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Human Biomonitoring: from group to personalized exposure assessment in occupational settings

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Evaluation methods in occupational health

1. External Monitoring:

   - Inhaled air — Reference: OEL (mg/m^3)
   - Work surfaces — Reference: SCL ($\mu g/100\ cm^2$)
   - Skin — Reference: DOEL ($\mu g/cm^2$)

2. Biomonitoring :

   Blood, urine, exhaled air, saliva, hair, nails, ..

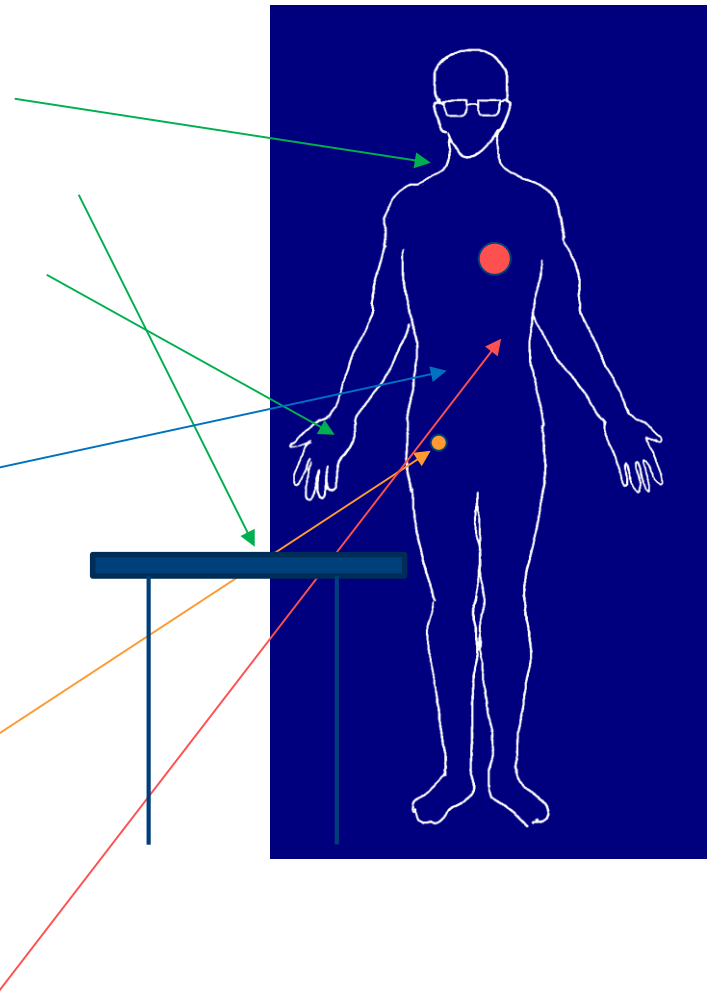
   Reference: BEI (mg/L, mg/m^3, ...)

3. Biological-effect Monitoring:

   Pre-pathologic effect (DNA adduct, epigenetic changes ….)

4. Health-effect Monitoring:

   Effect of stress factors (lung function, ….)



OEL = occupational exposure limit; SCL = surface contamination limit; DOEL = dermal OEL; BEI : biological exposure indices

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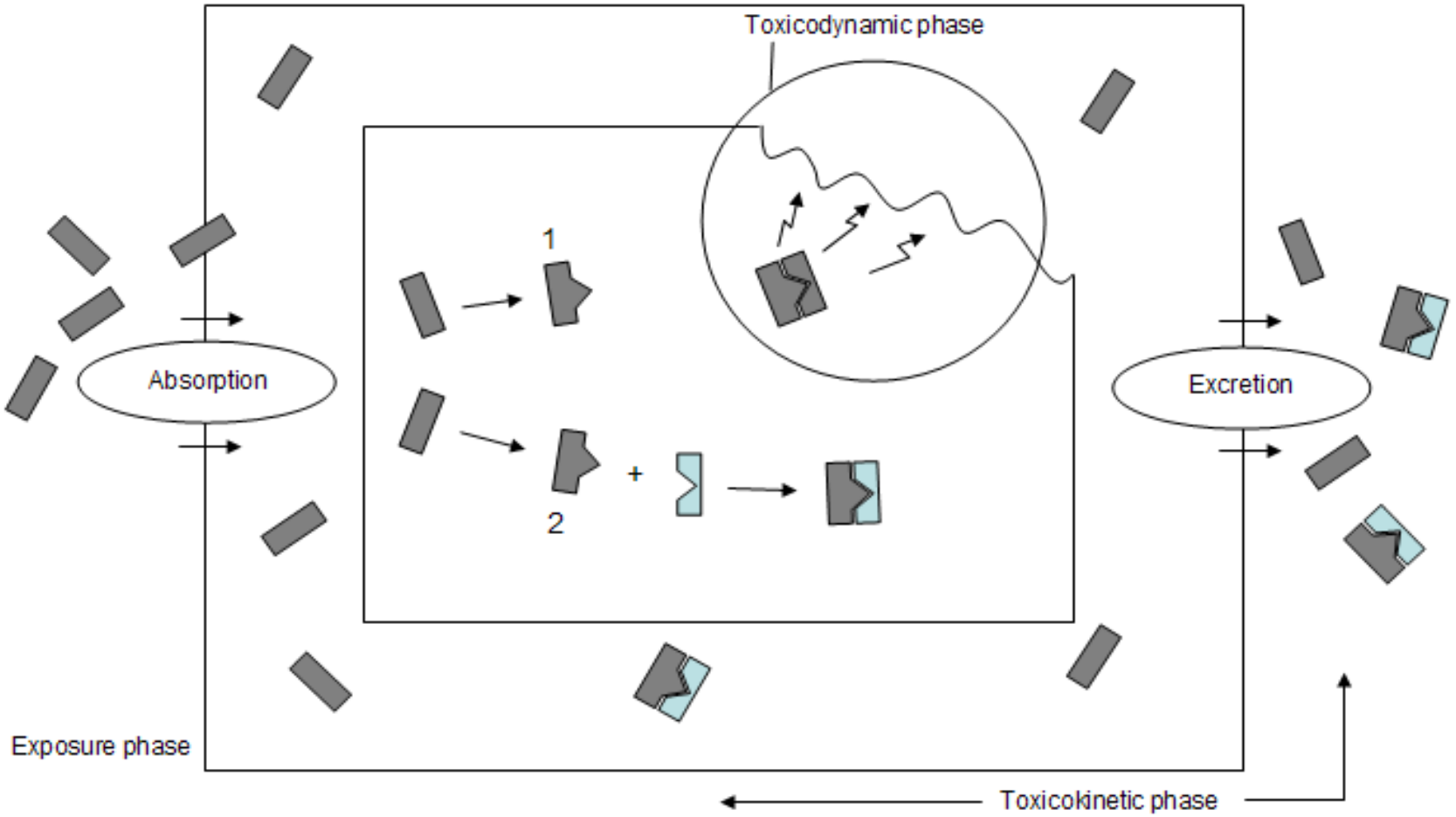
Biological monitoring (biomonitoring)

…is the standardized and repeated systematic collection, pretreatment, storage, analysis of body tissues to assess the internal dose of a xenobiotic substance by analysis of the parent substance and/or a product of bioformation.

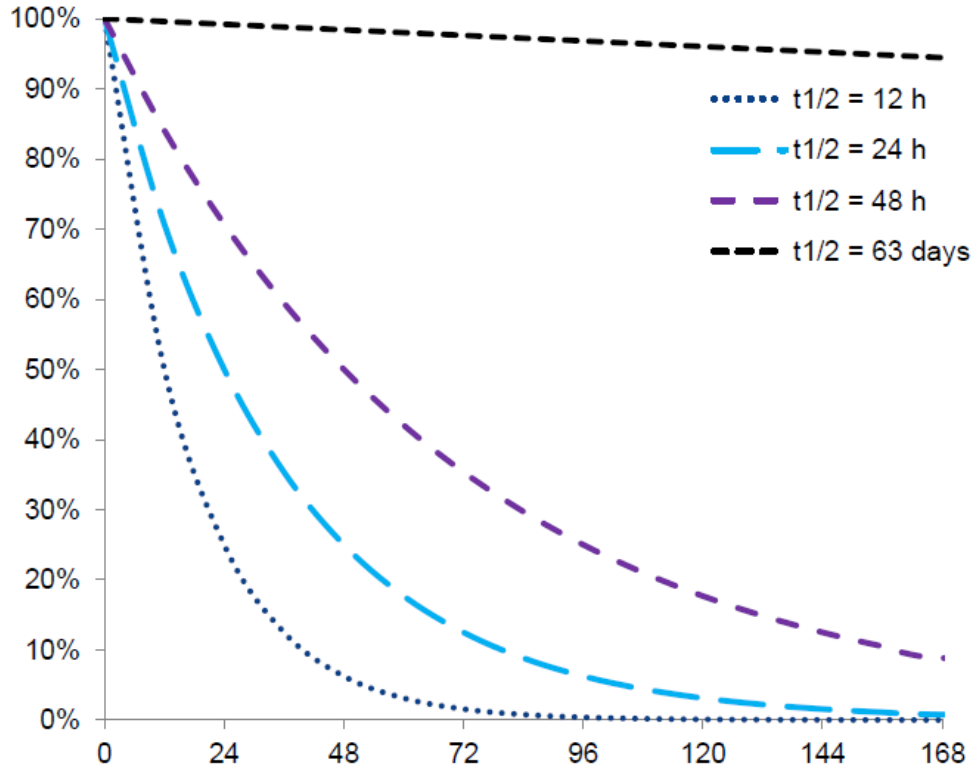
Toxicokinetics - toxicodynamics

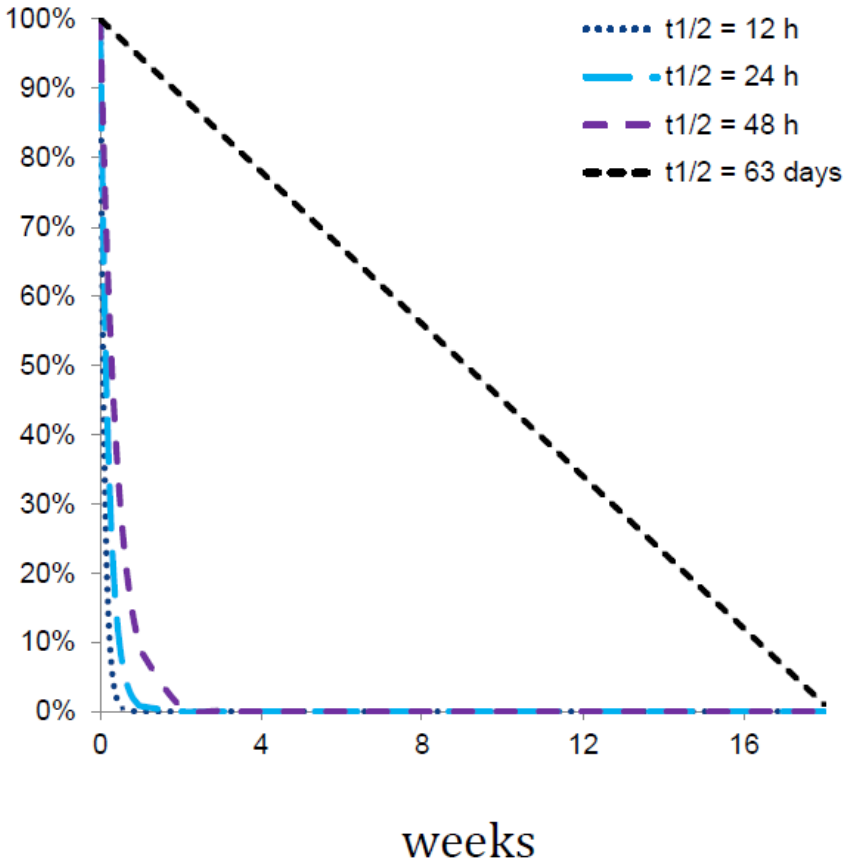


Toxicokinetics

- Toxicodynamics = working mechanisms
- Toxicokinetics = uptake, distribution, storage, metabolism and excretion
  - Biomonitoring is a form of applied toxicokinetics
  - Knowledge of half-life time is required:
    - To know if the substance is accumulating
    - To determine the correct sampling moment
  - Knowledge on the metabolism and the most appropriate parameter(s)
  - Knowledge on the excretion routs for the appropriate sample medium

