Preliminary exposure scenarios for taxol

a range finding study

Paul Scheepers

Research Lab Molecular Epidemiology

Dept Epidemiology Biostatistics and Health Technology Assessment

Ruud Wolberink

Wolberink & Den Dekker Arbo- en Bedrijfsgezondheidsdienst

Radboud University Nijmegen

Background

- In an R&D environment studies are carried out to improve bioavailability of formulations of taxol.
- In an old production building a pilot production facility is used for small scale R&D work.
- There are plans for building a new C-lab-like facility especially for these activities
- WdD and RUNMC support this process by:
  - Performing risk assessments
  - Developing methods for air sampling, wipe testing
  - Performing analyses of air and wipe samples
  - Support interpretation of outcomes of these occupational hygiene data in terms of health risk

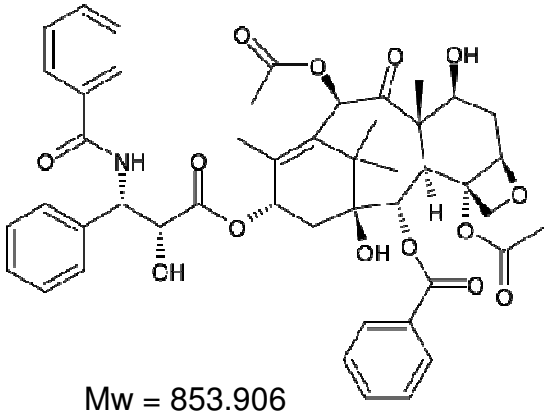
Introduction

- How to link occupational exposure to internal dose?
- How to interpret workplace contamination values?

➔ Missing link: exposure scenarios that can be used in a computer model that can generate probability estimates for internal exposure

The case of taxol

- Taxol (paclitaxel) member of the familiy of taxanes
- First isolated from the bark of the Pacific yew tree, *Taxus brevifolia*
- Stabilizes the structure of microtubili during cell division acting as a mitotic inhibitor because it disturbes the flexibility of the microtubili while positioning chromosomes in daughter cells
- Used to treat patients with lung, ovarian, breast, head and neck cancer
- Some of the more serious side effects are related to the use of Cremophor EL a castor oil that is used as an excipient, improving the bioavailbility to target tissues. In literature it is suggested that Cremophor EL may give rise to allergic responses in patients.



Mw = 853.906

Exposure modelling using a four step approach

1. Determine a critical internal dose (body burden)
2. Determine scenarios for
   a) Inhalation uptake
   b) Dermal uptake
   c) Oral uptake
3. Calculate probability dose estimates
4. Find critical ‘reference’ ranges for
   a) Air concentrations
   b) Skin contamination
   c) Contamination of objects/surfaces

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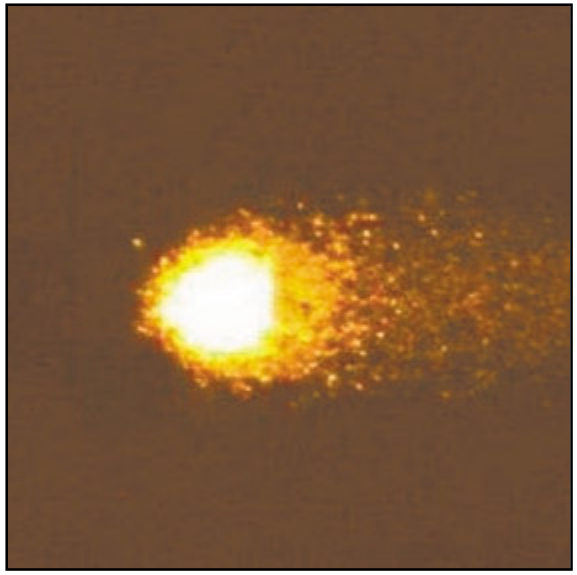
Step 1: Determine a critical internal dose (body burden)

Source: RTECS
Record: Taxol DA 8340700
Studies: 113
Relevant: 14

Lowest toxic dose observed in human lymphocytes: 100 nM (100 nmol/L plasma) by *in vitro* exposure to taxol during 2-6 h. Toxic effect: Comets determined by SCGE [a]

[a] Branham et al. (2004) Mutation Res 560:11-17



Comet assay: a single cell gel electophoresis (SCGE) showing DNA strand breaks and incomplete excision repair sites

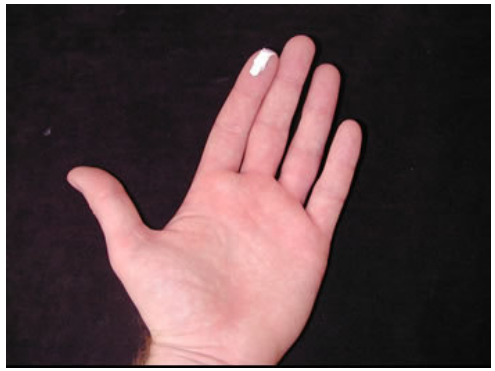
For an adult with a body weight of 70 kg a plasma concentration of 100 nM corresponds to a body burden of ~ 6 µg/kg (threshold)

