science and policy
for a healthy future

Building European knowledge on citizens' exposure to chemicals

—

HBM4EU

Greet Schoeters

VITO

Keeping an eye on chemicals

European Commission (2001): **Global production** of chemicals **increased 50 times from 1950 to 400 M t in 2001 and is expected to triple by 2050**.

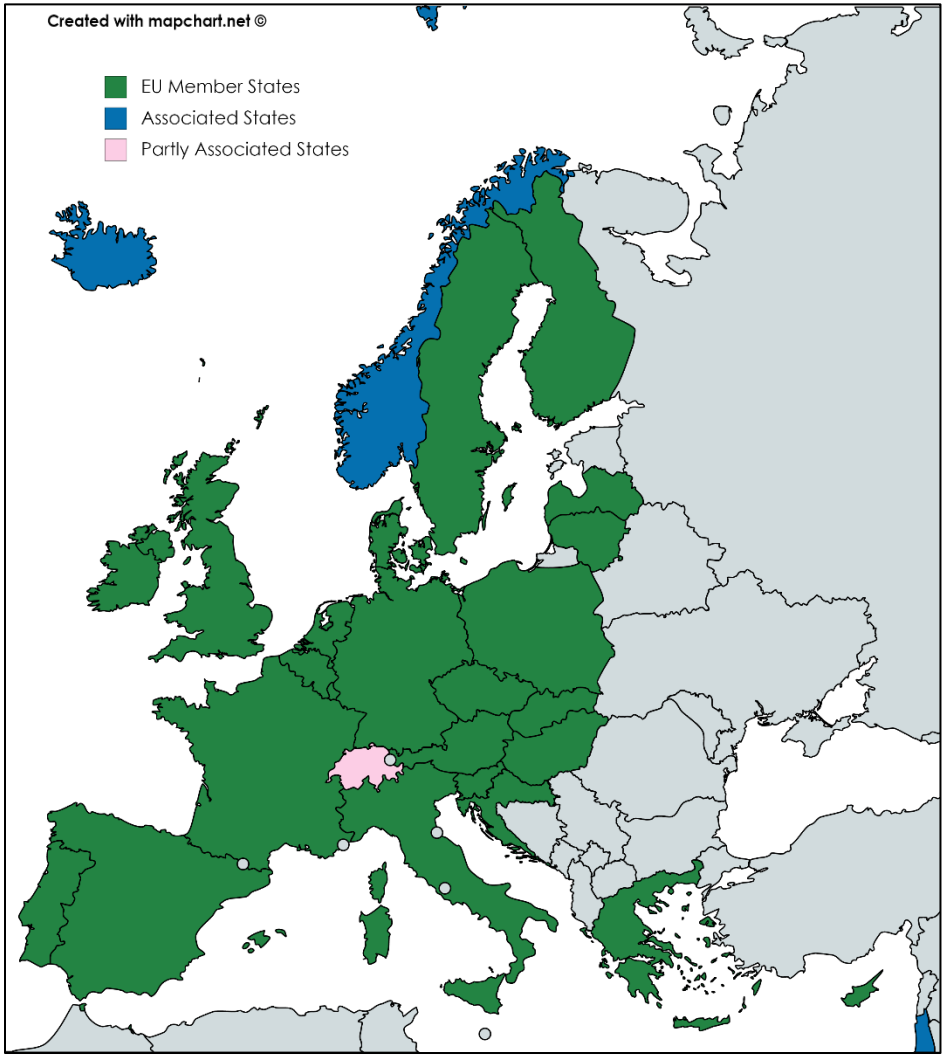
June 2015: Chemical Abstracts Service (CAS) assigned **100 Millionth CAS Registry Number®**.

Chemical industry is **Europe's 3rd largest** manufacturing industry.

Eurostat: about **30 M t of carcinogenic, mutagenic and reprotoxic** chemicals produced in 2009.

Source: CC Vision

Human Biomonitoring for Europe (HBM4EU)



Timeframe and budget:

- 5 years (2017-2021)
- European Joint Programme under Horizon 2020
- Total budget: € 74 million

