NEUROSOME

Exploring The Neurological Exposome

Exposure Modeling And Exposure Reconstruction For Cadmium

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Cadmium Neurotoxicity

1. Considered as a neurotoxin

2. Cd studies report associations between higher Cd concentrations and neurodevelopmental disorders (mental retardations, verbal IQ, learning disability)

3. Abnormal levels of Cd induce alterations in balance excitation/inhibition of the synaptic neurotransmission

- Excitatory neurotransmitters are decreased
- Inhibitory neurotransmitters are increased

4. Affects central nervous system (CNS), especially during fetal and neonatal development

- Cd is able to pass to the fetus via the placenta
- Cd is also detected in breast milk
- Blood-brain barrier is not fully mature in neonates.

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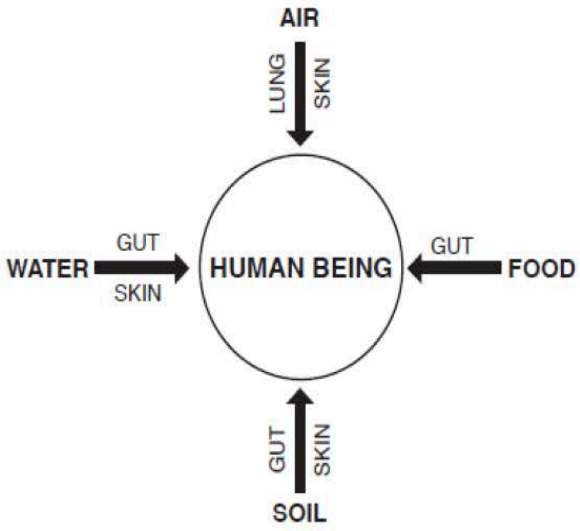
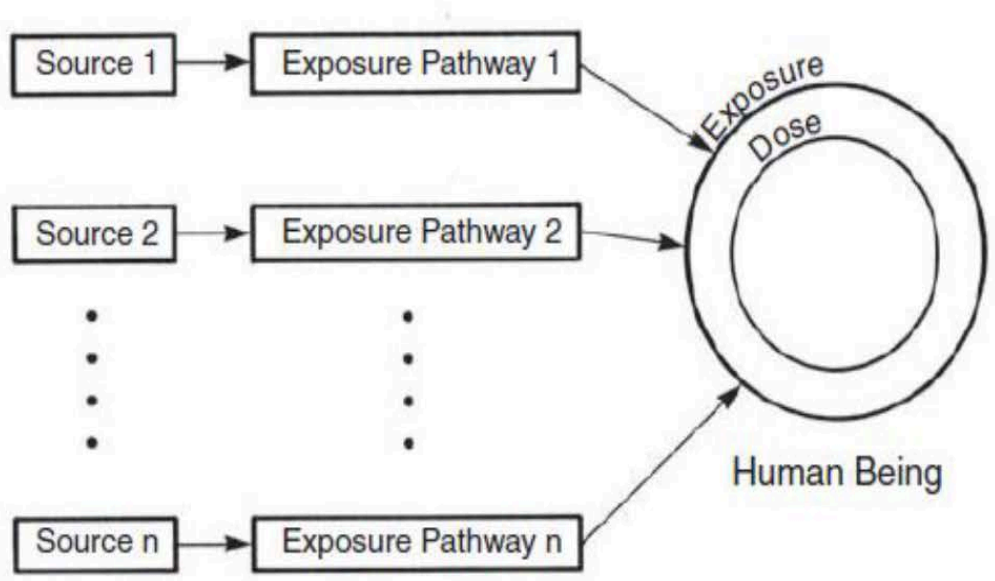
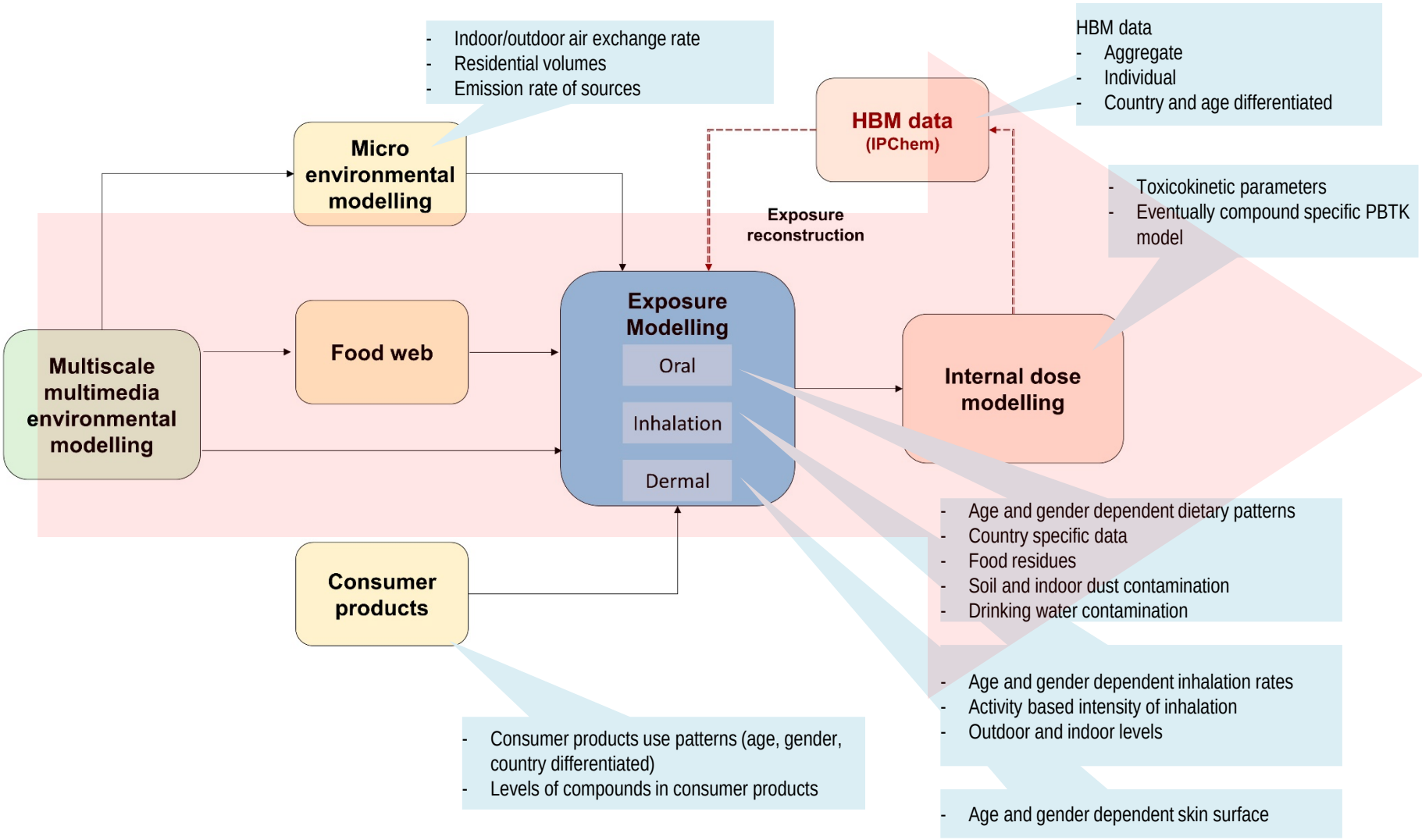
Seeks to provide the exposure contribution of each pathway to the total exposure by creating an exposure profile