Step 2: Determine exposure scenarios

a) Dermal exposure scenario

"Undetected skin contamination of finger tip, finger and hand palm"

Assumptions	Model setting
Amount (low – medium – high)	1.8, 18, 180 µg (50 %)
Exposed skin (low – medium – high)	1.8, 18, 180 cm^2
Solution of taxol (in ethanol)	20 g/L
Contact time	5.7 h/day [a]
Skin permeation value	3.4 x 10^{-6} cm/h [b]



[a] This corresponds to 40/7: 8 hours/day, 5 days/wk

[b] Calculated using SkinperX (W. ten Berge et al.)

Step 2: Determine exposure scenarios

b) Inhalation exposure scenario
"Undetected release of cytostatic-containing aerosols"

Assumptions	Model setting
Emission (low – medium – high)	3.8, 19, 380 µg (50 %)
Ventilation rate	2 h^{-1}
Room volume	315 m^3
Particles are respirable	Fraction absorbed = 100 %
Purity	98 %
Room temperature	20 ± 5 °C
Inhalation rate	23.2 ± 6 (m^3/day)
Exposure duration	5.7 h/day [a]

[a] This corresponds to 40/7: 8 h/d, 5 d/wk

Step 2: Determine exposure scenarios

c) Oral exposure scenario

"Mouth contact (- chewing) on a contaminated pen"

(example of a finger shunt scenario)

Assumptions	Model setting
Contamination amount (low-medium-high)	1, 10, 100 ng (50 %)
Contamination (low-medium-high)	0.5, 5 and 50 ng/cm^2
Contact duration (worst case)	30 min
Migration rate	10 ng/cm^2/min [a]

[a] Any value > 1.7 ng/cm^2/min will be sufficient to release 100 % of the contamination in the high exposure scenario.

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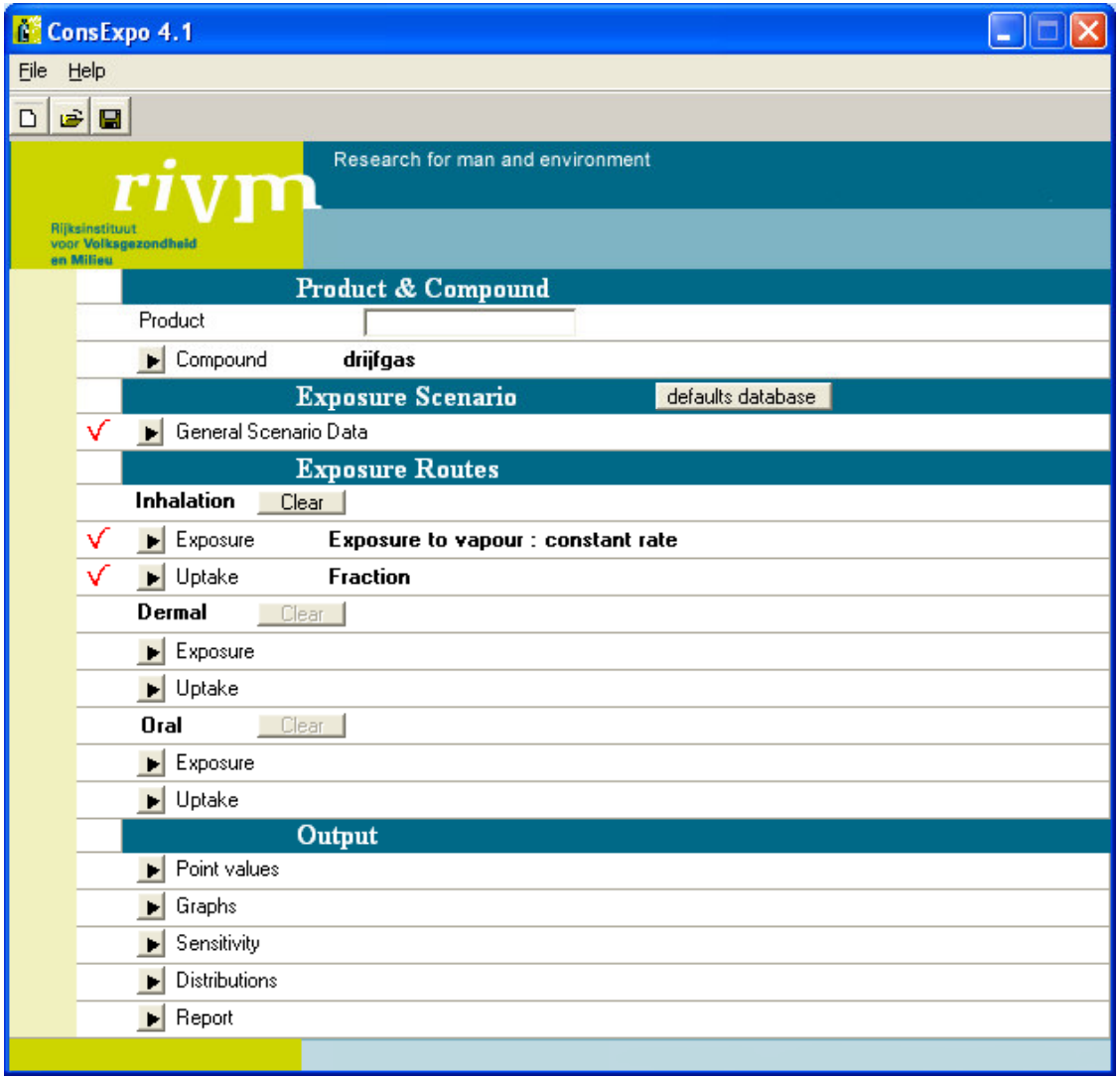
ConsExpo 4.1

