HBM4EU

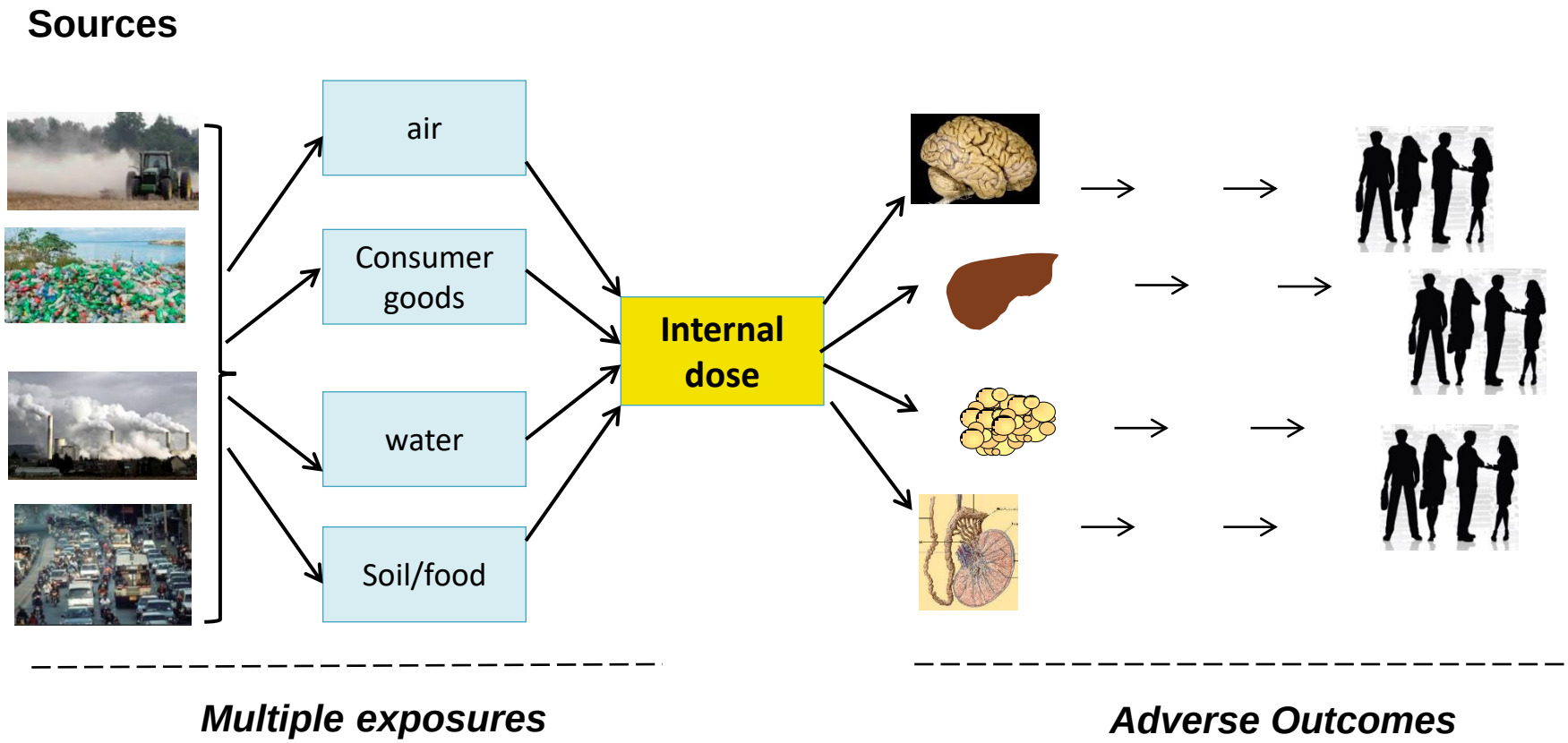
science and policy
for a healthy future

Advisory Board Meeting 2018

Report of Pillar 3 - Exposure & Health

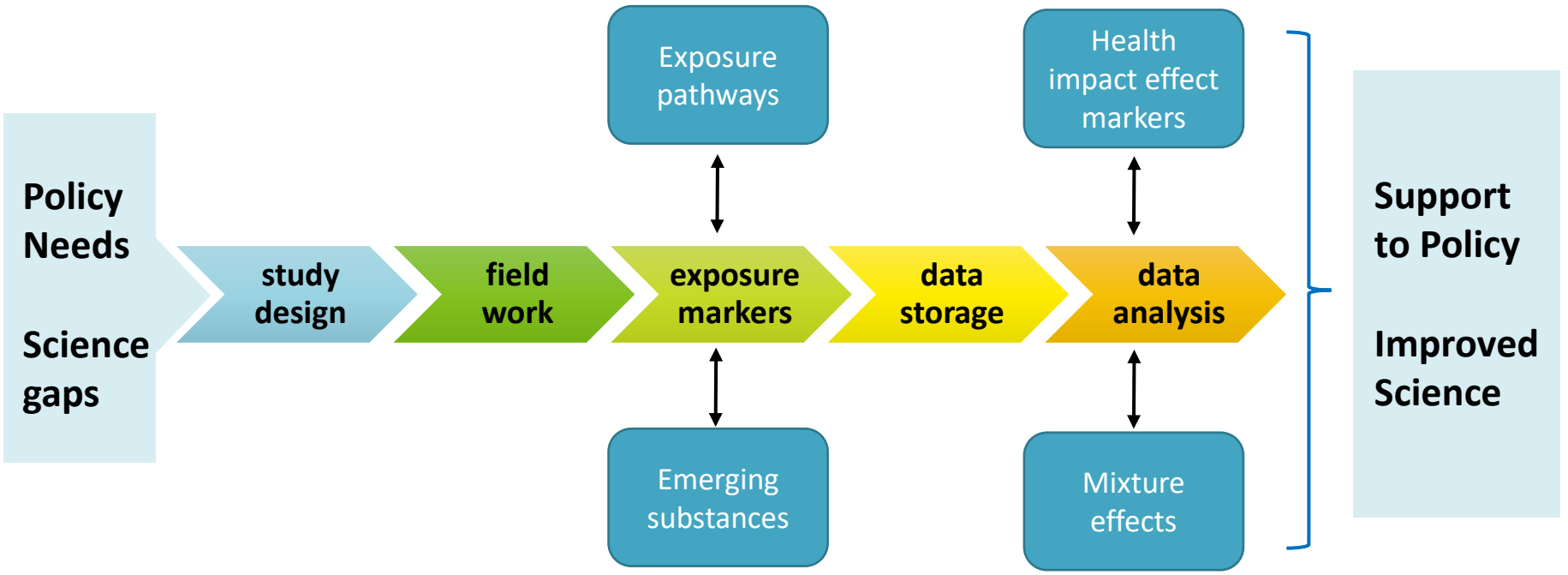
Robert Barouki, INSERM

Internal dose determination is central in Environment and Health sciences and policies