Half-life time – $T_{1/2}$





$T_{1/2}$ and importance for sample collection

- Moment of sampling is determined by $t_{1/2}$
  - Biomarkers with a short $t_{1/2}$
    - Very rapid changing levels, not useful for BM
  - Biomarkers with $t_{1/2} < 5h$
    - Sample collection at the end of the work shift
    - Values reflect very recent exposure
    - No accumulation
  - Biomarkers with $t_{1/2}$ between 5h and 10h
    - Sample collection at the end of the work shift and the end of the work week
    - Values reflect exposure during the work week
  - Biomarkers with $t_{1/2} > 10h$
    - Sample collection at the end of the work shift and the end of the work week
    - Values reflect both recent as previous exposure. Hence accumulation.

Biomonitoring of human exposure

“Classical” matrices

Urine

Advantages:

- important sample volume
- molecules are already in a liquid phase
- extensive knowledge of sample preparation and compounds analysis

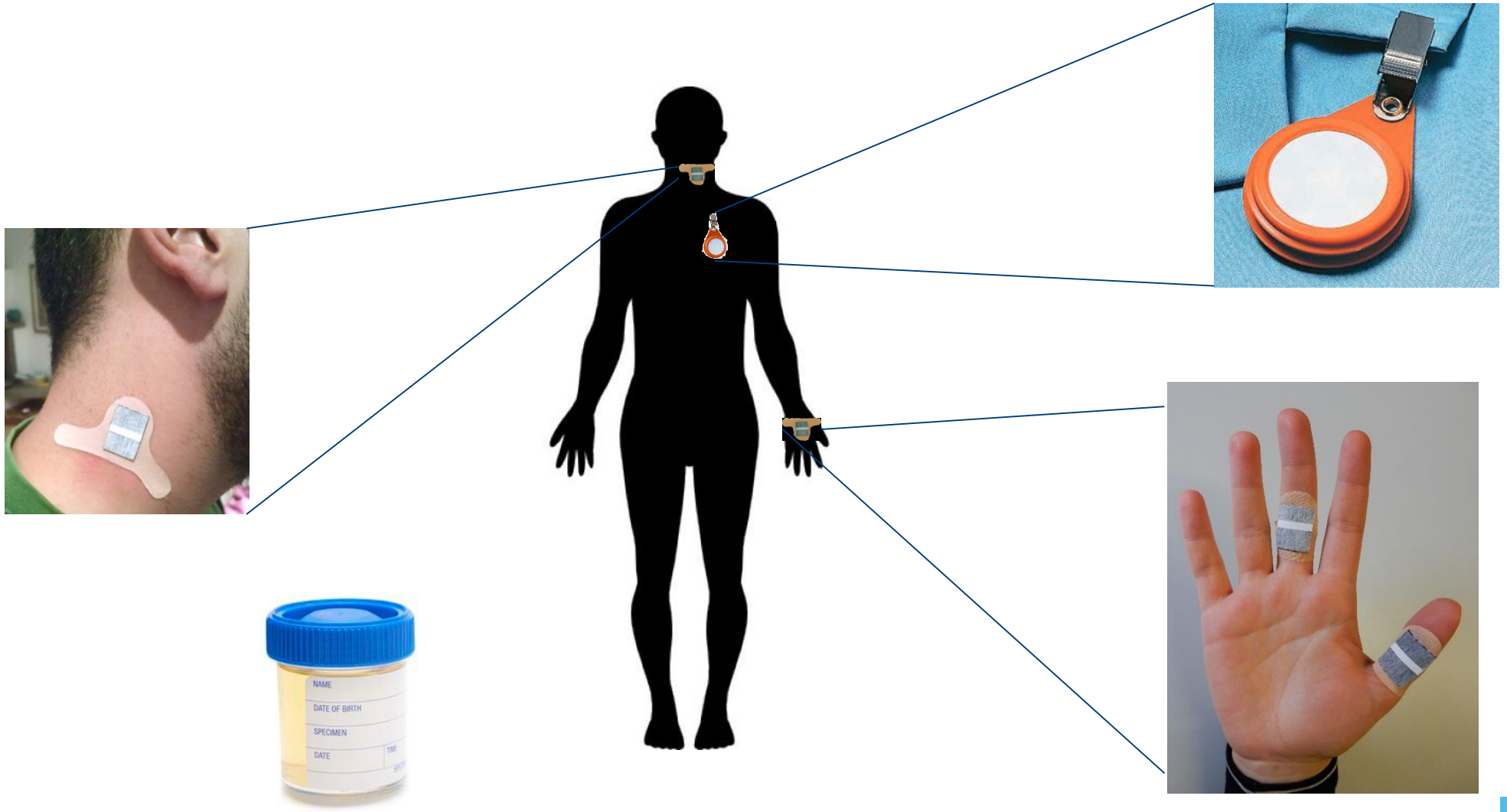
Field study - Thermoplastic panels factory

38 workers

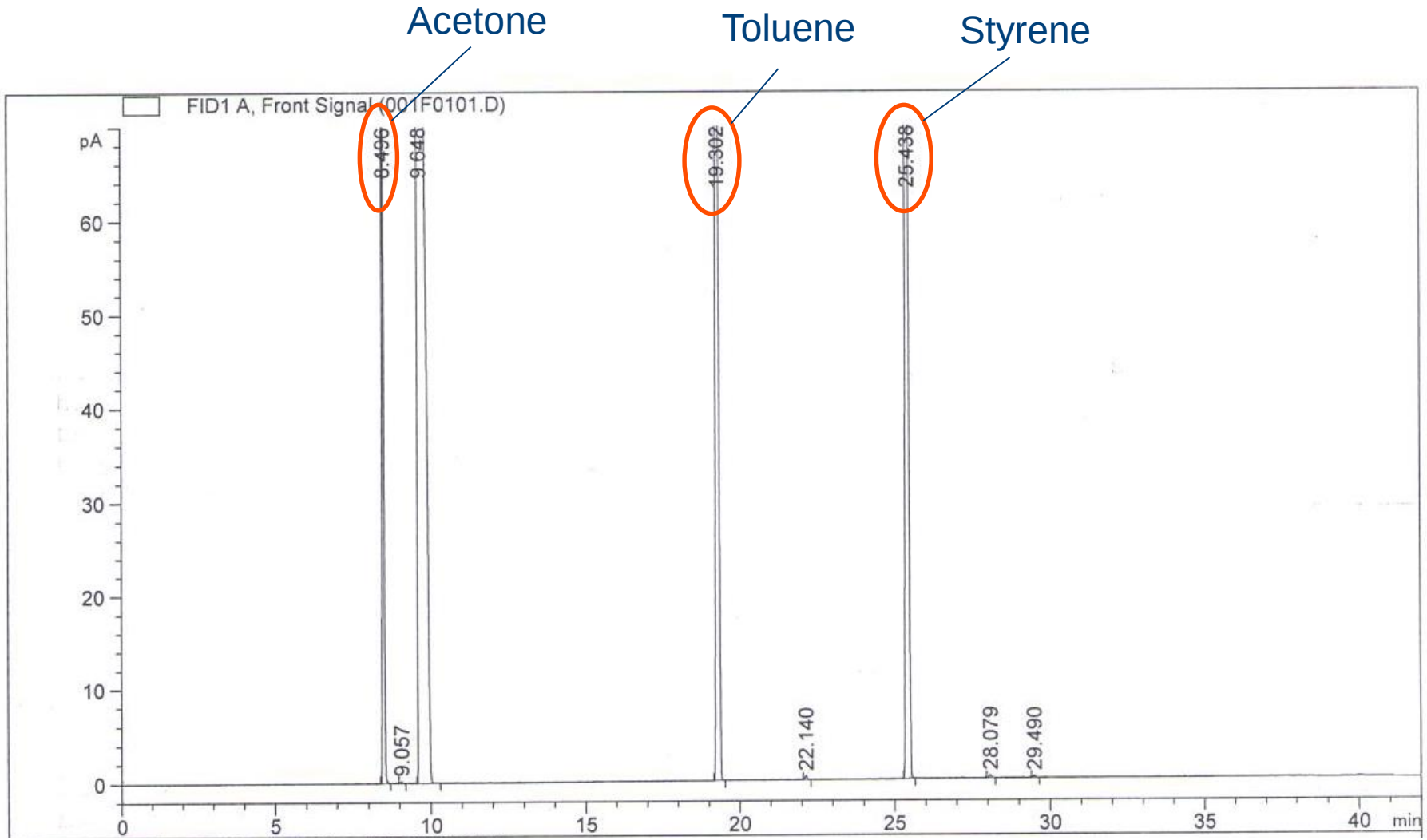
Jobs performed:

- “Sheet molding composite” workers (SMC) (n= 8)
- Hydraulic press workers (n= 14)
- Mechanics (n= 5)
- Office workers (n= 11)

