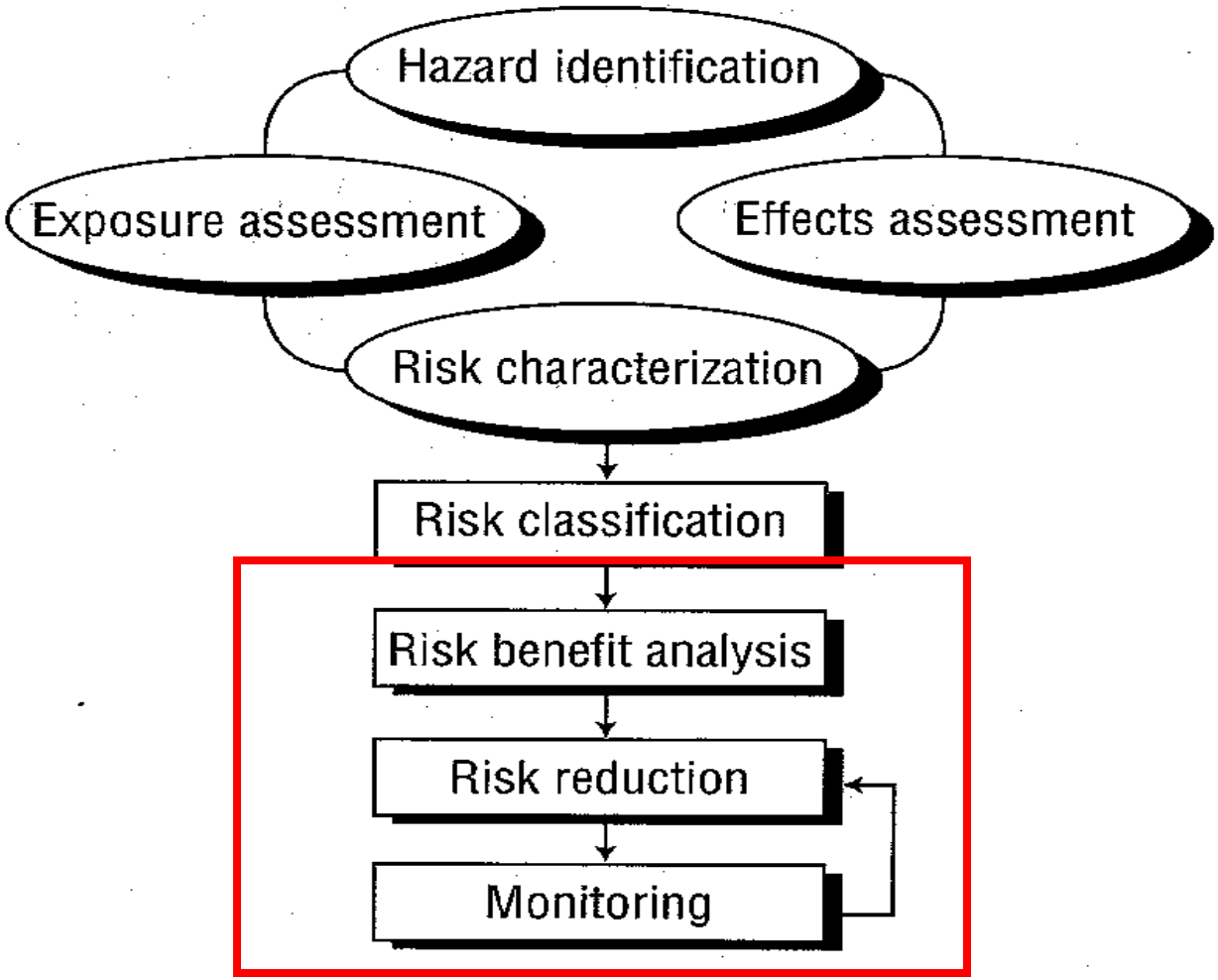

Figure 1.3. Steps in the risk management process.

CYTOTOXIC DRUGS
ASSESSMENT and MANAGEMENT of RISKS

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Safety of cytotoxic drugs – example EU (Czech Rep.)

- **Occupational / work safety**
  (current laws no. 309/2006 coll., 361/2007 coll.)

General work with any type of carcinogen
(cystostatics are considered carcinogens)

→ Employer duties

- manipulation in controlled & protected areas
- to **adapt measures that minimize exposures**
- e.g. break after 2h of work, minimum 15min …
- *analytical procedures to detect contamination*
- *monitoring of workers' health status*

! No details on analytics, monitoring …

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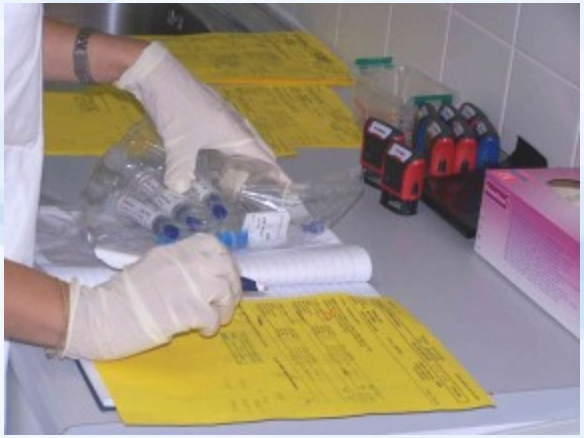
Hazardous activities → EXPOSURE

- Drug preparation
- Storage
- Transport
- Administration
- Waste management
- Sanitation



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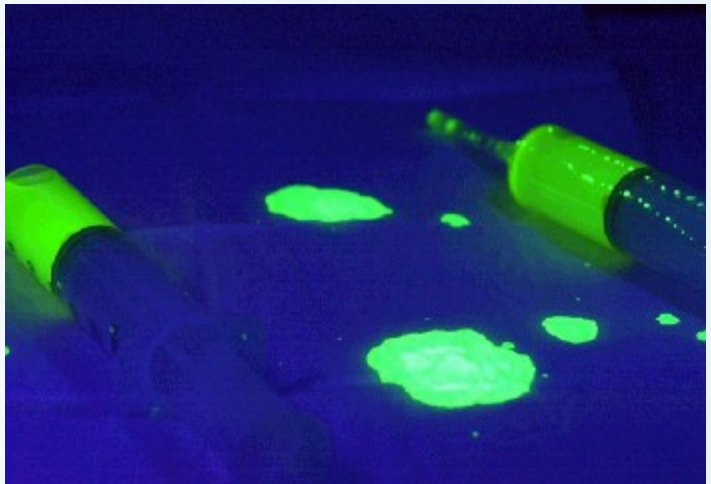
EXPOSURE PATHWAYS

Major routes of exposure to cytotoxic drugs

- **AIR**
  - **Aspiration of drugs**
    (gaseous phase, bound to particules, aerosols)

- **Surfaces - hand contamination**
  - Direct **permeation of skin**
  - Hands -> mouth
    : **food** - accidental ingestion



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Assessment of the exposure - MONITORING

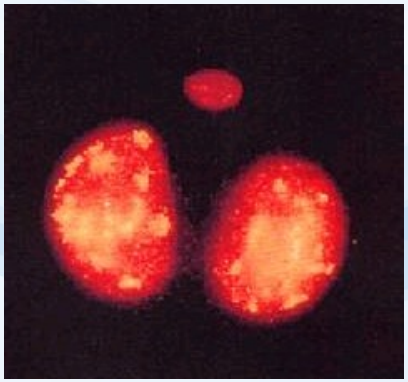
What to monitor ?

- **Drug levels**
  - In the air
  - On the surfaces
  - In workers (blood, urine)

- **Effects** (? of the drugs or other factors ?)
  - Health status
  - Biomonitoring (e.g. lymphocyte cytogenetics)

Notes on biomonitoring

- **„Genotoxic" changes in exposed persons**
  - Chromosomal aberations in blood leukocytes
  - Micronuclei formation
  - DNA damage (comet assay)
  - … and many others



- Rather non-specific
  - Cannot be directly linked to occupational exposures
  - Other variables more significant (e.g. smoking, lifestyle)
- Relationships to health consequences (?)
  - *DNA damage does not mean cancer*

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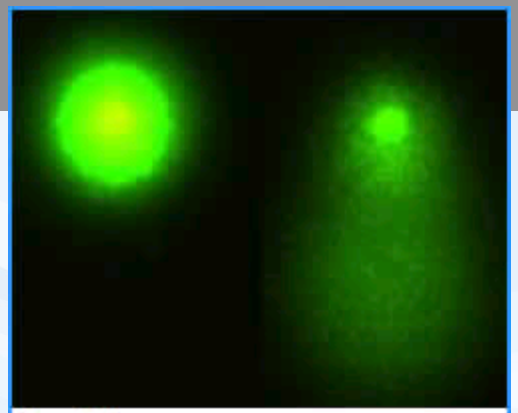
Biomonitoring DNA damage (comet assay)



Comet Assay
Illustration produced in the laboratory of Dr Al Rowland, Massey University

Int Arch Occup Environ Health (2006) 80:134-140

DNA damage in lymphocytes

Group	Lymphocytes	
	Tail moment (mean ± SD)	*P* values; Student *t* test
Pharmacy technicians ($n = 5$)	20.8 ± 10.1	0.3
Day hospital nurses ($n = 12$)	15.5 ± 9	0.8
Ward nurses ($n = 13$)	14.7 ± 7.9	0.6
Controls ($n = 30$)	16.1 ± 8.1	

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AIR CONTAMINATION (?)