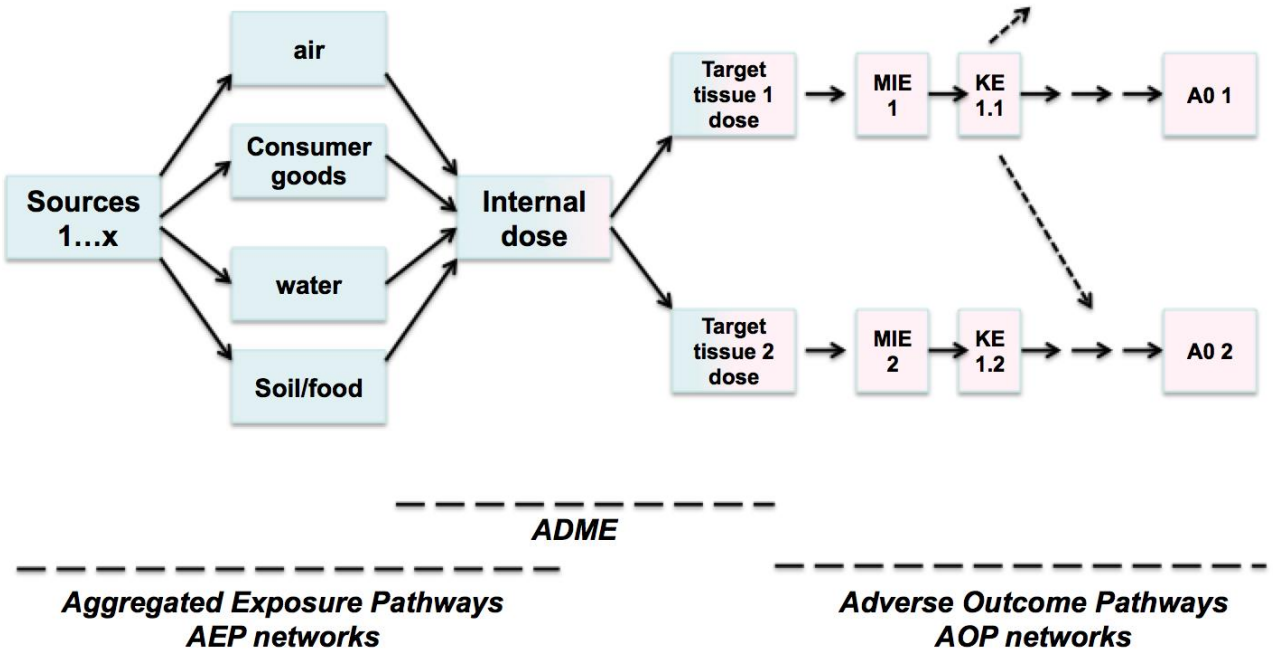


Expected major future developments:
- Analytical capacities
- Computational capacities
- Exposure and health links