Methodology



Air exposure



Chromatogram obtained for 3M monitors analysis

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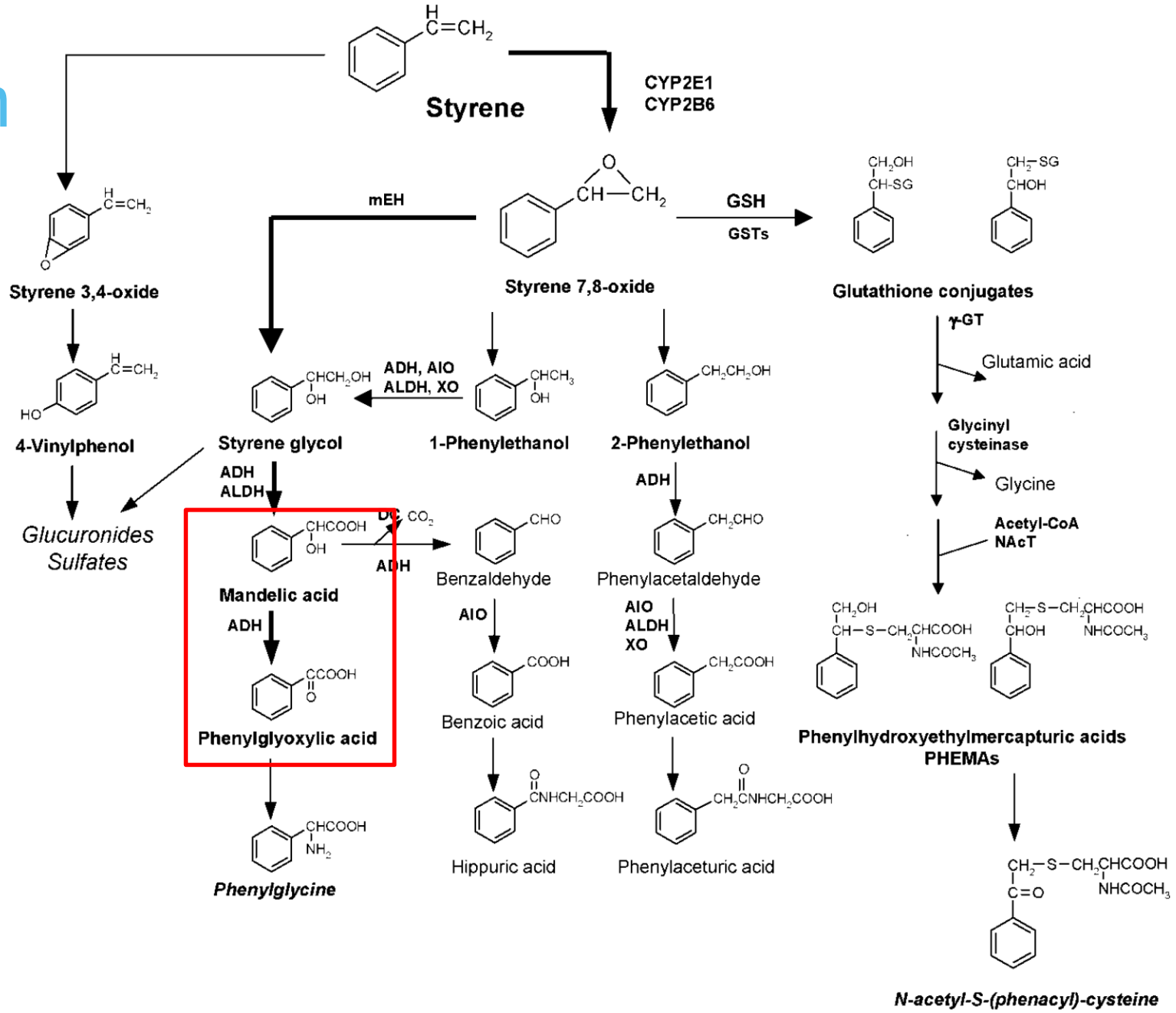
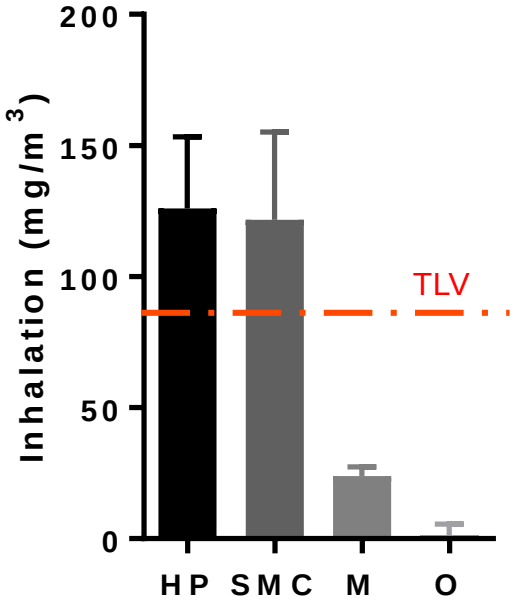
Styrene metabolism

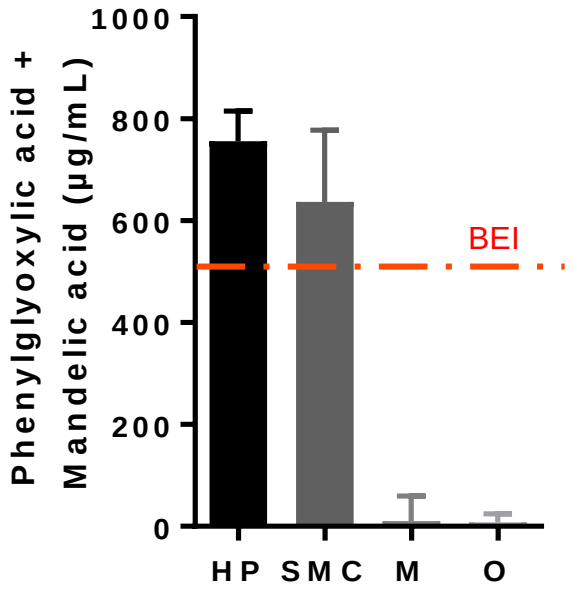


Results

Exposure to styrene

TLV-TWA= 85 mg/m^3 styrene
BEI= 520 µg/mL MA+PGA





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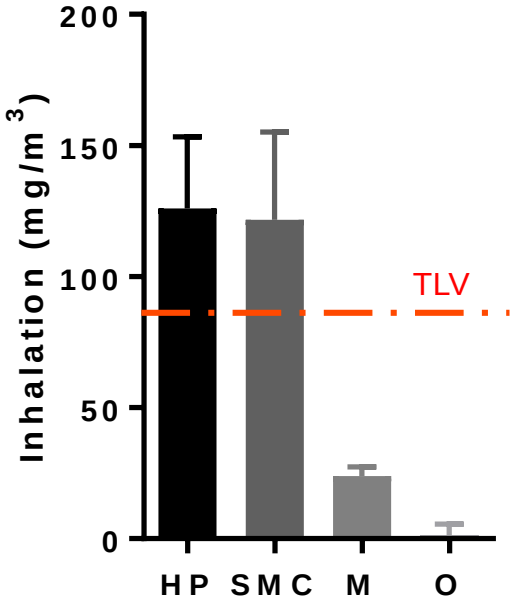
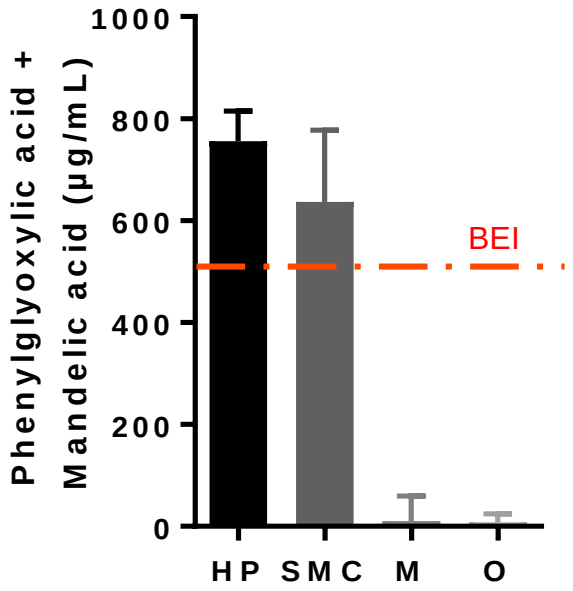
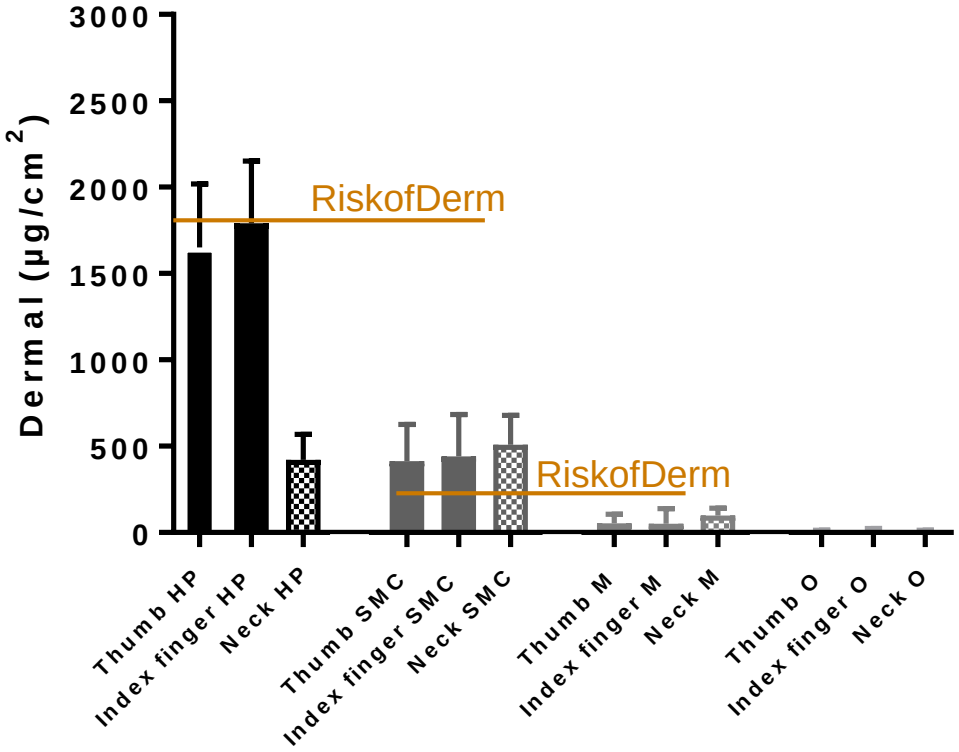
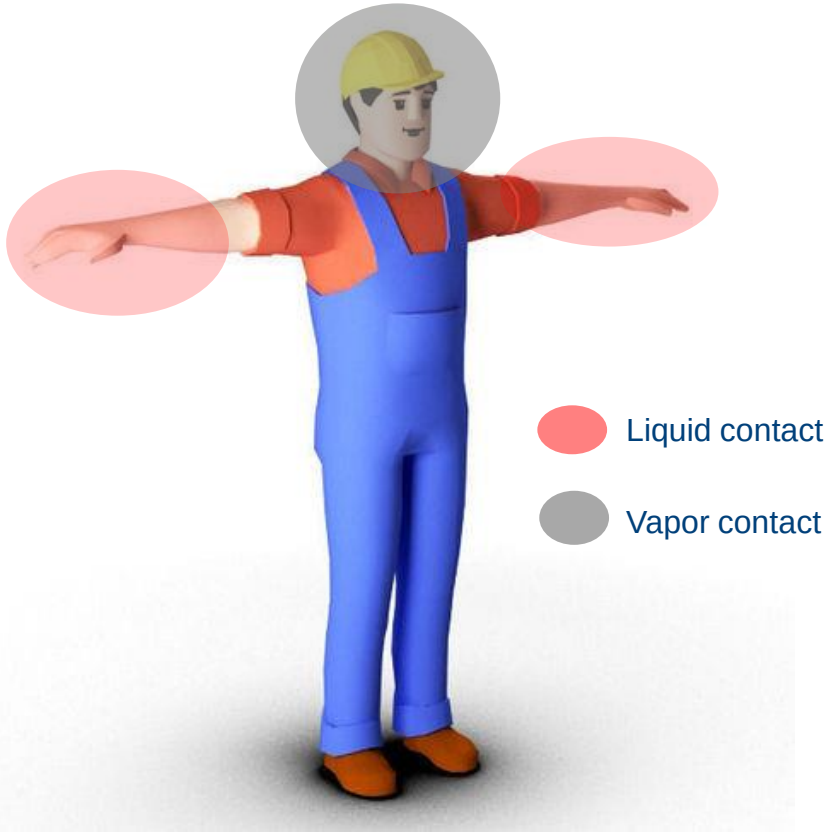






