
science and policy
for a healthy future

# HBM4EU project

Case studies: Use of HBM in cancer risk assessment

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3rd HBM4EU Training School 2019

# *Substances*

1. Hexavalent chromium
2. Anilines: o-toluidine
3. PAHs

# Hexavalent chromium

Assessment of occupational lung cancer risk in plating activities using HBM

# *CrVI compounds are known lung carcinogens*

- Use subject to authorisation under REACH
- However, occupational exposure **remains a relevant concern**: CrVI compounds still widely used in authorised industrial applications
  - Superior in producing hard and corrosion tolerant coatings
- CrVI fumes are also formed, e.g., in manufacturing and welding of stainless steel
  - Such process-generated fumes not covered by REACH, but fall under CMD (carcinogens and mutagens directive)

# *Lung cancer risk due to exposure to Cr(VI)*

Good quality, quantitative human epidemiological data available on the lung cancer risk caused by Cr(VI)

- Seidler et al. 2013 Int Arch Occup Environ Health 86(8): 943-955:
  - Evaluated the data in 5 high-quality epidemiological studies (including the 'Baltimore-' or 'Painesville'-cohorts) and investigated the dose-response for lung cancer caused by exposure to CrVI
  - Conclusion on a correlation: $RR=1.75\times C+1$

    RR=Relative Risk, C=Cumulative exposure in $mg/m^3$-years

# *Biomonitoring of chromium*

- Biomonitoring has been used for long to assess the exposure to hexavalent chromium at workplaces
- U-Cr (total chromium) standard method for the biomonitoring of hexavalent chromium
- Sample typically taken post-shift in the end of the workweek

# *Cancer risk assessment based on HBM data*

- Approach used for the risk assessment:
  - There are published equations to convert the measured urinary HBM data (representing internal exposure) into corresponding air levels (estimate of corresponding external exposure)
  - These are based on the occupational studies measuring both air and biomarker levels at workplaces

→ External exposure (as mg/m3) and lung cancer risks calculated based on these published equations

# *Material: HBM data used*

## Data originating from a FIOH database

- Consists of the urinary total chromium (U-Cr) samples sent to FIOH for exposure monitoring by occupational health care units

  Altogether > 42,000 U-Cr samples

## Cumulative exposure essential in CrVI related cancer incidence increase

- HBM data covering a ~40-year period (1980–2016) used

# *Calculation of external exposure estimates*

Published equations were used to convert the urinary HBM data into corresponding air levels

- Two correlation equations used, both for chromium plating [1)]:
  - Lindberg et al 1983: $[Cr_{air}]$ (µg/m$^3$)=0,43+0,013×$[Cr_{urine}]$ (nmol/l) r=0.71, n=57
  - Chen et al 2002: $[Cr_{air}]$ (µg/m$^3$)={$[Cr_{urine}]$ (µg/g cr)+0.33}/1.86 r=0.81, n=30
- Atmospheric samples taken over the whole working day, urine samples taken on 2nd working day (Lindberg et al 1983) or at end of week and end of shift (Chen et al 2002)

[1)] *Lindberg et al 1983 Scand J Work Environ Health 9: 333-340, Chen et al 2002 J Occup Health. 44: 46-52*

# Data (internal exposure estimates converted to external exposure estimates)

| Job title | Years | n | Urine-Cr, p95 (µmol/l) | Converted to air concentrations (µg/m3) using two different equations[1)] | |
|---|---|---|---|---|---|
| Plating | 1980-1989 | 771 | 0.46 | 6.4 | 11.4 |
| | 1990-1999 | 857 | 0.33 | 4.7 | 8.3 |
| | 2000-2009 | 4657 | 0.20 | 3.1 | 5.2 |
| | 2010-2016 | 3631 | 0.12 | 2.0 | 3.2 |

[1)] Left: *Lindberg et al 1983*
Right: *Chen et al 2002*

# Cumulative lung cancer risk for platers

| | **40 years exposure** External exposure estimation using the **Lindberg et al 1983 equation** | **40 years exposure** External exposure estimation using the **Chen et al 2002 equation** |
|---|---|---|
| Cumulative exposure level ($mg/m^3$) over 1980–2019 | 0.162 | 0.282 |
| RR (=1.75×C+1) | 1.28 | 1.49 |
| AR (%) (=100%×(RR-1)/RR) | 22.1 | 33.0 |

AR=Attributive Risk

# *Uncertainties related to the use HBM data in this case*

Uncertainties which may result in overestimation of risks?