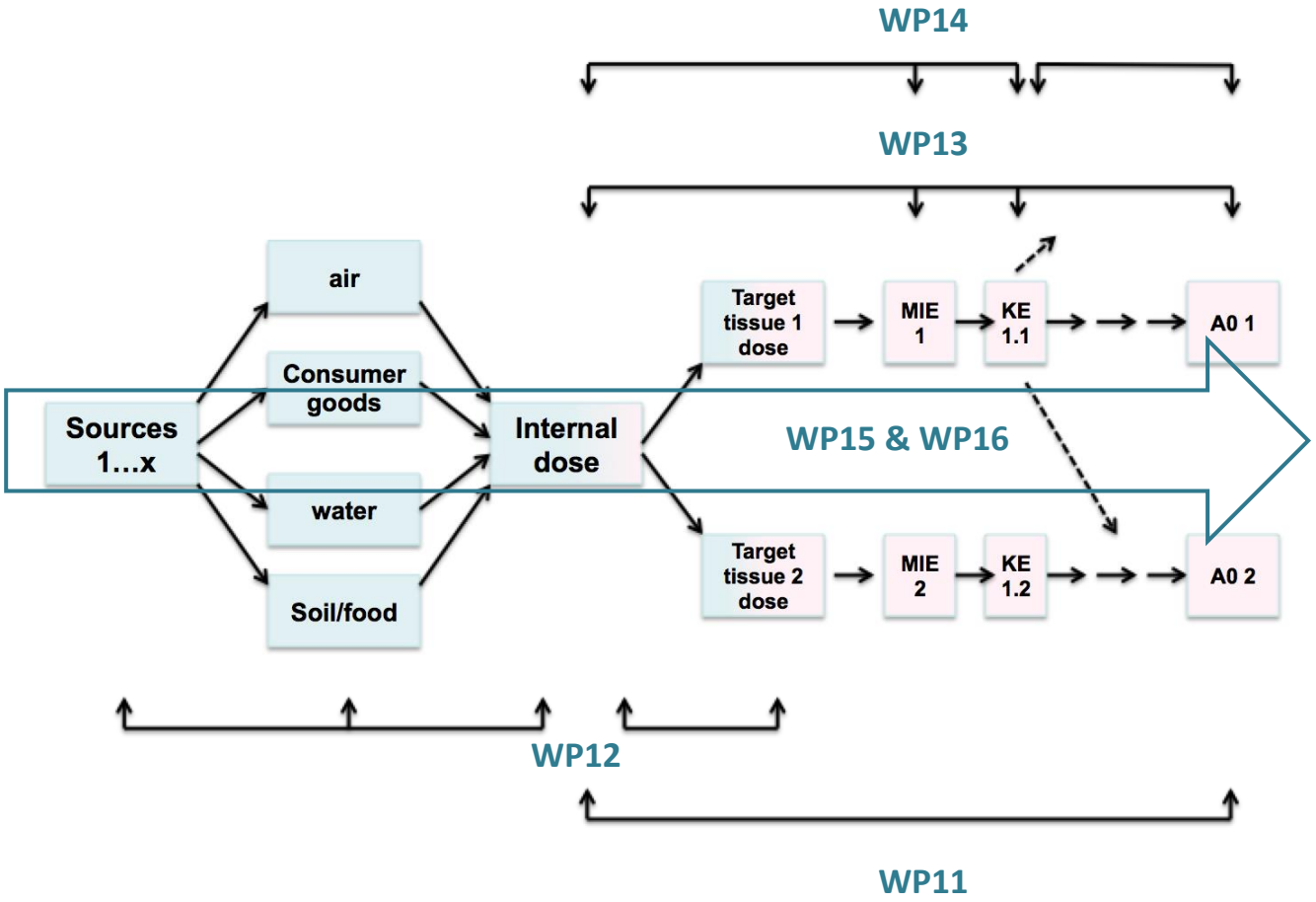
The HBM4EU activities



The triple A vision

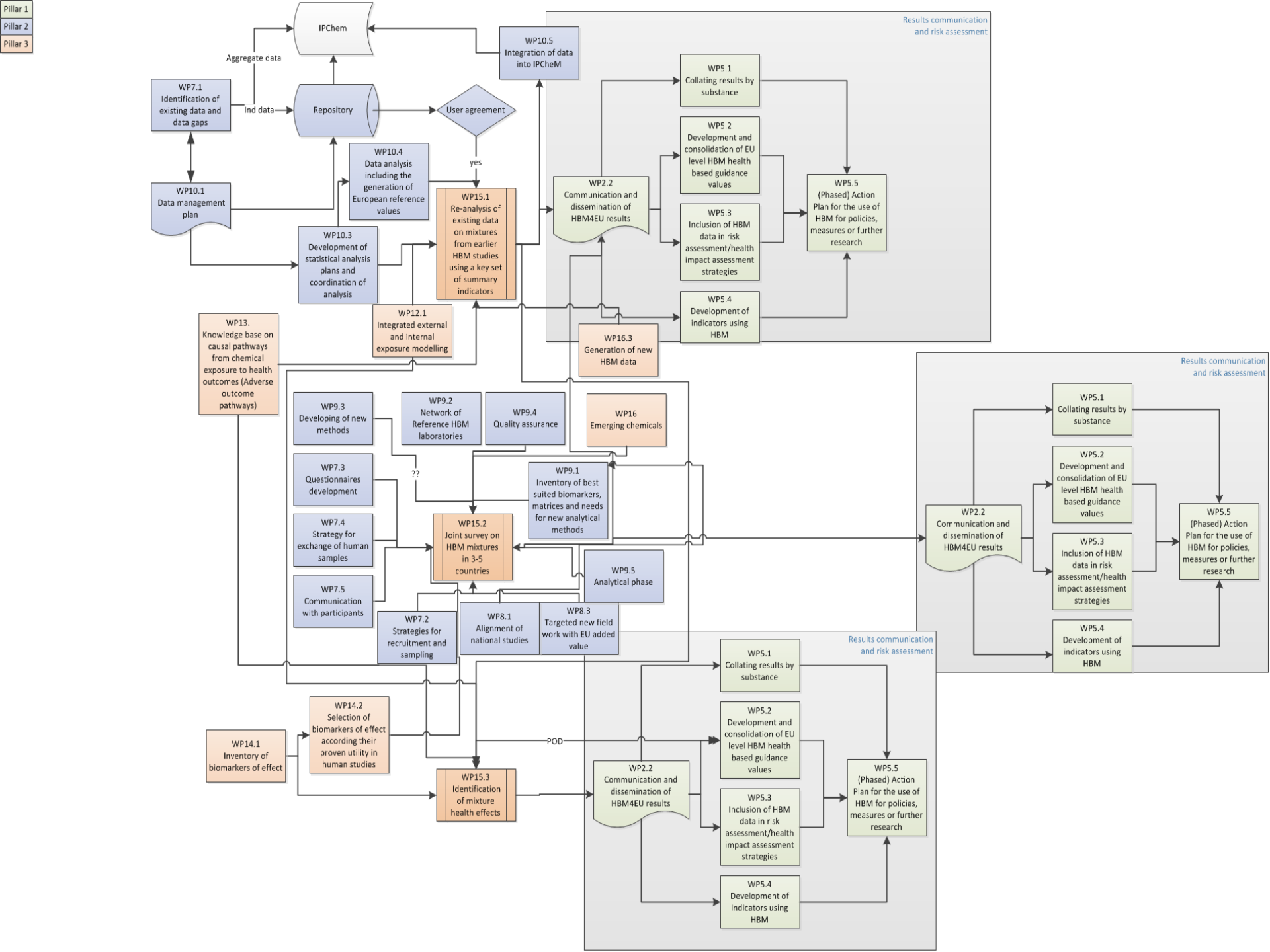


Pillar 3 WPs contribution



Interactions of Pillar 3 WPs with other WPS

WP	4	5	7	8	9	10	11	12	13	14	15	16
11			HBM-HES design	HBM-HES fieldwork	HBM-HES assays	HBM-HES data		HBM-HES Link to exposure	Inventory			
12	Priority & ADME & exposure	Exposure sources routes kinetics	Exposure models & HBM studies				HBM-HES Link to exposure		Exposure models cohorts		ADME interactions in mixtures	ADME of emerging subst
13	Priority & AOP toxicity	AOP HBM-GV goup subst Causality	Study cohort inventory				Inventory	Exposure models cohorts		Effect markers from AOP Test in cohorts	AOP applied to mixtures& cohorts	AOP of emerging subst
14		proxy for active exposure		Effect markers in HBM studies					Effect markers from AOP Test in cohorts		Effect markers of mixtures	Emerging derived from effect markers
15	Priority & mixture effect	HBM-GV of mixtures	Joint mixture study design	Joint mixture study fieldwork	Joint mixture study assays	Joint mixture study analysis		ADME interactions in mixtures	AOP applied to mixtures & cohortes	Effect markers of mixtures		Emerging mixtures
16	emerging subst and new priorities	HBM-GV of emerging susbt			New assays	Data analysis emerging		ADME of emerging subst	AOP of emerging subst	Emerging derived from effect markers	Emerging mixtures	


