For our Environment

RASS MSS Webinar - January 11, 2017

German Environmental Survey and Specimen Bank and the use of the human biomonitoring data for risk assessment

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German Environment Agency
(Umweltbundesamt)
Keeping an eye on chemicals

European Commission (2001): **Global production** of chemicals increased from 1 M t in 1930 to 400 M t in 2001.

June 2015: Chemical Abstracts Service (CAS) assigned **100 Millionth CAS Registry Number®**.

Chemical industry is **Europe’s 3rd largest** manufacturing industry.

Eurostat: about **30 M t of carcinogenic, mutagenic and reprotoxic** chemicals produced in 2009.
Why do we need HBM data?
Bisphenol A production and human exposure

- Overestimation of risk
- Overestimation of success

**Data Source:** German Environmental Specimen Bank (ESB)
The German HBM System:
Answering key questions concerning human exposure to chemicals

Cooperation for the promotion of HBM
- new analytical methods for chemicals of interest

German Environmental Survey
- population-representative
- ambient monitoring
- interviews

German Environmental Specimen Bank
- retrospective monitoring
- time trends background exposure

Exposure quantifiable?
Variation in population?
(Risk groups, sources, etc.)
Regulation and voluntary measures sufficient?
Exposure health-relevant?
Sound HBM data for science and policy

German Environmental Survey (GerES)

<table>
<thead>
<tr>
<th>Survey</th>
<th>Period</th>
<th>Age</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>GerES I</td>
<td>1985 - 86</td>
<td>25 - 69</td>
<td>2,700</td>
</tr>
<tr>
<td>GerES II a</td>
<td>1990 - 92</td>
<td>25 - 69</td>
<td>4,000</td>
</tr>
<tr>
<td>GerES II b</td>
<td>1990 - 92</td>
<td>6 - 14</td>
<td>730</td>
</tr>
<tr>
<td>GerES III</td>
<td>1997 - 99</td>
<td>18 - 69</td>
<td>4,800</td>
</tr>
<tr>
<td>GerES IV</td>
<td>2003 - 06</td>
<td>3 - 14</td>
<td>1,790</td>
</tr>
<tr>
<td>GerES V</td>
<td>2014 - 17</td>
<td>3 - 17</td>
<td>2,505</td>
</tr>
</tbody>
</table>

Environmental Specimen Bank (ESB)

- Greifswald (since 1995)
- Münster (since 1977)
- Halle/S. (since 1995)
- Ulm (since 1997)
Instruments

GerES

ESB
Study design and sample of GerES V

2,505 children and adolescents from 167 locations in Germany

Age range: 3 to 17 Years

Representative according to age, gender and community size.

Randomly selected from the 2. wave of the KiGGS study (the German Health Interview and Examination Survey for Children and Adolescents), conducted by the Robert Koch Institute (RKI)
Exploration of associations

State of health

Environmental influences

more than 2,000 pieces of information per child/adolescent
Ambient monitoring

Drinking water

anorganic and organic compounds (from plastic pipes)

Indoor monitoring

- ultrafine particles, particulate matter PM$_{2.5}$ and PAH
- house dust: „new“ plasticizers and flame retardants
- VOC and aldehydes

Noise

noise level, subjective annoyance

Integration of GIS data
Design of the German ESB (human samples)

Since 1997:
regular standardized sampling at **4 locations**
approx. 120 healthy male and female adults (20 - 29 yrs.) in each city

**No specific exposure**

- **Urine** (24 hrs.)
- **Blood** (whole blood, serum)

Self-administered questionnaire
Dental anamnesis
Cryo-archiving of samples: retrospective analyses
Biobanking

According to obligatory standard operation procedures (SOP)

Operated by Fraunhofer IBMT on behalf of the German Environment Agency

Sampling planning  Sampling  Anamnesis Analyses Storage

Source: Fraunhofer IBMT
Specimen regularly collected by the ESB

Environmental specimen

- Soil
- Spruce/Pine
- Beech/Poplar
- Earthworm
- Pigeon
- Deer
- Suspended sediment
- Zebra mussel
- Bream
- Blue mussel
- Eelpout
- Herring gull