- Physico-chemical properties of the compound determine evaporation, aerosol formation etc.
  - limited data available

- Stability in the air ?
  (? Oxidation, photodegradation ?)
- Air circulation & distribution, air-conditioning ?
  - site specific, usually no information

Protection (partial) - Safety cabinets, isolators

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Studies of the AIR CONTAMINATION

	Vapour pressure [Pa]
Paclitaxel	0.024
Doxorubicin	0.002
Dacarbazin	0.004
Ethanol	5 851

Generally low numbers … BUT ! IN EQUILIBRIA (closed system) values correspond to **milligrams / m3**

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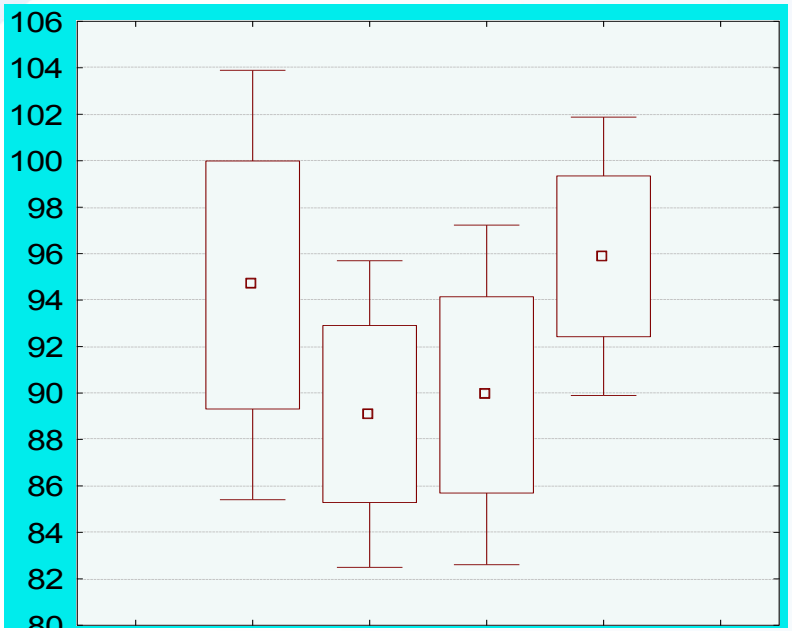
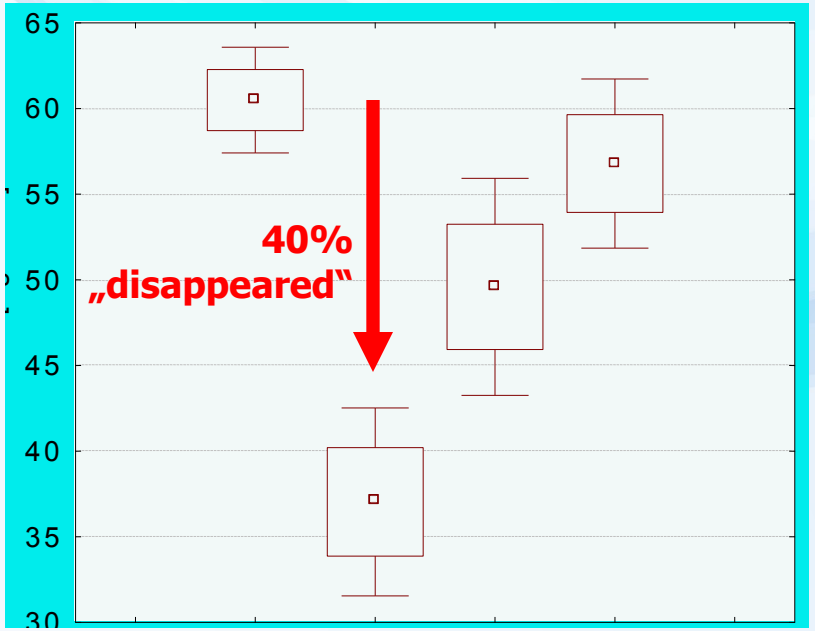
Studies of the EVAPORATION (steel)

PACLITAXEL
(VP=0.024)



DOXORUBICIN
(VP=0.002)



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AIR contamination - results

Table 4: Surface and airborne contamination of the working area studied

	Storage area			Praparation room			Outpatient clinic		
	N pos.	Median	Range	N pos.	Median	Range	N pos.	Median	Range
Surface contamination (pg/cm^2)									
Table	2	< 2	< 2-19	5	58	45-418	5	175	133- 273
Floor	1	< 2	< 2-2	5	73	57-207	5	5311	2032-15476
Phone	0	< 8	< 8	3	56	< 8-404	5	293	234-821
Shelf	0	< 2	< 2						
Refrigerator				5	267	159-399			
IV pump							5	866	836-6341
Floor at the toilet							5	1274	188-1830
Air contamination (ng/m^3)									
Vapours	0	< 0.05	< 0.05	0	< 0.05	< 0.05	5	0.68	0.26-4.29[a]
Aerosols	0	< 0.05	< 0.05	0	< 0.05	< 0.05	0	< 0.05	< 0.05

[a] overview of the concentrations measured: 0.68; 3.14; 4.29; 0.35; 0.26 ng/m^3

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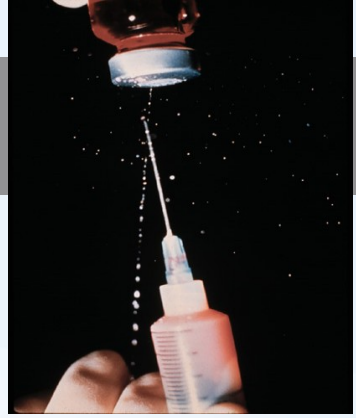
AIR contamination - conclusion



Levels in the air ?

AIR SAMPLING - complicated

LEVELS usually low - sensitive analytical methods needed

- often: negative results
- maximum observed levels 200 ng / m3
(8h continuous exposure, 100% intake ~ 672 ng/person)

CONCLUSION - AIR CONTAMINATION:

air contamination by cytotoxic drugs should be considered but further research is needed to develop reasonable methods

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Exposure: SURFACES

More data available than for air

Several studies

- Preparatory rooms
- Vials (external surfaces)

Other areas - less information

- Storage rooms
- Manipulation and transport
- Drug administration
- Toilets, sanitary areas …

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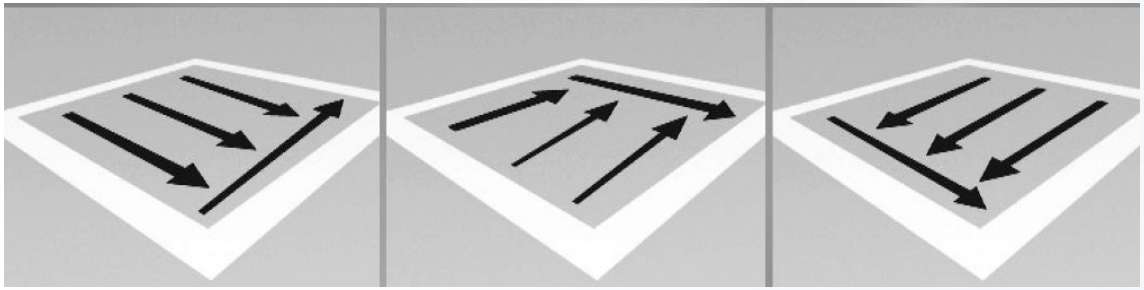
Exposure assessment - SURFACES

1) SAMPLING

- Standardized procedures are being adopted

  e.g. MEWIP project - Germany
  http://www.pharma-monitor.de/



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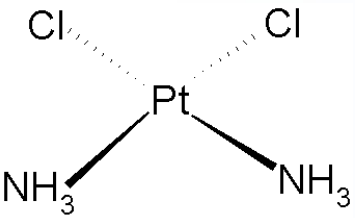
2) ANALYSES

- each drug needs specific methods
  - GC, HPLC, AAS, voltametry …

- recent developments
  - **Mass Spectrometry** (GC-MS/MS…)
    - more affordable (lower prices), low detection limits

(use of bioassays - e.g. genotoxicity of wipe samples)



