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

HBM4EU

science and policy for a healthy future

Workshop on policy uptake of HBM-results

Brussels - Nov 2018

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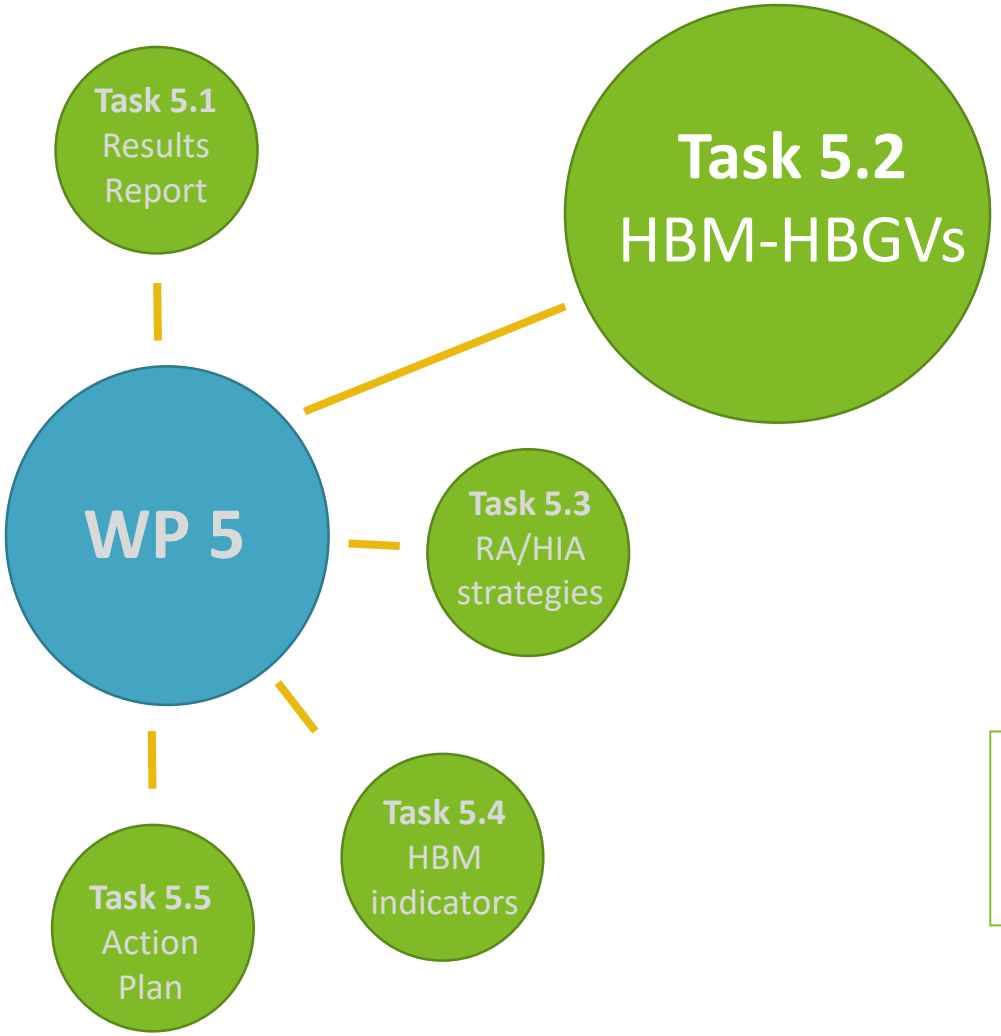
UBA

anses
French agency for food, environmental and occupational health & safety

Investigate, evaluate, protect

WP 5 – Translation of Results into Policy



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

anses
French agency for food, environmental and occupational health & safety
Investigate, evaluate, protect

