HBM4EU project

Calculation of European reference values

Eva Govarts - VITO

2nd HBM4EU Training School 2018

Calculation European reference values

What is a reference value (RV)?

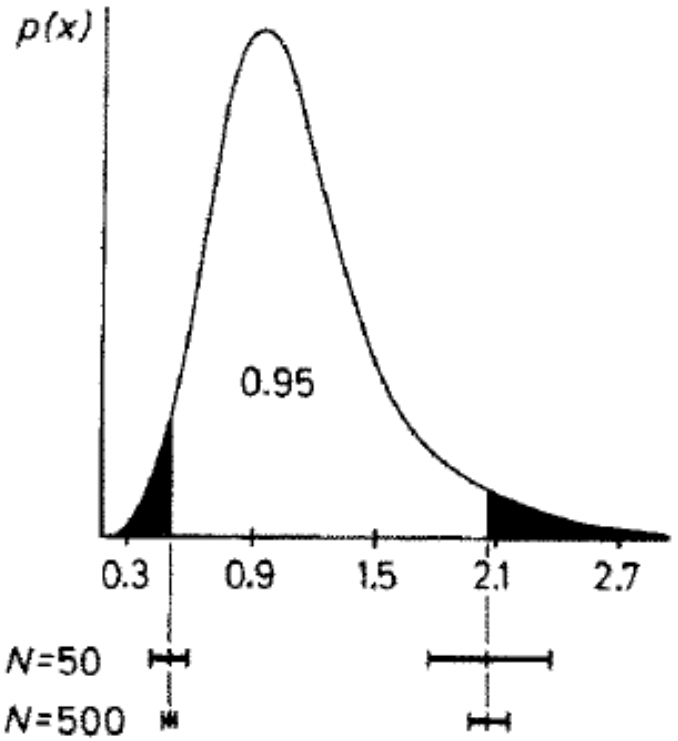
- RVs are statistical estimates from data collected in HBM studies
- Indicates the upper margin of background exposure to a given chemical at a given time
- Not related to any health effect

Calculation European reference values

What is a reference value (RV) used for?

- Specify from which level of exposure an individual is unusually high exposed
- Interpret levels of exposure to chemical substances (hot spots)
- Follow the time trend evolution of exposure levels
- Help public health policies to set a target in a reduction of exposure to chemicals

Selection of the 95th percentile



Convention in hypothesis testing where the 5% highest values indicate unusually high values

IFCC* defined the reference interval of a biological measurement distribution as the 0.95 central inter-fractiles interval between the 2.5 and the 97.5 percentiles. It can be moved to the left side of the distribution and, by consequence, the upper limit is moved from the 97.5 to the 95th percentile.

To ensure a better comparability with international RVs

*IFCC = The International Federation of Clinical Chemistry and Laboratory Medicine

Establishing reference values

Existing HBM data

= heterogeneous data

- Different matrices
- Different time periods
- No EU coverage
- Not always access to individual data
- Different study populations
- No analytical quality assurance

HBM data aligned studies

= more homogeneous data

- Same matrix (only check alignment of type of urine sample (morning, spot, 24h), blood sample (fasting/non-fasting, serum/plasma))
- Time period 2014-2018
- EU coverage
- Access to individual data
- Selected study populations
- Quality assurance labs

Different strategy depending on homogeneity of the data!!

Different strategy

Heterogeneous HBM data ⟷ Homogeneous HBM data

DATA

- Aggregated data calculated with the HBM4EU R-script
- Individual data → pooled dataset

STATISTICAL ANALYSES

- Exposure distributions across data collections (comparison over time, region, …)
- Reference value calculations by applying exclusion criteria (specific food intake) and/or partitioning criteria (age, sex, EU geographical region)

Exposure distributions ⟷ European Reference Values (ERVs)

Exposure distributions

R-script developed by WP10 data management team

→ harmonized aggregated descriptive statistics

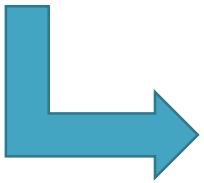
- Whole population + stratified by some parameters (sex, age, educational level, season, smoking status, sampling year)
- Values below LOD/LOQ imputed assuming normal/log-normal distribution
- Descriptive statistics
  - N
  - % below LOD-LOQ
  - Percentiles (P5, P10, P25, P50, P75, P90, P95) and 95% CI
  - Mean, standard deviation/error, 95% CI
  - Geometric mean and its 95% CI

Three steps approach

- Step 1: Inventory of available HBM data collections

- Step 2: Construction of a suitable pooled dataset

- Step 3: Authorization to derive a valid ERV



valid ERV

Inventory of available HBM data collections

→ Selection of homogeneous HBM data

- Type of substance / biomarker / matrix
- Type of population
- Time period
- Sampling
- Representativeness (national, regional, etc.)
- Quality assurance and comparability analytical methods

Construction of a suitable pooled dataset

- Constitution of one dataset by pooling all data coming from the selected data collections (reference sample)
- Apply splitting criteria to focus on a dataset for which it's relevant (and possible) to derive an ERV
  - Exclusion criteria: exclude participants that are not considered appropriate to be derived an ERV from (e.g. pregnant status)
  - Partitioning criteria: create sub-groups to derive sub-ERVs when relevant (when sub-ERVs are significantly different for sub-groups of the population) (e.g. sex, age)

Authorization to derive a valid ERV

- Sufficient sample size: 120 individuals to calculate 95% CI for the 95th percentile
- Representativeness: is the dataset representative of the population for which the ERV is derived?

 If authorization criteria are not met → **return to previous step to modify dataset**

Once dataset is built:

→ percentiles of reference distribution may be estimated by non-parametric methods

→ UBA, ANPS, VITO will work on a R-script to calculate ERVs in a harmonized and uniform way

Deliverable on exposure distributions and ERVs

Annual reports

- Deliverable D10.4 (November 2018)
- Deliverable D10.6 (November 2019)
- Deliverable D10.9 (November 2020)
- Deliverable D10.11 (October 2021)

Depending on the availability of the data and the level of homogeneity: exposure distributions and/or ERVs will be calculated for the 1st and 2nd set substances

Thank you for your attention

If you have any questions about the approach for exposure distributions and ERVs

Don’t hesitate to contact the following HBM4EU WP10 partners!

VITO: eva.govarts@vito.be

UBA: nina.vogel@uba.de

ANSP: loic.rambaud@santepubliquefrance.fr

Contacts

Eva Govarts: eva.govarts@vito.be
Sylvie Remy: sylvie.remy@vito.be
Liese Gilles: liese.gilles@vito.be
Greet Schoeters: greet.schoeters@vito.be

Speaker's information

Eva Govarts works as researcher – biostatistician at the Flemish Institute for Technological Research (VITO), Mol, Belgium. She received training in biomedical sciences, applied and biostatistics. In HBM4EU she is task leader of task 10.4 on the data analysis and generation of European reference values (RVs) and together with Greet Schoeters she is co-leading WP10.

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