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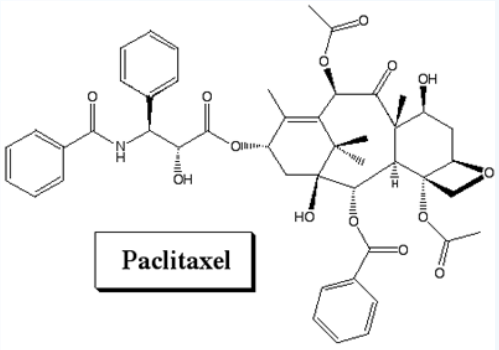
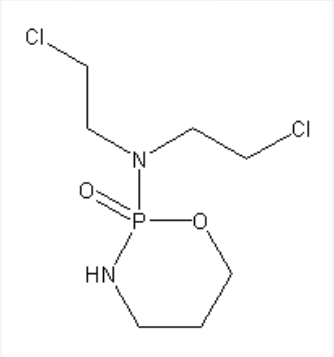
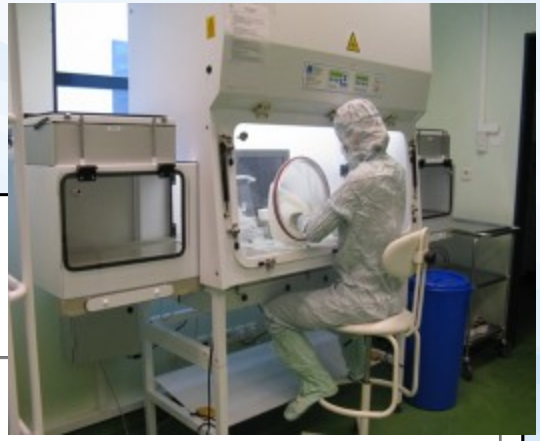




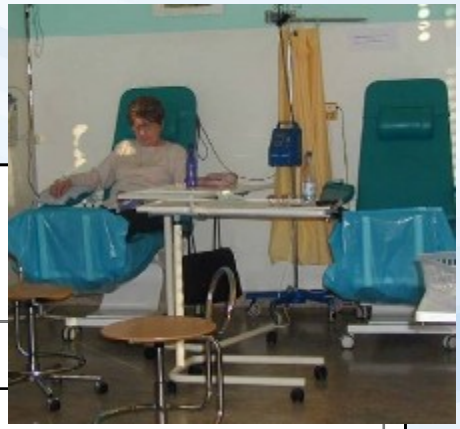
Examples - contamination

Brno 2008 - **clean preparatory room**
(3 sampling periods)



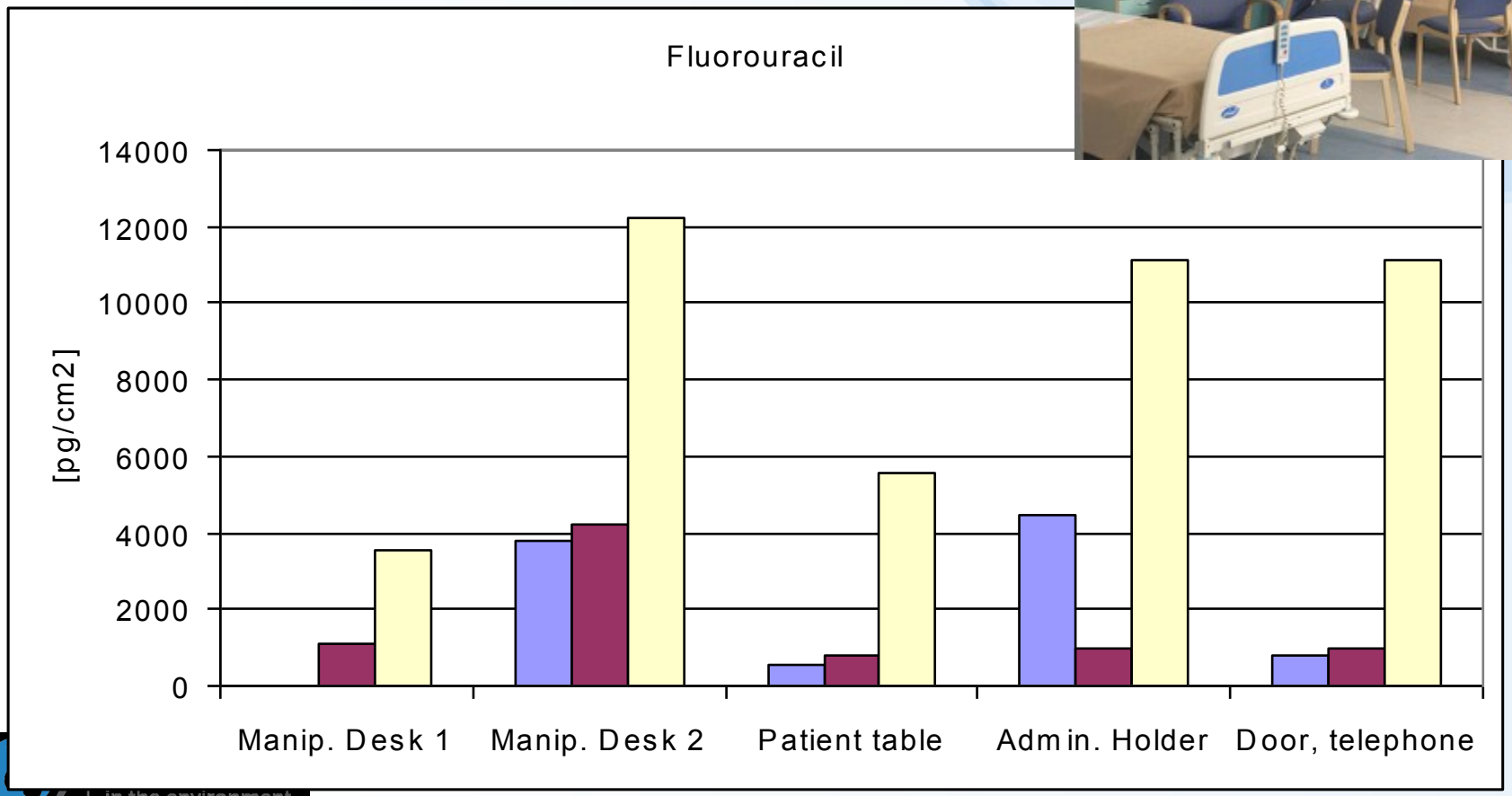
Examples - contamination

Brno 2008 – **daily outpatient clinic administration room** (3 sampling periods)



Examples - contamination

Brno 2008 - **hospital room (patient bedroom)**
(3 sampling periods)



RESULTS – surfaces contamination

	Cyclophosphamide			Platinum		
	Pd*	Median	Min/Max Value	Pd*	Median	Min/Max Value
Preparation room						
Working table	7/7	65	10/440	7/7	9	3/82
Floor	6/7	52	<2/81	7/7	8	4/46
Phone	4/4	7	5/32	4/4	2	0,6/2,3
Negativ press. cabinet	3/3	1150	**900/3400**	3/3	60	**13/1300**
Storage area						
Working table	3/7	<2	<2/8	4/7	0,8	<0,5/3,1
Reception table	4/4	150	**60/380**	2/4	<0,5	<0,5/1,3
Floor	0/3	<2	<2/<2	3/3	1,8	1,5/40
Phone	0/4	<2	<2/<2	0/4	<0,5	<0,5/<0,5
Shelf	4/4	42	**8/250**	4/4	2	0,8/3,9
Outpatients clinic						
Working table	7/7	21	7/75	7/7	33	20/52
Floor	6/7	650	**<2/11800**	7/7	480	**290/650**
Phone	4/4	5	3/11	2/4	0,7	<0,5/1,4
WC-floor	7/7	380	**80/2700**	7/7	680	**220/8100**
Nursing clinic						
Working table	1/7	<2	<2/2	4/7	1	<0,5/3,9
Floor – by sickbed	2/7	<2	<2/3	6/7	36	<0,5/95
Phone	0/4	<2	<2/<2	0/4	<0,5	<0,5/<0,5
Floor – by waste	1/7	<2	<2/2	7/7	22	2/96