IHSkinPerm

Body parts	Surface (cm^2)
Hands + forearms	2000
Neck + face	1100



Styrene

	Liquid contact			Vapor contact		
	Exposure	Fraction absorbed	Amount absorbed	Exposure	Fraction absorbed	Amount absorbed
HP workers	1720 mg/hour	6,49%	714 mg	125 mg/m3	97,70%	0,685 mg
SMC workers	410 mg/hour	22,90%	601 mg	121 mg/m3	97,70%	0,663 mg
Mechanics	52 mg/hour	23,30%	77,5 mg	24 mg/m3	97,70%	0,130 mg

W. ten Berg et al., 2011. IH-SkinPerm, an Advanced Skin Absorption Model. Dermatitis, 22 -5-p 287.

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Biomonitoring of human exposure

“Classical” matrices

Urine

Advantages:

- important sample volume
- molecules are already in a liquid phase
- extensive knowledge of sample preparation and compounds analysis

Limitations:

- reflecting only recent exposure

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Methodology

	Mo.	Tu.	We.	Th.	Fr.
Pres-shift	X	X			X
After-shift	X	X			X

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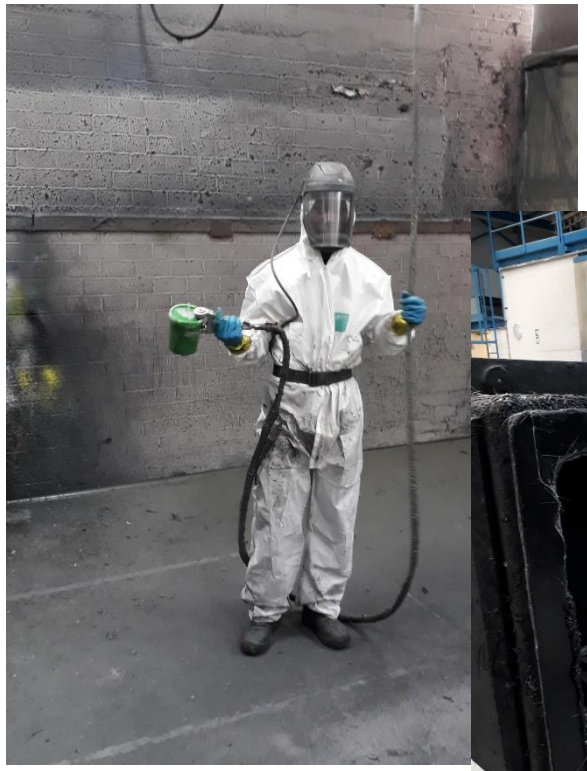
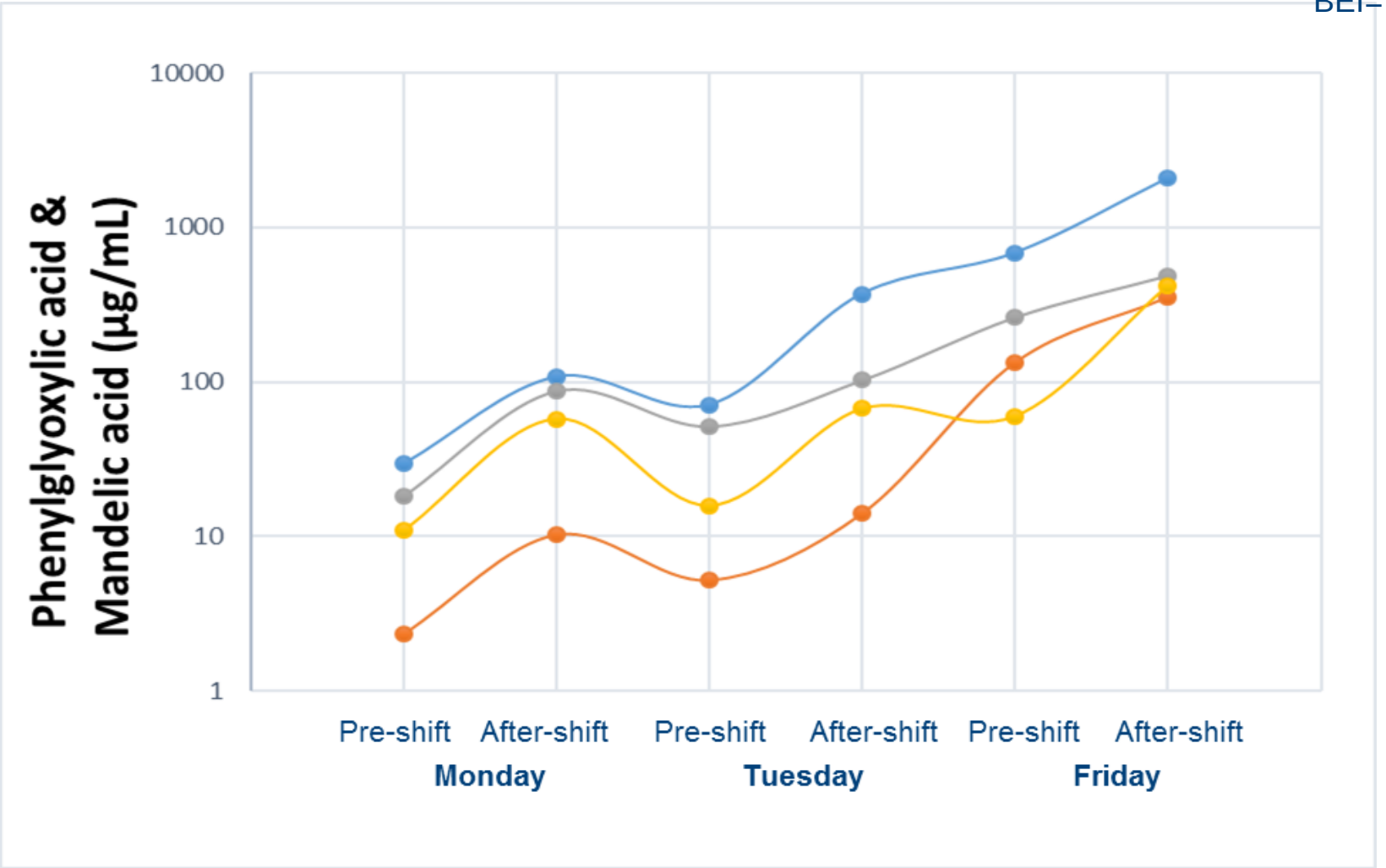
Field study - Factory of composites car bodyparts