UBA

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

Task 5.2 – Overall objectives

Task 5.2
HBM-HBGVs

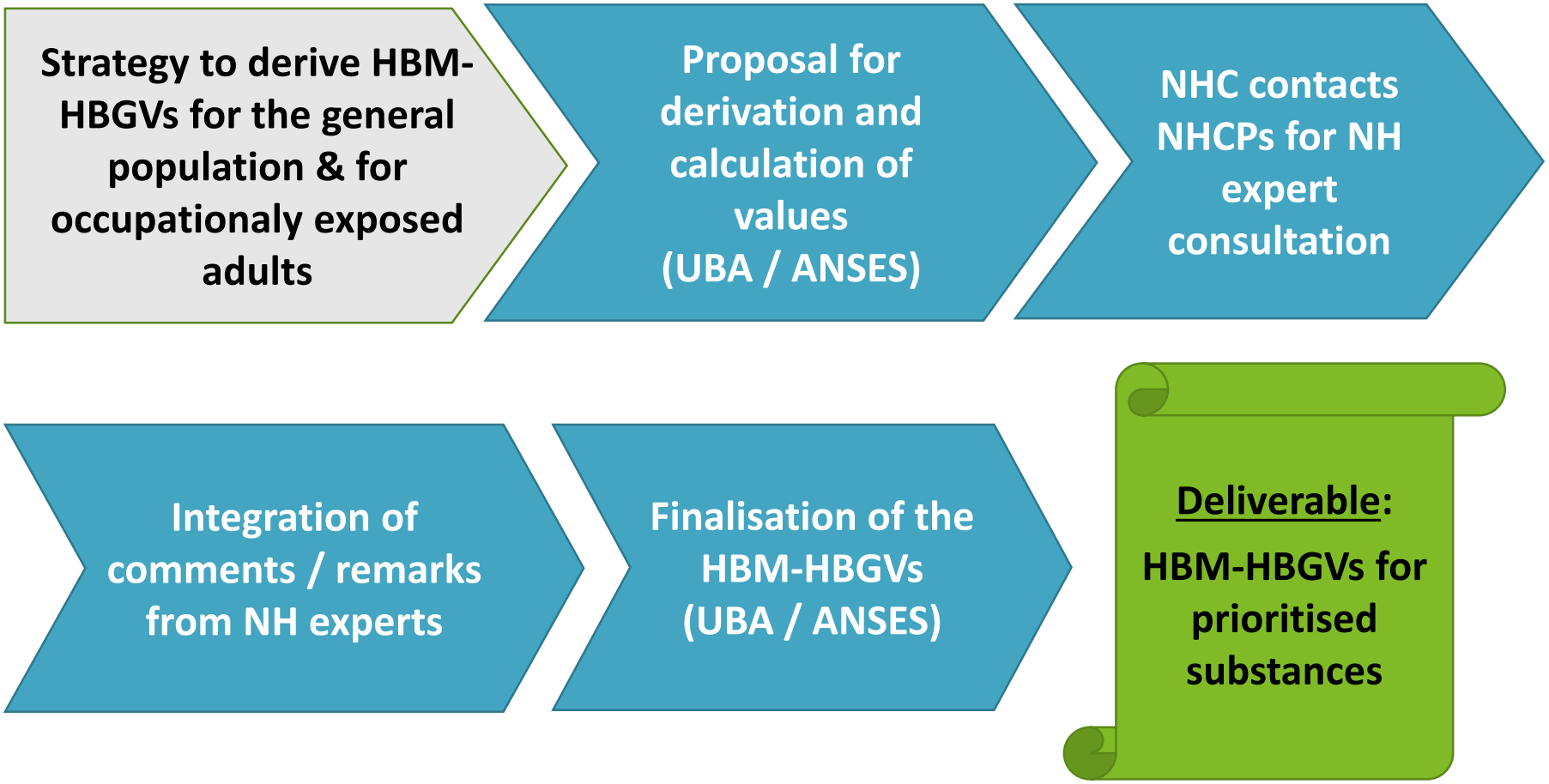
A) Establishment of a methodology to derive HBM-HBGVs

- for the general population (HBM-HBGV$_{GenPop}$)
- for workers (HBM-HBGV$_{Workers}$)
- 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



Definition of derived HBM-HBGVs

Values derived according to current knowledge

HBM-HBGV$_{GenPop}$

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$_{Workers}$

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})

