Human biomonitoring to support risk assessment and chemical policies in Europe: Results from HBM4EU

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Challenges for chemical risk assessment

- More than 100,000 different chemicals on the market
- 4.7 trillion US dollars revenues in 2021
- 302 million tonnes of chemicals consumed in the EU in 2020
- About 10% of chemicals consumed in EU are carcinogenic, mutagenic or reprotoxic (Eurostat 2020)

*Persson, Environ. Sci. Technol. 2022, 56, 3, 1510–1521*
EU chemicals strategy for sustainability

By 2050, pollution is reduced to levels no longer considered harmful to health and natural ecosystems:

- Banning and restricting – except for essential uses
- Substituting with substances of less concern
- Tackling “cocktail effect”
Chemical Risk assessment

Human biomonitoring makes pollution personal

Measures chemicals and their reaction products directly in urine, blood,..

Integrates exposures from inhalation, ingestion, dermal uptake

Human biomonitoring makes pollution personal
The European Human Biomonitoring Initiative – HBM4EU

5.5 years, extended (2017-2022), European Joint Programme under Horizon 2020
Total budget: ~ 74 million €

30 countries (25 EU Member States, 3 associated countries, Switzerland) and the European Environment Agency

116 Partner organisations

Coordinated by the German Environment Agency (UBA)

Co-coordinated by VITO

Answer open policy-relevant questions

Improve chemical risk assessment in the EU through the effective use of HBM data

Harmonize procedures and tools for HBM at EU level

Develop novel methods to identify human internal exposure and establish the causal links with human health effects

The science policy nexus in HBM4EU

We started the dialogue with policy makers: national and at EU level

- What are the policy questions?
- What are the priorities?
- Input from policy context?
- Uptake in policies?

Clearly communicate science

Deliver at the right moment.

- Farm to fork-transition of farming and diet
- Sustainable chemical’s strategy
- Zero pollution ambition

From Policy to science: prioritisation and capturing policy questions

- What is the current exposure of the EU population?
- Are exposures different between countries? Why?
- Are exposure levels above any health relevant health assessment values?
- Has European regulation an effect?
- Should the substance be subject to (further) regulation?

The HBM4EU network: The HBM platform

- Big step towards harmonisation of human biomonitoring in Europe
  - Knowledge Exchange,
  - Highest quality standards,
  - Collaboration
  - Capacity Building

166 laboratories: 45% of them HBM4EU qualified

152 biomarkers
9 chemical groups

Existing and new HBM studies and data

https://ipchem.jrc.ec.europa.eu/
https://www.hbm4eu.eu/eu-hbm-dashboard/
**HBM4EU aligned studies: harmonization in 21 countries**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ General population</td>
<td>!no hotspot areas</td>
</tr>
<tr>
<td>✓ Samples collected between 2014-2021</td>
<td>! Specific targeted populations e.g. patient groups</td>
</tr>
</tbody>
</table>

### Geographical coverage

- North 21% → 2
- East 11% → 1
- South 28% → 3
- West 40% → 3/4

### Domains for which reliable data are needed:

#### Age

- ✓ Children (6-11y)
- ✓ Teenagers (12-19y)
- ✓ Adults (20-39y)

#### Geographical coverage

- ✓ North 21% → 2
- ✓ East 11% → 1
- ✓ South 28% → 3
- ✓ West 40% → 3/4

#### Sex

- ✓ Male
- ✓ Female

→ 50:50 ratio

### Domains with minimal prevalence (10%):

#### SES socio-economic status

- ✓ Educational level (ISCED- classification from UNESCO)
- ✓ Level 0-6

#### Subject living environment

- Inhabitants of
  - ✓ Low
  - ✓ Medium
  - ✓ high density communities

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Geographical differences

### Acrylamide biomarkers

<table>
<thead>
<tr>
<th>Country</th>
<th>GAMA in urine (µg/g crt) of children in Europe by mean value (P50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEB II - Norway</td>
<td>8.32</td>
</tr>
<tr>
<td>NAC II - Italy</td>
<td>30.74</td>
</tr>
<tr>
<td>GerES V - Germany</td>
<td>13.19</td>
</tr>
<tr>
<td>ESTEBAN - France</td>
<td>11.89</td>
</tr>
</tbody>
</table>

### PFOS+PFOA+PFHxS+PFNA

Geographical differences in exposure to PFOS in blood (µg/L) of teenagers in Europe (2014-2021) by median value (P50)

- NEB II - Norway: 3.39
- NAC II - Italy: 2.01
- GerES V - Germany: 2.20
- ESTEBAN - France: 2.20
- ESTBAN - France: 2.01
- INSEF-ExpoQuim - Portugal: 25.01
- ESB - Germany: 7.13

### Chemical regulation at EU level but national implementation

- **Sustainable** HBM with comparable data is necessary on European level!