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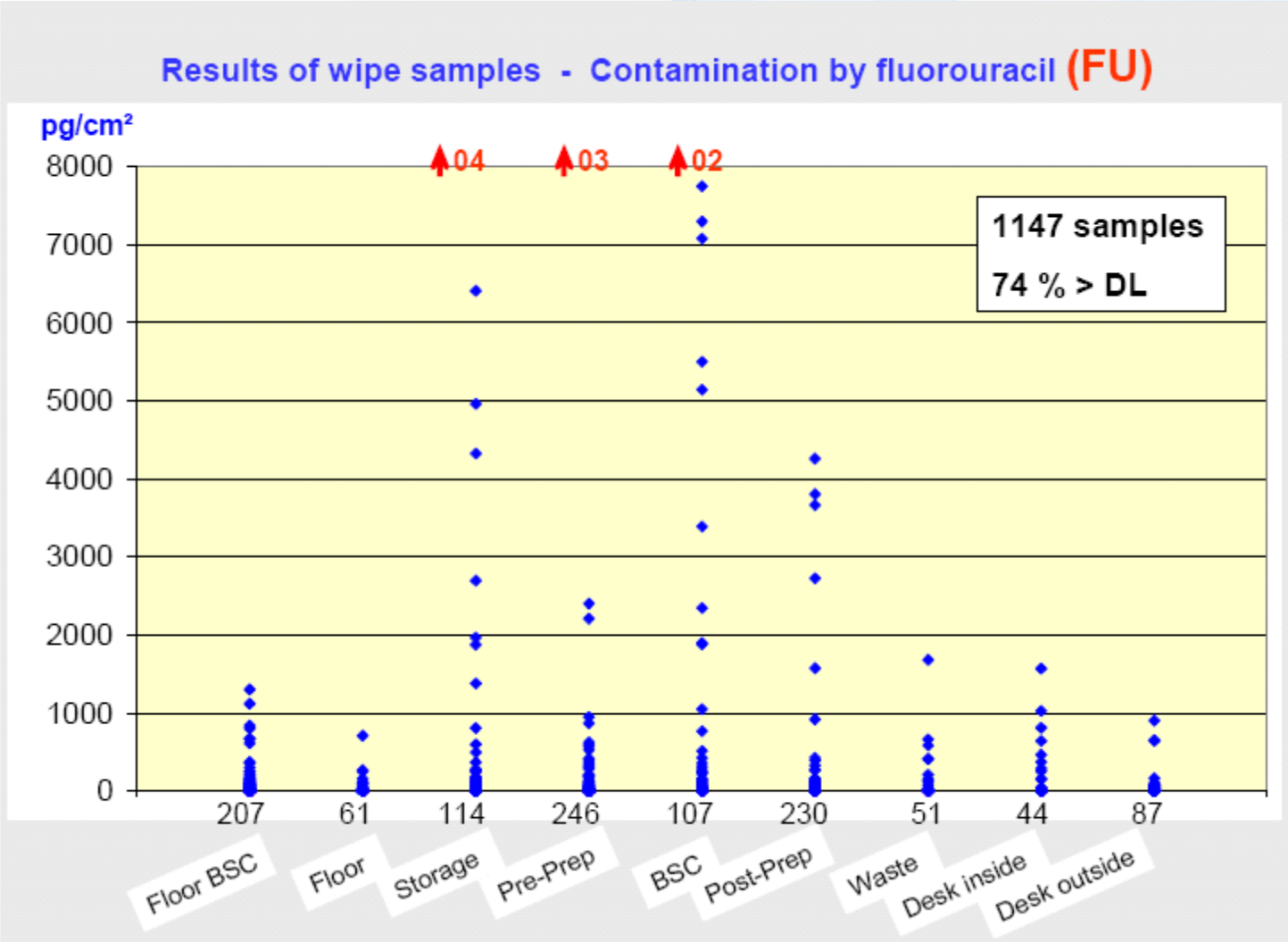
Exposure levels - SURFACES

Dr. Rudolf Schierl (Munich, Germany)

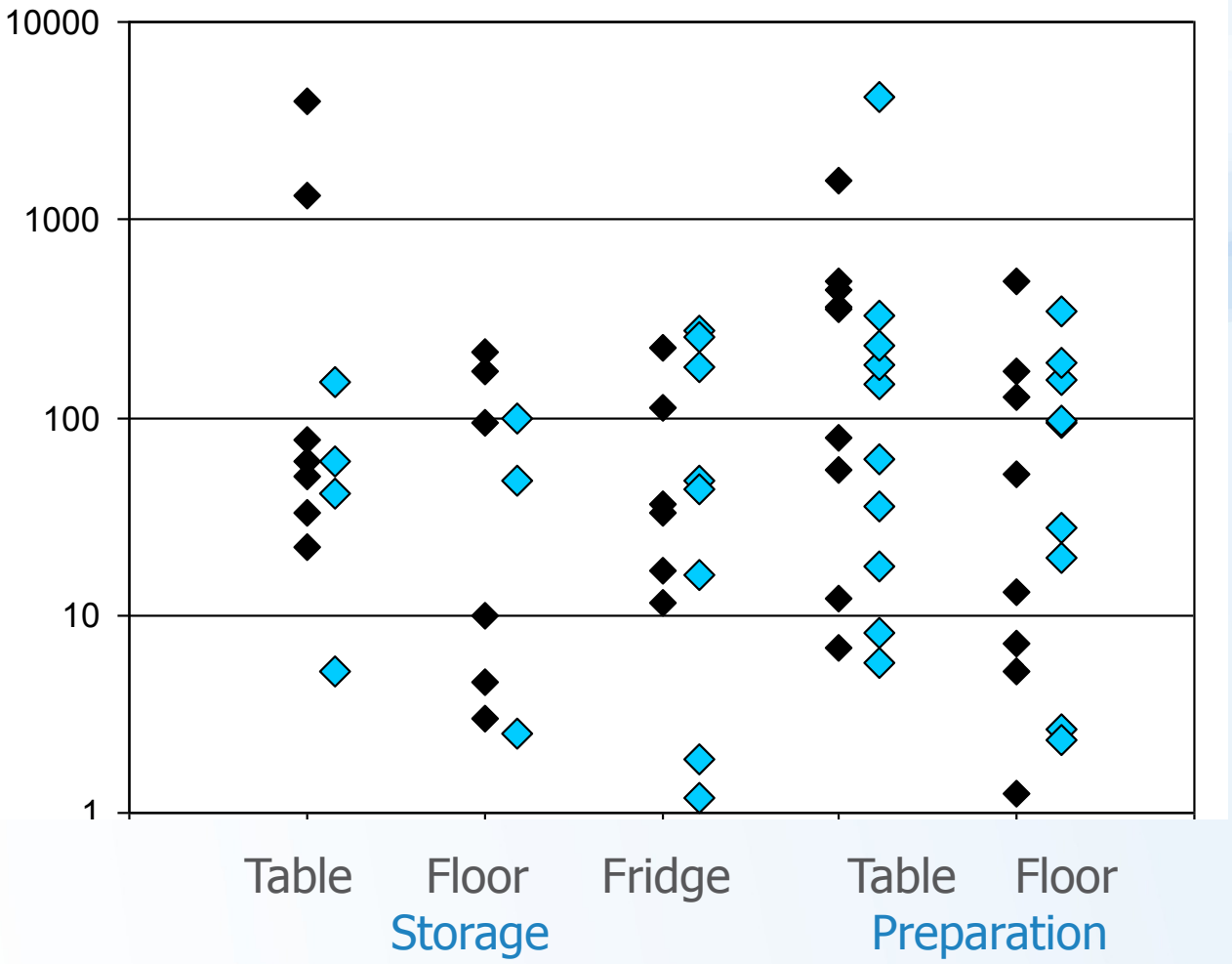


in the environment

RESULTS – surfaces contamination

Cyclophosphamide – two sampling campaigns
15 pharmacies (Czech Rep.)

[pg/cm2]



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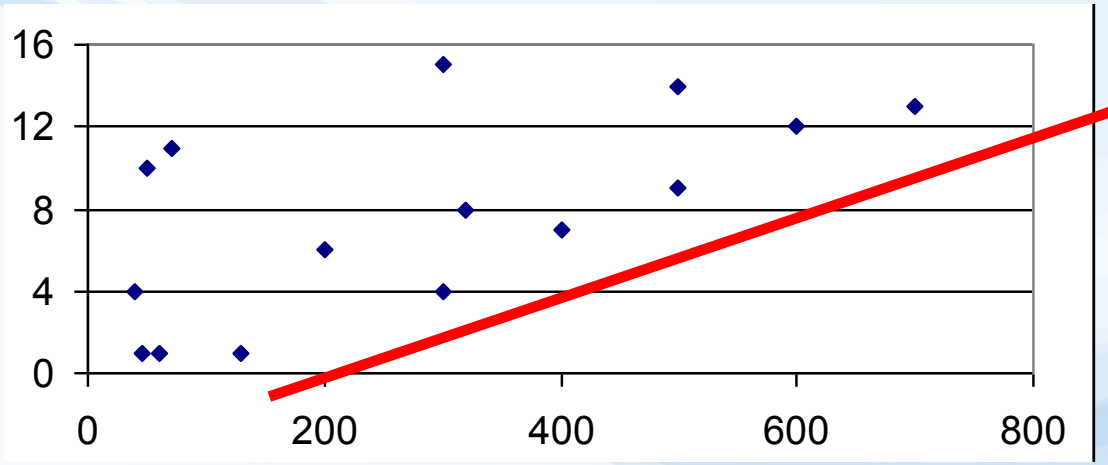
Surface **contamination vs. Work-load**

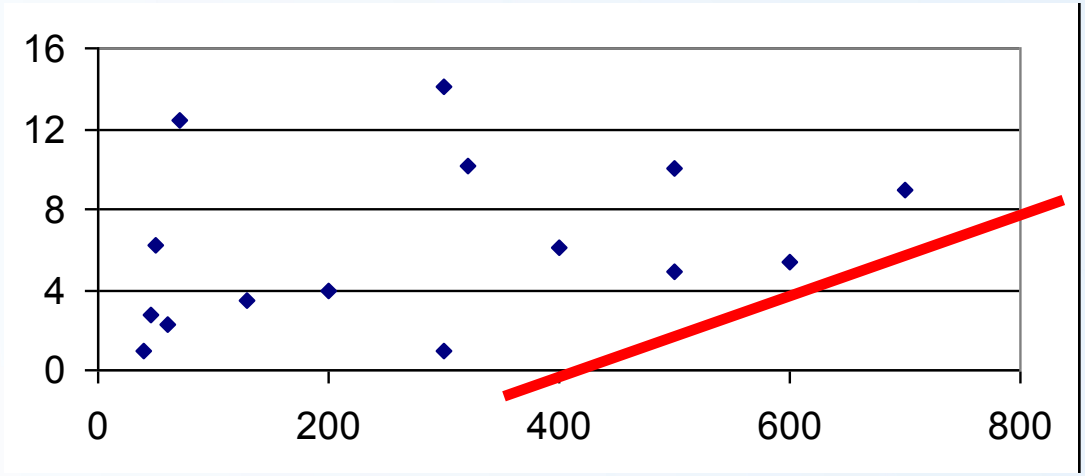
„contamination“

Cyclophosphamide



„contamination“

Platinum



numbers of drug preparations per day

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Contamination example – an accident