Key objective – To evaluate exposure models and reconstruct exposure for Cadmium



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Cadmium Toxicokinetics

1. Cadmium absorption routes

- Inhalation (In cigarette smoke Cd has higher absorption efficiency)
- Oral (Increased absorption for individuals with poor iron status)
- Dermal

2. Cadmium metal and salts are not well absorbed

- About 25%, 1-10% and <1% of the dose respectively for each route

3. After absorption, Cadmium widely distributes throughout the body

4. Cadmium does not undergo any direct metabolic reaction, such as oxidation, reduction or alkylation

5. Absorbed Cadmium is excreted very slowly with urinary and fecal excretion

- Approximately 0.007% and 0.009% of the body burden per day

6. Kidneys are the main site of Cadmium's accumulation

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Data for evaluating the models

1. Data related to Cadmium

- contamination levels in several environmental matrices such as ambient air, indoor air, water, soil, dust
- food residues in various food items
- concentration in consumer products

The data were collected and stored disaggregated by geographical location within Europe.

2. Data that are not chemical specific: This includes data related to consumer behaviour

- food and drinking water consumption
- inhalation rates
- time activity patterns
- dust ingestion rates, soil ingestion rates
- frequency of use of consumer products
- hand to mouth and object to mouth behaviour data

Data of this type were also disaggregated by gender and age class.

3. Exposure modifier data were included along with their respective geographical location such as country and city and stratified by population, age and gender.

Why HBM data?

1. Data Paucity - Quality

- Lack of data supporting integrated exposure models or measured data (environmental matrices, food residues, exposure factors) with poor quality might result in overestimation or underestimation of exposure pathways (e.g. ingestion of dust for infants) over other important pathways (e.g. dietary exposure)

2. Insufficient information about exposure mechanisms

- Conservatism of exposure factors (e.g. consumer products' coefficients that describe the migration of the product through mouthing or contact) leads to inaccurate exposure estimation
  - Overestimation due to bottom up approaches
  - Underestimation in case of completely ignoring exposure mechanisms because of insufficient data

3. Model integration is best described with HBM data of certain quality and relevance.

4. HBM data includes the contribution from all sources, pathways and routes.

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Observations

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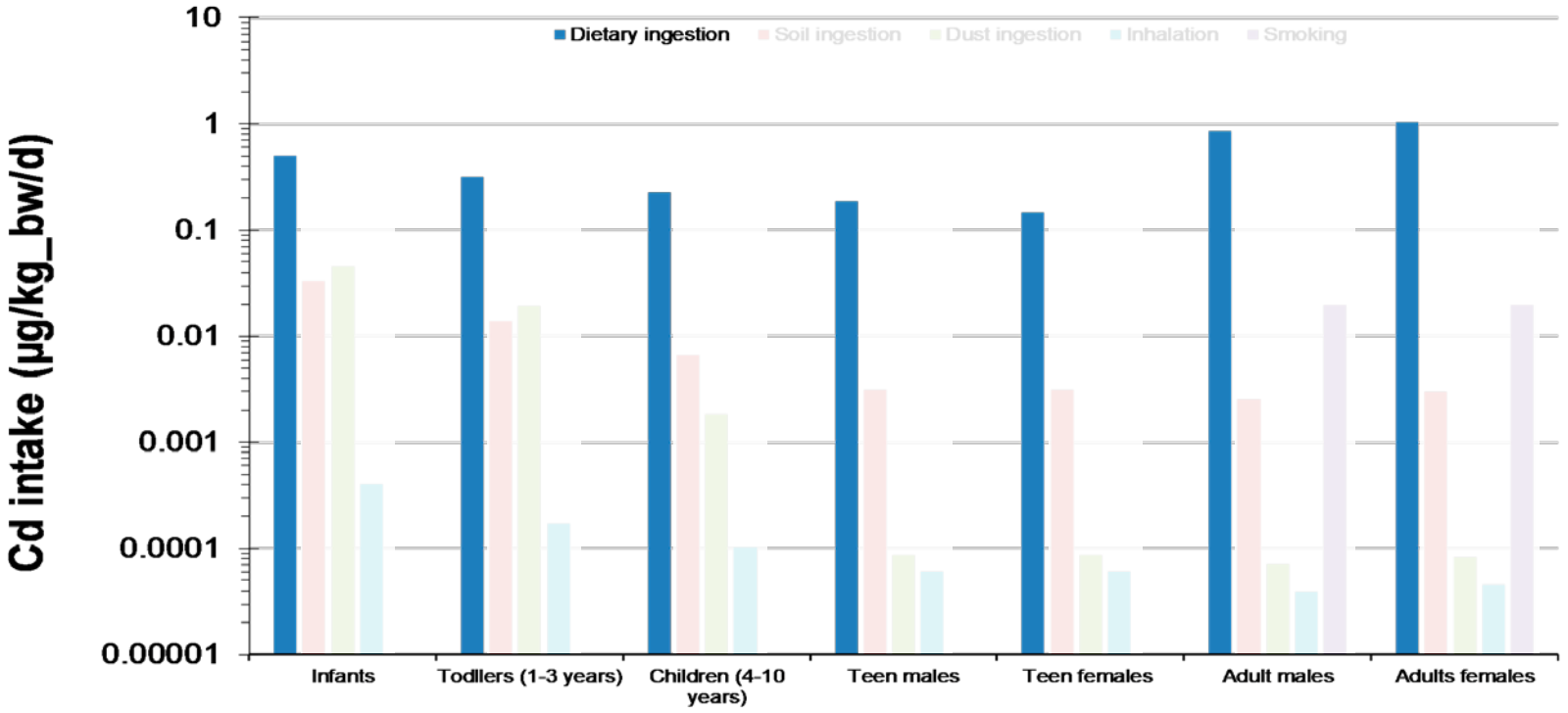
2. Diet is the main source of exposure
3. Smoking is the second source of exposure for adults