1. General scenario
2. Inhalation
3. Dermal
4. Oral



ConsExpo 4.1: output

	Point estimate	Probability estimate
Input	Assumed (fixed) value for each parameter	Measured or assumed distribution of values for each parameter
Output	Fixed number	Calculated distribution

ConsExpo 4.1: output

Distributional or probabilistic calculations account for:

- Uncertainty: variation due to imperfect/incomplete knowledge
- Variability: natural variation in a parameter

Allan explains variability

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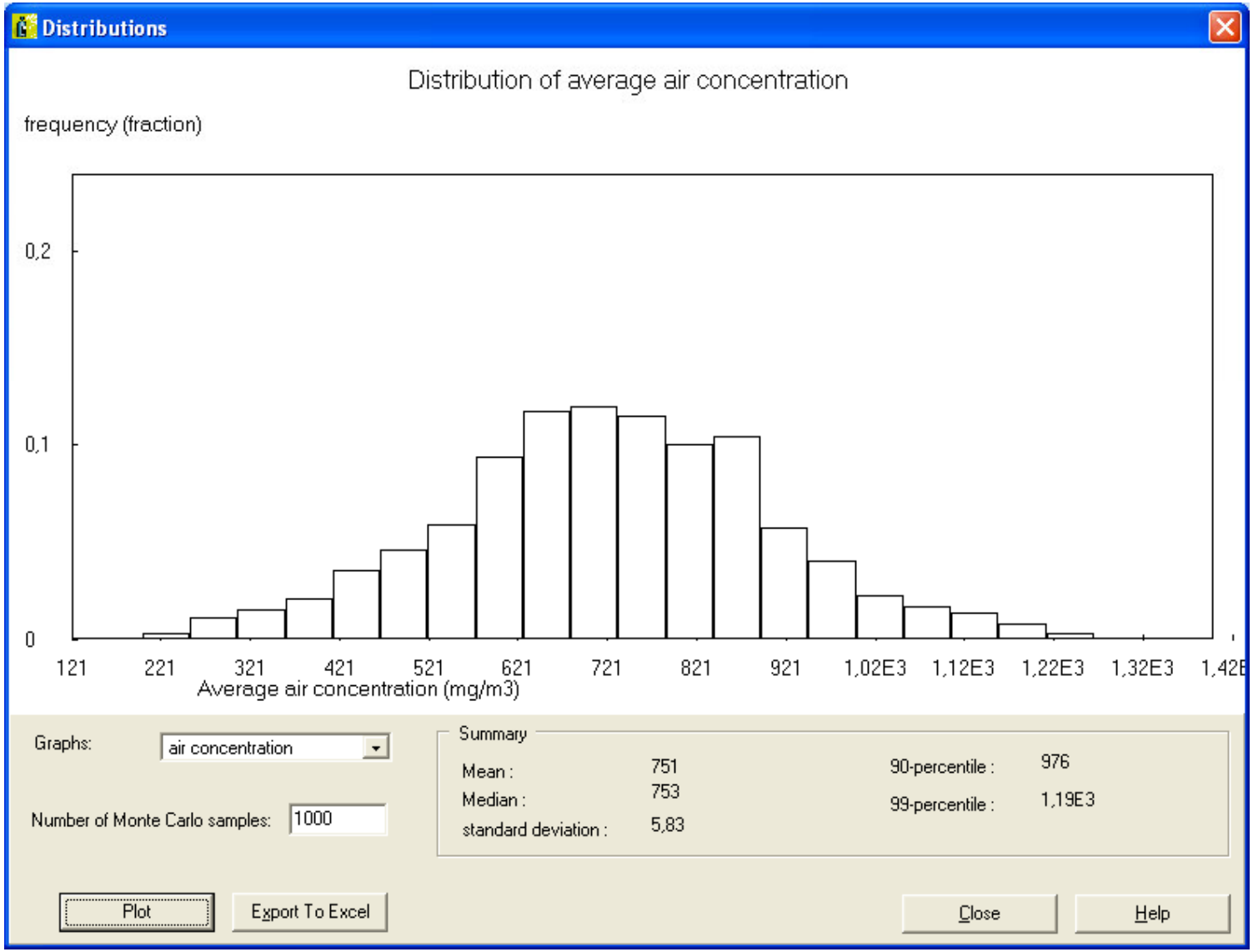