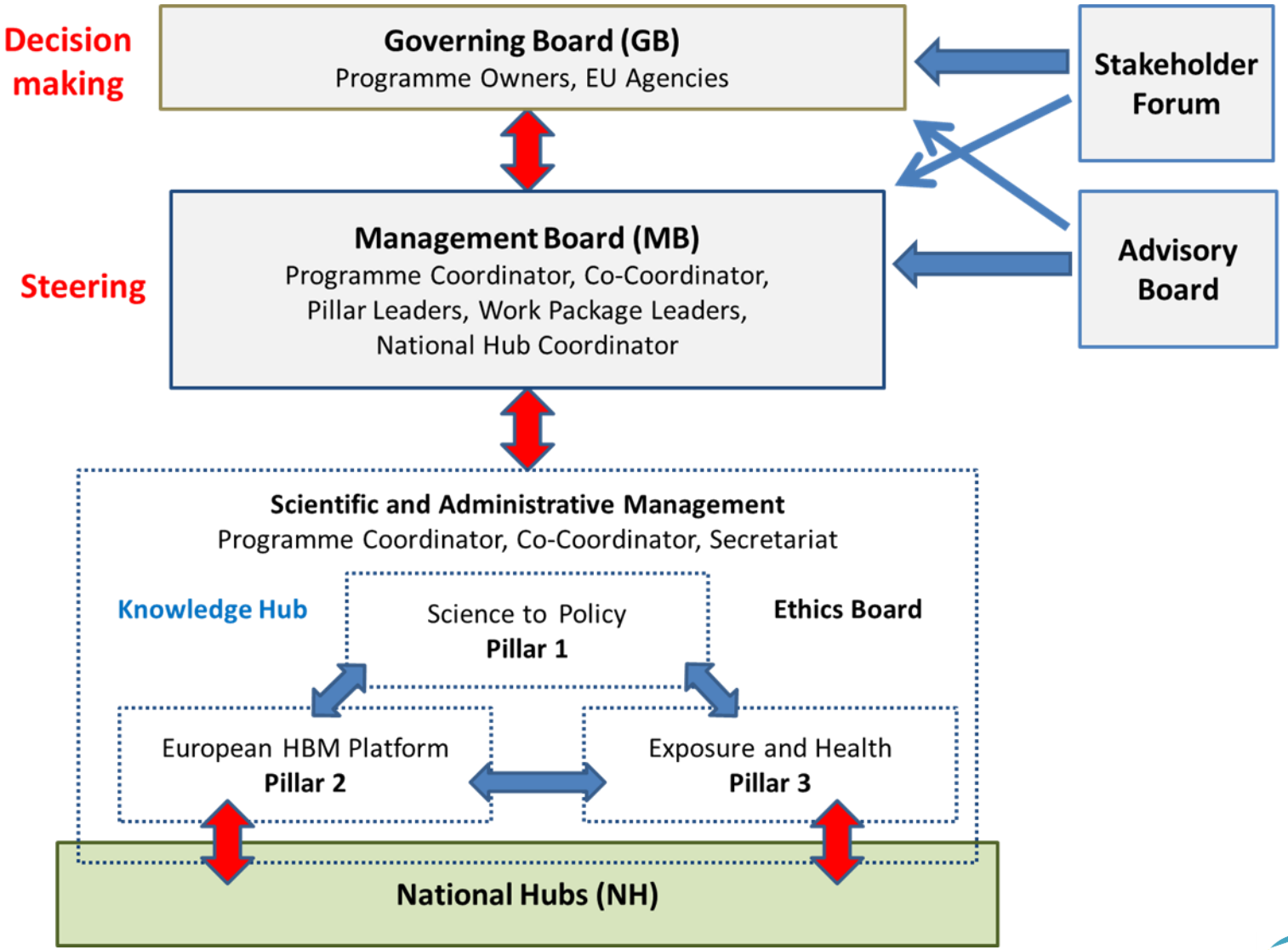
28 countries and the European Environment Agency:

- 24 EU Member States
- 3 associated countries
- Switzerland

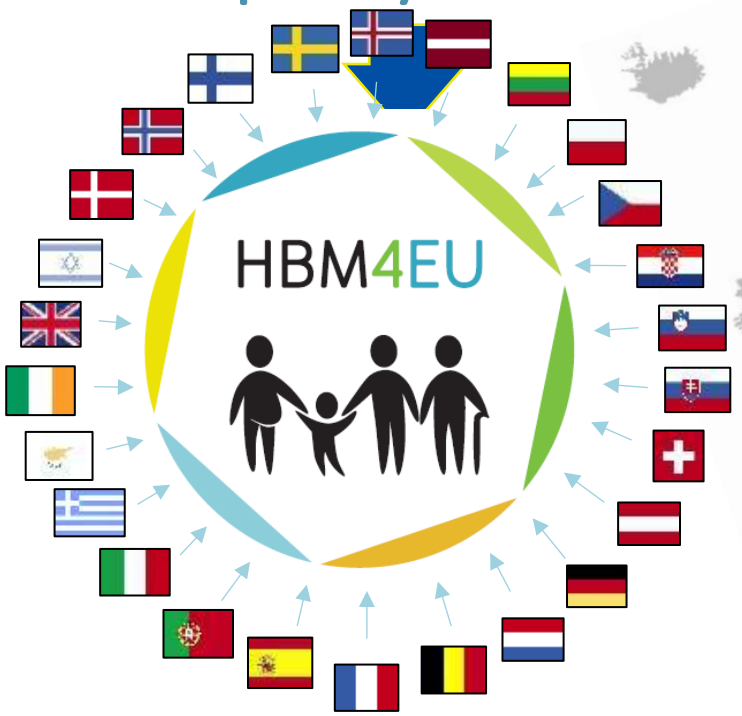
Coordinated by the German Environment Agency (UBA)

Umwelt Bundesamt

Governing Structure of HBM4EU



Science policy interface



science and policy
for a healthy future

Answer open policy relevant questions as defined by EU Services and partner countries

Give policy makers a fast and easy access to results and data

Bridge the gap between science and policy

Science policy interface

Science policy

EU level

ENV
chemicals legislation (e.g. REACH), air/water pollution, noise

EMPL
worker safety, exposure to chemicals

RTD R&I
framework programme

SANTE
food contaminant, pesticides, biocides, EDs

GROW
product safety, cosmetics, REACH

JRC
scientific and technical support

ECHA
REACH regulation

EEA
environment data, information, assessment

EFSA
risk assessment for food and feed

National hubs

Ministries/

Policy Leads in Environment and Human Health

Stakeholders:

Citizens

National NGOS, Industry representatives

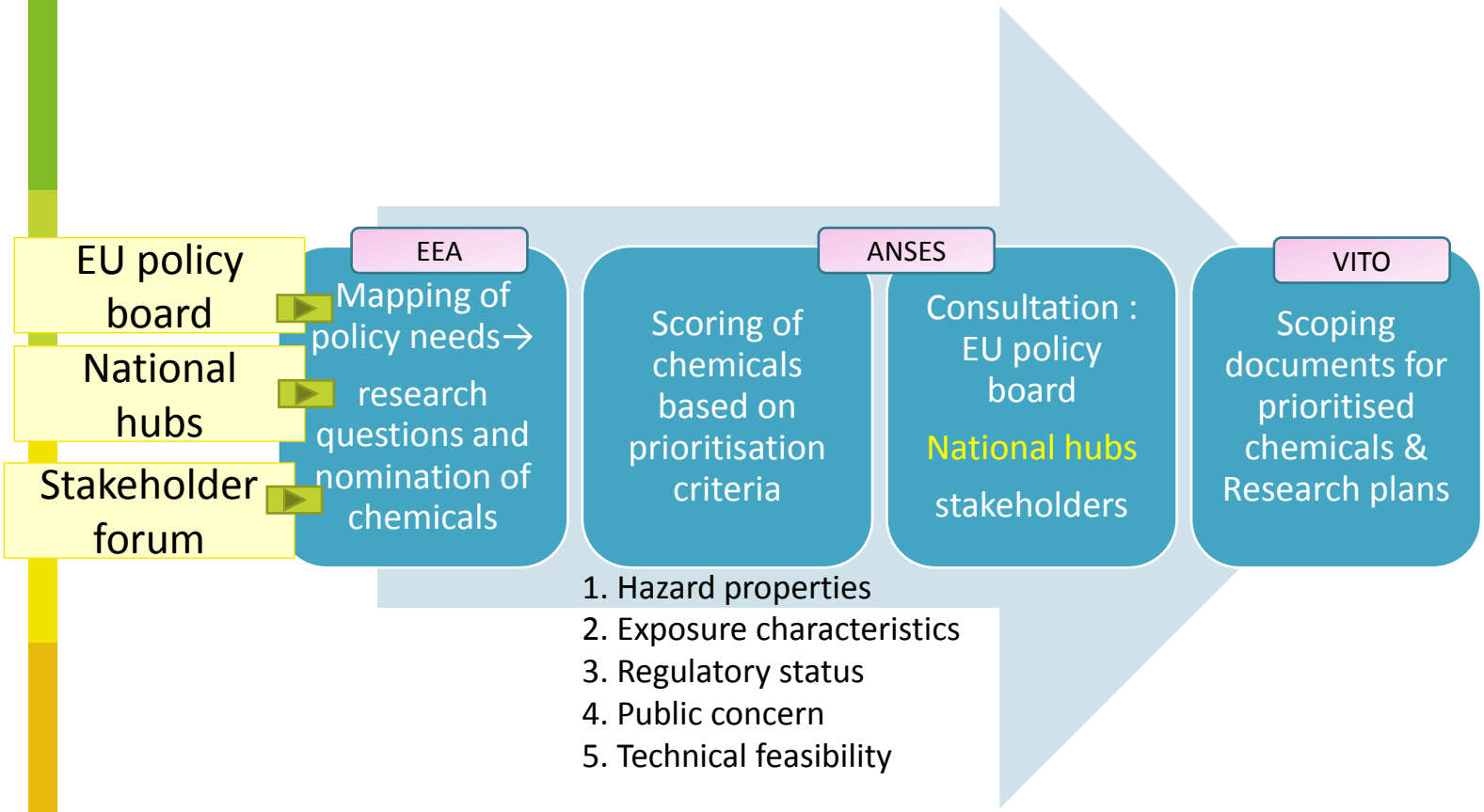
Research institutes:

National Expertise

HBM4EU Partner

From policy to science: prioritising chemicals

Transparancy and participation



Priority substances first round

Chemical family/Substances	Goals
Phthalates & Hexamoll®DINCH®	time trends, focus on substitutes
Poly/per-fluorinated compounds	baselines, time trends, support regulation, biomarkers of exposure and effect
Brominated & organophosphate flame retardants	baselines, time trends, support regulation, research on health impact
Bisphenol A, S and F	overall human exposure and exposure sources, possible further regulation
Cadmium and Chromium(VI)	overall human exposure and exposure sources, Cr(VI): possible geogr. variation
8 carcinogenic PAHs in REACH, 16 USEPA priority PAHs	overall human exposure, impact of PAHs on public health
Aniline derivatives	exposure of workers
Mixtures	identification of chemical mixtures, assessment of effects
Emerging substances	screening for new substances, non-targeted analysis

Policy questions

- What is the current exposure of the EU population?
- Are exposures different between countries? Why?
- Can we detect a significant decrease in levels after REACH?
- Are exposure levels above any health relevant health assessment values?
- Should the substance be subject to (further) regulation ?

Science policy

From science to policy

Translation of science into policy advice

1. Health Based Guidance Values for exposure biomarkers:

2. Improve risk assessment strategies

3. HBM based indicators to follow spatial and time trends

4. Participative and deliberative process to translate results in policy options

European HBM Platform: comparable HBM data

HBM platform

Survey design

- Map existing HBM data and identify gaps
- Protocols for field work, questionnaires, informed consents,
- biobanking and sample exchange

Ulrike Fiddicke

Umwelt Bundesamt

Targeted fieldwork surveys

- Aligning current studies
- New targeted surveys
- Analysis of biobanked samples

Ovnair Sepai

Public Health England

Protecting and improving the nation's health

Lab analysis and quality assurance

- Networks of laboratories
- Quality assurance and quality control
- Develop new analytical methods
- Harmonised analysis of biomarkers

A. Castaño&M.Esteban

cnsa Centro Nacional de Sanidad Ambiental

isc Instituto de Salud Carlos III

Data management and analysis

- Data management and statistical analysis
- Derive EU-wide reference exposure values
- Make HBM data available via IPCHEM

G. Schoeters & E. Govarts

vito

Aligning existing and planned studies collect data that will provide EU wide coverage