Cadmium intake for different age groups

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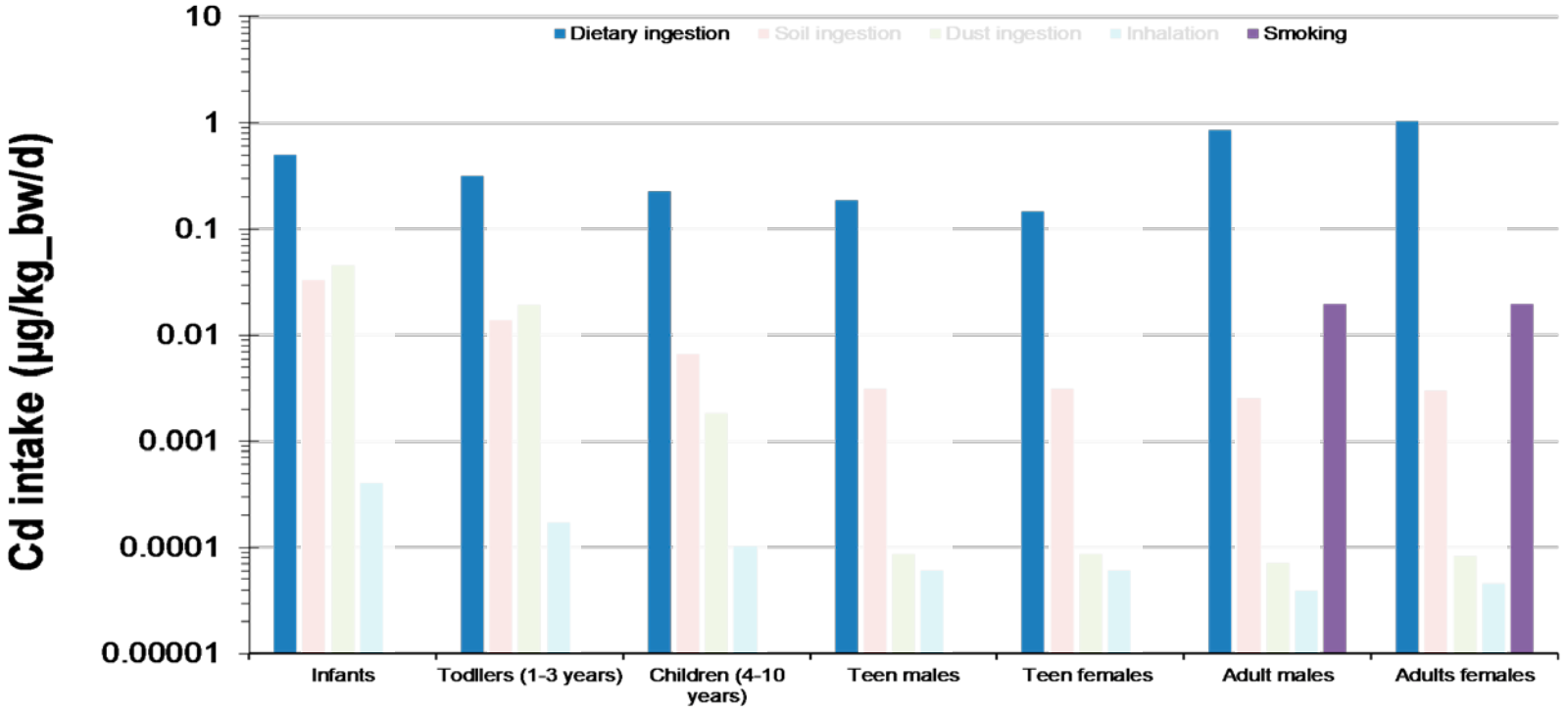