Dr. Rudolf Schierl (Munich, Germany)

Example (1) floor contamination

4 broken vials Holoxan 2 g (liquid)

Correct use of spill kit

14 days later: wipe samples

Place of accident: 260 000 pg/cm² Ifosfamid

5 m away: 37 500 pg/cm² Ifosfamid

Cleaning with methanol

Place of accident : 92 000 pg/cm² Ifosfamid

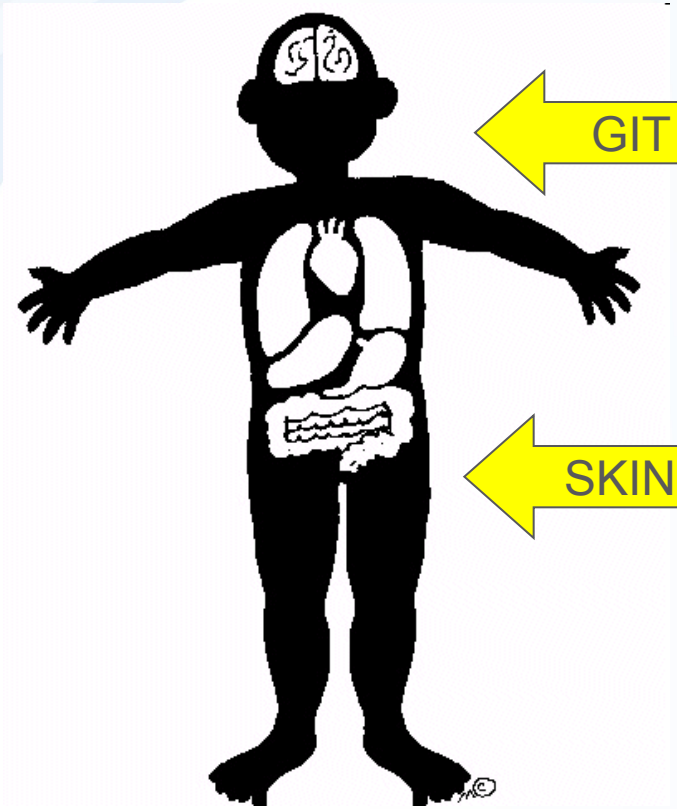
5 m away : 3 000 pg/cm² Ifosfamid

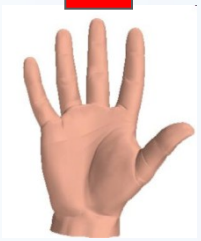
4 months normal daily cleaning

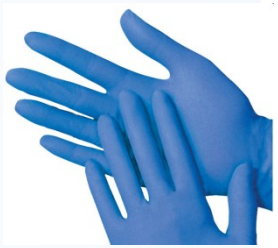
Place of accident : 450 pg/cm² Ifosfamid

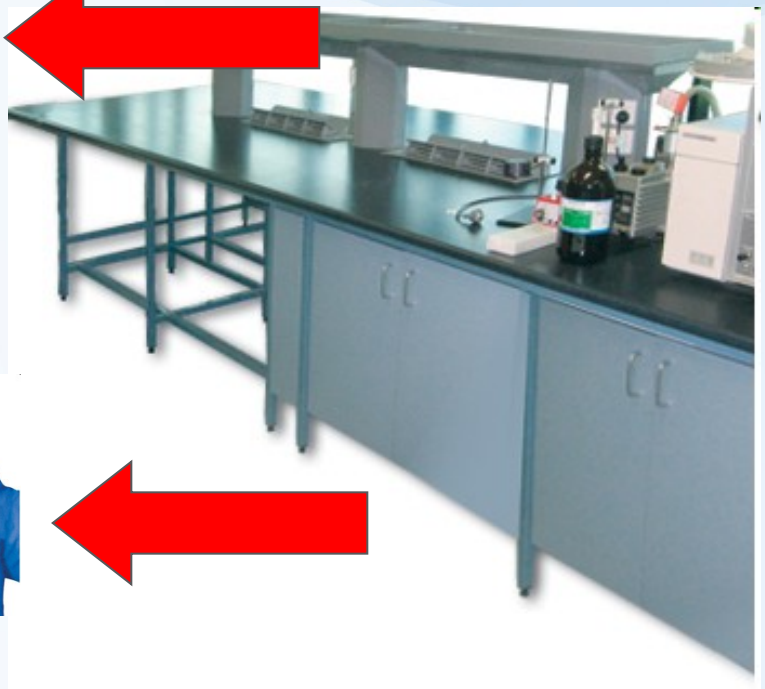
5 m away : 50 pg/cm² Ifosfamid

Exposure pathway: Surfaces → Hands → Body exposure









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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

GLOVES PERMEATION

		Breakthrough time [min]			
	[mm]	CP	PX	DX	FU
Vinyl	0.12	**60**	**240**	n.d.	n.d.
Latex	0.16-0.3	**60-360**	n.d.	n.d.	n.d.
Nitrile	0.14	n.d.	n.d.	n.d.	n.d.

		Max. permeability [ng/cm^2.min]			
	[mm]	CP	PX	DX	FU
Vinyl	0.12	**160**	**3**	**n.d.**	**n.d.**
Latex	0.16-0.3	**5-72**	**n.d.**	**n.d.**	**n.d.**
Nitrile	0.14	**n.d.**	**n.d.**	**n.d.**	**n.d.**

Cheaper gloves permeated – rather by small molecules

CP, PX: vinyl, latex / 160 ng/cm2.min

Nitrile gloves (seems) to provide sufficient protection

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Contamination of HANDS

Median & Maximum values for cyclophosphamide (CP) and platinum (Pt)
Pd – frequency of the positive samples

			Storage area			Prepar. room			Outpatient clinic		
		LoD[1]	Pd[2]	Med	Max	Pd[2]	Med	Max	Pd[2]	Med	Max
Surface cont. (pg/cm²)											
Working table	CP	3	3/12	<LoD	9	12/12	65	490	12/12	58	270
	Pt	1	5/12	<LoD	3	12/12	8	92	12/12	39	81
Floor	CP	3	4/12	<LoD	14	12/12	67	210	11/12	2700	15500
	Pt	1	6/12	<LoD	44	12/12	6	51	12/12	500	203000
Telephone	CP	9	0/9	<LoD	<LoD	7/9	56	400	9/9	230	820
	Pt	4	0/9	<LoD	<LoD	7/9	14	23	6/9	4	36
Air contamin.	CP	0.1	0/5	<LoD	<LoD	0/5	<LoD	<LoD	5/5	0.8	4.7
(ng/m³)	Pt	nd[3]	nd[3]	nd[3]	nd[3]	nd[3]	nd[3]	nd[3]	nd[3]	nd[3]	nd[3]
Hands	CP	5	4/12	<LoD	100	0/12	<LoD	<LoD	7/13	12	360
(ng/hands)	Pt	0.5	4/12	<LoD	7	11/12	1	8	11/11	2	40

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Cyclophosphamide in the URINE

Table 2: Cyclophosphamide excretion by workers from different oncological departments (µg/24h)

Department	Pd.[1]	Median	Maximum
Hospital pharmacy	1/13	<0.030	0.100
Nursing clinic	0/9	<0.030	<0.030
Outpatient clinic	2/8	<0.030	0.140

[1] Number of positive samples/total number of samples

Table 4: Summary of the results and estimated biological uptakes (µg/24h)

x 100

Analyte	Pd.[1]	Excretion		Biological uptake	
		Median	Max	Median	Max
Cyclophosph.	3/30	<0.030	0.140	3	14
Platinum	30/30	0.005	0.210	0.01	0.42

[1] Number of positive samples/total number of samples

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Hirst et al. 1984. The Lancet 323(8370), 186-188

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

RISK CHARACTERIZATION - cyclophosphamide

ADDITIONAL CANCER RISK - cyclophosphamide

„Extra cancer cases“ in exposed workers

34 – 986 cases / million workers / year

Vandenbroucke,J; Robays, H. 2001: How to protect environment and employees against cytotoxic agents, the UZ Ghent experience Journal of Oncology Pharmacy Practice 6: 4,146-152

17 – 100 cases / million workers / year

Sessink, P. J. M., Kroese, E. D., Vankranen, H. J., & Bos, R. P. 1995a. Cancer Risk Assessment for Health-Care Workers Occupationally Exposed to Cyclophasphamide. International Archives of Occupational and Environmental Health, 67(5), 317-323

„Acceptable“ risk **Strive risk ……. 1 extra case**

„Not acceptable“ **Prohibitory risk …. > 100 extra cases**

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RISK CHARACTERIZATION - cyclophosphamide

ADDITIONAL CANCER RISK - cyclophosphamide

MEASURED VALUES
Czech Republic (CYTO project) ~ **0.14 ug CP in urine / day**

MEASURED VALUES
(*Dr. Paul Sessink (Exposure Control B.V., NL) , www.exposurecontrol.nl)*

Technicians **- 0.18 ug CP** in urine/day
(~ **1.4 - 10 extra cancer cases**/million workers a year)

Nurses **- 0.8 ug CP** in urine/day
(~ **10 - 50 extra cancer cases**/million workers a year)

? Acceptable risk ?