HBM platform

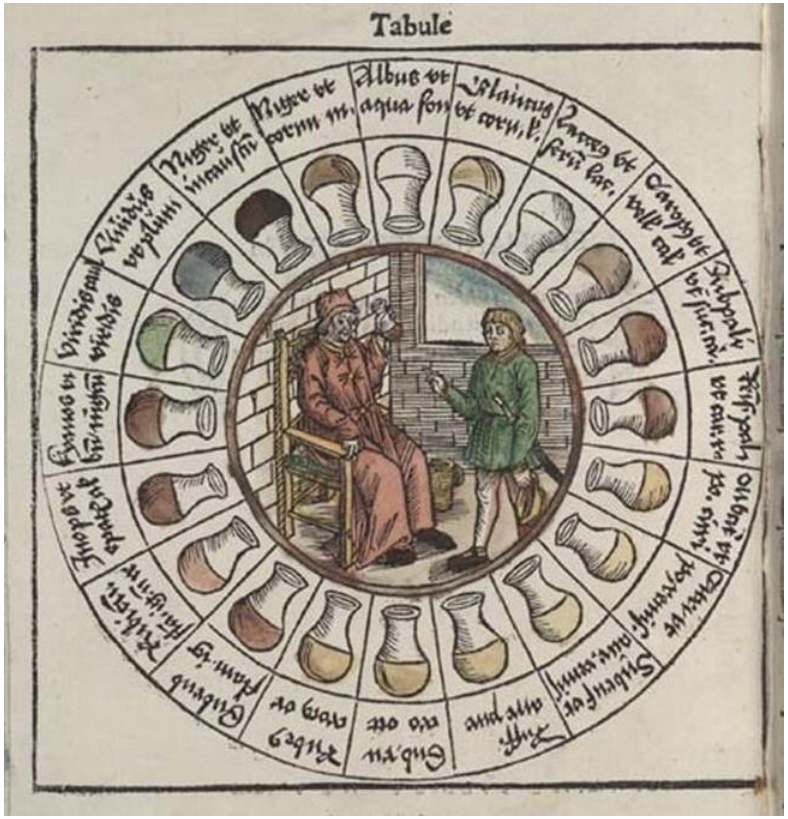
Geographical region of Europe % of European population	North 21%	West 40%	South 28%	East 11%	Substances
	Denmark Finland Iceland Ireland Latvia Lithuania Norway Sweden UK	Austria Belgium France Germany Luxembourg (The Netherlands) Switzerland	Croatia Cyprus Greece Italy (Portugal) Slovenia Spain	Czech Republic Poland Slovakia Hungary	
Representative samples					
2600 Children (6-11y)	NO,DK	FR, DE,NL	IT,SL/EL	HU,SK,PL	phthalates + DINCH flame retardants
2600 Adolescents (12-19y)	SE,NO	FR,DE,BE	ES,SL/EL	CZ,PL	Phthalates + DINCH per-fluorinated compounds
2300 Adults (20- 39y)	DK,IS,FI	FR*,CH,BE	HR,	CZ,PL	bisphenols occupational: Cd, PAH

Input from NH

Quality and comparability of the analytical results

HBM platform

- **Inventory of laboratories in Europe with experience in HBM analysis**
- **Laboratories for organising the QAQC**
- **Laboratories for analysis of HBM samples**
- **Laboratories for development of new methods**