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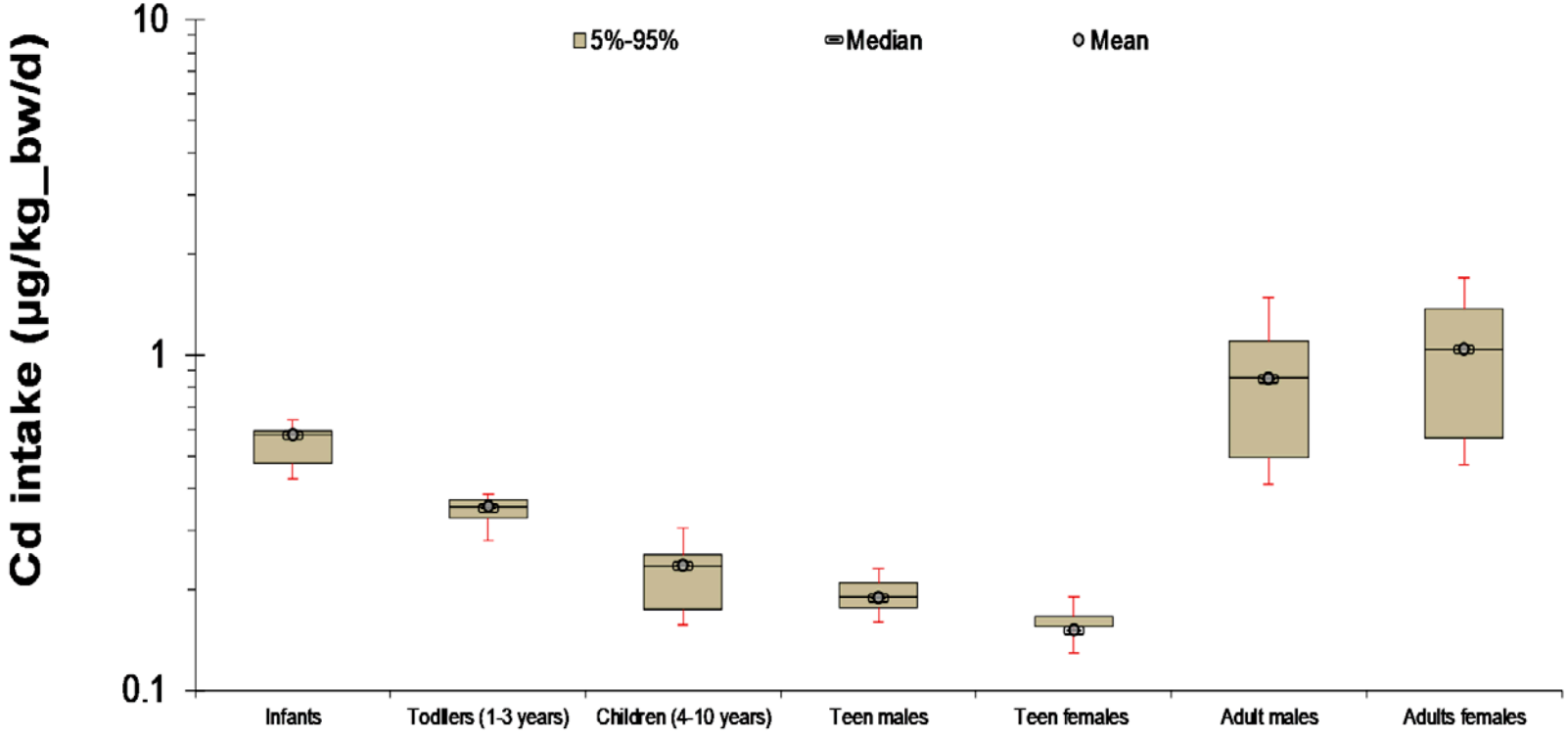
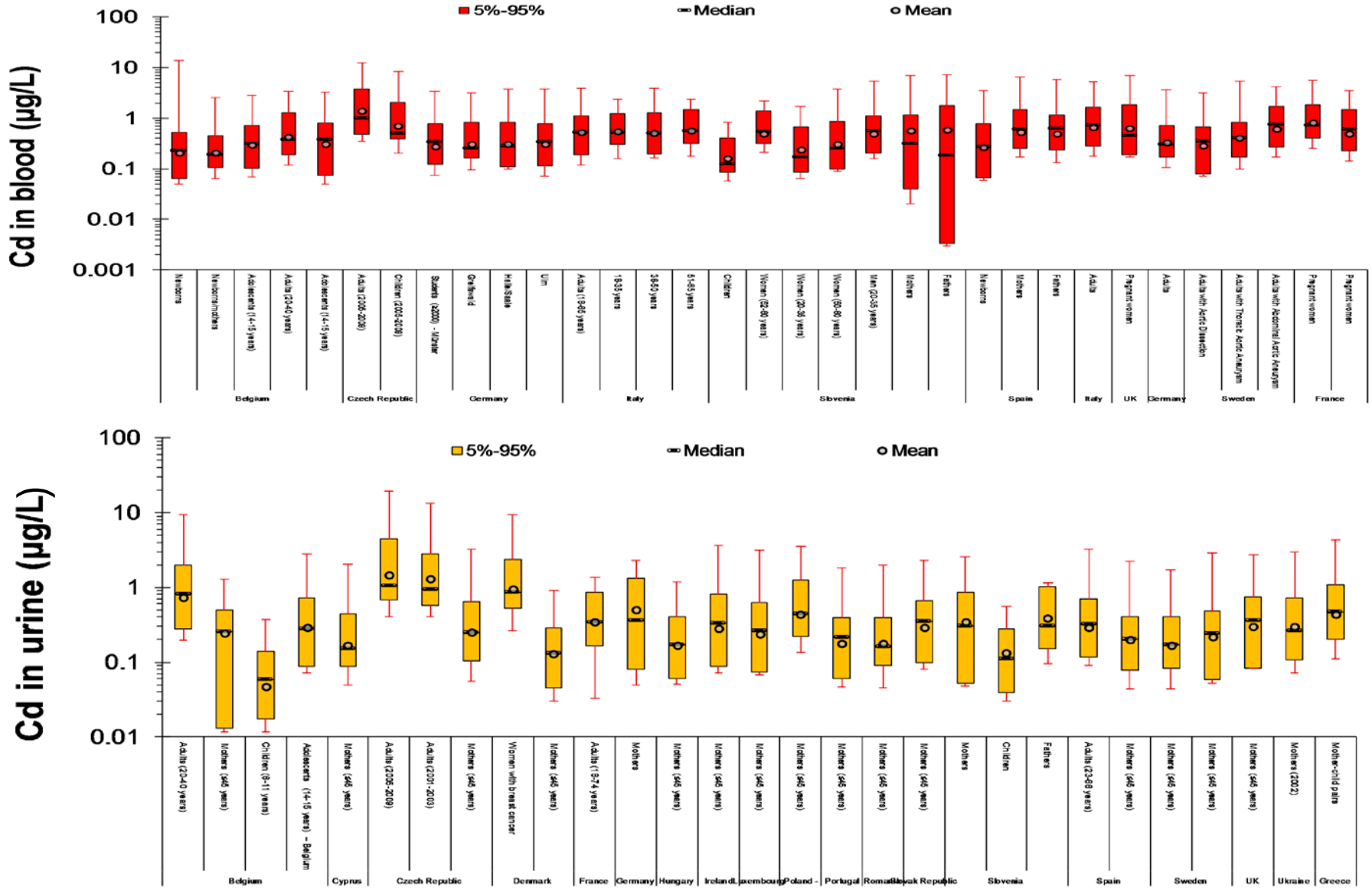