Step 3: Calculate dose estimates

Scenario	Low	Medium	High
Emission (µg)	3.8	19	380
Air concentration (ng/m^3)	1.0	5.0	100.0
Median acute systemic dose	0.000001	0.00019	0.0039
99 Percentile	0.0001	0.60	6.2
Median chronic systemic dose	0.00039	0.0019	0.038
99 Percentile	1.1	7.5	143

Well below threshold | In the same range | Above threshold

Step 3: Calculate dose estimates

b) Dermal dose (µg/kg)

Scenario	Low	Medium	High
Amount on skin (µg)	0.018	0.18	1.8
Exposed surface (% of total body surface)	0.01 (finger tip)	0.1 (finger)	1 (palm)
Skin exposure (ng/cm^2)	10	10	10
Median acute systemic dose	0.00025	0.0025	0.025
99 Percentile	0.0097	0.096	0.98
Median chronic systemic dose	0.0025	0.025	0.25
99 Percentile	0.26	2.5	20

Well below threshold | In the same range | Above threshold

Step 3: Calculate dose estimates

c) Oral dose (µg/kg)

Scenario	Low	Medium	High
Product amount (ng)	1	10	100
Contamination (ng/cm^2)	0.5	5	50
Median acute systemic dose	1.4×10^{-7}	1.4×10^{-6}	1.4×10^{-5}
99 Percentile	9.5×10^{-5}	9.7×10^{-4}	8.4×10^{-3}
Median chronic systemic dose	1.4×10^{-6}	1.4×10^{-5}	0.00014
99 Percentile	0.0014	0.0074	0.205

Well below threshold | In the same range | Above threshold

Step 4: Range finding for taxol

Preliminary (range) findings for Taxol:

Inhalation is the most important risk:

- Daily exposure to 5 ng/m^3 over (less than) one year could lead to an unacceptable (accumulated) internal exposure

- Exposures to 100 ng/m^3 could lead to an unacceptable exposure within one working period

➔ Target level is < 0.1 ng/m^3 (action level 0.5 ng/m^3)

Step 4: Range finding for taxol

Preliminary (range) findings for Taxol:

Dermal exposure can become critical in specific scenarios:

- Contamination of a door handle or a telephone receiver of 2000 ng could lead to substantial accumulated uptake exceeding the guideline of 6 µg/kg.

➔ Taxol could spread (by surface-to-surface transfer) to places where one does not expect this toxic substance (and thus does not wear skin protection)

- Cleaning after a spill could involve a serious risk because skin contamination may exceed 10 ng/cm^2 (e.g. splashes/spatters of a 20 g/L solution!).

➔ Cleaning (after a spill) requires additional skin protective equipment

Step 4: Range finding for taxol

Preliminary (range) findings for Taxol:

Oral uptake is unlikely to be a problem

- This scenario does not contribute very much compared with inhalation and skin routes of uptake

➔ Normal personal hygiene procedures for a tox unit (all materials in the unit should be considered to be contaminated)