- …
- ….

Uncertainties which may result in underestimation of risks?

- ….

How about applying the same approach for other tasks with Cr(VI) exposure? E.g. welding?

# *Conclusions*

- HBM provides a useful tool for assessing risks of adverse health effects, as it reflects actual dose absorbed into the body (e.g. takes into account the use of RPE)
- However, uncertainties related to the interpretation of biomarker levels needs to be taken into account and their potential impact needs to be evaluated
  - The calculations depend on the quality of the correlation equations used
  - "Applicability domain" of the correlation equations needs to be considered
  - U-Cr reflects total Cr exposure, while only CrVI is carcinogenic
  - HBM reflects exposure also via other than the inhalatory route, which are not particularly relevant to lung cancer
  - Use of HBM data may in some cases result in overestimation of risk, which needs to be recognized



# o-Toluidine

Cancer risk assessment for workers/general population

# *Background*

- Animal carcinogen, classified to cat 1B according to CLP. Human data on the carcinogenicity limited.
- Has been added in year 2012 to the candidate list for eventual inclusion in Annex XIV to REACH
- Cancer dose-response data from animal studies
  - Benchmark Dose Level causing 10 % tumour incidence above background level (BMDL10) was 42.2 mg/kg bw per day in rats

# *Cancer risks*

- For occupational exposure (SCOEL 2017):
  - A tumor risk of 1 : 10 at the $BMD_{10}$ of 210 mg/$m^3$ (48 ppm)
  - A tumor risk of 1 : 1000 at 2.10 mg/$m^3$ (0.48 ppm)
  - A tumor risk of 1 : 10 000 at 0.210 mg/$m^3$ (0.048 ppm)
  - A tumor risk of 1 : $10^6$ at 2.10 µg/$m^3$ (0.00048 ppm)

- Corresponding risk levels for general population, continuous exposure (after allometric scaling)
  - A tumor risk of 1 : 10 at ~10 mg/kg bw
  - A tumor risk of 1 : 1000 at 0.1 mg/kg
  - A tumor risk of 1 : 10 000 at 0.01 mg/kg
  - A tumor risk of 1 : $10^{-6}$ at 0.1 µg/kg

# *Biomonitoring of o-toluidine*

- o-toluidine is excreted in urine conjugated metabolites
- Total o-toluidine can be measured after hydrolysis of conjugates from urine samples (post-shift samples in the case of occupational exposure)
- Since o-toluidine can be absorbed also via the skin, biomonitoring is an important method to estimate the exposure
- However, no correlations based on measured data between external intake and urinary levels has been published

# *Estimating external intake on the basis of biomarker levels*

- Calculating the dose/BEs for different risk levels using urinary mass balance approach (Angerer et al., 2011, IJHEH, 214)

$$Css = \frac{\mathrm{D} \times \mathrm{BW} \times \mathrm{Fue}}{\mathrm{V24}} \text{ or } \qquad D = \frac{\mathrm{Css} \times \mathrm{V24}}{\mathrm{Fue} \times \mathrm{BW}}$$

# *Biomonitoring data on o-toluidine*

- Occupational data:
  - Study on German rubber workers (Korinth et al., 2007) showed median and 95th percentile U-o-toluidine levels of 6 and 292 µg/L in post-shift samples
  - In French liquid SO2 plant polluted with ortho-toluidine. Pre-shift, the urine concentration of o-toluidine ranged between 1.7 ± 1.5 µg/L while the post-shift levels increased to 523 ± 321.6 µg/L (Labath et al., 2006).
- General population data:
  - The 95th percentile of urinary o-toluidine (total of free and conjugated) among the non-smoking general population is approximately 0.2 µg/l (Kütting et al. 2009; Weiss and Angerer 2005).
  - Smoking can increase o-toluidine levels 2-5 times in general population.

