Strategies for health interpretation: development of HBM health-based guidance values for individual phthalates and BPA

Workshop on policy uptake of HBM-results
Brussels - Nov 2018

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WP 5 – Translation of Results into Policy

Task 5.1 Results Report

Task 5.2 HBM-HBGVs

Task 5.3 RA/HIA strategies

Task 5.4 HBM indicators

Task 5.5 Action Plan

Development and consolidation of human biomonitoring health-based guidance values (HBM-HBGVs)

+ possibility for HBM4EU-countries experts to feed in their personal expertise

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Task 5.2 – Overall objectives

A) Establishment of a methodology to derive HBM-HBGVs

- for the general population (HBM-HBGV\textsubscript{GenPop})
- for workers (HBM-HBGV\textsubscript{Workers})
- based on existing derivation schemes of UBA and ANSES
- taking into account comments of National Hub experts
- Publication in peer-reviewed journal

B) Derivation of HBM-HBGVs for substances prioritized under HBM4EU

- Documentation as reports (deliverables) including fact sheets summarizing the relevant information used for the derivation of the values
- Taking into account comments of National Hub experts
- Publication in peer-reviewed journal
Task 5.2 – Overall working process

- Strategy to derive HBM-HBGVs for the general population & for occupationaly exposed adults
- Proposal for derivation and calculation of values (UBA / ANSES)
- NHC contacts NHCPs for NH expert consultation
- Integration of comments / remarks from NH experts
- Finalisation of the HBM-HBGVs (UBA / ANSES)

Deliverable: HBM-HBGVs for prioritised substances

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Definition of derived HBM-HBGVs

Values derived according to current knowledge

**HBM-HBGV\textsubscript{GenPop}**

Similar to the HBM-I value from the German Biomonitoring Commission

- concentration of a substance or its metabolites in human biological material ≤ which there is no risk of health impairment anticipated
- verification or control value
- rather a screening tool for health risk assessment on population level, should be used with reasonable care at the individual level
- not for non-threshold carcinogens

**HBM-HBGV\textsubscript{Workers}**

Similar to the Biological Limit Value (BLV) from ANSES

- concentration of a substance or its metabolites in human biological material aiming to protect workers exposed regularly and over the course of a working life from the adverse effects related to medium- and long-term exposure
- screening tool for occupationally exposed adults health risk assessment
- also possible to derive for non-threshold carcinogens, as additional life time risks ($10^{-4}$, $10^{-5}$, $10^{-6}$)

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Derivation strategy – Prerequisites

- Reliable toxicokinetic information in humans
- Analytical traceability of the selected specific biomarker(s)
- Quality assured & relevant epidemiological and/or toxicological data on the substance of concern to select a critical dose
Derivation strategy – Methodology

3 options to derive HBM-HBGVs

1. Derivation from human data based on internal concentration and health effects relationship
2. Derivation of HBM-HBGV_{GenPop} based on a defined tolerable intake (e.g. ADI, TDI, DNEL)
3. Derivation of HBM-HBGV_{Worker} based on an occupational exposure limit (e.g. 8h-OEL, MAK value)

4. Derivation from data based on critical effect seen in animal studies (POD as NOAEL, LOAEL or BMDL)

Preference

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Scheme of derivation option nº2 based on a defined tolerable intake/external exposure value (for urinary biomarkers)

External Dose

Animal POD

AF_A

Human Equivalent POD

AF_H

Relevant Internal Dose

Monitored Biomarker

Estimated metabolite output using excretion fraction data; divide by average daily creatinine excretion or urinary volume

Defined tolerable intake/external exposure value (e.g. TDI, DNEL, OEL..)

HBM-HBGV

Adapted from Aylward et al. 2009
Scheme of derivation option n°3 based on a animal POD (for urinary biomarkers)

Adapted from Aylward et al. 2009

- External Dose
  - Animal POD
  - $AF_A$
- Relevant Internal Dose
- Monitored Biomarker
  - Human Equivalent POD
  - Estimate metabolite output using excretion fraction data; divide by average daily creatinine excretion or urinary volume
  - $AF_H$
  - HBM-HBGV

Human Internal conc.
Limitations and Uncertainties

- Data from epidemiological and animal studies vary in quality and focus.
- Data on metabolite excretion/TK data often coming from studies with few volunteers, sex or age-specific differences or potential dependency on exposure level often not considered.
- Intra- and inter-individually variability of urinary daily volume or creatinine excretion rates.