Styrene exposure

BEI= 520 µg/mL MA + PGA



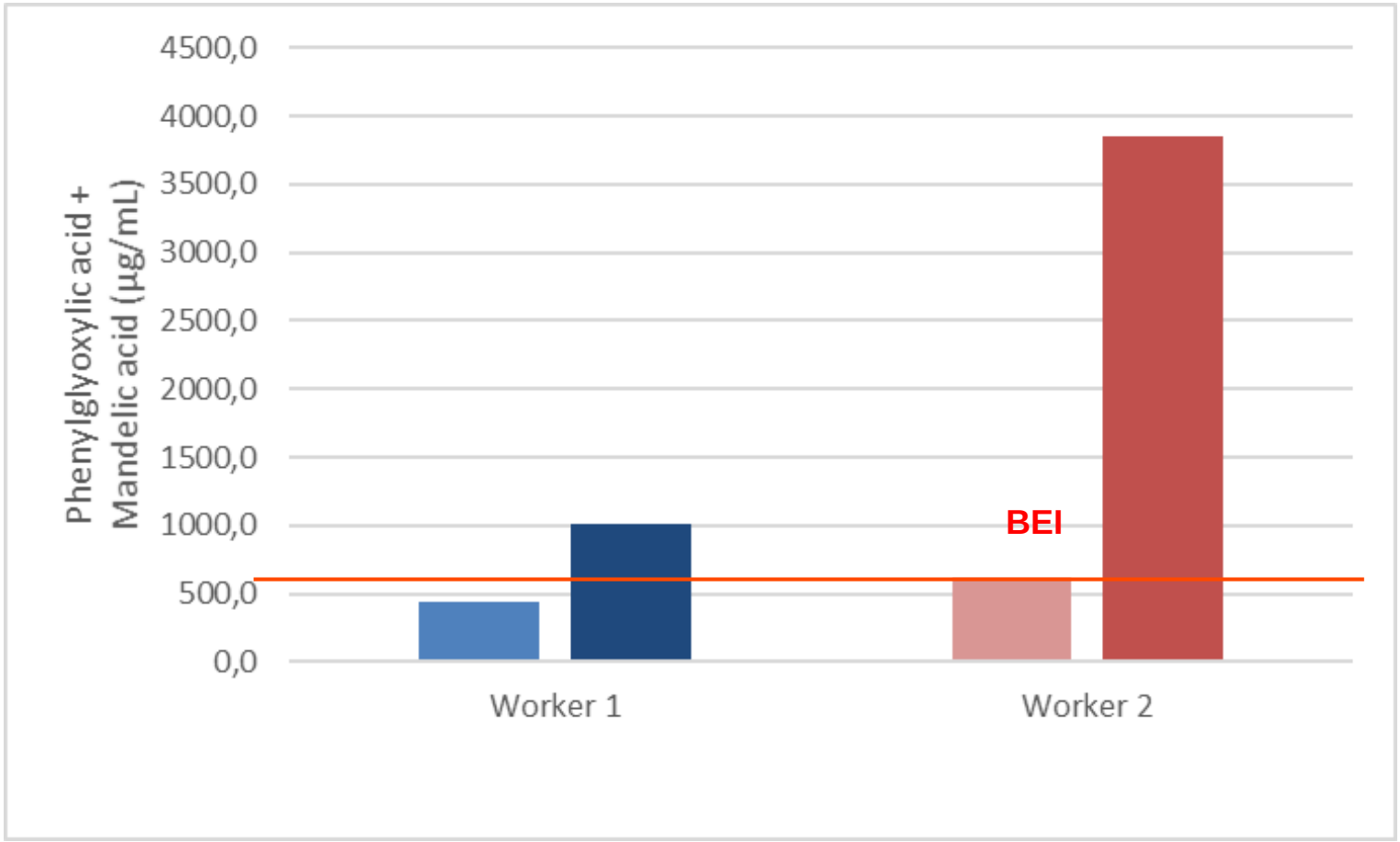
Styrene exposure

Worker 1

Worker 2

Urine biomonitoring

BEI= 520 µg/mL MA+PGA



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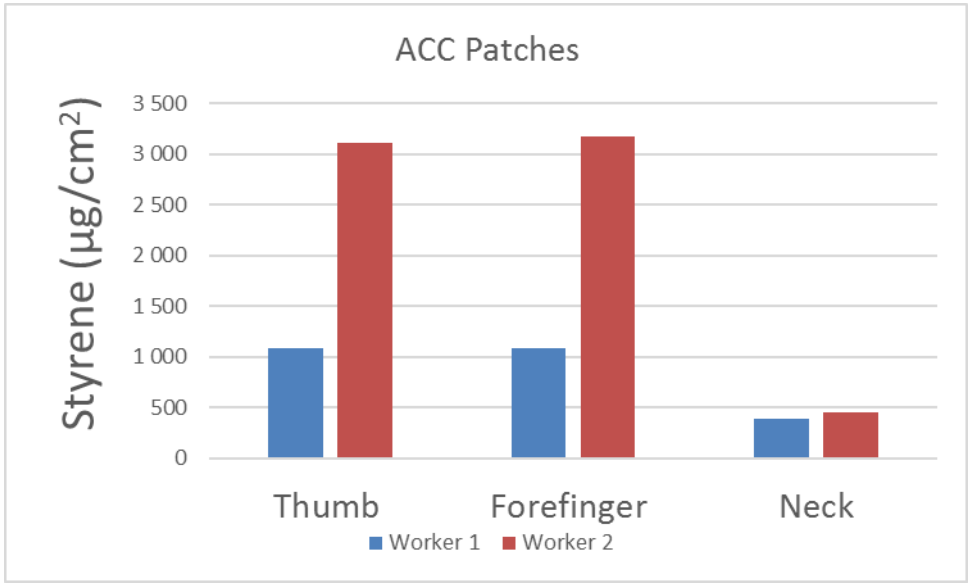
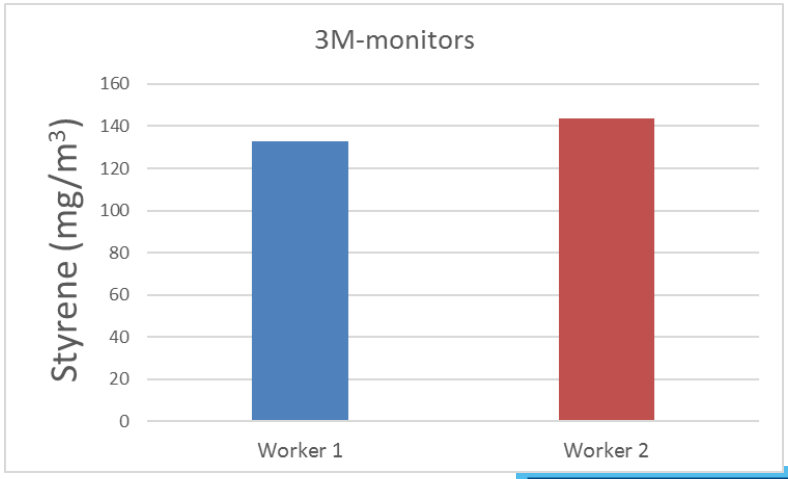
Styrene exposure

Worker 1

Worker 2



Washed daily with an acetone based mixture



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Biomonitoring of human exposure

“Classical” matrices

Blood

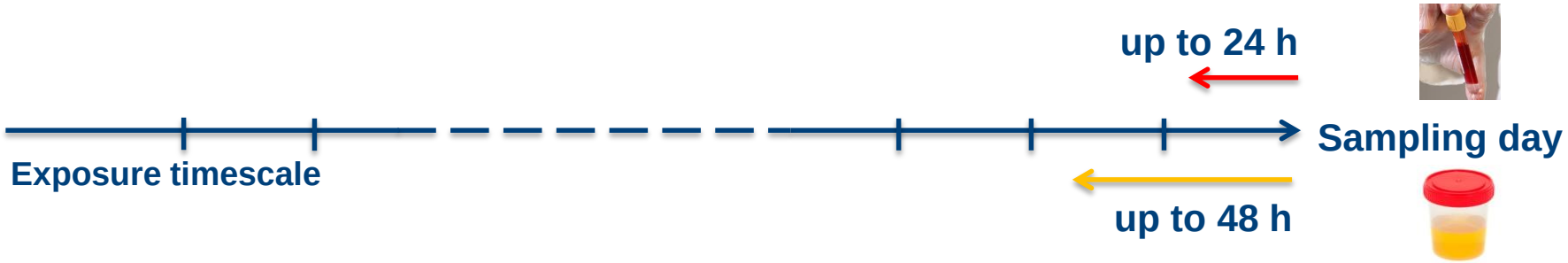
Urine

Advantages:

- important sample volume
- molecules are already in a liquid phase
- extensive knowledge of sample preparation and compounds analysis

Limitations:

- reflecting only recent exposure
- invasive sampling and difficulties to collect blood out of a medical context



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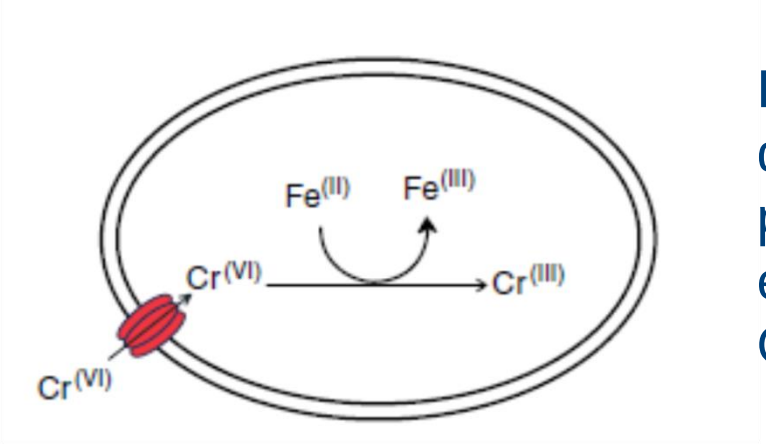
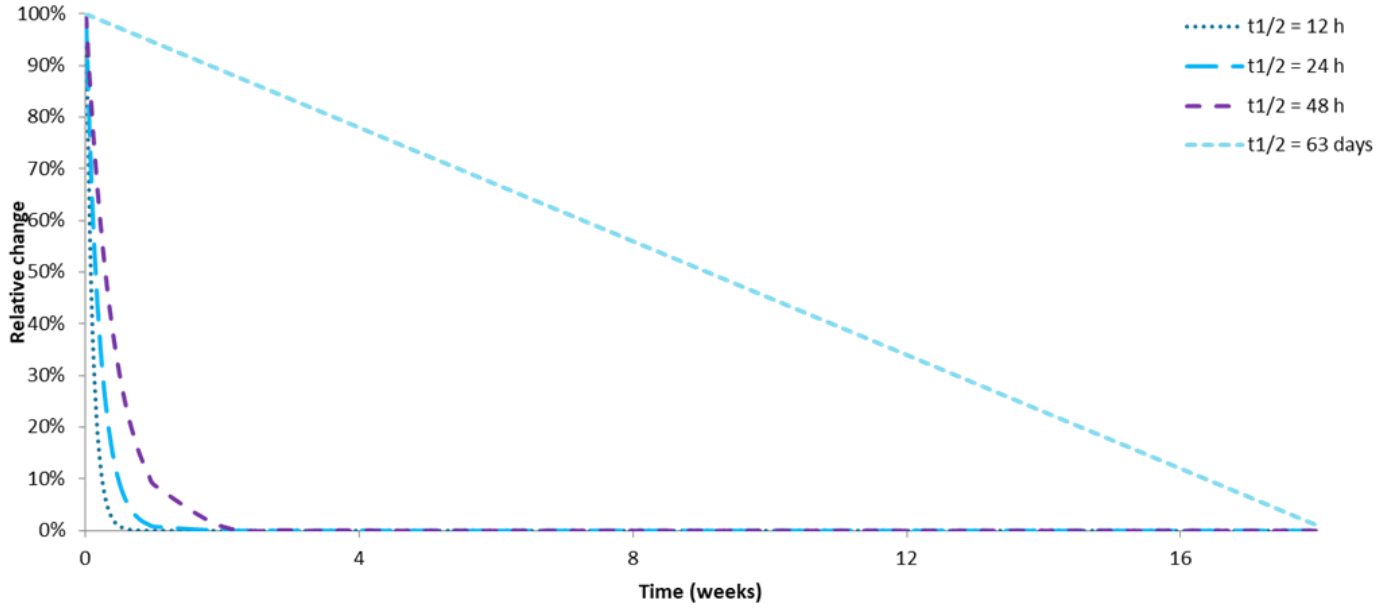
Chromium in erythrocytes (RBC)

Blood



Lewalter et al. (1985) Chromium bond detection in isolated erythrocytes: a new principle of biological monitoring of exposure to hexavalent chromium. Int Arch Occup Environ Health 1985;55(4):305-18.



Netherlands Welding Study

Question	References (N = 20)	Welders (N = 53)
Age in years (median + range)	40 (26-56)	38 (18-57)
Smokers (%)	20	36
Persons with dental fillings (%)	85	85
Average number of dental fillings per person (median + range)	8 (0-16)	5 (0-16)
Persons with dental prostheses (%)	5	4
Persons with tattoos (%)	5	4
Welding during off-work hours (%)	0	24
Persons with contacts with Cr-containing materials during off-work hours (%)	10	40
Number of consumptions of Cr-containing foodstuffs in past 4 months (median + range)	20 (0-103)	3 (0-150)

SS = stainless steel; MS = mild steel; HGS high alloy steel

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Scheepers et al.,Toxicol Lett. 2008;178(3):185-90.

Netherlands Welding Study

Biomarker	Exposure	References (n = 20)			Welders (n = 53)		
		Median	0.95-Perc.	Range	Median	0.95-Perc.	Range
Cr in urine (μg/g creatinine)	Pre-shift	<0.1	0.21	<0.1 – 0.22	0.26***	2.0	<0.1-2.6
	Post-shift	<0.1	0.22	<0.1 – 0.22	0.30***	2.9	<0.1-3.7
	Increase shift	0.00	0.02	-0.08 – 0.02	0.00	1.5	-0.68-2.7
Cr in plasma (μg/L)	Recent	0.23	0.44	0.11 – 0.45	0.44***	1.5	0.16-2.2
Cr in red blood cells (μg/L)	Past 4 months	0.07	0.14	<0.06 – 0.14	0.10**	0.33	<0.06-1.0

** p < 0.005; ***p < 0.001

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Scheepers et al.,Toxicol Lett. 2008;178(3):185-90.