Pillar 1
Pillar 2
Pillar 3
IPChem
Aggregate data
Ind data
Repository
User agreement
yes
WP10.5 Integration of data into IPCheM
WP7.1 Identification of existing data and data gaps
WP10.1 Data management plan
WP10.4 Data analysis including the generation of European reference values
WP10.3 Development of statistical analysis plans and coordination of analysis
WP15.1 Re-analysis of existing data on mixtures from earlier HBM studies using a key set of summary indicators
WP12.1 Integrated external and internal exposure modelling
WP13. Knowledge base on causal pathways from chemical exposure to health outcomes (Adverse outcome pathways)
Results communication and risk assessment
WP2.2 Communication and dissemination of HBM4EU results
WP5.1 Collating results by substance
WP5.2 Development and consolidation of EU level HBM health based guidance values
WP5.3 Inclusion of HBM data in risk assessment/health impact assessment strategies
WP5.4 Development of indicators using HBM
WP5.5 (Phased) Action Plan for the use of HBM for policies, measures or further research
WP16.3 Generation of new HBM data
WP9.3 Developing of new methods
WP9.2 Network of Reference HBM laboratories
WP9.4 Quality assurance
WP16 Emerging chemicals
??
WP7.3 Questionnaires development
WP9.1 Inventory of best suited biomarkers, matrices and needs for new analytical methods
WP7.4 Strategy for exchange of human samples
WP15.2 Joint survey on HBM mixtures in 3-5 countries
WP9.5 Analytical phase
WP7.5 Communication with participants
WP7.2 Strategies for recruitment and sampling
WP8.1 Alignment of national studies
WP8.3 Targeted new field work with EU added value
WP14.1 Inventory of biomarkers of effect
WP14.2 Selection of biomarkers of effect according their proven utility in human studies
POD
WP15.3 Identification of mixture health effects

Main policy & Science issues - Connection to Pillar 3 WPs (1)

Exposure sources and pathways	• WP12 (exposure models)
Combining HBM and health surveys	• WP11 (procedures for HBM and Health surveys) • WP14 (effect markers to be added to surveys)
Evidence for causality (supporting evidence-based risk assessment)	• WP12 (kinetics, metabolism dynamics), • WP13 (AOP, cohorts) • WP14 (effect markers)

Main policy & Science issues - Connection to Pillar 3 WPs (2)

How to assess mixtures?	• WP15 (mixture studies) • WP13 (AOP) • WP12 (kinetics) • WP14 (effect markers)
Vulnerable groups	• WP13 (cohorts, key events in AOP) • WP12 (metabolism) • WP14 (effect markers & key events),WP15 (mixture hotspots) • WP16 (workplace)
Emerging substances	• WP16 (targeted and untargeted approaches)

Pillar 3 – Activities underway

Pillar 3: Exposure and Health

- WP11: Linking HBM to health surveys and registers
- WP12: From HBM to exposure
- WP13: Establishing Exposure Health relationships
- WP14: Effect Biomarkers
- WP15: Mixtures, HBM and human health risk
- WP16: Emerging Chemicals

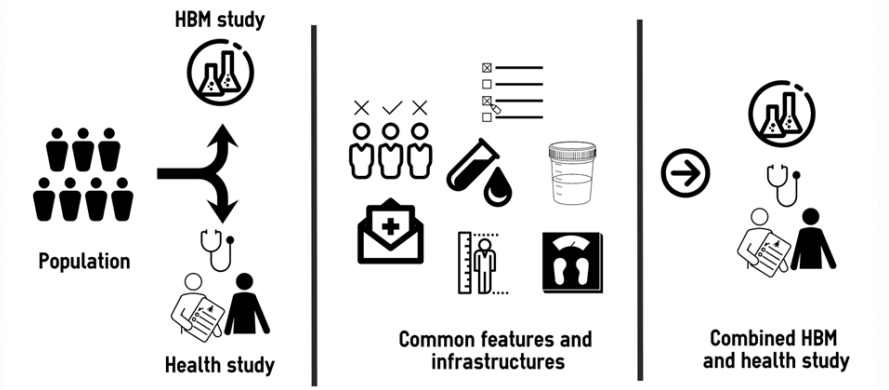
WP11 – Linking HBM, Health studies and Registers

Selection of feasibility studies through the first Internal Call (2018):

- UK National Hub Proposal: Integrating a human biomonitoring (HBM) module into the Health Survey for England (HSE)
- Integration of an HBM module in the follow-up of the population based LIFE-Adult Cohort: A feasibility study (Germany)