⇒ Level of confidence is attributed to each derived HBM-HBGV: low or medium or high.
Why do we need HBM-HBGVs?

- Improve risk assessment of chemicals by using HBM data
- Perform this HBM-based risk assessment consistently within the EU
- Helping policy makers to prioritise action
- Support for policy action and risk management measures

- Easy-to-use screening tools for health risk assessment (should be used with reasonable care at the individual level)
- Not to be considered as a stand-alone diagnostic criteria

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**Relation to other existing internal limit values**

**Biomonitoring Equivalent (BE)** (developed as part of a collaboration between Summit Toxicology, US EPA, Health Canada & multiple industry trade groups):

⇒ concentration of a chemical in blood or urine that corresponds to an allowable exposure guidance value (such as a USEPA Reference Dose or ATSDR Minimal Risk Level or Acceptable Daily Intake) considered safe by regulatory agencies

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**The BE derivation process includes:**

- Compiling existing tolerable exposure reference values;
- Compiling and reviewing existing pharmacokinetic information;
- Reviewing information on the MOA;
- Assessing available biomarkers for specificity and relevance;
- Deriving BE values for the POD and the exposure reference value \((BE_{POD}, BE)\);
- Independent peer-review of the BE;
- Publishing the BE dossier in the peer-reviewed literature;
- Development of chemical-specific communications materials
Relation to other existing internal limit values

⇒ If derived from a defined tolerable intake value, then HBM-HBGVs derived within HBM4EU are functionally identical to Biomonitoring Equivalents, however:

➤ the corresponding allowable exposure guidance values selected are values considered safe by an European (regulatory) agency (e.g. EFSA, ECHA, SCOEL...) as a priority

⇒ If HBM-HBGVs are derived from an animal POD (and then converted to a ‘TDI-like’ value or converted to a Human Equivalent POD and then to a Human Equivalent concentration):

➤ assessment factors (AFs) applied are preferably the ones recommended by ECHA¹ (if not, choice and magnitude of the AFs will be explained)

Task 5.2 – Output so far

2017

May

Methodology document for deriving HBM-HBGVs submitted for consultation with NH-experts

Gathering of comments received, revision of the document and publication still ongoing

August

Documents on HBM-HBGVs derivation for DINCH & DEHP sent to consultation with NH-experts

Oct

Revision of documents on HBM-HBGVs for DINCH & DEHP according to the comments received

Dec

D5.2 “1st substance-group specific derivation of HBM-HBGVs for DINCH/DEHP” uploaded by coordinator

https://www.hbm4eu.eu/deliverables/
Proposal of HBM-HBGVs for **DPHP & DBP** to NH-nominated experts for review, deadline for commenting on **31 Oct 2018**

Proposal of HBM-HBGVs for **DiBP & BBzP** to NH-nominated experts for review, resubmission to UBA/ANSES expected end of **January 2019**

Proposal of HBM-HBGVs for **Bisphenol A** and **Cadmium** to NH-nominated experts for review, resubmission to UBA/ANSES expected end of **February 2019**

D5.6 (A to C): “Derivation of consolidated HBM-HBGVs for selected phthalates, for Bisphenol A, for Cadmium”
Phthalates

 shown to result in disturbances in androgen-mediated development of the reproductive system in males (in utero) with biological pathways leading to common effects characterized by the spectrum of effects of the rat phthalate syndrome (ECHA 2017, Danish EPA 2016):

- inhibition of foetal testosterone production
- reduction of male anogenital distance
- decrease of gene expression related to steroid biosynthesis
- increase permanent nipple retention in male offspring
- increase incidence of genital malformations (hypospadias and cryptorchidism)
- delay puberty onset
- reduction of semen quality
- cause testicular changes (decreased testes and epididymides weight, tubular atrophy and Leydig cell hyperplasia)

⇒ Relevant for male humans
Approaches for deriving HBM-HBGVs for phthalates mixtures?