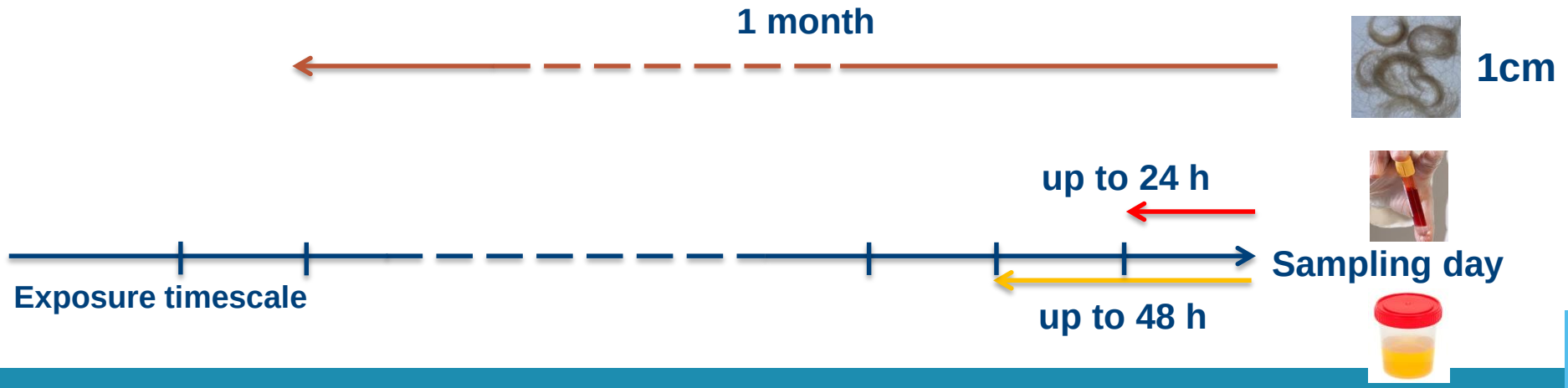
Biomonitoring of human exposure

“Alternative” matrices

Hair

Advantages:
- access to an extended detection window
- non-invasive and easiness of sampling

Limitations:
- analytical limitations
- external contamination
- reflection of exposure levels



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Hair biomonitoring in forensic

European Workplace Drug Testing Society

Drug and Alcohol Testing in Hair, Collection and Analysis

Ethylglucuronid (EtG) alcohol marker

Smoking / drugs marker

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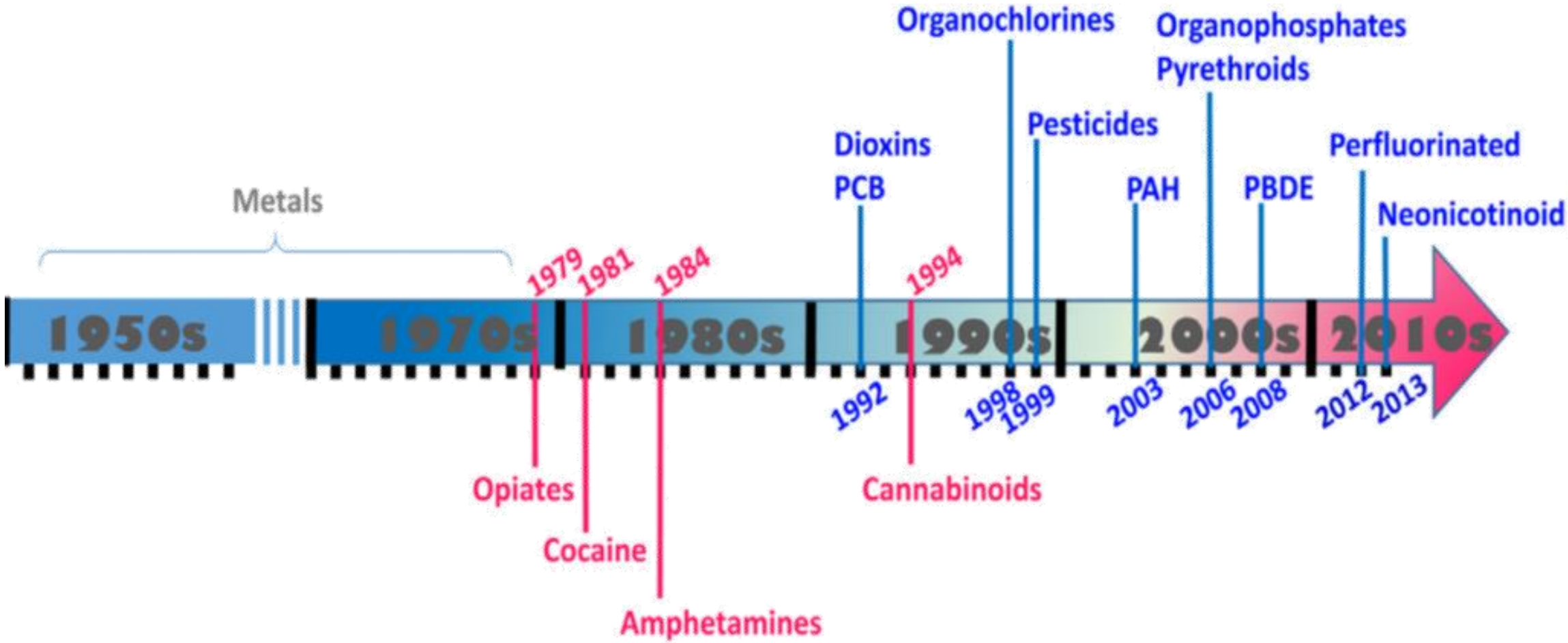

Appenzeller, 2015; In book: Hair Analysis in Clinical and Forensic Toxicology, pp.179-196

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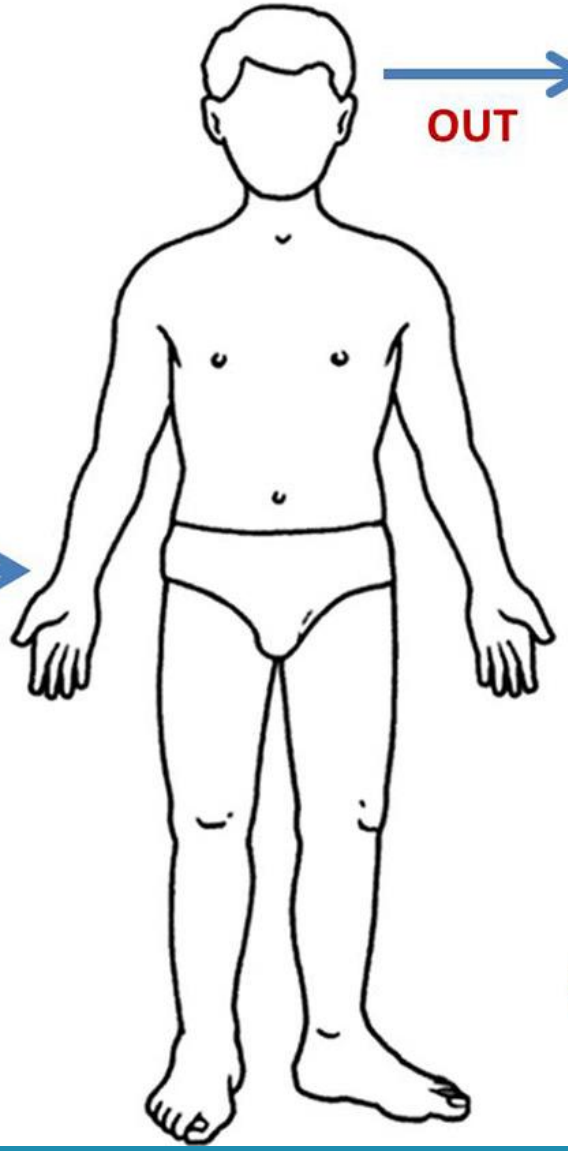
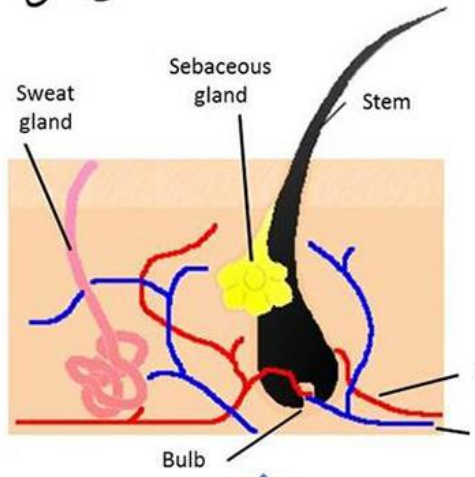
Hair biomonitoring in vineyard workers