HBM platform

Comparable HBM data in Europe

Alignment of sampling and field work protocols

Quality and comparability of the analytical results

Sharing data

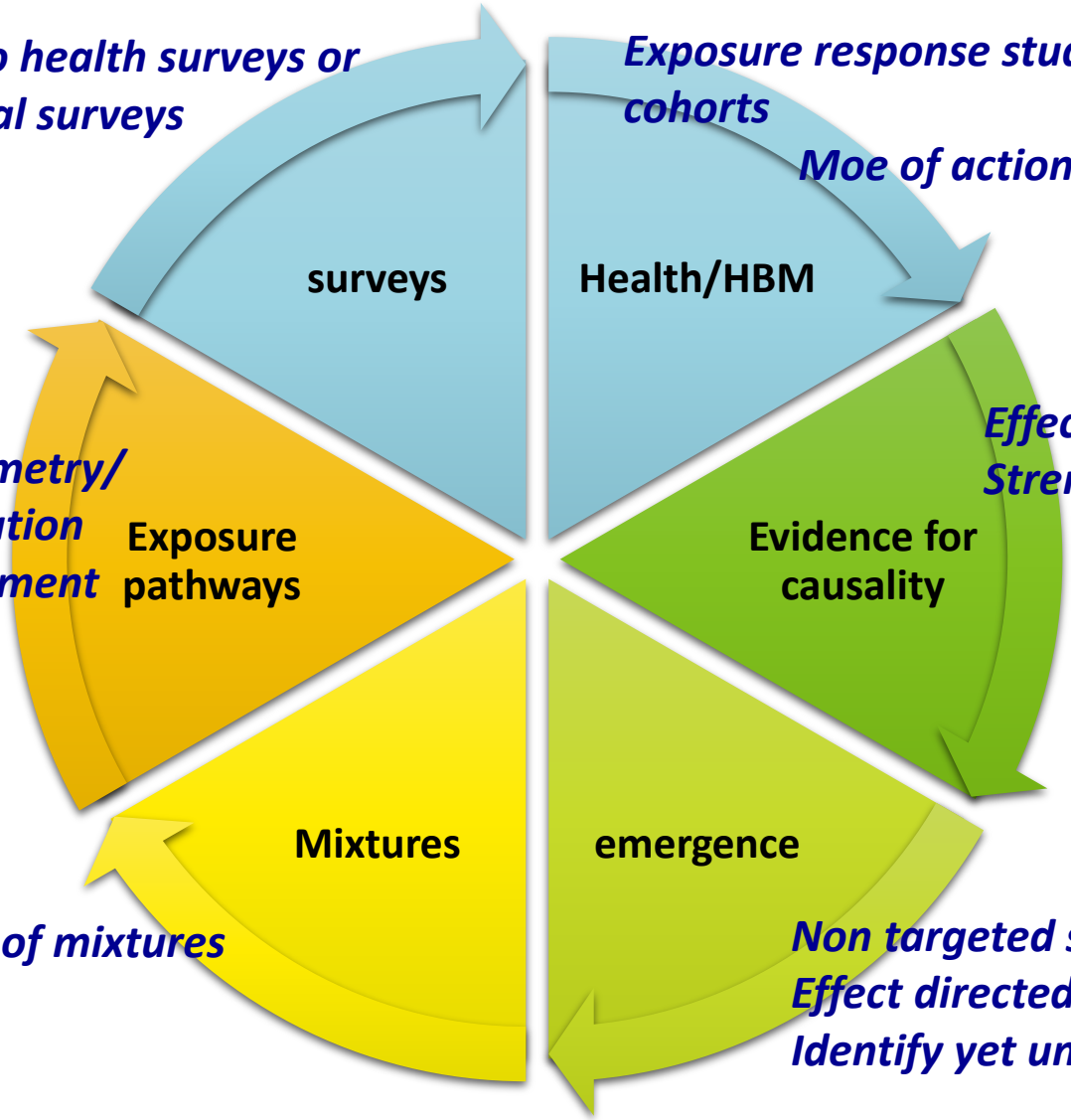
HBM4EU Repository

Pseudonymous data

Metadata
Aggregated data
Anonymous data

From exposure to health effect

Research



Linking to health surveys or nutritional surveys

Exposure response studies in longitudinal cohorts

Moe of action Adverse outcome pa

Effect biomarkers
Strengthen weight of evi

Non targeted screening
Effect directed screening
Identify yet unknown hazards

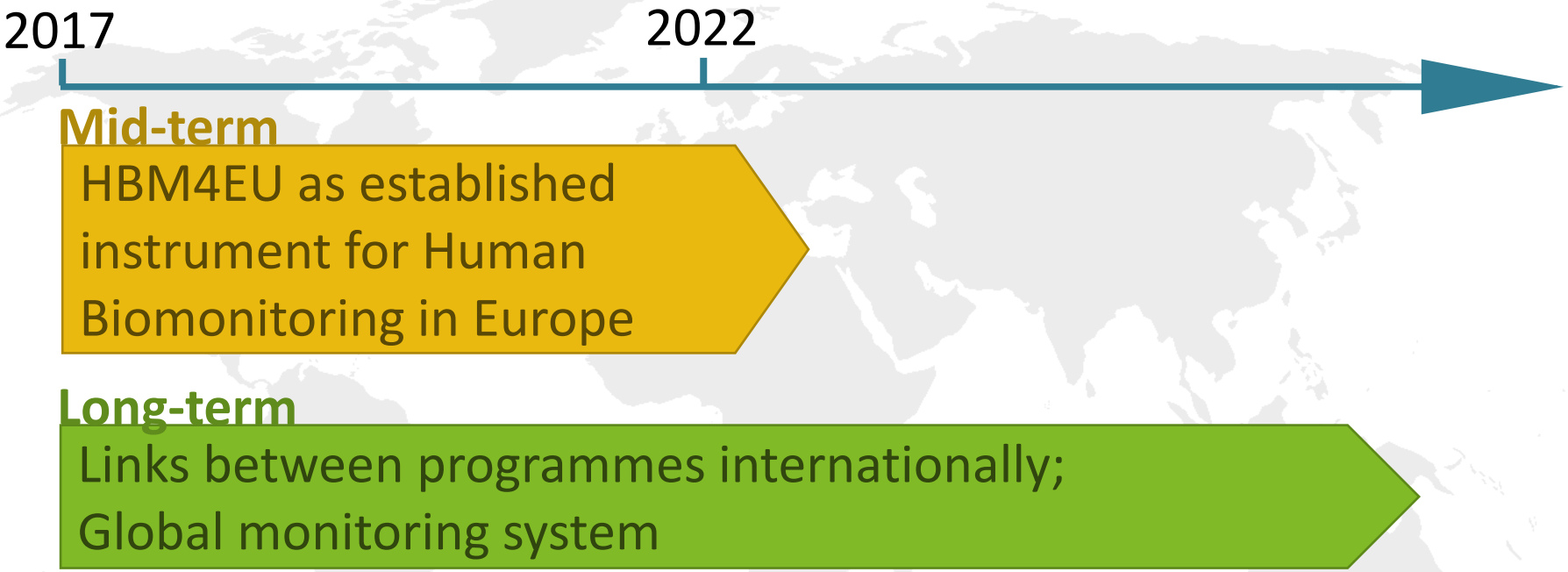
Capture real exposures

Inform regulation of mixtures

Modelling
PBTK/ reverse dosimetry/ integrating information
Improve risk assessment

HBM4EU – International Level?

Various international programmes to cooperate with



Prerequisites: harmonization, quality assurance, data sharing

Thank you

HBM4EU is coordinated by the German Environment Agency,

Email: HBM4EU@uba.de

co-coordinated by VITO
Email: HBM4EU@vito.be

https://www.hbm4eu.eu/

https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html

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

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First round

Priorisation 2016

9 substance groups:

1. Phthalates/DINCH
2. Bisphenols
3. Per-/Polyfluorinated compounds
4. Flame Retardants
5. Cadmium & Chromium
6. PAHs and air pollutants
7. Anilin family: MOCA
8. Chemical mixtures
9. Emerging chemicals

Second round

Priorisation 2018

9 substance groups:

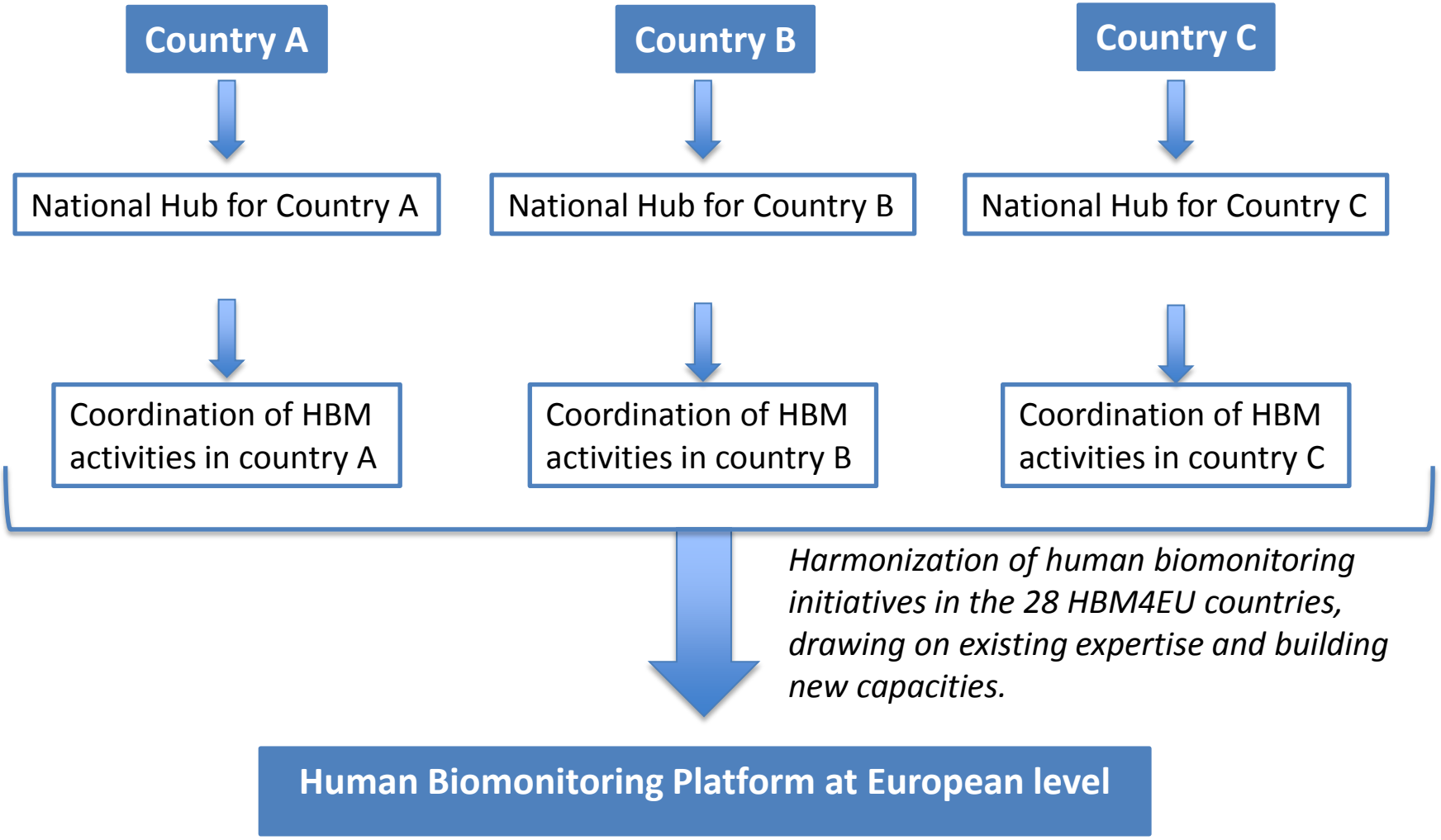
1. Acrylamide
2. Aprotic solvents
3. Arsenic
4. Diisocyanites
5. Lead
6. Mercury
7. Mycotoxines
8. Pesticides
9. UV filters

National Hub for Human Biomonitoring – Portugal (HBM NH-PT)