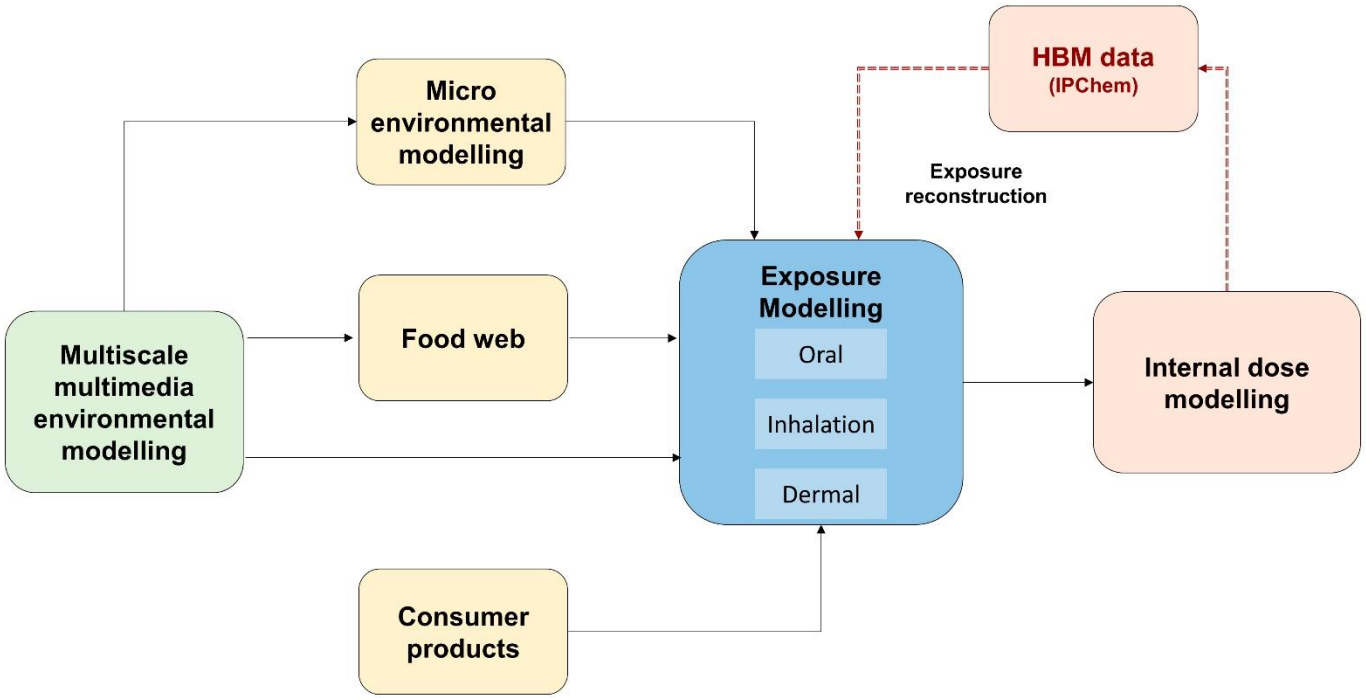
- Feasibility study on linking HBM and health studies in Finland under Task 11.4.

Learn more about **opportunities** & **obstacles** in different settings



WP12 – From HBM to Exposure

Design of the integrated HBM4EU computational platform including different modules:



WP12 – From HBM to Exposure

Progress on Bisphenols (BPA and substitutes)

So far:

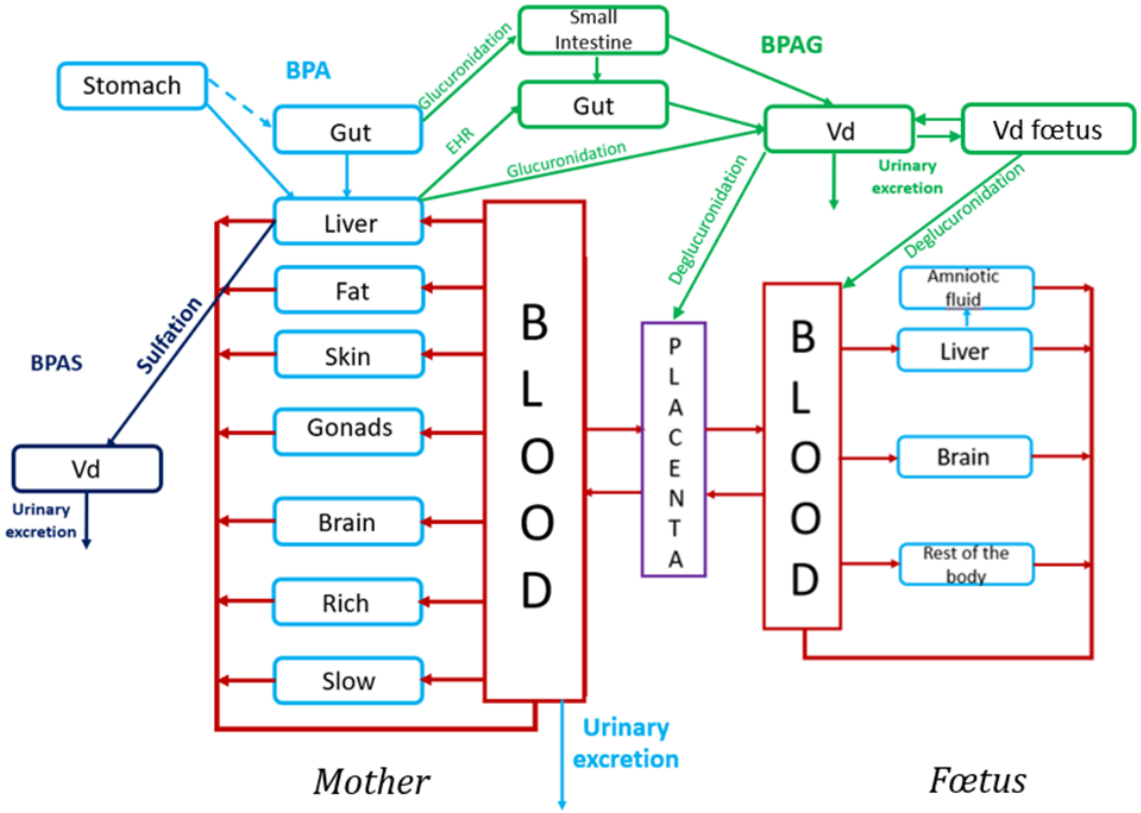
- **Review of the existing PBPK models for bisphenols** (delivered in M12)
- **Data collection on metabolism and half-live of all bis**phenols (submitted in July 2018)
- **Identification of HBM studies** to analyze (The data of the HBM4EU project are not available yet. It was decided to first work with national/local studies). (June 2018)
- **First case study on BPA in pregnant women of the French ELFE cohort** (September 2018) → estimation of the external exposure and dosimetry in the foetus