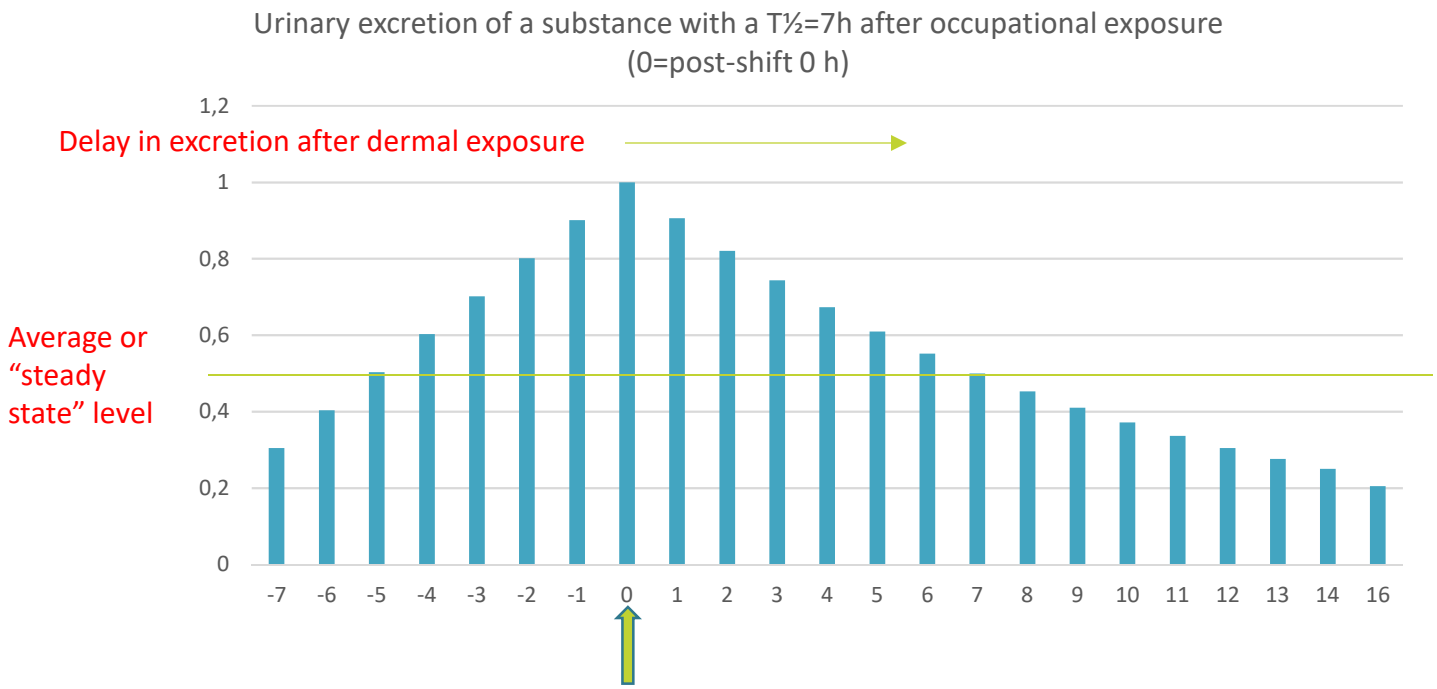
# *Cancer risk caused by the measured urinary levels*

- German rubber industry workers
  - urinary o-toluidine levels (95th percentile level) of 292 µg/L correspond intake of 8 µg/kg. This corresponds the cancer risk level of 1 : 37 000 (or $2.7*10^{-5}$).
- French liquid $SO_2$ plant polluted with o-toluidine
  - Post-shift urine of 523 ± 321.6 µg/L correspond average intakes of 15 µg/kg. This corresponds to approximate tumor risk level up to 1 : 20 000 (or $5*10^{-5}$).
- The 95$^{th}$ percentile of urinary o-toluidine among the non-smoking general population of 0.2 µg/l corresponds an intake of 6 ng/kg bw/day. This indicates a tumor risk well below 1 : $10^{-6}$.

Uncertainties in the assessment? Needs for refinement?