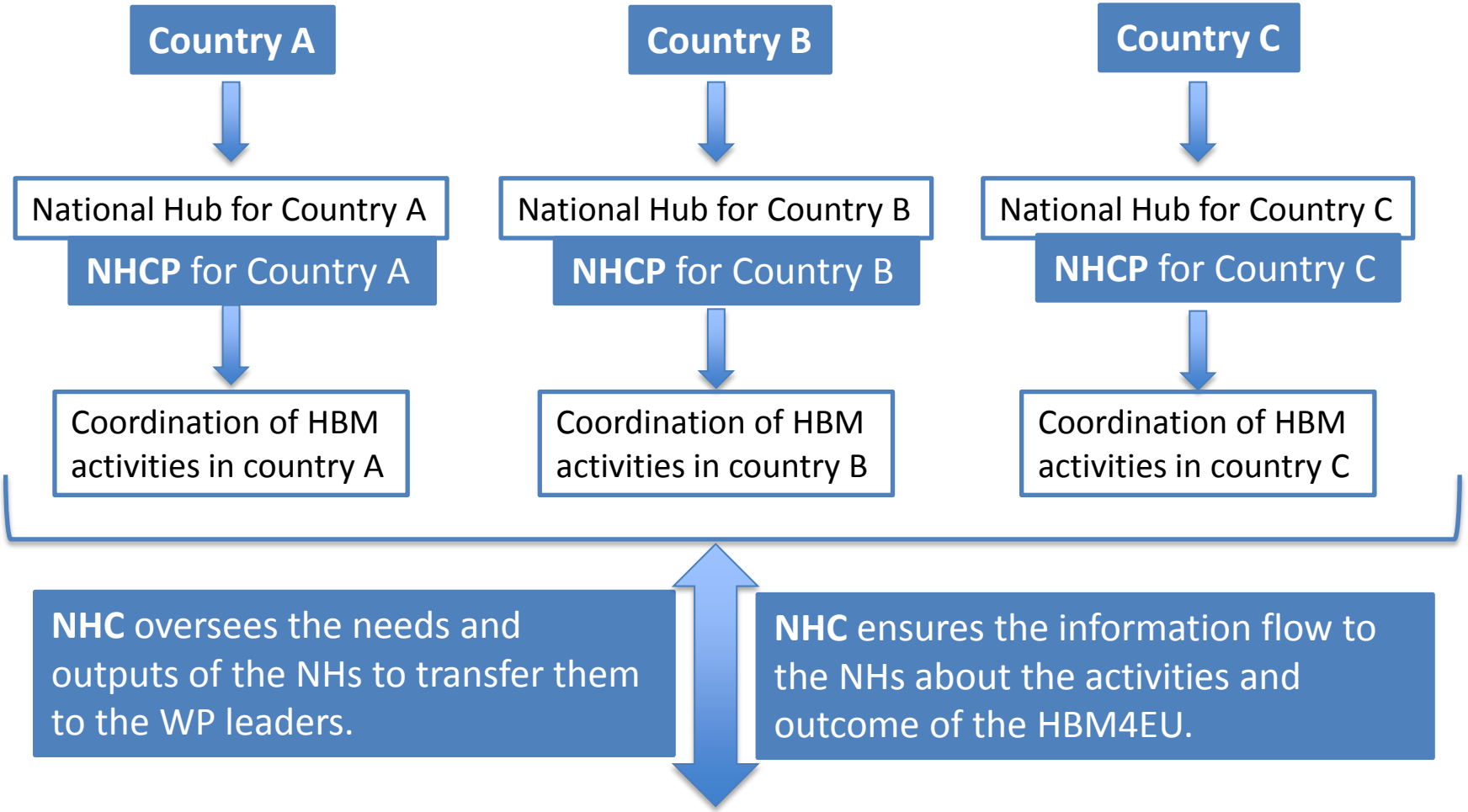
Rita Cavaleiro (*National Hub Contact Point*)
Fundação para a Ciência e a Tecnologia

1st Workshop on Human Biomonitoring in Portugal (1st HBM-PT), INSA, 11 May 2018

HBM4EU National Hubs



HBM4EU National Hubs



NHCP = National Hub Contact Point

NHC = National Hub Coordinator
(Public Health England: Department of Health – DH)

The Portuguese National Hub for HBM

- HBM4EU Programme Owners* and/ or Managers**:

- HBM4EU Linked Third Parties:

** Programme Owners: national/regional ministries/authorities responsible for defining, financing or managing research programmes carried out at national or regional level.*

*** Programme Managers are typically research councils or funding agencies or other national or regional organisations that implement research programmes under the supervision of the programme owners. Their participation has to be mandated by the national/regional authorities in charge (normally the responsible Ministry).*

The Portuguese National Hub for HBM: Structure

National Hub Ambassador

Advisory Board

General Assembly (APA / DGS / FCT / INSA)

Management Board (APA / DGS / FCT / INSA)

Scientific and Administrative Management

Coordination: APA / DGS / FCT / INSA

Executive Secretariat: APA / DGS / FCT / INSA

- **WP1:** Coordination and Management — APA / DGS / FCT / INSA
- **WP2:** Dissemination — APA / DGS / FCT / INSA
- **WP3:** Internal Calls — FCT
- **WP17:** Ethics Requirements — INSA

Pillar 1

Science-Policy Interface

Coordination: APA / DGS / FCT / INSA

- **WP4:** Priorization — APA / DGS / FCT / INSA
- **WP5:** Translation of Results into Policy — APA / DGS / FCT / INSA
- **WP6:** Sustainability and Capacity Building — APA / DGS / FCT / INSA

Pillar 2

Human Biomonitoring Platform

Coordination: APA / DGS / FCT / INSA

- **WP7:** Survey dDsign — ESTeSL / FMUL / INSA
- **WP8:** Survey Implementation — ESTeSL / FMUL / INSA
- **WP9:** Laboratory Analysis and Quality Assurance — APA /FMUL / INSA
- **WP10:** Data Management and Analysis — DGS / INSA