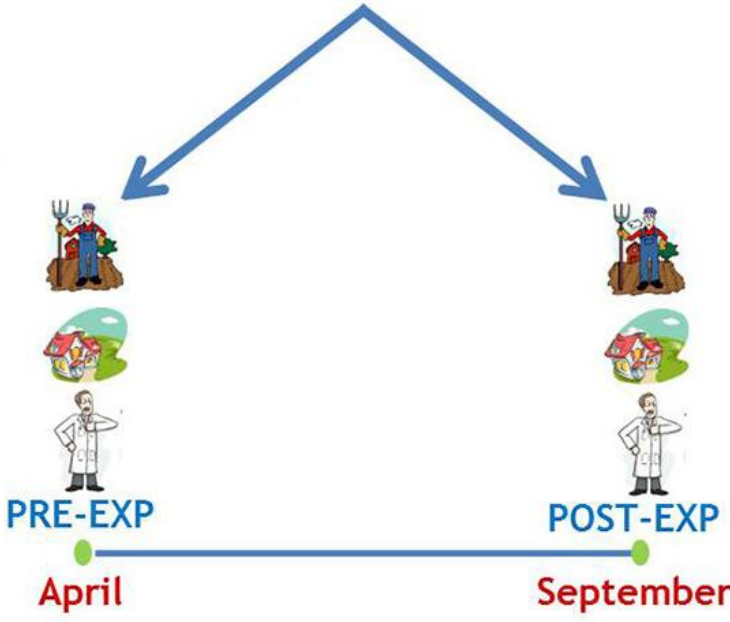
IN

OUT



HAIR SAMPLE





Polledri et al. Sci Total Environ 2019

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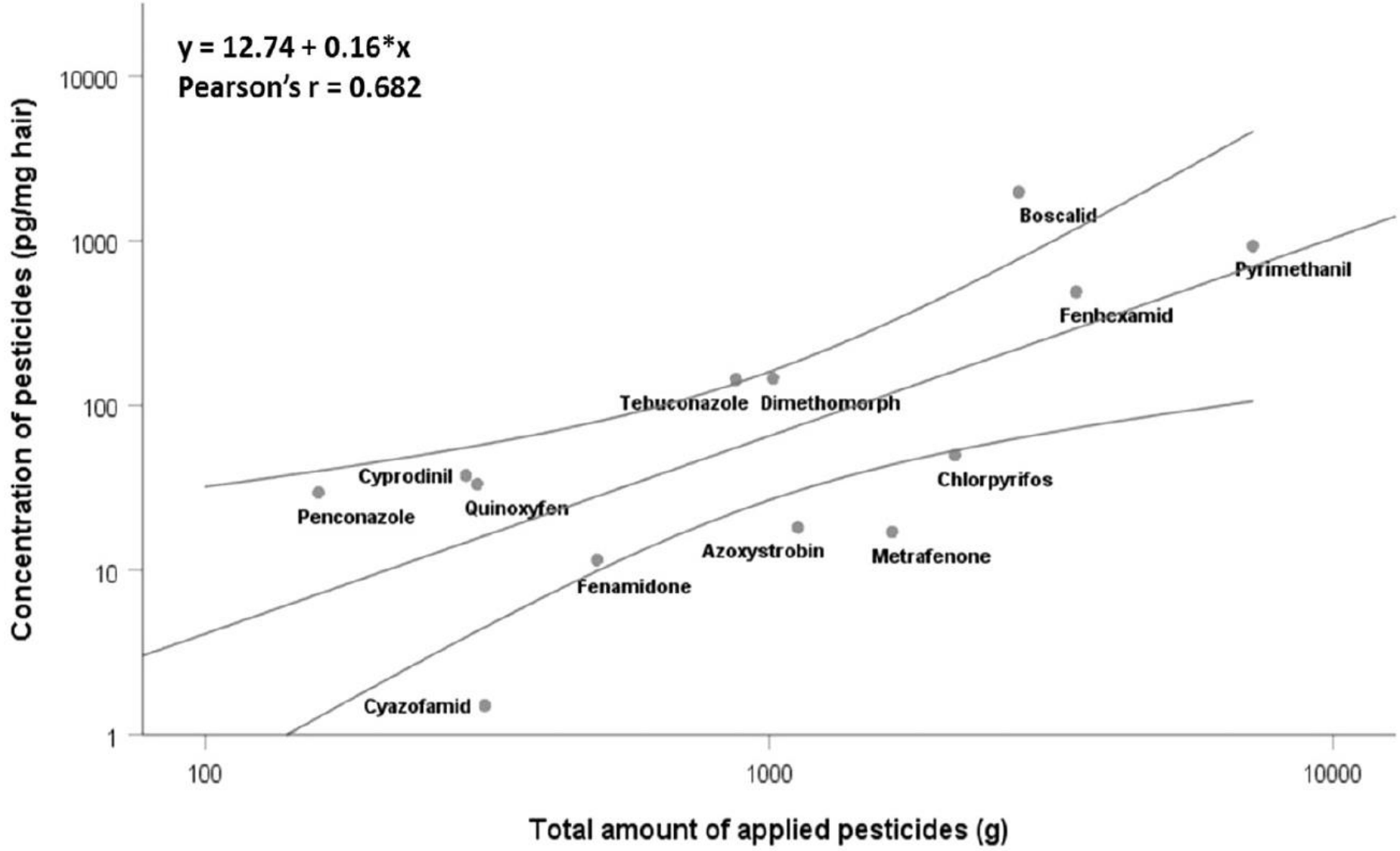
Hair biomonitoring in vineyard workers



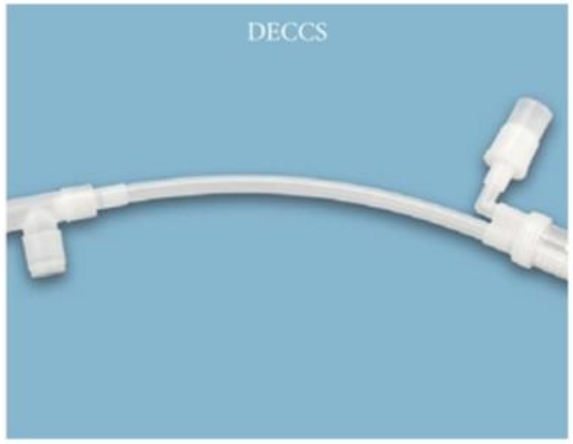
Polledri et al. Sci Total Environ 2019

Biomonitoring of human exposure

“Alternative” matrices

Hair

Exhaled Breath Condensate (EBC)



Disposable Exhaled Condensate Collection System (DECCS)

Turbo –DECCS, Medivac, Parma, Italy

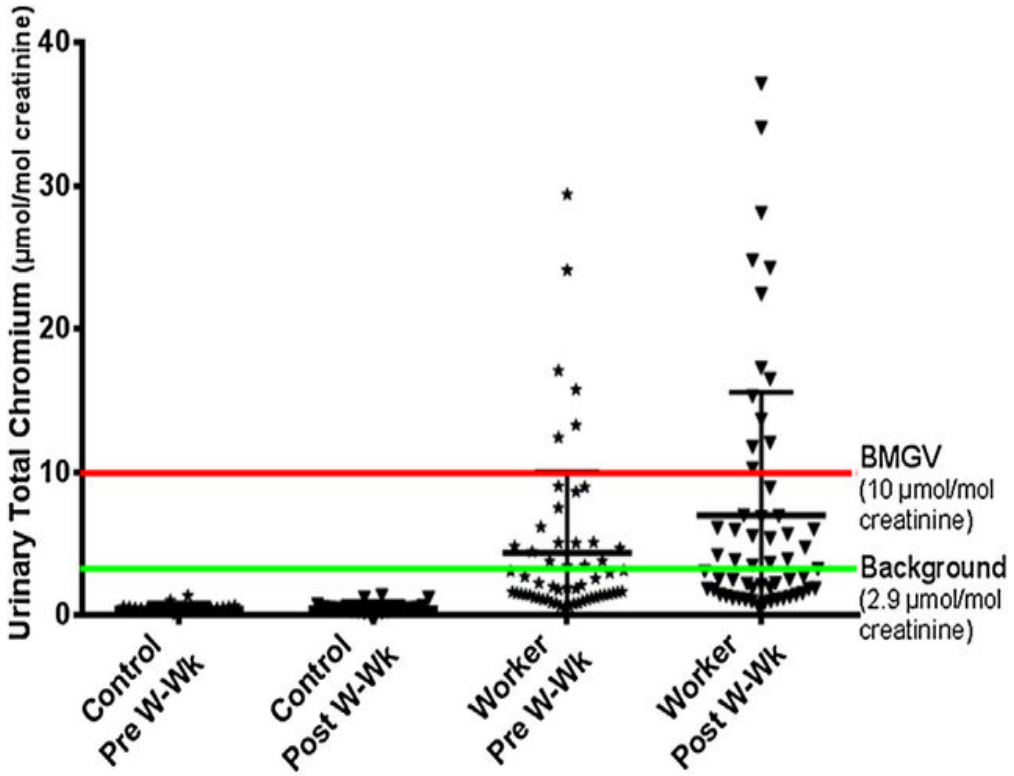
Exhaled Breath Condensate (EBC)

Workers (N=58):
- Cr workers (N=35)
- Non-Cr metal workers (N=12)
- Other workers (N=11)

Controls (office workers) (N=22)

Males and females
Smokers and non-smokers

BMGV = BioMonitoring Guidance Value



Exhaled Breath Condensate (EBC)

Workers (N=58):

- Cr workers (N=35)
- Non-Cr metal workers (N=12)
- Other workers (N=11)

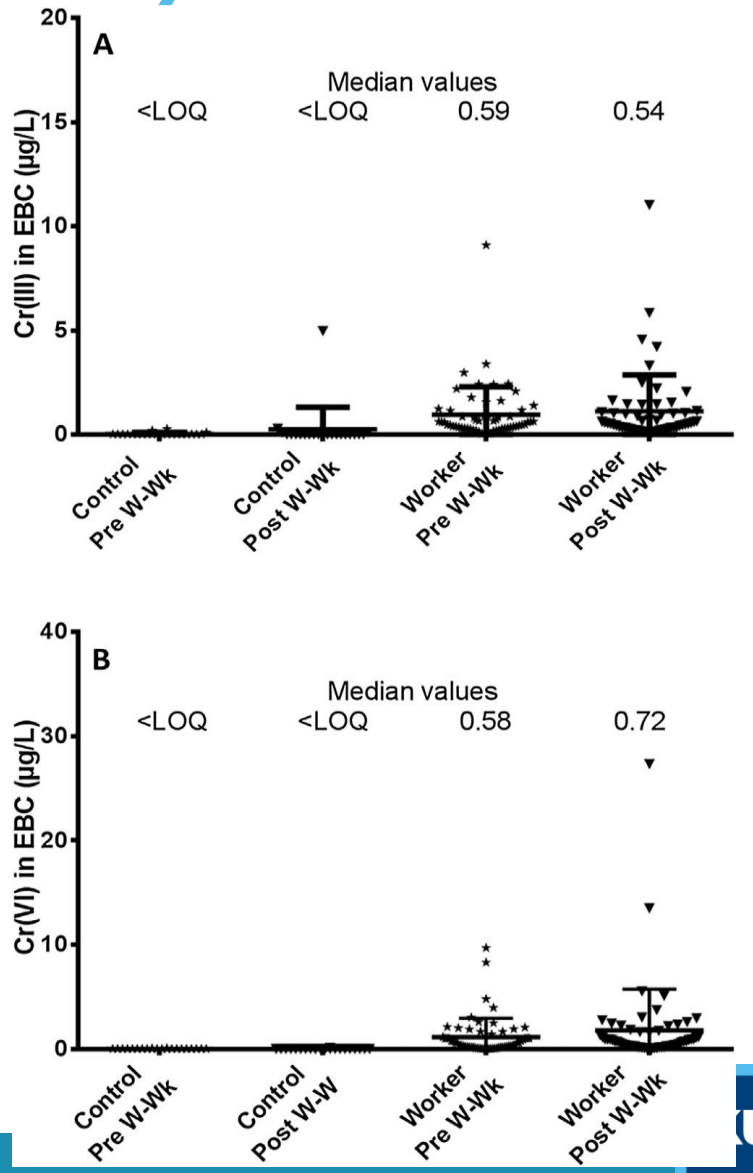
Controls (office workers) (N=22)

84 % < LOQ for Cr III

91 % < LOQ for Cr VI

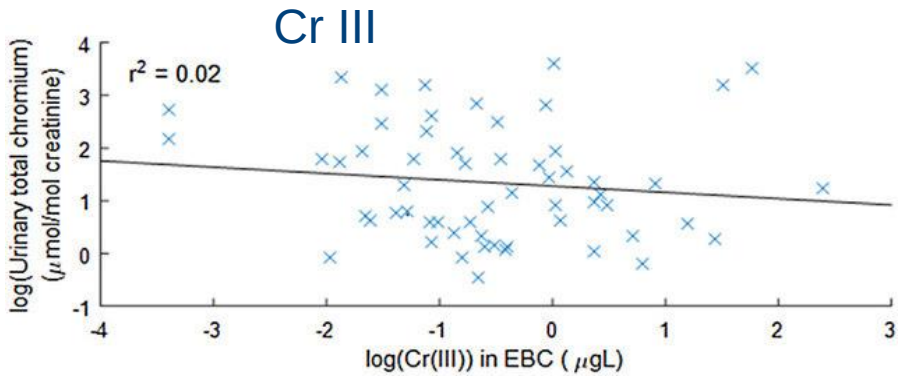
Males and females

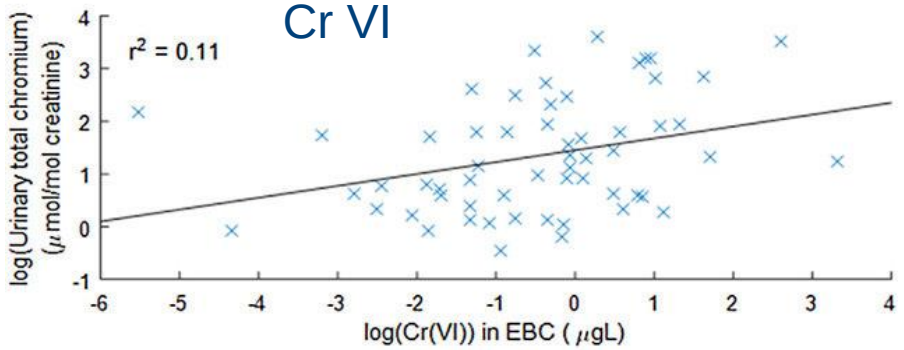
Smokers and non-smokers

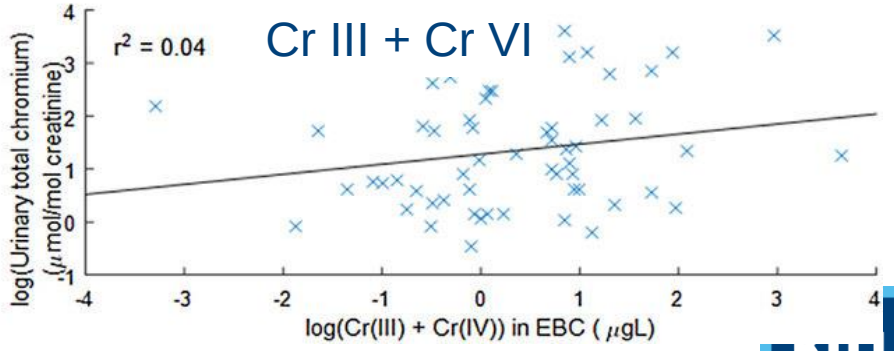


Exhaled Breath Condensate (EBC)

Correlations of log transformed data between Cr in post working week urine and post working week EBC samples.