Range finding study taxol

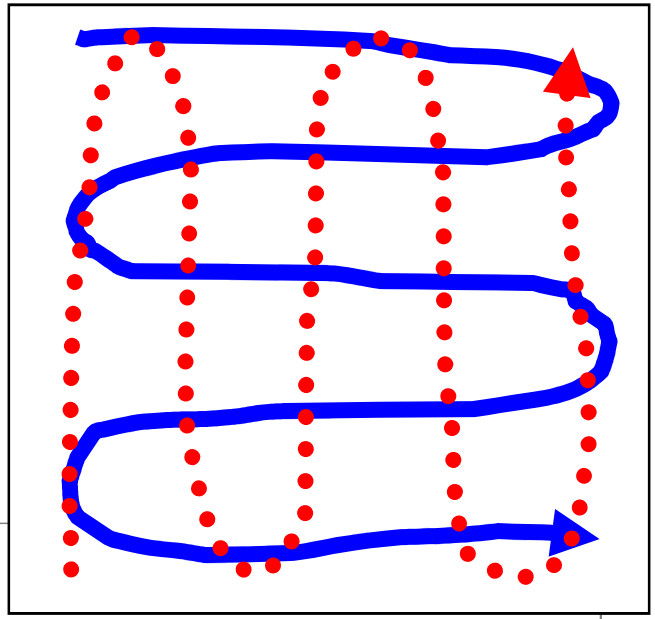
Surface contamination

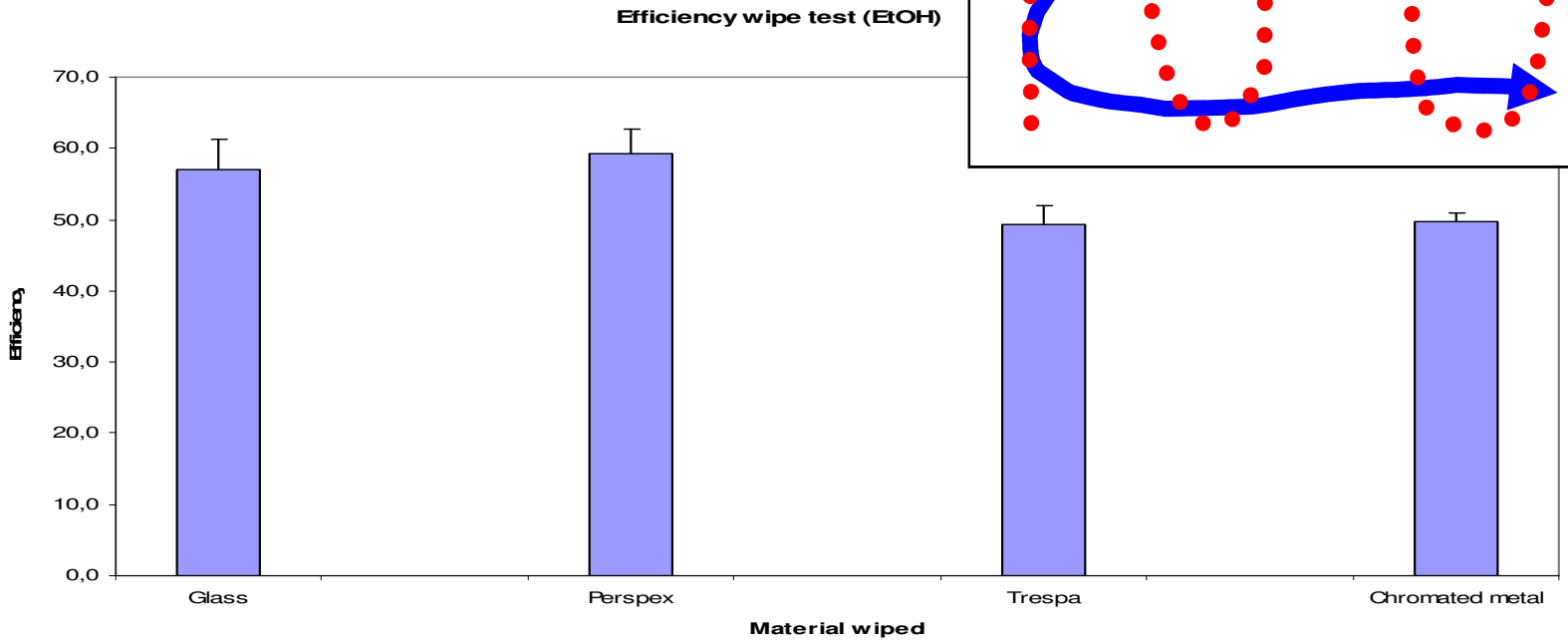
<u>Procedure wipe test</u>

Medical gauze

Alcohol

20 x 20 cm





Surface contamination < 2000 ng

Contamination of surfaces that could be touched without proper protection (amounts in ng of taxol)