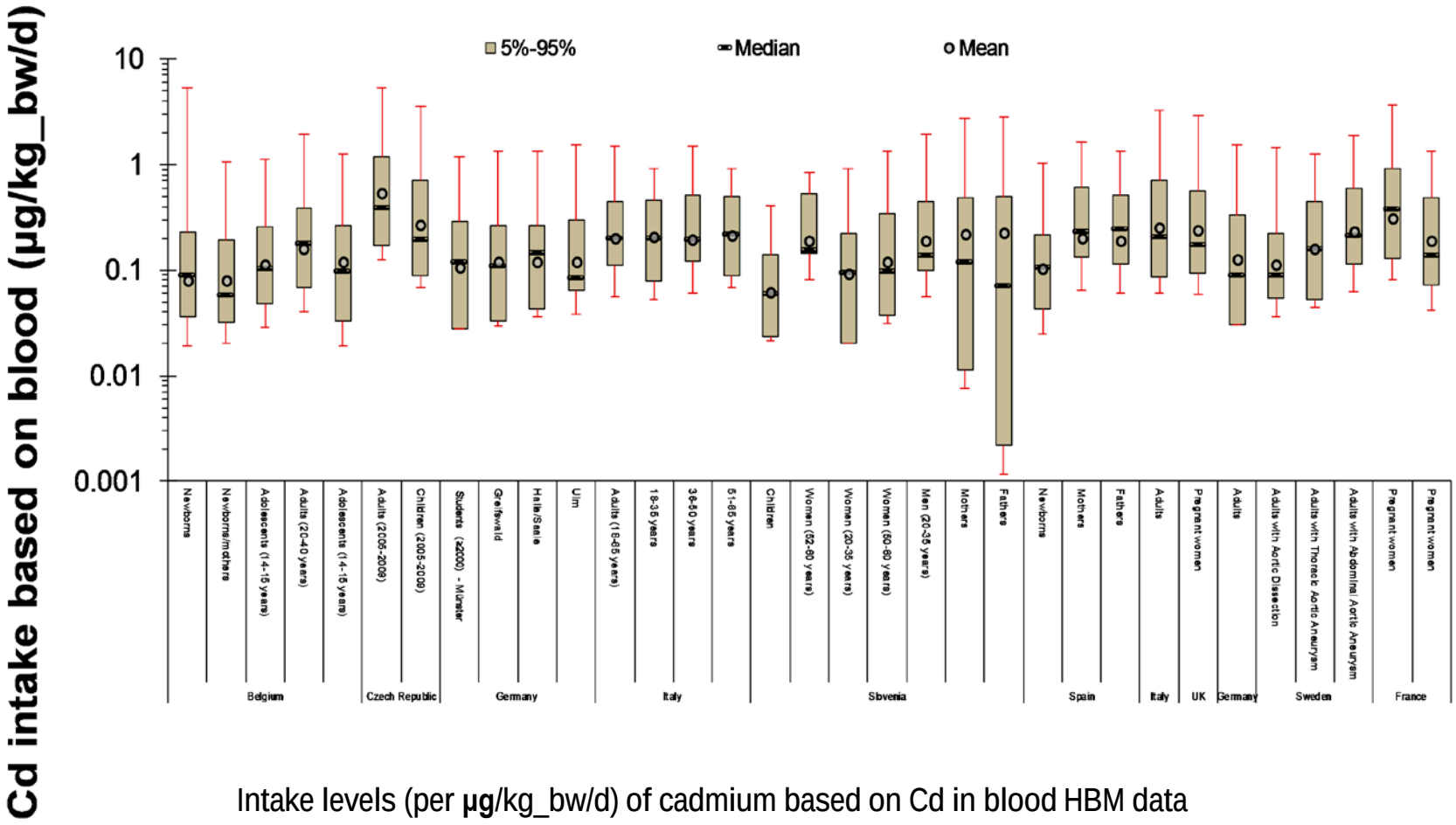
Cadmium intake for different age groups

Aggregate Cd intake for all age groups

Levels of Cd in urine and blood used for exposure reconstruction

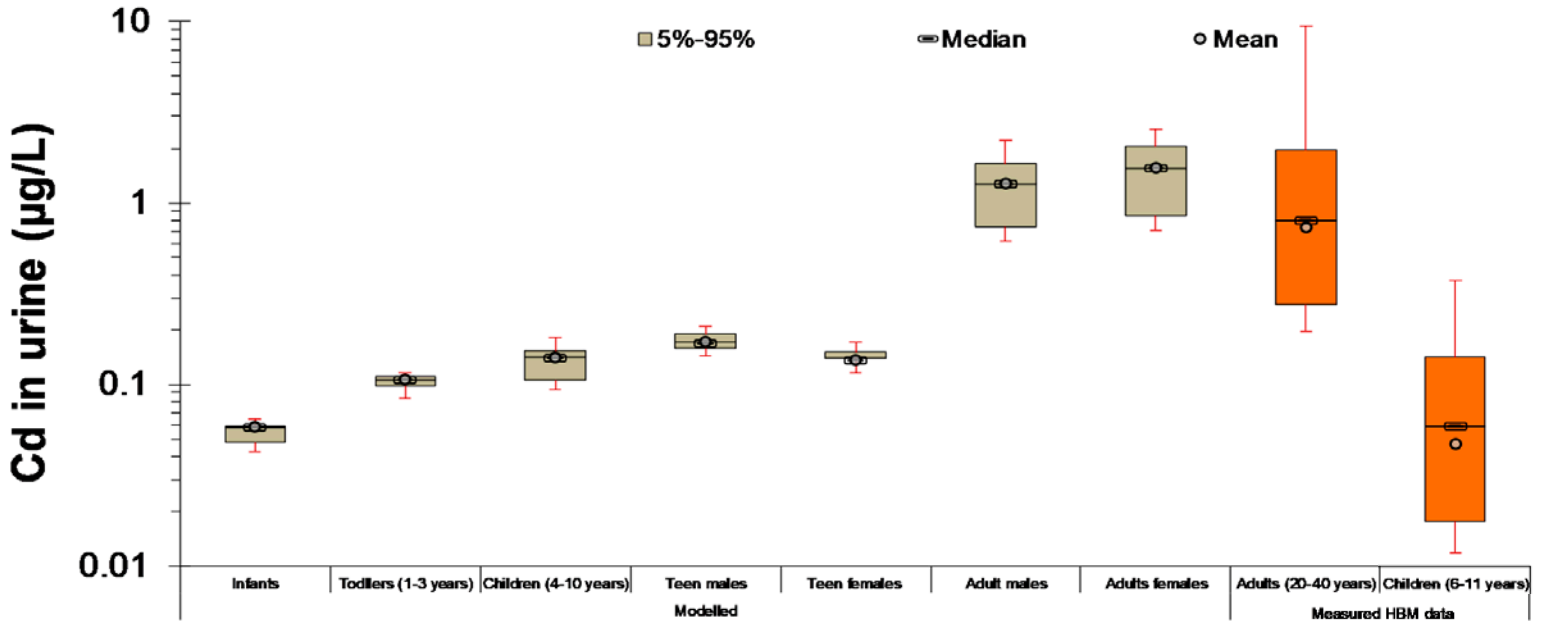


Intake levels of Cadmium based on HBM data



Intake levels (per **µg**/kg_bw/d) of cadmium based on Cd in blood HBM data

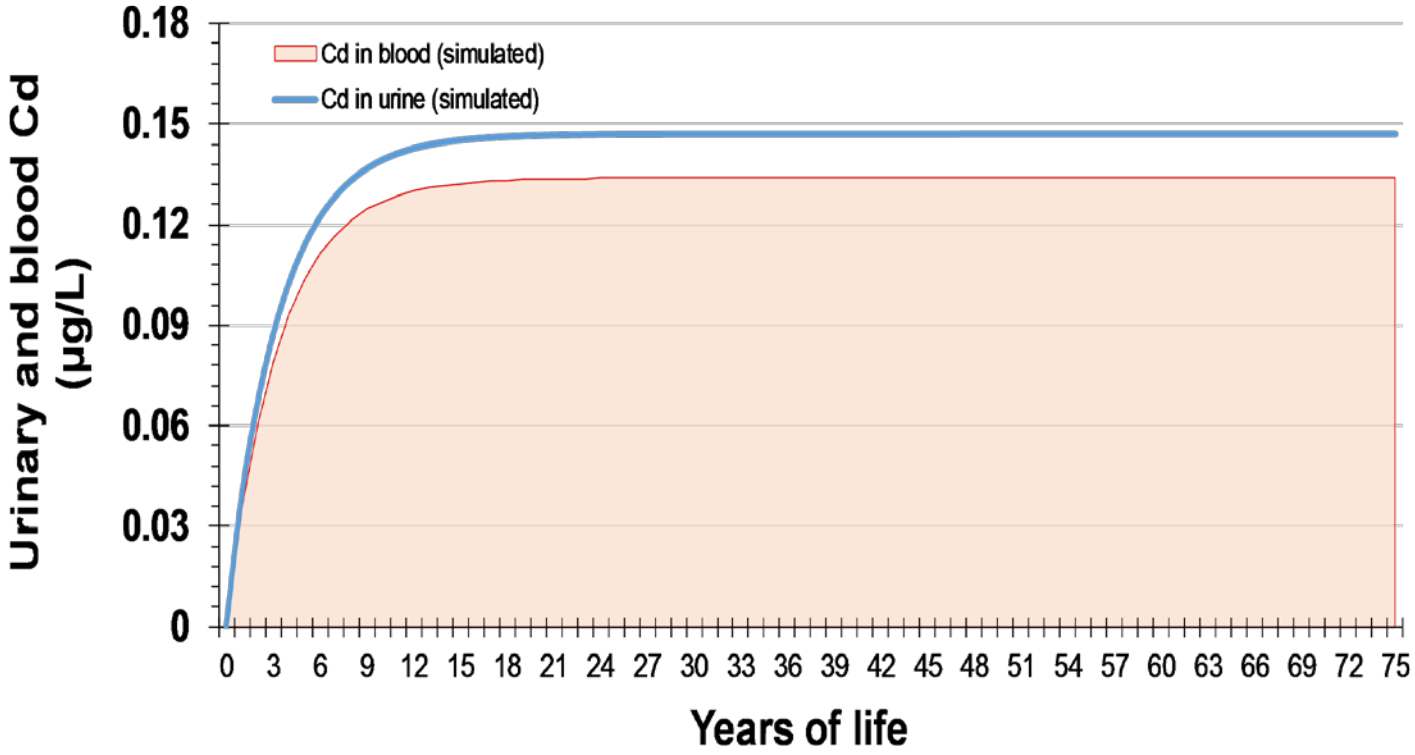
Comparison of Cd urinary concentrations against measured HBM data



Expected and indicative measured Cd levels in urine for all age groups

Remarks

1. Cadmium levels increase during lifetime
2. Steady state in about 20 years – accumulation of cadmium in the body
3. Negligible intra-day variability



Urinary and blood cadmium lifetime course based on a typical dietary exposure

Contents

Discussion

1. Daily intake ranges between 0.2 and 1 µg/kg_bw/d

2. Diet is the main source of exposure for all age groups
- Secondary sources
  - Smoking for adults
  - Soil ingestion for infant and toddlers (1-3 years)
  - Dust ingestion for children (4-10 years) and teens

3. Cadmium accumulates through life span