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Dr. Paul Sessink (Exposure Control B.V., NL)
www.exposurecontrol.nl

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

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RISKS TO WORKERS – **metaanalysis** study

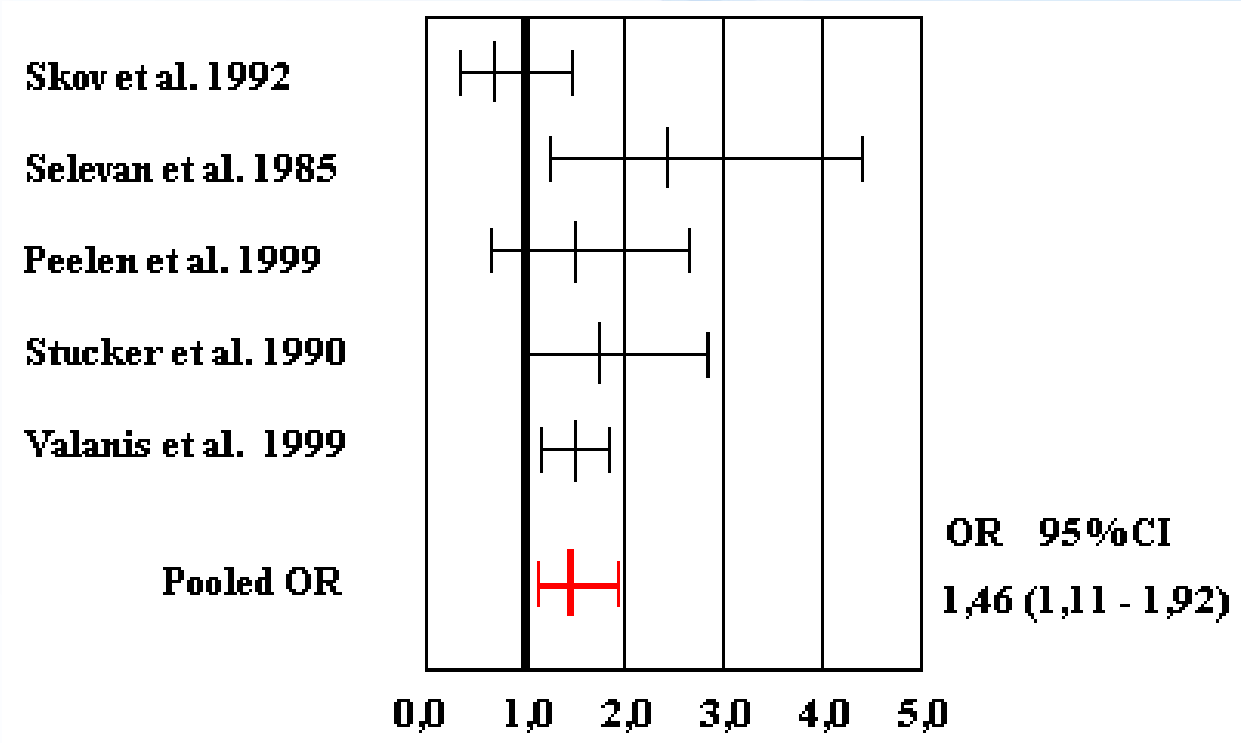
- G. Dranitsaris et al. Are health care providers who work with cancer drugs at an increased risk for toxic events? Systematic review and metaanalysis of the literature. J Oncol Pharm Practice 2005; 11: 69-78

  - 14 studies found (1966-2004); 7 valid and further analyzed

  - Some results (statistically non-significant)
    - Developmental malformations RR = 1,64, 95% CI = (0,91 - 2,94)
    - Dead newborns RR = 1,16, 95% CI = (0,73 – 1,82)
    - Acute effects
    - Carcinogenicity

RISKS TO WORKERS – **metaanalysis** study

- G. Dranitsaris et al. 2005
  - **Spontaneous miscarriage RR = 1,46 95% CI = (1,11 – 1,92)**



Conclusion:
Sufficient plausibility of health effects related to cytostatics

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Final notes on MONITORING

Why to monitor ?

What to monitor ?

How to monitor ?

How to use monitoring data ?

Final notes on MONITORING

Why to monitor ?

- check yourself (QA/QC in drug safety as well as in drug preparation)

- results of the monitoring minimize contamination

- MEWIP study (Germany)
- CYTO project (Czech Republic)

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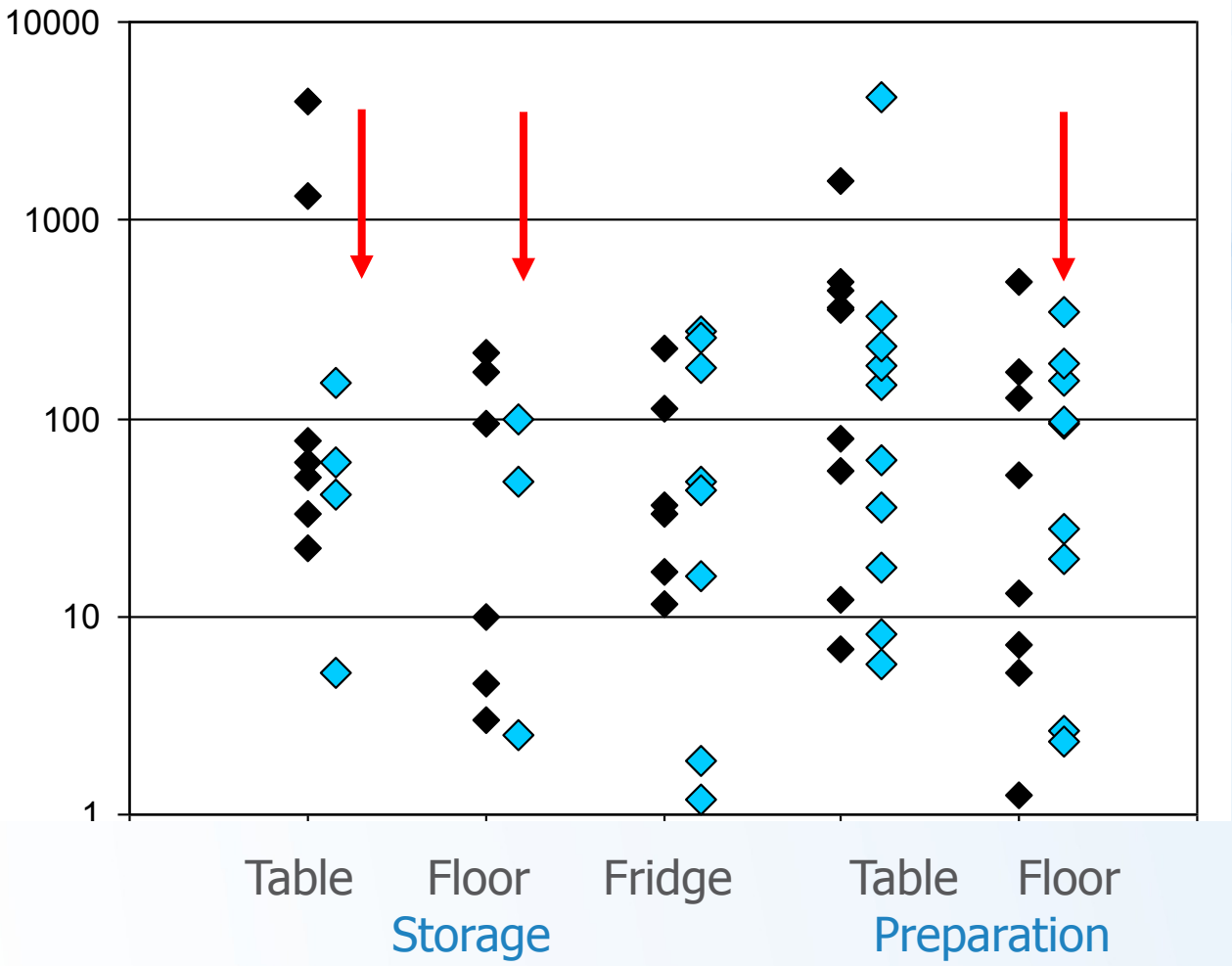
MONITORING - rising awarness – improving situation

Cyclophosphamide – two sampling campaigns
15 pharmacies (Czech Rep.)

[pg/cm2]



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Final notes on MONITORING

What to monitor ?