Evidence from the recent peer-reviewed scientific literature shows that:
- phthalates produce mixture effects;
- the effects are often predicted well by using the dose-addition concept

Existing methods for cumulative risk assessment

- Toxic Unit Summation (TUS)
- Hazard index (HI)
- Point of departure index (PODI)
- Toxic equivalent factors (TEF)/ Relative potency factor (RPF)
- Similar mixtures risk indicator (SMRI)

Methods to be assessed next for phthalate mixtures (linked to WP15)
Thanks for your attention

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Farida Lamkarkach
Eva Ougier

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## HBM-HBGVs for DEHP (Bis(2-ethylhexyl)phthalate)

<table>
<thead>
<tr>
<th>For the general population</th>
<th>For occupationally exposed adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected TK data</strong></td>
<td><strong>1) Anderson et al. (2011) for urinary excretion fractions of metabolites</strong>&lt;br&gt;20-volunteers oral single-dose study using labelled-DEHP&lt;br&gt;<strong>2) Koch et al. (2005) for the excretion half-lives (DEHP + metabolites)</strong>&lt;br&gt;1-volunteer high single-doses labelled-DEHP oral study</td>
</tr>
<tr>
<td><strong>Selected BM(s)</strong></td>
<td><strong>Σ [urinary 5-oxo-MEHP + 5-OH-MEHP]</strong>&lt;br&gt;or&lt;br&gt;<strong>Σ [urinary 5cx-MEPP + 5-OH-MEHP]</strong></td>
</tr>
<tr>
<td><strong>Derivation method</strong></td>
<td><strong>From an external toxicological guidance value + TK extrapolation (based on urinary mass balance)</strong></td>
</tr>
<tr>
<td><strong>Selected external tox guidance value or POD</strong></td>
<td><strong>TDI from EFSA (2005): 0,05 mg/kg bw/d</strong>&lt;br&gt;Based on multigenerational reprotox oral rat study by Wolfe and Layton (2003): NOAEL of 4,8 mg/kg bw/d for developmental impairment; AFs = [10 · 10] = 100</td>
</tr>
<tr>
<td><strong>HBM-HBGV</strong></td>
<td><strong>Σ urinary [5-oxo-MEHP + 5-OH-MEHP]</strong>&lt;br&gt;Children (6-13y): 340 µg/L&lt;br&gt;Adults: 500 µg/L</td>
</tr>
<tr>
<td></td>
<td><strong>Σ urinary [5cx-MEPP + 5-OH-MEHP]</strong>&lt;br&gt;Children (6-13y): 380 µg/L&lt;br&gt;Adults: 570 µg/L</td>
</tr>
</tbody>
</table>
## HBM-HBGVs for DEHP (Bis(2-ethylhexyl)phthalate)

### For the general population

<table>
<thead>
<tr>
<th>HBM-HBGV</th>
<th>Level of confidence attributed to the derived DEHP HBM-HBGV_{GenPop}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Σ urinary [5-oxo-MEHP + 5-OH-MEHP]</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>Children (6-13y):</td>
<td>340 µg/L</td>
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<tr>
<td>Adults:</td>
<td>500 µg/L</td>
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<tr>
<td>Σ urinary [5cx-MEPP + 5-OH-MEHP]</td>
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<td>Children (6-13y):</td>
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<td>Adults:</td>
<td>570 µg/L</td>
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</table>

### For occupationaly exposed adults

<table>
<thead>
<tr>
<th>HBM-HBGV</th>
<th>Level of confidence attributed to the derived DEHP HBM-HBGV_{Workers}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary [5cx-MEPP] at the end of the workshift</td>
<td>LOW</td>
</tr>
<tr>
<td>Workers:</td>
<td>620 µg/L</td>
</tr>
</tbody>
</table>
### HBM-HBGVs for DINCH (Diisononylcyclohexane-1,2-dicarboxylate)

**For the general population**

<table>
<thead>
<tr>
<th>Selected TK data</th>
<th>Koch et al. (2013) for metabolites fractional urinary excretion ratios + excretion half-lives 3-volunteers high single-dose DINCH oral study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected BM(s)</td>
<td>$\Sigma$ [urinary OH-MINCH + cx-MINCH]</td>
</tr>
<tr>
<td>Derivation method</td>
<td>From an <strong>external tox guidance value</strong> + TK extrapolation (based on urinary mass balance)</td>
</tr>
</tbody>
</table>
| Selected external toxicological guidance value | **TDI from EFSA (2006):** 1,0 mg/kg bw/d  
Based on 2-generation reprotox oral rat study by BASF (2003)  
NOAEL of 100 mg/kg bw/d for nephrotoxicity; AFs = [10 · 10] = 100 |

### HBM-HBGV

| Children (6-13y) | 3 mg/L  |
| Adults:          | 4.5 mg/L |

**Level of confidence attributed to the derived DINCH HBM-HBGV**

GenPop LOW