- Steady-state in about 20 years
- Slow elimination
- Negligible intra-day variability

4. Model evaluation
- Comparable levels of Cd in modelled and measured data

THANK YOU FOR YOUR ATTENTION

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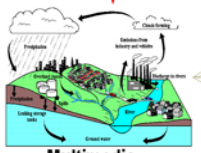
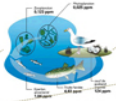
Enhanced multimedia modelling incorporating additional environmental processes and local to local and regional to regional interactions



Multimedia environmental contamination

Occupational Exposure (ART model)

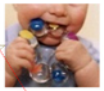


Bioaccumulation

Agriculture

Food contamination

Drinking water contamination



Non-dietary oral exposure

Consumer products

In house building materials, objects and activities

Direct skin application

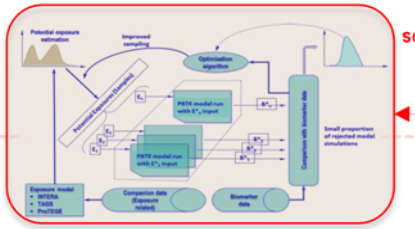
Water contamination

Indoor air

Outdoor air

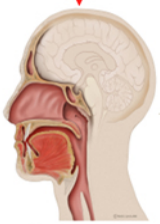
Active smoking

Other microenvironments



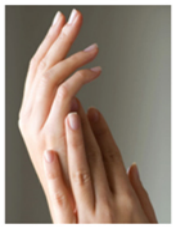
Advanced reverse dosimetry scheme for exposure reconstruction