Future work:

- Parameterize the generic PBPK model for BPA substitutes
- Finalize the ELFE case study: improvement of the exposure scenarios
- Analyze the project data (dose reconstruction and internal dosimetry)
- Dissemination (2 papers are already planned)

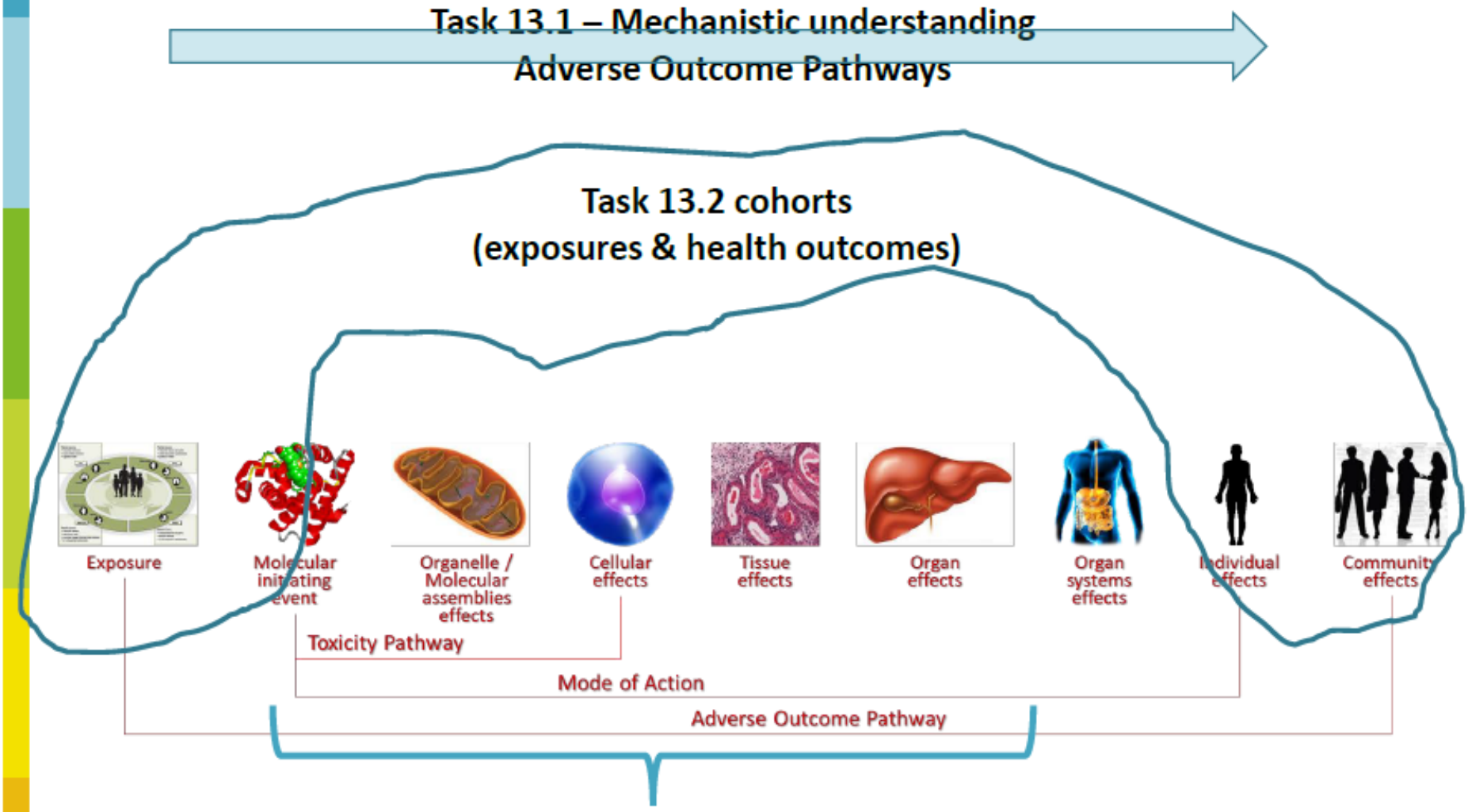
WP12 – From HBM to Exposure

Case Study - ELFE cohort : BPA exposure in pregnant women and foetus

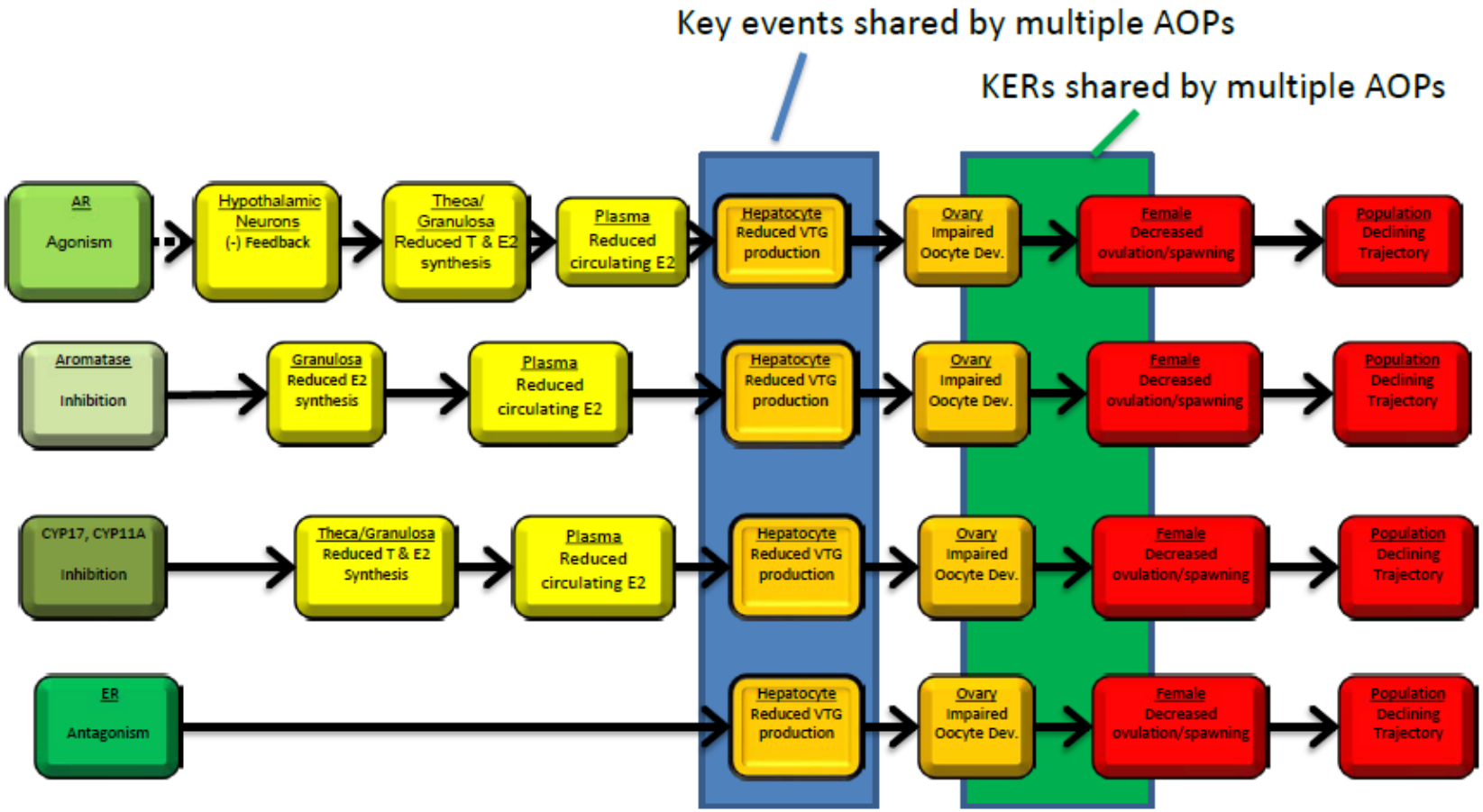


The PBPK model for BPA in mother and foetus

WP13 – Establishing Exposure Health Relationships



4. For most real-world applications, AOP networks are the functional unit of prediction



WP14 – Effect Biomarkers

Identification and inventory of key effect biomarkers through literature search for the 1st round priority substances

Classical (and studied) effect biomarkers

Reproductive Hormones: LH, FSH, TT, E2, SHBG

Thyroid Hormones: TSH, T3, T4

Glucose metabolism: (FBG + Insulin = HOMA-IR) + HbA1c

Serum lipids: Total cholesterol, LDL, HDL, TG

Blood pressure

Anthropometric measurements: Height/Weight; Waist-to-hip ratio; Percentage of Body fat; Skinfold-thickness; Birth weight; Head circumference; Birth lenght; Anogenital distance (AGD)

Neuropsychological tests

Classical (less studied) effect biomarkers

HPAdrenal-Axis: CRH – ACTH - Cortisol + Adrenal Androgens (DEAH-S)

Adipokines: Leptin and Adiponectin