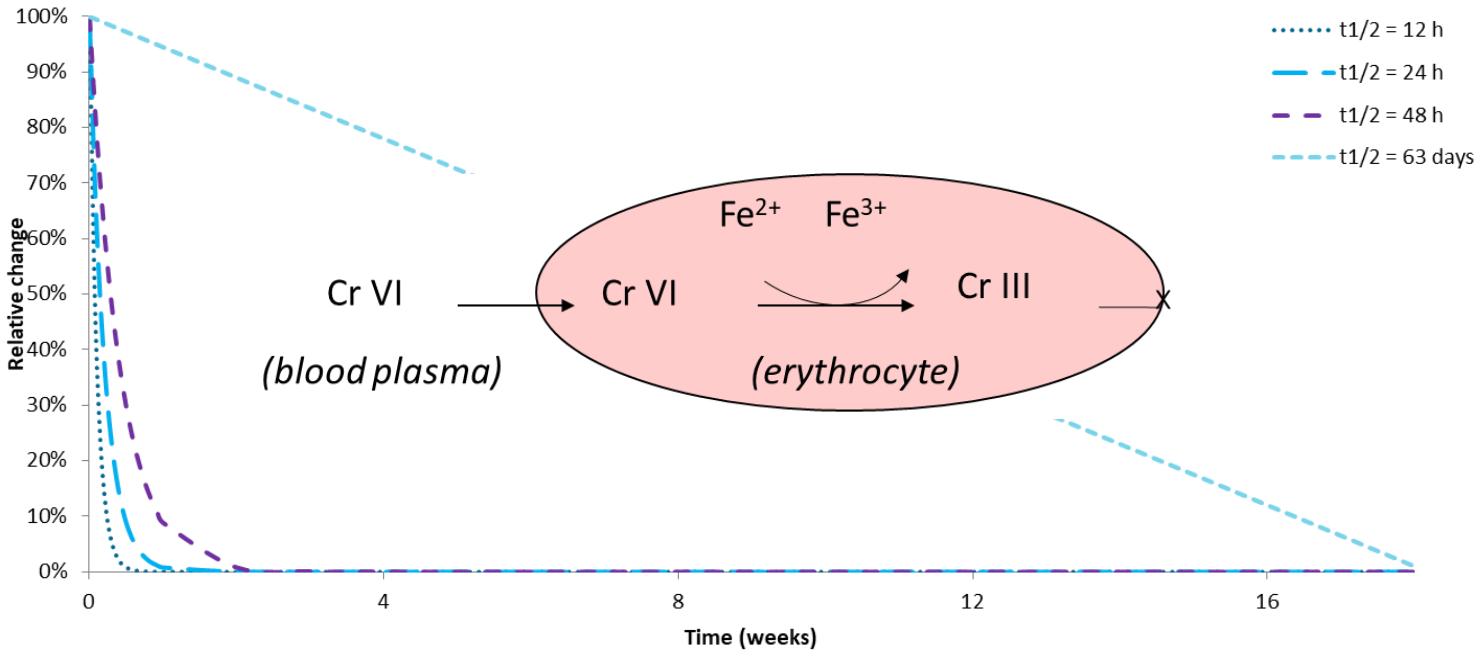




Leese et al. (2017) Int J Hyg Environ Health. 220:415-423

First and zero order kinetics

Cr-RBC and Cr-EBC primarily reflect exposure over a longer timeframe (days-weeks-months).



Perspectives – ongoing studies

HBM4EU science and policy for a healthy future

Setting up a collaborative European human biological monitoring study on occupational exposure to hexavalent chromium

Tiina Santonen[1], Alessandro Alimonti[2], Beatrice Bocca[2], Radu Corneliu Duca[3], Karen S. Galea[4], Lode Godderis[3,5], Thon
Kiilunen[1], Holger
Porras[1], Alain Ro
Wasowicz[10], Arg

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Occupational exposure group from HBM4EU

Tiina Santonen, Finland
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Radu Duca, Belgium
Kate Jones. UK
Karen S. Galea, UK
Susana Viegas, Portugal
Ivo Iavivancoli, Italy
Paul Scheepers, Netherlands
Wojciech Wasowicz, Poland
Beata Janasik, Poland
Maria Silva, Portugal
Simo Porras, Finland

Liz Leese, UK
Alessandro Alimonti, Italy
Thomas Göen, Germany
Ogier Hanser, France
Alain Roberts, France
Lode Godderis, Belgium
Bruno Gomes, Portugal
Henriqueta Louro, Portugal
Rob Anzion, Netherlands
Maurice van Dael, Netherlands
Flavia Ruggieri, Italy
Ovnair Sepai, UK

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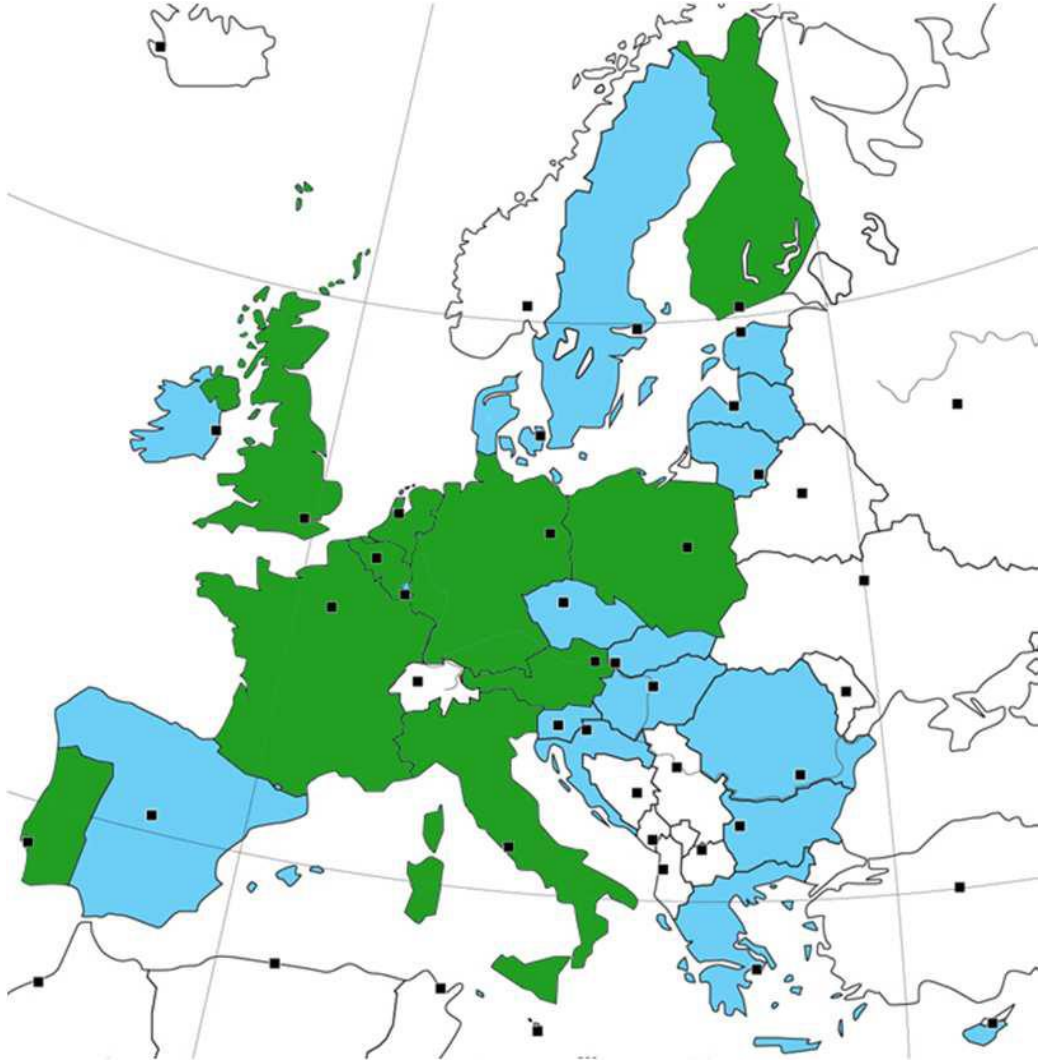
Occupational Bio[redacted]toring Study

Participating countries (green) under WP8.5

Samples will be collected f[redacted]
Finland, Belgium, Netherla[redacted]ria,
Portugal, France, Poland, Germany,
UK and Italy.



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Occupational Biomonitoring Study

Sample collected

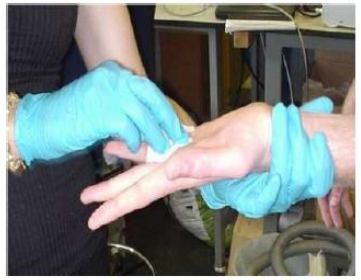
Biological samples

urine

blood

EBC

Industrial hygiene samples



Wipe

air

Occupational Biomonitoring Study

Biological samples and biomarkers

Exposure biomarkers

Urine: Cr-U; Ni-U; Mn-U

EBC: Cr(VI)/Cr(III)-EBC ; and optionally Ni, Mn-EBC

Plasma: Cr; PFAS

Red Blood cells: Cr-RBC

Effect biomarkers (optional)

Urine: oxidative stress (e.g. malondialdehyde, 8-isoprostane, 8-hydroxy-2-deoxyguanosine) and epigenetic changes (e.g. DNA methylation).

Whole blood: genotoxicity (micronucleus assay), oxidative stress and epigenetic changes (e.g. DNA methylation).

Choosing the most suitable biological media

Medium	Biomarkers	Reflected timeframe	Collection	Burden	Repeats	Analytical challenge
Blood	All systemic	Acute (some chronic)	-	---	---	-
Urine	Water soluble/ volatile	Acute and chronic	+	+	+	+
Exhaled air	Volatile	Acute	++	+	++	++
Condensed air	Water soluble	Acute	++	+	++	++
Hair/nails/ teeth	Some metals	Chronic	+	+/-	+/-	---