# *Conclusions*

- Approach good for screening => can be easily seen if there is a reason for concern
- Naturally, there are uncertainties, especially when this steady state based –approach is applied for short half-life substances in occupational exposure



# PAHs

Challenges in the use of HBM in PAH risk assessment

# *Cancer risks of PAHs*

- Cancer risk in occupational exposure:
  - Meta-analysis by Armstrong et al 2003, 2004 (combining data from different industries) usually used as a basis for dose-response curve
  - E.g. ECHA/RAC (2018)

| Cumulative Exposure One Year TWA BaP concentration (µg/m³) | Cumulative exposure (40 years × TWA exposure) (µg/m³) | Excess bladder cancer risk in EU workers |
|---|---|---|
| 100 | 4 000 | $4 \times 10^{-1}$ |
| 10 | 400 | $4 \times 10^{-2}$ |
| 1 | 40 | $4 \times 10^{-3}$ |
| 0.1 | 4 | $4 \times 10^{-4}$ |
| 0.01 | 0.4 | $4 \times 10^{-5}$ |
| **0.001** | **0.04** | **$4 \times 10^{-6}$** |
| 0.0001 | 0.004 | $4 \times 10^{-7}$ |

# *Cancer risks of PAHs*

- For general population dietary exposure cancer risks have been estimated on the basis of animal data
- EFSA (2008), ECHA (2018):

**PAH4: ELCR = 0.1 × 7/340 = 2.06 × $10^{-3}$ per µg/kg bw/day**

**PAH8: ELCR = 0.1 × 7/490 = 1.43 × $10^{-3}$ per µg/kg bw/day**

*Calculated on the basis of the animal study by Culp et al 1998 with coal tar pitch, which could be used to identify a BMDL10.

# *Biomonitoring*

- 1-hydroxypyrene most commonly used biomarker for PAH exposure in occupational settings
- Correlations between air B[a]P levels and 1-OHP levels based on measured data published

$$concentration\ of\ airborne\ B[a]P = \frac{(\text{concentration}_{1-OHP}) - 1.13)}{11.1}$$

- Correlations available also for air B[a]P and urinary 3-OHB[a]P levels

$$concentration\ of\ airborne\ B[a]P = \frac{(\text{concentration}_{3-OHBaP}) - 0.1729)}{0.001835} \quad / 1\ 000$$

Ref. ECHA/RAC 2018
https://echa.europa.eu/documents/10162/13637/ctpht_rac_note_en.pdf/a184ee42-0642-7454-2d18-63324688e13d

# *Use of HBM data in risk assessment of PAH*

- Uncertainties, occupational exposure:
  - 1-OH-PYR: proportion of pyrene vs B[a]P varies depending on exposure source
  - Equations not accurate in the lower exposure range and cannot estimate very low exposure levels e.g. those with urinary 1-OH-PYR values below 1.13 µmol/mol

⇒ do not work at the exposure levels seen in general population

# *General population oral exposure*

- It is possible to back calculate from 1-OHP levels pyrene intake
  - This has been done in WP12 (estimated EU average pyrene intake 0.045 µg/kg bw/d
  - Most of the pyrene intake in humans is expected to come from food sources
- However, cancer dose responses are for 4 or 8 PAHs, not for pyrene => additional uncertainty
  - If these back calculated pyrene levels are used as a surrogate, assessment is probably overestimating the cancer risk because pyrene levels in food are higher than those of e.g. B[a]P

# *Conclusions*

- Different approaches to use HBM data in cancer risk assessment
- Uncertainties needs to be recognized
- Remember that alternative approaches include also uncertainties, which may be even higher (e.g. when using exposure modelling)

# Contacts

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## Speaker's information

Tiina Santonen, MD, PhD, MSc in Applied Toxicology, ERT, works as Chief Specialist at Finnish Institute of Occupational Health. Her main tasks at the institute relate to chemical risk assessment and biomonitoring. She is the former member of Scientific Committee on Occupational Exposure limits (SCOEL) and a member of ECHA Risk Assessment Committee (RAC). In HBM4EU she is responsible for tasks 5.3 related to the better use of HBM in the risk assessment of chemicals and task 8.5 related to targeted occupational surveys.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.