HBM dtabase



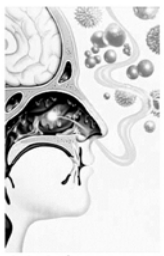
Oral exposure

More detailed GI absorption

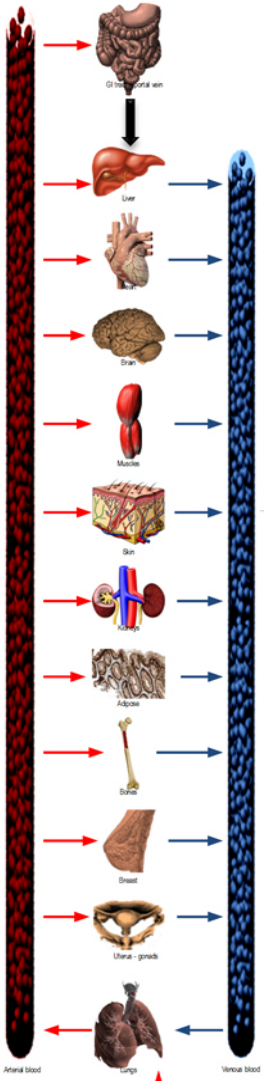


Dermal exposure

More detailed skin absorption model

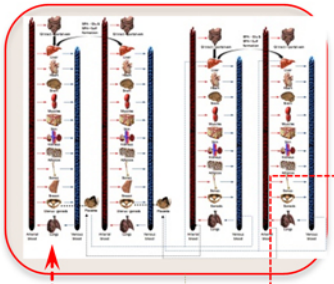


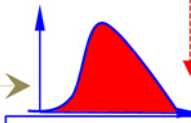
Inhalation exposure



Additional number of metabolites

Life-stage PBTK model including gestation and lactation





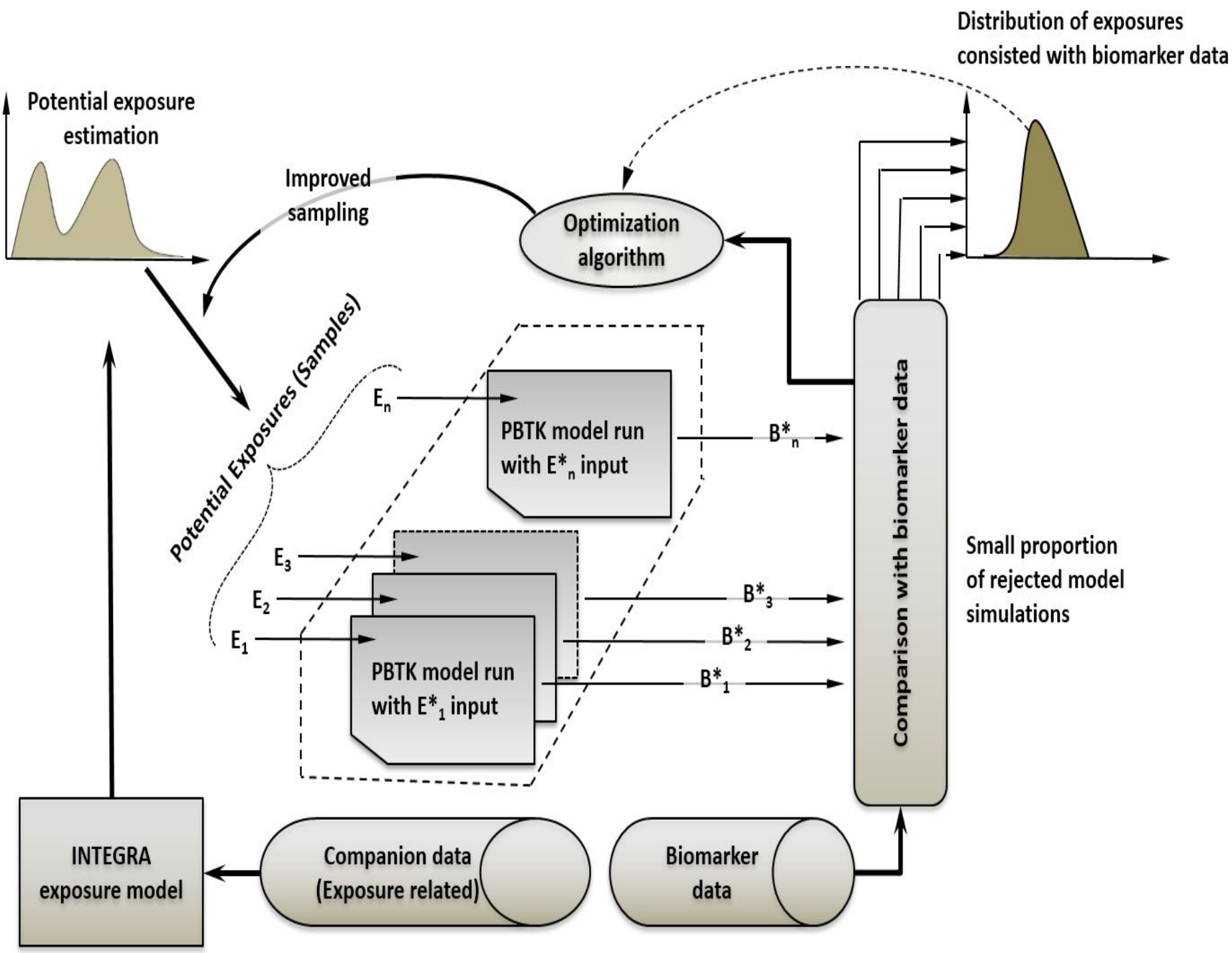
Internal exposure (probabilistic assessment)

Metabolic/systemic compartments

Bio-accumulative compartments

Simpler PK model for data poor chemicals

Additional links to QSARs and ToxCast Phase I


Distribution of exposures consisted with biomarker data
Potential exposure estimation
Improved sampling
Optimization algorithm
Potential Exposures (Samples)
E_n
PBTK model run with E^*_n input
B^*_n
E_3
E_2
E_1
PBTK model run with E^*_1 input
B^*_3
B^*_2
B^*_1
Comparison with biomarker data
Small proportion of rejected model simulations
INTEGRA exposure model
Companion data (Exposure related)
Biomarker data