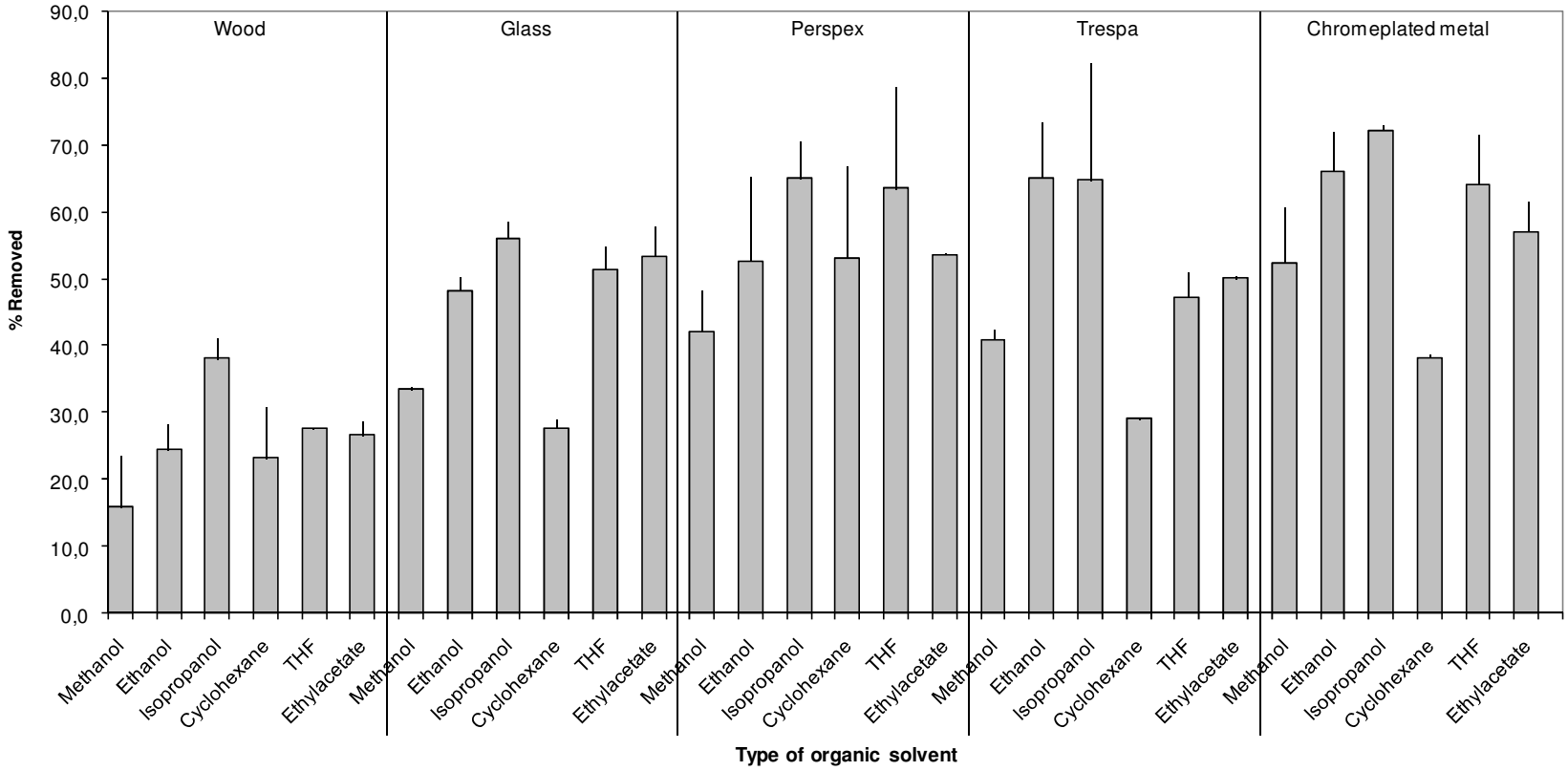
Cleaning

	Material	24-11-06	21-12-06	23-05-07	25-05-07	27-08-07	19-10-07
Telephone receiver	Plastic	150	10,900	13.6	15.3	20.8	nd
Handle of fume cupboard	Wood	69	46.7	-	48.7	18.2	15.5
Water tap handles	Metal	34.9	28.3	117.4	85.3	6.1	15
Door handles	Metal	10	6.2	20.4	17.2	3.6	nd