Human specimen

- Whole blood/Plasma
- 24 h sampling urine

Sources: Projektgruppe Trier (10), Fraunhofer IBMT (2), Fraunhofer IME (1), UBA (1)
German Initiative to further develop HBM

The German Chemical Industry Association (VCI)

Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety

German Environment Agency

Federal Institute for Occupational Safety and Health (BAuA)

Federal Institute for Risk Assessment (BfR)

HBM relevant Chemicals

Potential exposure of the general population

+ Potential health relevance

development of new chemical-analytical HBM methods
Human biomonitoring & interview monitoring

*first application of newly developed analytical methods*

- **Plasticiser**: Hexamoll® DINCH, DPHP, ASE/ASEP („Mesamoll“), Tri(2-ethylhexyl) trimellitat TOTM, diethylhexylterephthalat DEHTP, Di-isononyladipat DINA, Di-2-ethylhexyladipat DEHA/DOHA
- **Antioxidant**: butylated hydroxy-toluene BHT
- **Sun screens**: 4-MBC, OMC, octisalate, octocrylene
- **Biocides**: CIT/MIT, climbazol
- **Fragrances**: geraniol, lysmeral, 7-hydroxycitronellal
- **Polyurethane ingredients**: TDI (2,4-TDI+ 2,6-TDI), MDI
- **Technical solvents**: NMP, NEP
- **Vulcanisator**: 2-MBT
- **Glyphosate**
The German Human Biomonitoring Commission

Protection of the health of the population who is exposed to chemical substances from the environment by scientific assessment and derivation of guidance values:

• Statistically derived Reference values

• Toxicologically/epidemiologically based Human Biomonitoring Values (HBM I = alert value & HBM II = action value)

New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission.

Int J Hyg Environ Health. 2016 Sep 17, DOI: 10.1016/j.ijheh.2016.09.007.2
GerES IV: Identification of a possible impact on health I

Phthalates metabolites in urine of children aged 3 to 14

DEHP - Diethylhexylphthalat
TDI*: 50 µg/(kg KG∙d)
1.4

DnBP - Di-n-butylphthalat
TDI*: 10 µg/(kg KG∙d)
11.7

DiBP - Di-iso-butylphthalat
TDI*: 10 µg/(kg KG∙d)
9.1

* TDI: Tolerable Daily Intake
GerES IV: Identification of a possible impact on health II

∑ weighted intake rates of 5 phthalates

85% Exceedance of TDI (DnBP)

GerES (2003-2006): children aged 3 to 14
Weighting according to factors described by Earl Gray, US-EPA
Intake rates: daily intake related to volume calculated by Wittassek
Phthalates: decision on measures and control of success

Exposure of the general population, children, GerES IV:
- single substances: exceedance of HBM-I or TDI by 2% to 12% per substance
- aggregate exposure: exceedance by more than 50%

Regulation:
- Several steps: toys for children, cosmetics, food
- Danish proposal to ban phthalates rejected
- Authorisation since 2/2015

Toxicology:
- reproductive toxicants → Substances of Very High Concern
  DEHP, DnBP, BBzP: SVHC in 2008; DiBP: SVHC in 2010

HBM Values DEHP sum of metabolites 5oxo-MEHP and 5OH-MEHP in urine:
- Children, aged 6 - 13: HBM-I 500 µg/l
- Women in childbearing age: HBM-I 300 µg/l
- Others: HBM-I 750 µg/l

→ assessment of aggregate exposure required
ESB time trend phthalates 1988 to 2015

Exposure to metabolites of 4 SVHC has decreased by 67-96%, they are still to be detected in every single sample. DINP increased by 56%.