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

Preference

3 2 1

- Derivation from hu ed on internal concentratio effects relationship

IF NOT AVAILABLE

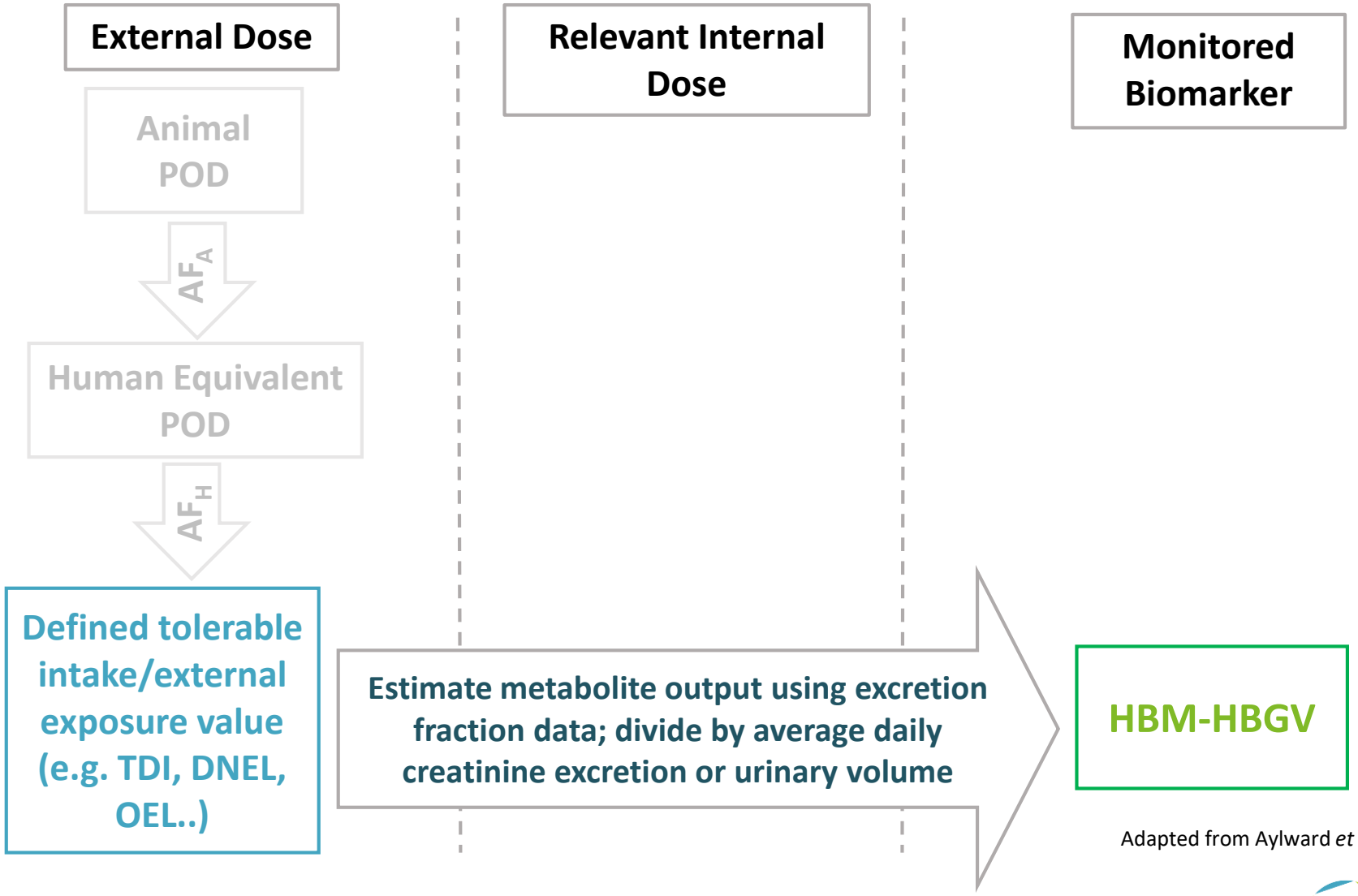
- Derivation of HBM-HBGV$_{GenPop}$ bas d on a defined tolerable intake (e.g. ADI, TD