Problem: residual contamination

Surface contamination

Cleaning efficiencies of taxol for different solvents used on different surfaces



Range finding study taxol

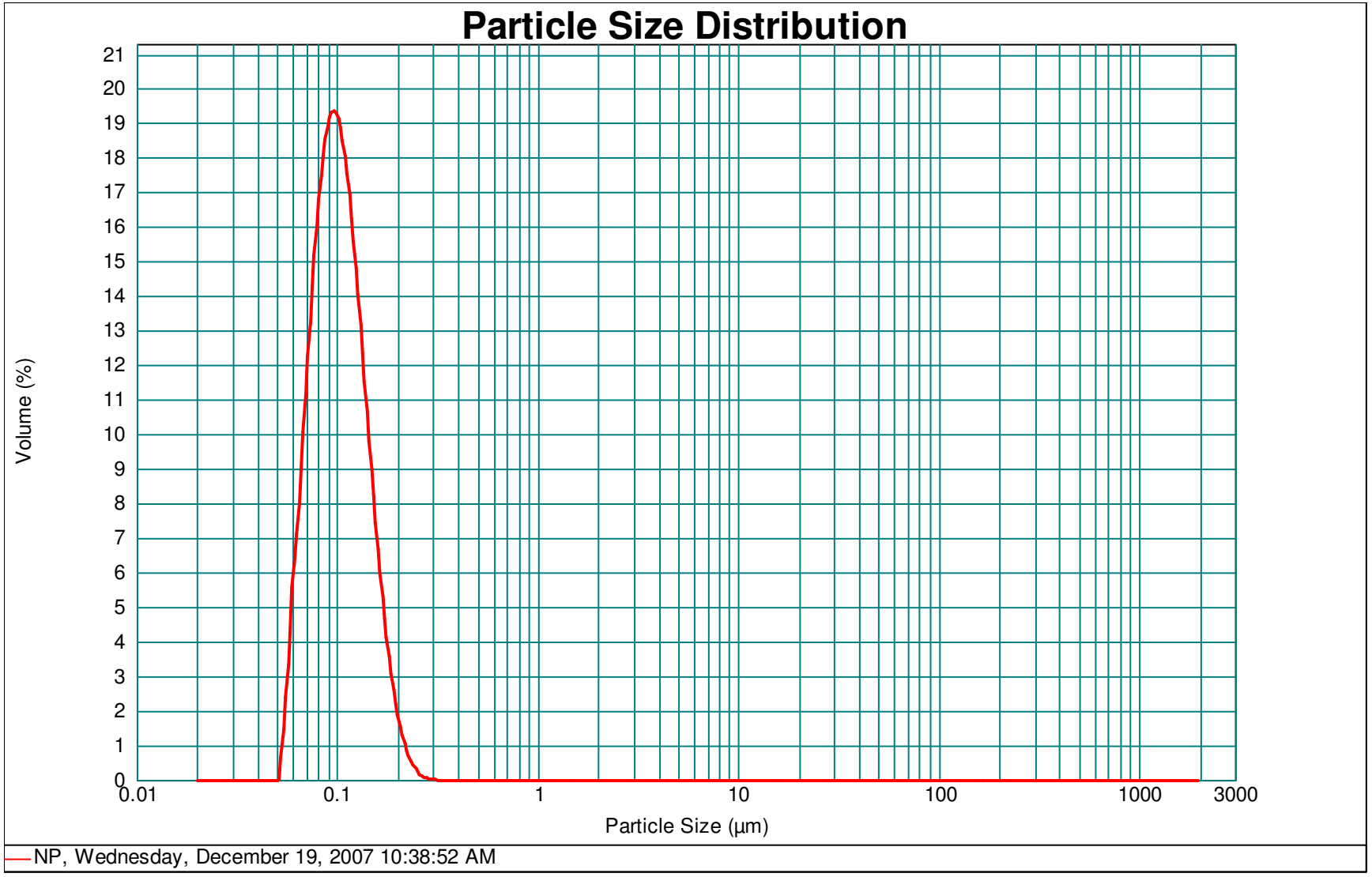
Surface contamination < 10 ng/cm^2

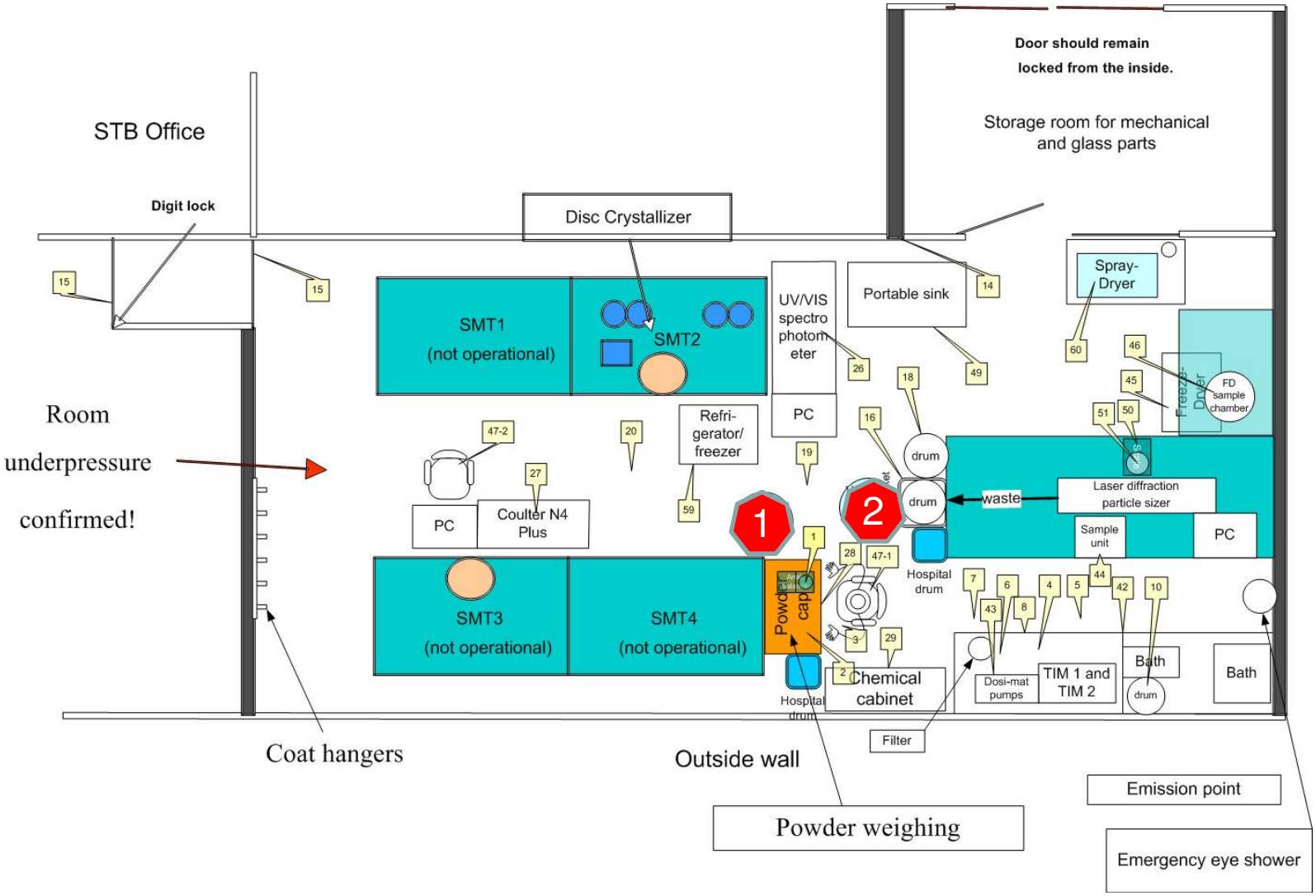
Contamination of surfaces that could be touched without proper protection (amounts of taxol in ng/cm^2)