Measured by Holger Koch, IPA, and Thomas Göen, IPASUM
N-Methyl-2-pyrrolidone (NMP)

**Use:**
Technical solvent

**Exposure of the general population:**
• by using paint and graffiti remover,
• indoors via paints and carpets

**Exposure pathway:** inhalative, dermal

**Toxicology:**

a) specific metabolites in urine: 5-hydroxy-NMP (5-HNMP) and 2-hydroxy-N-methylsuccinimide (2-HMSI)

b) reproductive toxicant → Substance of Very High Concern (SVHC, 2011)

**HBM Values,** sum of metabolites 5-HNMP + 2-HMSI in urine:
- Children: HBM-I = 10 mg/l, HBM-II = 30 mg/l
- Adults: HBM-I = 15 mg/l, HBM-II = 50 mg/l

**Substitute:** N-Ethyl-2-pyrrolidone (NEP)

**CAVE:** similiar toxicological profile

→ *assessment of aggregate exposure required*
The internal exposure of the reprotoxic SVHC did not decline.
Time trend of NEP-metabolites in 24h-urine

The internal exposure of the reprotoxic substitute declines

Measured by Holger Koch, IPA
**Glyphosate**

**Use:**
- Broad spectrum systemic herbicide
- Used for crop desiccation

**Toxicology:**
- IARC: probably carcinogenic to humans (Group 2A)
- EFSA: Acceptable Daily Intake (ADI) 0.5 mg/kg bw/d

clarification by the different agencies is indispensable

**Exposure of the general population:**
- By food
- Home use for gardening

**Analytical method:**
- GC-MS/MS, LOQ: 0.1 µg Glyphosate/L urine
Time trend glyphosate in 24h-urine

Fraction of quantifiable levels decreases after 2012? Result of changes in application?

Sex-related differences in exposure?
Analysis of population-representative GerES V samples
Multiple exposure in children: endocrine disruptors

HBM Data from the German Environmental Survey GerES IV (2003-2006)
Multiple exposure - conclusions

People are exposed to a large number of chemicals

Exposure consists of several chemicals with the same mode of action or affecting the same target organ

HBM reveals co-exposures

HBM helps to describe typical exposure situations

HBM demonstrates that single substance assessment does not reflect realistic exposure scenarios
Policy advice: the example of mercury

“The use of dental amalgam should be considered very cautiously for children under the age of 6.”
Reduction in amalgam use (as observed in GerES)

<table>
<thead>
<tr>
<th>GerES</th>
<th>No tooth</th>
<th>1 tooth</th>
<th>2 or more teeth</th>
</tr>
</thead>
<tbody>
<tr>
<td>II (1990/92)</td>
<td>37%</td>
<td>10%</td>
<td>53%</td>
</tr>
<tr>
<td>IV (2003/06)</td>
<td>92%</td>
<td>3%</td>
<td>5%</td>
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</tbody>
</table>

Exceedance of HBM assessment values for Hg (in %)
Mercury – Reduction in amalgam use (ESB)

Participants with amalgam fillings (in %)

Münster (West)
Mercury – multivariate analysis (ESB)

Contribution to Hg amount in 24h-urine (ng)

Source: Schulz, Rüdel, Uhlig, Hettwer, Kaltenbach (2015): Comparative examination of the human and environmental mercury exposure based on monitoring data derived from the German Environmental Specimen Bank (ESB)

https://www.umweltprobenbank.de/upb_static/fck/download/Endbericht_Integrierte_Bewertung_Hg_2015_08_10_Web.pdf [in German]
Mercury - conclusions

Internal mercury exposure decreased substantially in Germany.

Dental amalgam is a main exposure determinant.

As the use of dental amalgam has decreased, exposure via food became relatively more important.