- dozens of drugs administered
  - **„representative“ drug** should be selected

- selection criteria:
  - used often
  - in high amounts
  - analytical methods available
  - should be hazardous
  - literature data available

→ **CYCLOPHOSPHAMIDE**

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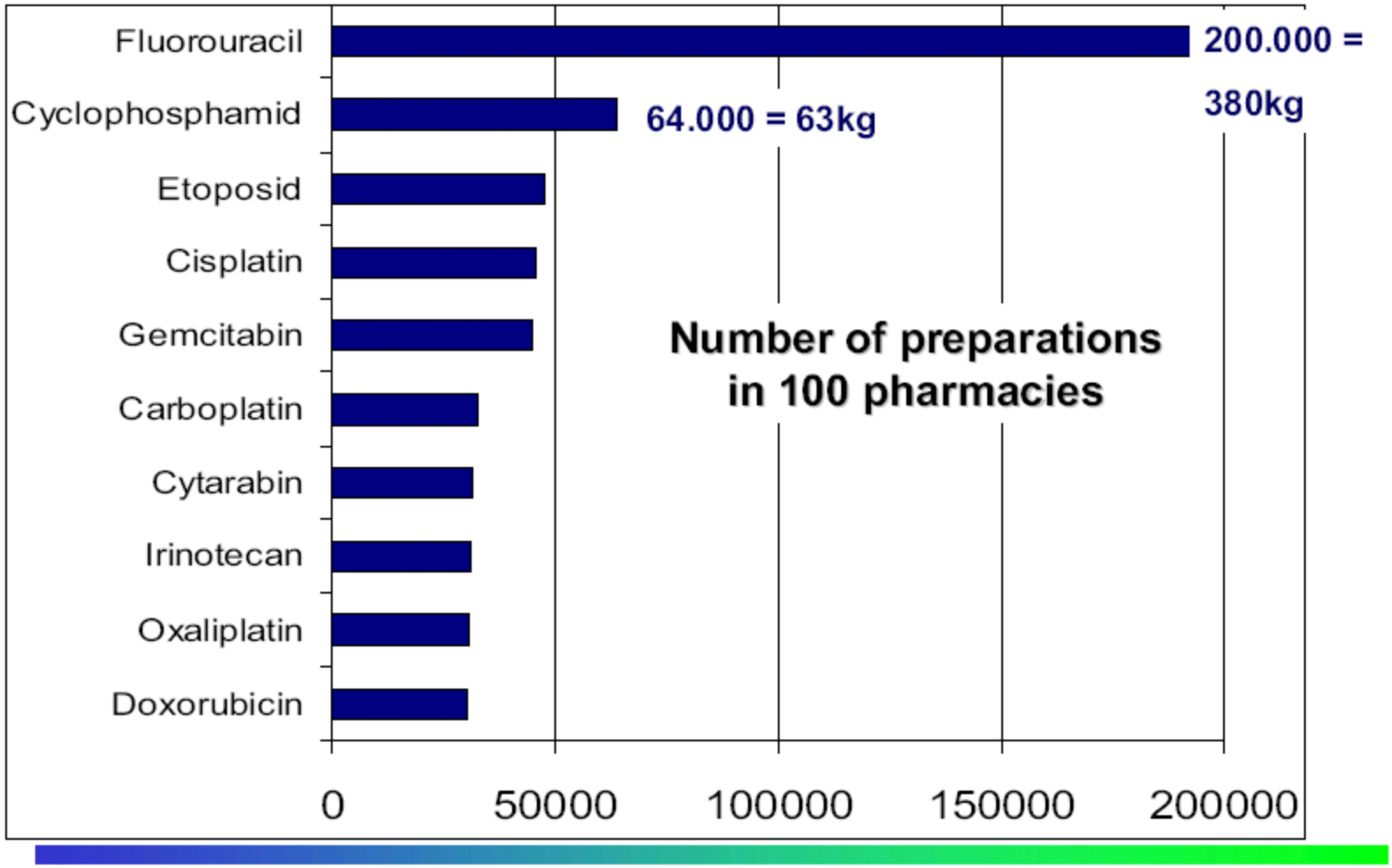
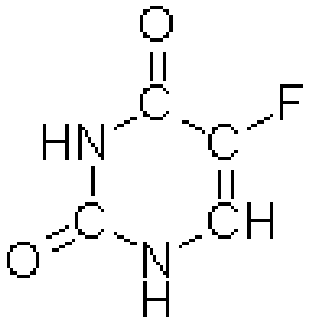
Results: Work practice

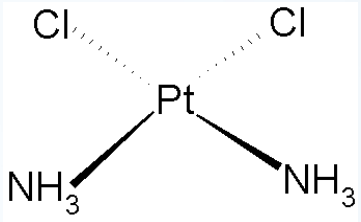


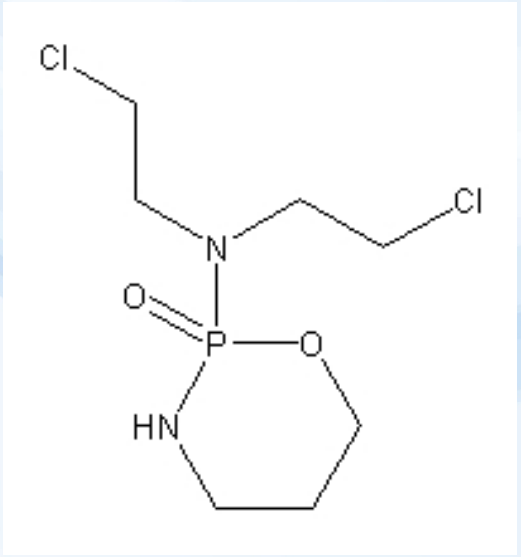
CYTO project model compounds

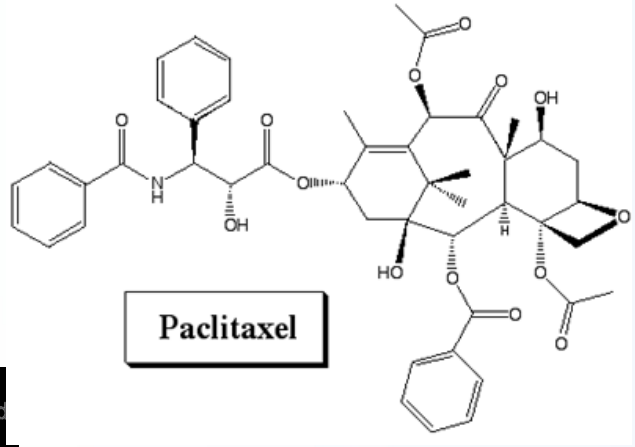
Models:

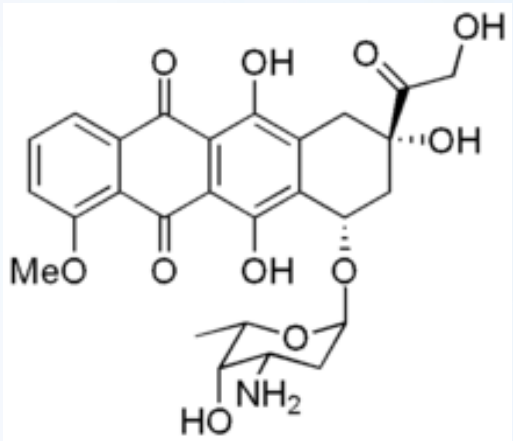
Fluorouracil, Cisplatin, Cyclophosphamide, Paclitaxel, Doxorubicin











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Final notes on MONITORING

How to monitor ? *(recommendations)*

- **surfaces**
  - easy and standardized sampling
  - correlate with exposures/doses
  - periodically - 1-2times/year
  - standardized and sensitive methods available

- **biomonitoring** (complementary)
  - cyclophosphamide in urine
  - passive sampler „dosimeters“
  - health status & cytogenetics

Final notes on MONITORING

How to use monitoring results ?

- **manage risks:** adapt procedures and protective measures to improve yourself (*periodic samplings)*

-> example

- **compare your situation** with others (anonymously)