Younger age groups have higher biomarker levels than older ages.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpyrifos</td>
<td>2.43</td>
<td>0.89</td>
</tr>
<tr>
<td>Pyrethroids</td>
<td>1.24</td>
<td>0.393</td>
</tr>
<tr>
<td>TCPY</td>
<td>0.645</td>
<td>0.162</td>
</tr>
<tr>
<td>3-PBA</td>
<td>0.844</td>
<td>0.186</td>
</tr>
</tbody>
</table>

Higher intake of food per kg body weight

Higher inhalation rate

*Tarazona et al, Toxics. 2022 doi: 10.3390/toxics10080451*
Younger age groups have higher biomarker levels than older ages.

Biomarkers of phtalates and DINCH in HBM4EU aligned studies
GM (95/CI)

<table>
<thead>
<tr>
<th></th>
<th>children</th>
<th>teens</th>
<th>children</th>
<th>teens</th>
<th>children</th>
<th>teens</th>
<th>children</th>
<th>teens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Σ(5cx-MEPP + 5OH-MEHP)</td>
<td>28.7</td>
<td>16.8</td>
<td>29.1</td>
<td>19.5</td>
<td>23.4</td>
<td>18.6</td>
<td>1.36</td>
<td>0.7</td>
</tr>
<tr>
<td>MBzP</td>
<td>3.88</td>
<td>2.07</td>
<td>2.3</td>
<td>1.79</td>
<td>1.36</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MiBP</td>
<td>19.5</td>
<td></td>
<td>1.86</td>
<td>1.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MnBP</td>
<td>18.6</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Protecting vulnerable ages: children & adolescents – transgenerational equity?

- Aprotic solvents
  - NMP highest in young children, NEP highest in adolescents

- Acrylamide
  - Levels are higher at younger ages

- Benzophenones
  - Levels are higher in teenagers than in adults

- Mycotoxins
  - Children have a higher exposure to the DON mycotoxin compared to adults

- Phthalates
  - Children have higher levels than teenagers except MEP

- Pyrethroids
  - HBM levels (P50 and P95) are higher in children compared to adults for 3-PBA, cis-DBCA, cis and trans DCCA

- Chlorpyrifos
  - Concern for health risk in some children populations with P95 higher than in adult studies

Protect children as they are often more exposed than older age groups
Changes over time

DiBP exposure of children P50 for the biomarker MiBP in µg/L.

Chemical regulation at EU level works to reduce exposure
Phthalates, BPA, PFOS and PFOA

BUT!!!!

Changes over time

DINCH exposure of children, P50 for the biomarker $\sum (OH$-MINCH + cx-MINCH) in $\mu$g/L

Substitutes pop up !!!

Rapid update of TDI(ADI) is needed if new toxicological information becomes available

Acrylamide in adults, urinary metabolites measured over time

Time trend analysis based on harmonized published data (2000-2015) and HBM4EU studies (2015-2021) show:

- An increasing of AAMA concentration over time from 2000 to 2017
- A decreasing of AAMA during 2018-2020

mitigation measures are not visible till 2017

BUT there is an indication of first slightly effect of the 2017 EU regulation mitigation measures only in ADULTS (no data on children)

AAMA: N-acetyl-S-(2-carbamoylethyl)-cysteine

FAIR data: making the data Findable, Accessible, Interoperable and Reusable via IPCHEM

https://ipchem.irc.ec.europa.eu/

via European HBM dashboard

https://www.hbm4eu.eu/eu-hbm-dashboard/
Risk quotients: fraction of the population at risk

➢ Comparison with health based guidance values
➢ Interpretation: adverse health effects cannot be excluded if health based guidance values are exceeded (based on current scientific knowledge)

➢ 27 HBM-GVs derived in HBM4EU

➢ Biomonitoring equivalents (Summit Toxicology)
➢ HBM I (German HBM commission)

HBM4EU data support current policy decisions

Share of European teenagers with chemical exposure levels (median) of PFASs with concerns for health.