IF NOT AVAILABLE

- Derivation of $_{Worker}$ based on an occupational ex sure limit (e.g. 8h-OEL, MAK value)

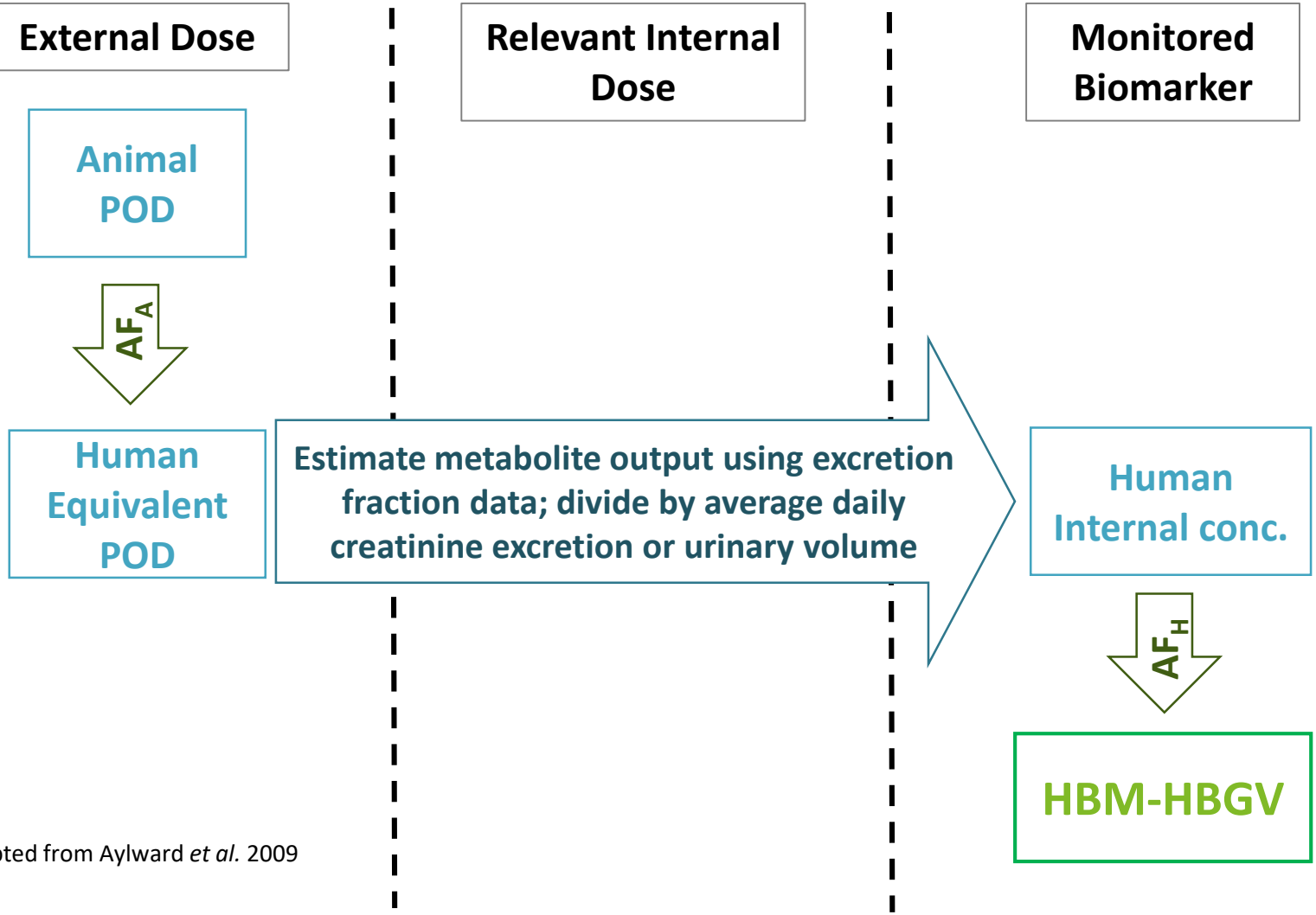
- Derivation from data based on critical effect seen in animal studies (POD as NOAEL, LOAEL or BMDL)

Scheme of derivation option n°2 based on a defined tolerable intake/external exposure value (for urinary biomarkers)



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

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

Source: oncnursingnews.com

Why do we need HBM-HBGVs?