-> example

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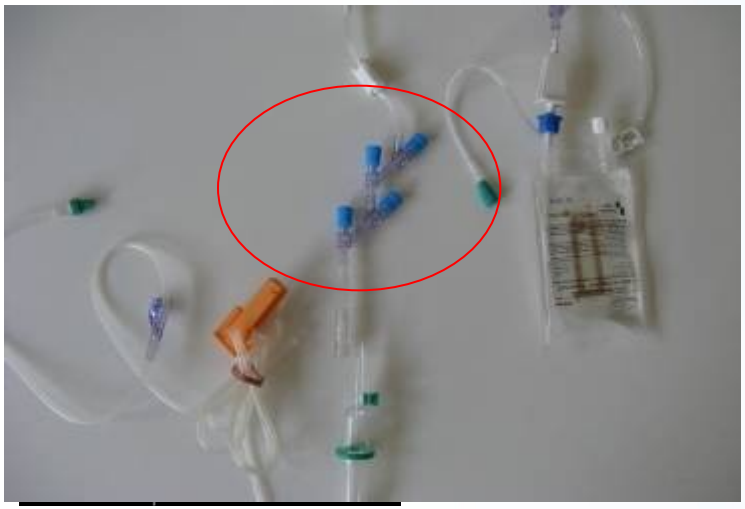
Managing exposure & risks – Czech examples

www.mou.cz

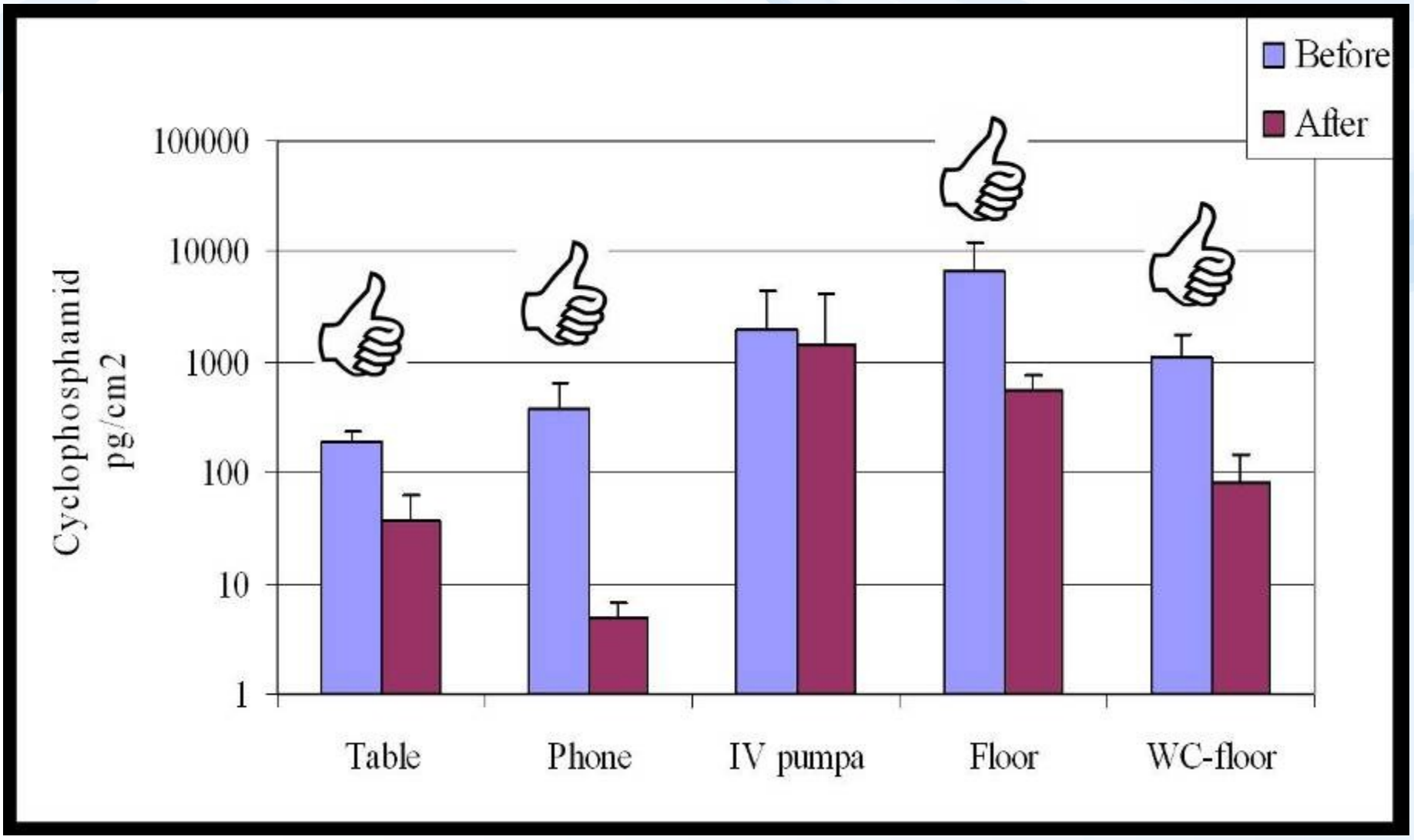
Wall-mounted holders

multi-channel administration sets



toilets with self cleaning seats

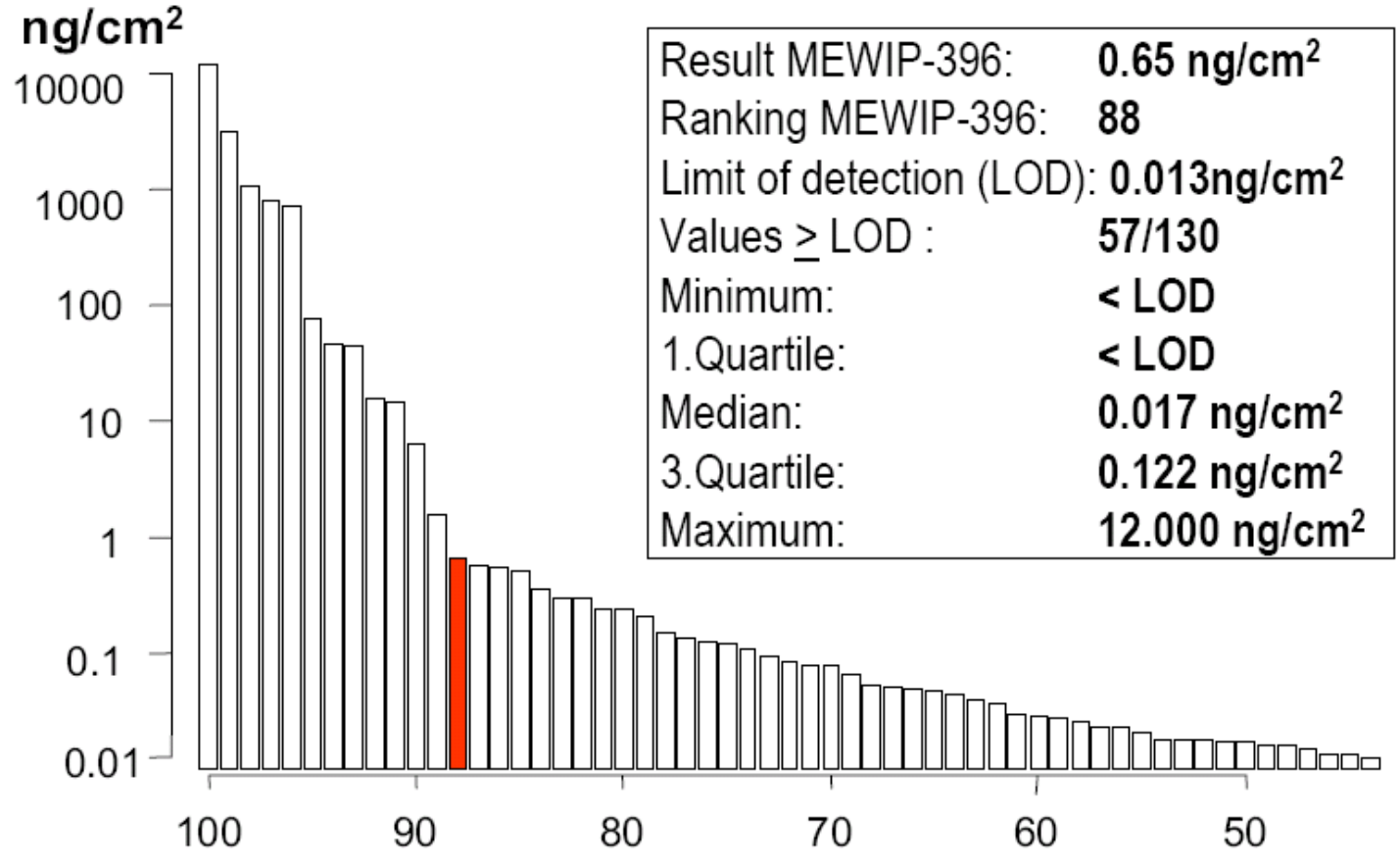
Surface contamination by cyclophosphamide (before / after of safety measure application)



Compare yourself with the others

Dr. Thekla Kieffmeyer (IUTA, Germany) - MEWIP project

Methods: Reports for participants

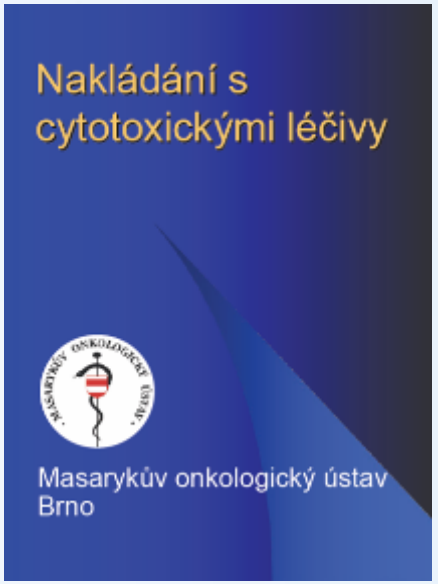


GENERAL SUMMARY

- Cytotoxic drugs represent **hazard** to workers
- **Risks** can be managed

- **Risk assessment and management tools**
  - Education and training (all personel)
  - Protective measures
  - Control mechanisms
    - Monitoring and biomonitoring

- **Further development**
  - Standardized procedures to be adopted



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