Inflammatory markers: hsCRP, IL-6…

Liver enzymes: AST, ALT, ALP, GGT, Bilirrubin

Renal function: Urinary albumin

Urinary 8-OHdG + 8-isoprostane

Others: IgE, vitamin D (25-OH-D)…

Novel Effect biomarkers

BDNF

Kisspeptin

Gene expression of nuclear receptors: ERα, ERβ, AR, ESRRA, ESRRB, PPAR-γ, AhR

OMICS/Epigenetic markers, such as DNA methylation and micro-RNAs, among others

WP 14: Biomarkers of effect (BPs group)

1. **Identification and prioritization of existing biomarkers of effect of bisphenol A and its analogues for HBM**
   - ✓Comprehensive literature search (> 11,500 articles) for relevant health endpoints
   - ✓Classification of biomarkers according to their novelty
   - ✓Prioritization of promising biomarkers for HBM
   - ✓Identification of gaps in knowledge

2. **Implementation of relevant biomarkers for HBM studies (in progress & next steps)**
   - ✓Method development to analyse selected biomarkers in blood/urine (2019)
   - ✓Design a study to implement these biomarkers in an European cohort

WP15 – Mixtures

Proposal of a plan for development of 5 case studies:

1. Developmental neurotoxicity beyond polybrominated diphenylethers (PBDEs)
2. Heavy metals and nephrotoxicity
3. Anti-androgenic chemicals and male reproductive health
4. Chromium (VI), nickel and polycyclic aromatic hydrocarbons and lung cancer
5. Addressing exposure misclassification in mixture studies