- **Improve risk assessment of chemicals by using HBM data**
- **Perform this HBM-based risk assessment <u>consistently</u> 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)

- <u>Not</u> to be considered as a stand-alone diagnostic criteria

Source: divassoftware.com

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**

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 recommanded by ECHA[1]** (if not, choice and magnitude of the AFs will be explained)

[1] (ECHA (2012). Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version: 2.1. https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

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/

Task 5.2 – Outlook

2018

August

Proposal of HBM-HBGVs for **DPHP** & **DBP** to NH-nominated experts for review, deadline for commenting on 31 Oct 2018

Dec

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

2019

January

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

April

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

Approaches for deriving HBM-HBGVs for phthalates mixtures ?

Work to perform

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)* **:**

Suppression of fœtal androgen action

- 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 ?

Work to perform

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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Back Up slides

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

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

Published

	For the general population	For occupationaly exposed adults
Selected TK data	**1) Anderson et al. (2011) for urinary excretion fractions of metabolites** 20-volunteers oral single-dose study using labelled-DEHP **2) Koch et al. (2005) for the excretion half-lives (DEHP + metabolites)** 1-volunteer high single-doses labelled-DEHP oral study	
Selected BM(s)	Σ [urinary 5-oxo-MEHP + 5-OH-MEHP] or Σ [urinary 5cx-MEPP + 5-OH-MEHP]	Urinary 5cx-MEPP
Derivation method	**From an external toxicological guidance value + TK extrapolation (based on urinary mass balance)**	**From a Point of Departure (POD) + TD and TK extrapolation (based on urinary mass balance)**
Selected external tox guidance value or POD	**TDI from EFSA (2005): 0,05 mg/kg bw/d** Based on multigenerational reprotox oral rat study by Wolfe and Layton (2003): NOAEL of 4,8 mg/kg bw/d for developmental impairement; AFs = [10 · 10] = 100	**POD: NOAEL of 5,8 mg/kg bw/d for bilateral aspermatogenesis** observed in the 2-y reproductive rat study of David et al. (2000) Allometric adjustement + TK extrapolation based on urinary mass balance + AFs = [2,5 · 5] = 10
HBM-HBGV	**Σ urinary [5-oxo-MEHP + 5-OH-MEHP]** **Children (6-13y): 340 µg/L** **Adults: 500 µg/L** **Σ urinary [5cx-MEPP + 5-OH-MEHP]** **Children (6-13y): 380 µg/L** **Adults: 570 µg/L**	**Urinary [5cx-MEPP] at the end of the workshift** **Workers : 620 µg/L**

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

Published

	For the general population	For occupationaly exposed adults
	Level of confidence attributed to the derived DEHP HBM-HBGV$_{GenPop}$ **MEDIUM**	Level of confidence attributed to the derived DEHP HBM-HBGV$_{Workers}$ **LOW**
HBM-HBGV	Σ urinary [5-oxo-MEHP + 5-OH-MEHP] Children (6-13y): 340 µg/L Adults: 500 µg/L Σ urinary [5cx-MEPP + 5-OH-MEHP] Children (6-13y): 380 µg/L Adults: 570 µg/L	Urinary [5cx-MEPP] at the end of the workshift Workers : 620 µg/L

HBM-HBGVs for DINCH (Diisononylcyclohexane-1,2-dicarboxylate)

Published

	For the general population
Selected TK data	**Koch et al. (2013) for metabolites fractional urinary excretion ratios + excretion half-lives** 3-volunteers high single-dose DINCH oral study
Selected BM(s)	Σ [urinary OH-MINCH + cx-MINCH]
Derivation method	**From an external tox guidance value + TK extrapolation (based on urinary mass balance)**
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	**Σ urinary [OH-MINCH + cx-MINCH]** **Children (6-13y): 3 mg/L** **Adults: 4,5 mg/L**

Level of confidence attributed to the derived DINCH HBM-HBGV$_{GenPop}$

LOW