The program offers a number of generally applicable models ranging from **multimedia environmental model** to indoor air quality model and from exposure models for the **different exposure routes** (inhalation, oral and dermal) to a **generic PBPK model to evaluate internal doses** in target tissues and a **database containing several types of data** ranging from human physiological parameters to emission data from consumer products, from human biomonitoring (HBM) data to physical/chemical properties and from indoor and outdoor concentration levels to building characteristics. Data are stored along with their geographical information in order to allow users to build realistic exposure scenarios to represent typical exposure conditions for specific countries and/or cities in Europe. Together, the database and models provide the tools to assess exposure for a wide range of scenarios, whereby only additional information on exposure determinants.

An exposure assessment in INTEGRA is a tiered process, starting with the basic information on **physical/chemical properties** of chemicals, products and the exposed population. Subsequently, **suitable models are selected per exposure route**, according to the product usage scenario. INTEGRA offers a number of well described exposure and uptake models to estimate inhalation, dermal and oral exposure to compounds. Three different levels of exposure assessment are implemented in the platform, starting from the occupational one (i.e. Tier 0), to the comprehensive environmental one (i.e. Tier 1) to a reverse dosimetry to determine the external exposure consistent with HBM data input data. INETGRA offers a number of well described multimedia and exposure and uptake models to estimate inhalation, dermal and oral exposure to chemicals. Furthermore, the software also accepts stochastic distributions as input to a wide range of exposure parameters assessed via Monte Carlo methods (probabilistic exposure assessment).

The modelling environment comprises several components, as follows:

1. Multimedia environmental modelling module to estimate the concentration of chemicals in different environmental matrixes (i.e. air, water, soil and food) taking into consideration the exchange between the different environmental media.
2. Emissions-concentrations module, linking sources to indoor concentrations, taking into account the physicochemical processes in indoor settings: dispersion, ventilation, gasparticle-dust partitioning, etc.
3. Exposure module including several models for the dermal, inhalation and oral routes, taking into account time-microenvironment-activity patterns and inhalation rates based on activity, gender and body weight.
4. Internal dosimetry module, which computes aggregate exposure by absorption factors for each route, links temporal patterns to internal dose through a generic Physiology Based ToxicoKinetic (PBTK) model. It estimates the internal doses of contaminants and their metabolites at the target tissue.
5. An exposure reconstruction module to assess backward the exposure which is responsible for the human biomarker values measured.
6. Uncertainty and variability of exposure and risk determinants are assessed along the full chain assessment through hierarchical modelling using Markov Chain Monte Carlo.

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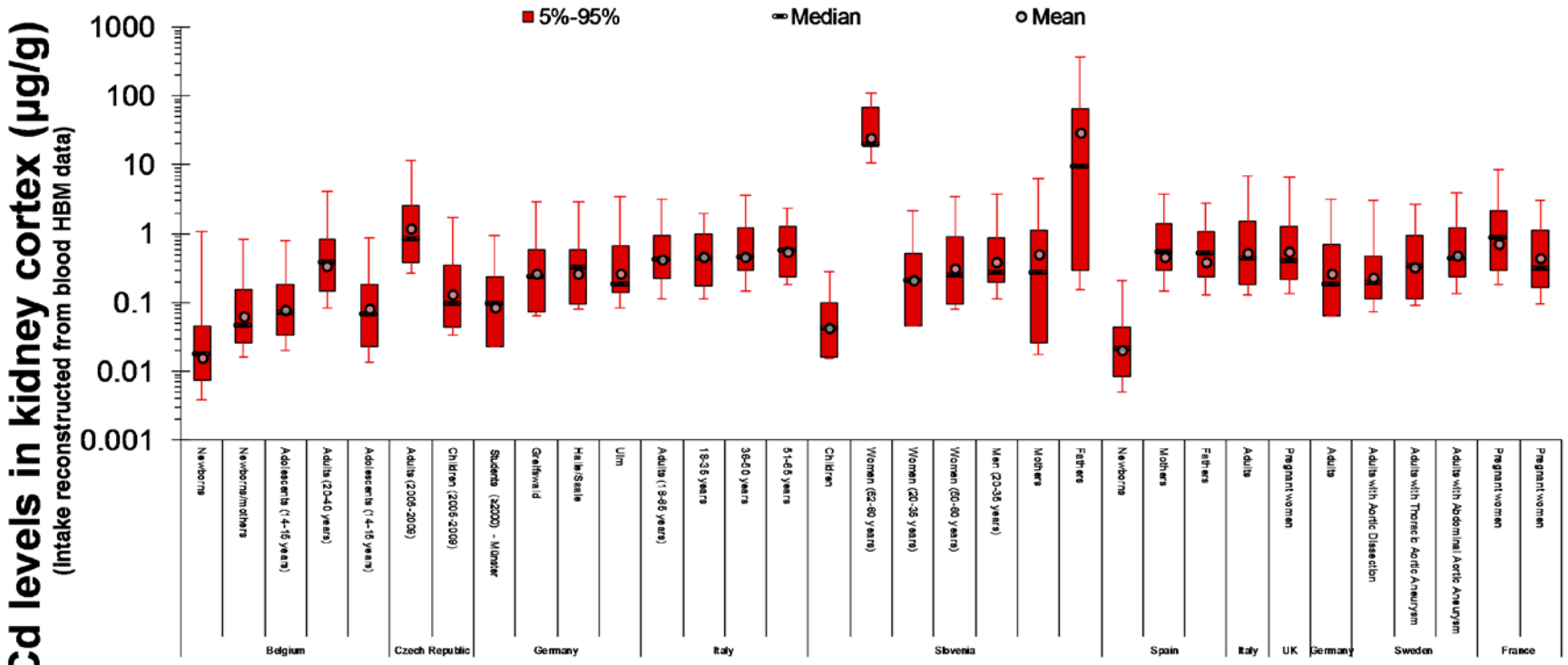
Reconstructed internal dose



Internal dose based on intake estimates calculated from available HBM data of cadmium in blood