	Material	24-11-06	21-12-06	23-05-07	25-05-07		27-08-07	19-10-07
Scale of balance	Metal	4.5	668	-	124.6		2.1	nd
Powder weighing	Plastic	34.5	12.6	1.5	2.6		0.2	0.1
Fume cupboard	Plastic	3.8	3.5	50.5	15.0		0.01	186
Floor	Concrete	0.2	0.8	2.3	0.8		1.5	0.2

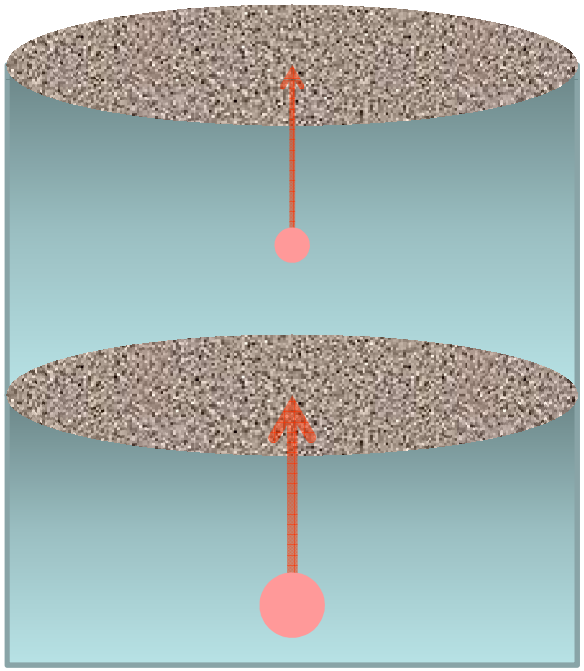
New cleaning procedure:
1. Soak (> 5 min) in 30 v% 1M NaOH in water with 70 v% methanol using a tissue
2, Dry with a tissue and clean 2-3x with isopropanol or n-propanol
3. Wipe 3 times with a tissue soaked in water

Undetected spill?


Particle Size Distribution
Volume (%)
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0.01
0.1
1
10
100
1000
3000
Particle Size (µm)
NP, Wednesday, December 19, 2007 10:38:52 AM


Door should remain
locked from the inside.
STB Office
Storage room for mechanical
and glass parts
Digit lock
Disc Crystallizer
SMT1
(not operational)
SMT2
UV/VIS
spectro
photom
eter
Portable sink
Spray-
Dryer
Freeze-
Dryer
FD
sample
chamber
Room
underpressure
confirmed!
Refri-
gerator/
freezer
PC
Coulter N4
Plus
drum
waste
Laser diffraction
particle sizer
Sample
unit
PC
Hospital
drum
SMT3
(not operational)
SMT4
(not operational)
Powder
cap
Chemical
cabinet
Dosi-mat
pumps
TIM 1 and
TIM 2
Bath
Filter
Coat hangers
Outside wall
Emission point
Powder weighing
Emergency eye shower

Air sampling on membrane filters



Back-up

Front

Range finding study taxol

Air concentration (ng/m^3)

Date	Sampling location 1		Sampling location 2	
	Front	Back-up	Front	Back-up
28.09.2007	0.1	.	0.2	.
03.10.2007	0.2	.	0.3	.
31.10.2007	0.02	0.004	0.007	-
03.12.2007	-	-	-	-
05.12.2007	0.4	-	0.5	-
10.12.2007	-	-	-	-

. No data
- Not detected

Only cleaning activities!

Discussion

- What is the critical internal dose?
- Are there more specific (‘realistic’) data that can be used as input data?
- Which percentile value of uptake distributions be used for determining the uptake of a scenario?
- What is the relationship between skin exposure and dermal uptake (sensitivity analysis)?
- Can this approach also be used for other cytostatic drugs (e.g. cyclophosphamide and cis-platina)?

Future challenges

- Move R&D activities to a new ‘C-lab’ environment
- Improve quantifiation of contamination measurements
- Development of a biological monitoring method for taxol