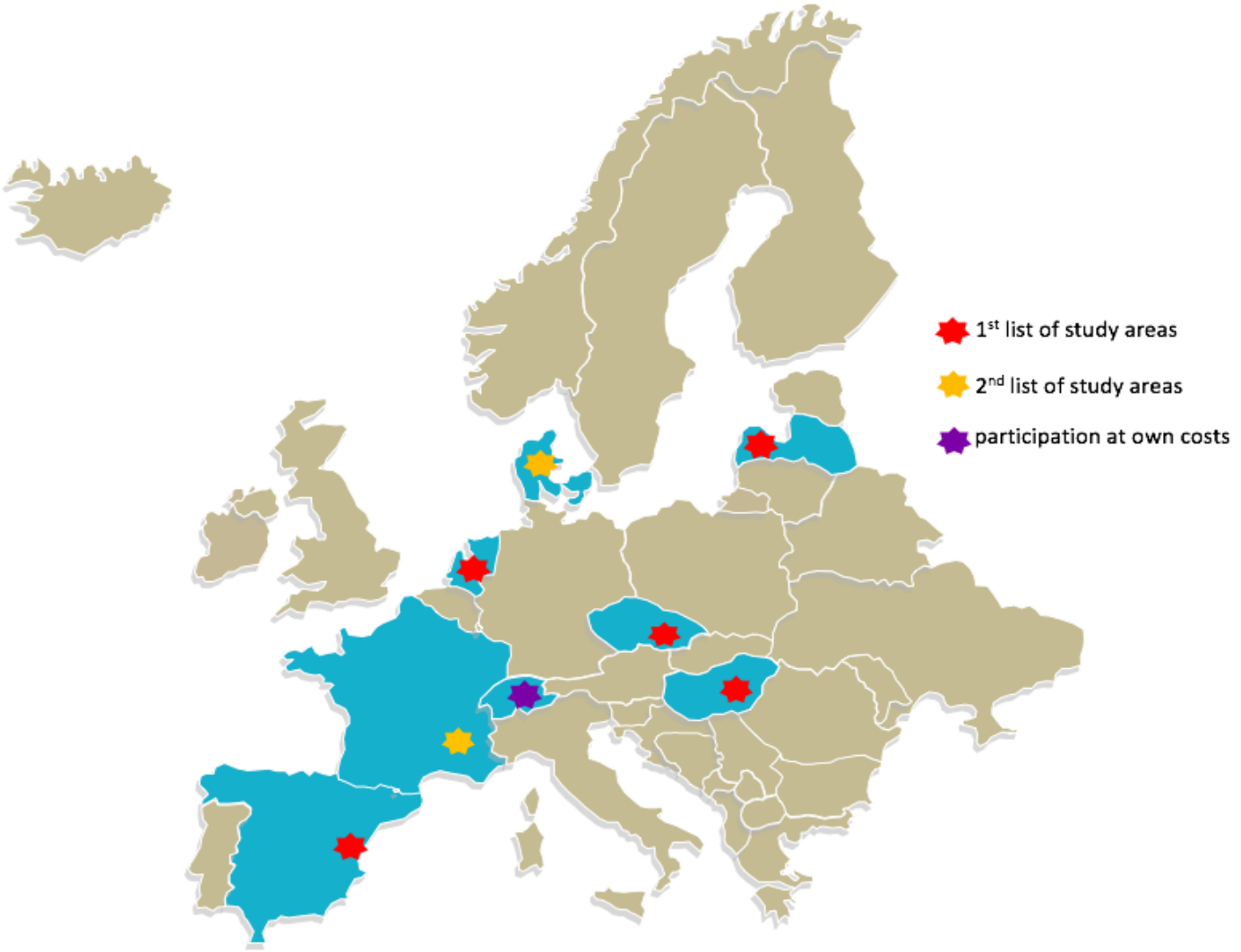
→ Case studies will deal with the question:

- What are the health risks of mixtures from combined chemical exposures and do predicted risks of such mixtures exceed the levels regarded as acceptable for humans?
  Through Hazard Index and Point of Departure Index approaches

WP15 – Mixtures

P

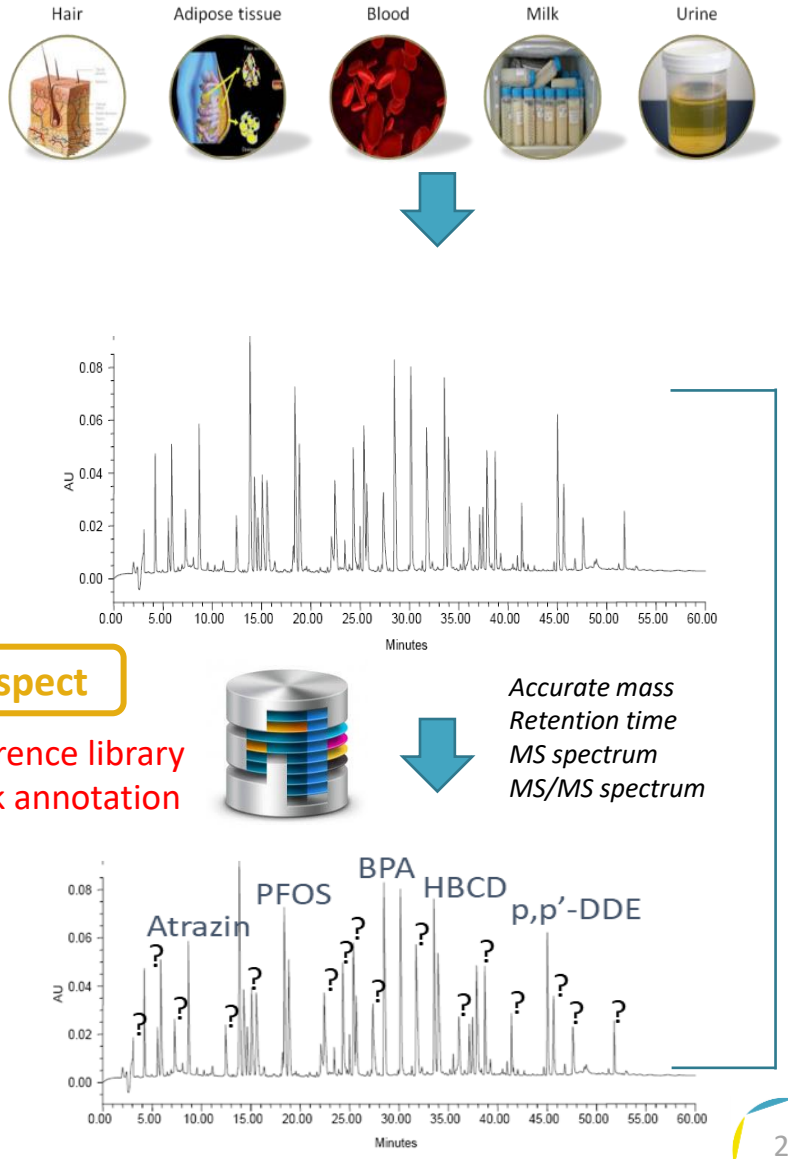
–



WP16 – Emerging substances

Development of harmonized methods in several laboratories for the detection of known emerging chemicals (suspect screening)

- Crossed sample preparation procedures
- Harmonized MS/MS data acquisition guidelines
- Consolidated QA/QC dispositions



Inserm

La science pour la santé
From science to health

Pillar 3 partners

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