<table>
<thead>
<tr>
<th>Chemical substance</th>
<th>% population exceeding guidance value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOA</td>
<td>7.66%</td>
</tr>
<tr>
<td>HBM-I: 2 µg/L</td>
<td></td>
</tr>
<tr>
<td>PFOS</td>
<td>9.40%</td>
</tr>
<tr>
<td>HBM-I: 5 µg/L</td>
<td></td>
</tr>
<tr>
<td>Σ(PFHxS + PFOS)</td>
<td>13.80%</td>
</tr>
<tr>
<td>EFSA opinion: 4.9 µg/L</td>
<td></td>
</tr>
<tr>
<td>Σ(PFOA + PFNA + PFHxS + PFOS)</td>
<td>14.26%</td>
</tr>
<tr>
<td>EFSA opinion: 6.9 µg/L</td>
<td></td>
</tr>
<tr>
<td>Σ(PFOA + PFNA)</td>
<td>19.01%</td>
</tr>
<tr>
<td>EFSA opinion: 2 µg/L</td>
<td></td>
</tr>
</tbody>
</table>

Results from HBM4EU: HBM-GV-exceedance shown by HBM4EU demonstrate necessity of regulatory actions!

Strong support for i.a. PFAS group restriction activities

The data presented are from teenagers 12-19 year collected across Norway, Sweden, Slovakia, Slovenia, Greece, Spain, Germany, France and Belgium. Values <LOD/LOQ are replaced by LOD/2 or LOQ/2. Sums are only calculated if one of the markers constituting the sum is detected for at least 60%.

Fraction of children (HBM4EU aligned study) at risk from phthalate and DINCH

Regulate substances of similar chemical classes at group level to prevent regrettable substitution

Fraction of the HBM4EU aligned study population at risk

- Current regulation is not enough to protect the population sufficiently
- Speed up decision making

Exceedance of health based guidance values

Adverse health outcomes cannot be excluded

Exposure and health relationship in the aligned studies

Exposure biomarker → Biochemical biomarker → Effect biomarker → Health outcome

**Molecular**
- TR Histone modification
- BDNF methylation

**Clinical**
- TSH, T3, T4
- LH, FSH
- TT, E2
- SHBG
- BDNF

**Health outcome**
- Neurobehaviour
- Neuropsychological tests

**Biochemical biomarker**
- ER, AR, PPARα, PPARγ
- Histone modification
- Kisspeptin methylation

**Effect biomarker**
- LH, FSH
- TT, E2
- SHBG
- Kisspeptin
- 8-OHdG

**Health outcome**
- Pubertal development
- Sexual maturation

**Biochemical biomarker**
- PPARα, PPARγ, GR, TR methylation
- Kisspeptin methylation

**Effect biomarker**
- Glucose and insulin
- TG, TC, HDL-C, LDL-C
- Leptin, adiponectin
- TSH, T3, T4
- Kisspeptin
- 8-OHdG

**Health outcome**
- BMI
- Waist circumference
- Body fat mass
- Glucose intolerance
- Diabetes
- Hypertension

The causal chain: Exposure biomarkers--- effect biomarkers --- health outcomes

At current levels of human exposure, biological changes and adverse health outcomes can be demonstrated


Regulatory actions needed – EU level

**Bisphenols**
- Regulate BPA substitutes and bisphenols as a group:
  - P95 of BPF is higher than P95 of BPA in 5 of 11 sampling sites (adults - aligned studies), median levels of urinary BPA substitutes are increasing in all European regions

**PFAS**
- PFAS as a group to further reduce exposure
  - Up to 23.8% of teenagers exceed the EFSA based guidance values for sum of 4 PFAS

A sustainable **surveillance** HBM network for Europe is needed

- A sustainable network of QA/QC laboratories
- Harmonisation of materials and procedures
- Accessible and comparable HBM data
Research and follow up is needed

- Develop early warning capacity for chemicals of emerging concern
- Monitoring of internal exposure to substitutes (BPA, OPFRs) as levels are increasing
- Improve capacity for suspect and non-target screening
- Patterns in real life internal exposures
- Mixture exposures and effects
Special Issue: Key results of the European Human Biomonitoring Initiative - HBM4EU
Edited by Marike KolossaGehring, Greet Schoeters, Douglas Haines, Argelia Castano, Robert Barouki, Alexandra Polcher, Philipp Weise

Special Issue “Analysis of Human Biomonitoring Data and Risk Assessment of Human Exposure to Environmental Chemicals: What Do We Learn for Prevention?”
https://www.mdpi.com/journal/toxics/special_issues/Human_Biomonitoring_Europe

https://www.hbm4eu.eu/
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National hubs
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