Source: marcel / Fotolia.com
HBM in the EU: preparatory phase and pilot study

Aims

• Preparation and conduct of a feasibility study
• Harmonization of methods, questionnaires, quality assurance, ...
• Measurement of comparable results
• Building up network & infrastructure
• Use of HBM for improving policy
DEMOCOPHES: exposure of children to DEHP

Dehp metabolite im urine (µg/L), adjusted to creatinin, age and gender

HBM I:
300 µg/L (mothers)
500 µg/L (children)
Σ(OH-MEHP, oxo-MEHP)

1,7% > HBM I

Cyprus
Luxembourg
Switzerland
Belgium
United Kingdom
Germany
Denmark
Slovenia
Portugal
Sweden

ALL

Hungary
Ireland
Czech Republic
Spain
Rumania
Poland
Slovakia

p < 0.001
p < 0.001
p < 0.001
p < 0.001
p < 0.001
p < 0.001
p = 0.001
p = 0.21
p = 0.54
p = 0.96

p = 0.004
p = 0.009
p < 0.001
p < 0.001
p < 0.001
p < 0.001
p < 0.001
Answer open policy relevant questions as defined by EU Services and partner countries

Give policy makers a fast and easy access to results and data

Bridge the gap between science and policy

science and policy for a healthy future

Source (map of Europe): © User:maix/Wikimedia Commons / CC-BY-SA 2.5
an ambitious EU research programme designed especially to answer policy relevant questions
Who we are - the HBM4EU partners

22 EU Member States
3 Associated States, Switzerland, and EEA

(3 candidates to join in later)

107 Partners
38 Grant Signatories

Financial volume: ~ 74 M €

🌟 Management Board Member
Prioritization process

**EU level**

- **ENV** - chemicals legislation (e.g. REACH), air/water pollution, noise
- **EMPL** - worker safety, exposure to chemicals
- **SANTE** - food contaminant, pesticides, biocides, EDs
- **GROW** - product safety, cosmetics, REACH
- **RTD R&I framework programme**

**JRC** - scientific and technical support
- ECHA - REACH regulation
- EEA - environment data, information, assessment
- EFSA - risk assessment for food and feed

**HBM4EU** - European joint programme on human biomonitoring
Prioritization process

Source: David Liuzzo, derivative work: MichaelBueker [CC BY-SA 3.0], via Wikimedia Commons
**Pillar 1: Science to Policy**

WP4: Prioritisation and input to the annual work plan

WP5: Translation of results into policy

WP6: Sustainability and capacity building

**Pillar 2: European HBM Platform**

WP7: Survey design and fieldwork preparation

WP8: Targeted field work surveys and alignment at EU level

WP9: Laboratory analysis and quality assurance

WP10: Data management and analysis

**Pillar 3: Exposure and Health**

WP11: Linking HBM, health studies, and registers

WP12: From HBM to exposure

WP13: Establishing exposure health relationships

WP14: Effect Biomarkers

WP15: Mixtures, HBM and human health risks

WP16: Emerging Chemicals

WP3: Internal Calls

WP17: Ethics Requirements

WP2: Knowledge Hub

WP1: Programme management and coordination

Scientific and Administrative Management

National and EU Stakeholders; Advisory Board
Activities on mixtures in HBM4EU

• Identification of most relevant chemical mixtures for risk assessment
  - development of aggregated mixture indicators
  - integration of various approaches and conventions of countries
  - database of existing HBM mixture data

• Joint survey on HBM mixtures in 3-5 countries, and apply overarching analysis across priority substances to get aggregated HBM profiles
  - study populations enrolled based on exposure gradient
  - priority substances and pesticides (due to EU/EFSA approach)

• Identification of mixture health effects
  - close co-operation with ongoing EU projects
  - liaison with EFSA activities
  - use and/or development of effect markers
Conclusions

The human exposure to various chemicals is a key aspect of environmental health.

- Evidence of toxicologically relevant properties alone does not automatically reduced use and exposure
- Safe or at least better substitutes can be identified
- Regulation supports reduction of exposure
- Control of the success of regulatory measures is necessary
- Admission to SVHC list does not automatically decrease human exposure
- HBM helps to set priorities
- Health risk assessment needs to include aggregate exposure

HBM helps bridging the gap between science and policy making
Supporting policy, but also the public ...

www.umweltprobenbank.de

www.uba.de/geres
Thank you very much for your attention.

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