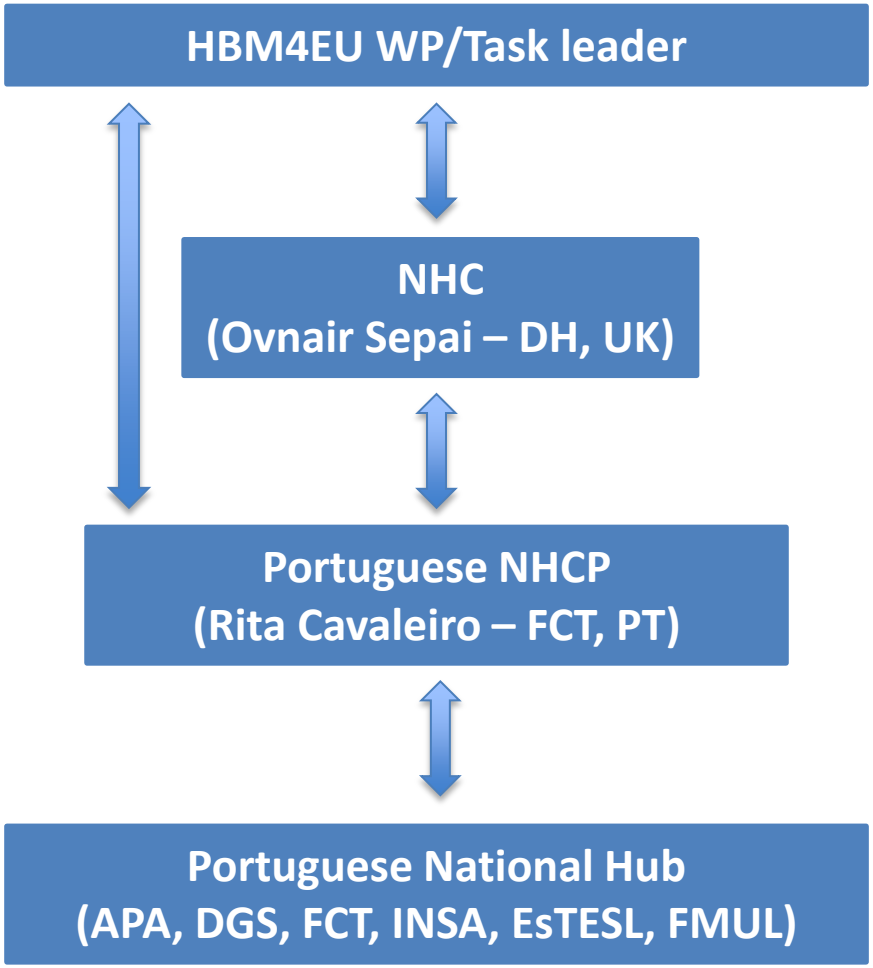
Pillar 3

Exposure and Health

Coordination: APA / DGS / FCT / INSA

- **WP11:** Linking HBM, Health Studies and Registers — FMUL/ INSA
- **WP12:** From HBM to exposure — FMUL / INSA
- **WP13:** Exposure-Health relationships — APA / DGS / FMUL / INSA
- **WP14:** Effect Biomarkers — INSA
- **WP15:** Mixtures, HBM and Human Health Riscks — DGS / INSA
- **WP16:** Emerging Chemicals — APA

The Portuguese National Hub for HBM: Flow of information between HBM4EU and NH-PT



NHCP = National Hub Contact Point

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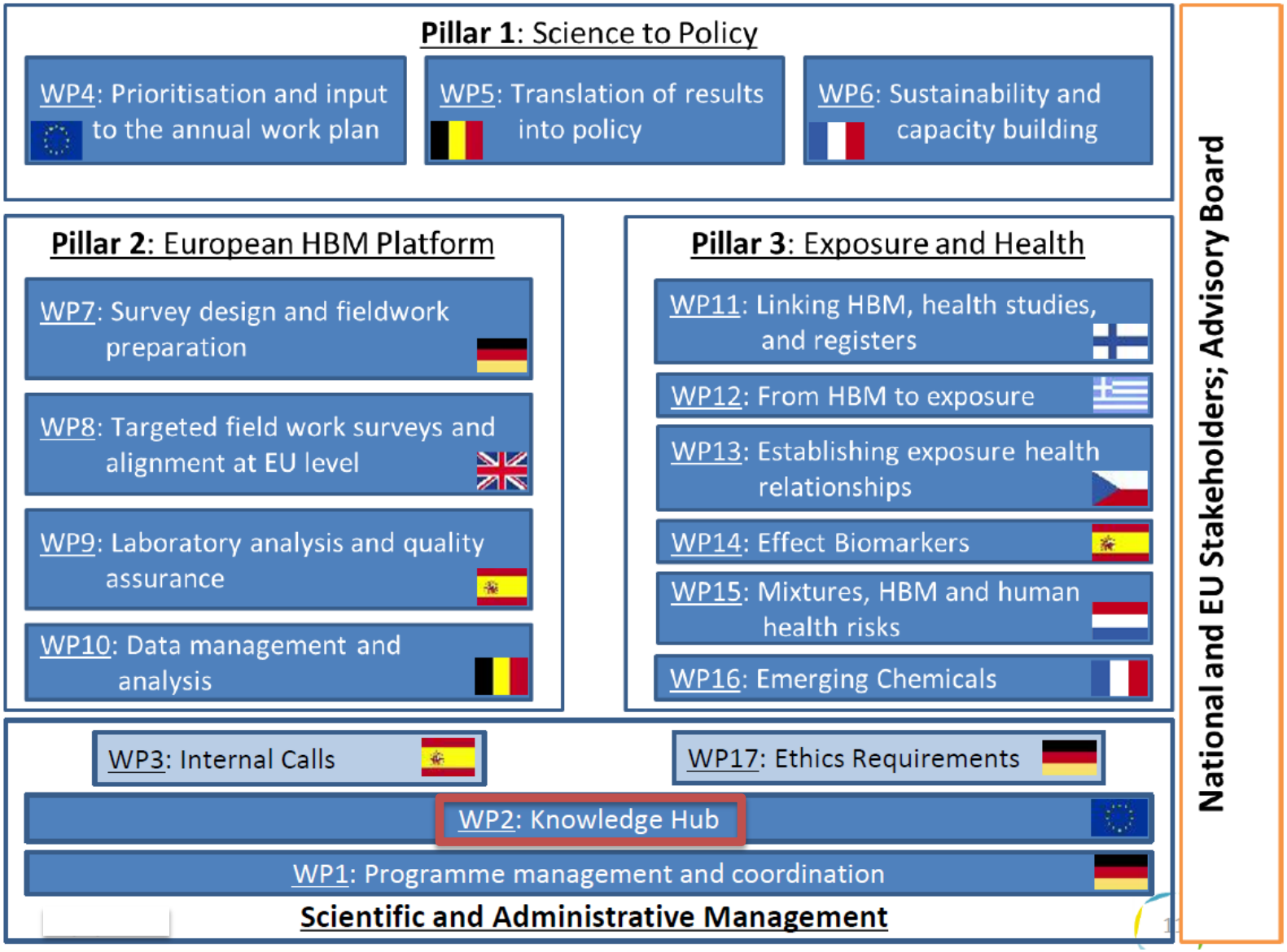
The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP2 – "Knowledge Hub"

(Leader: EEA – European Environment Agency, DK)

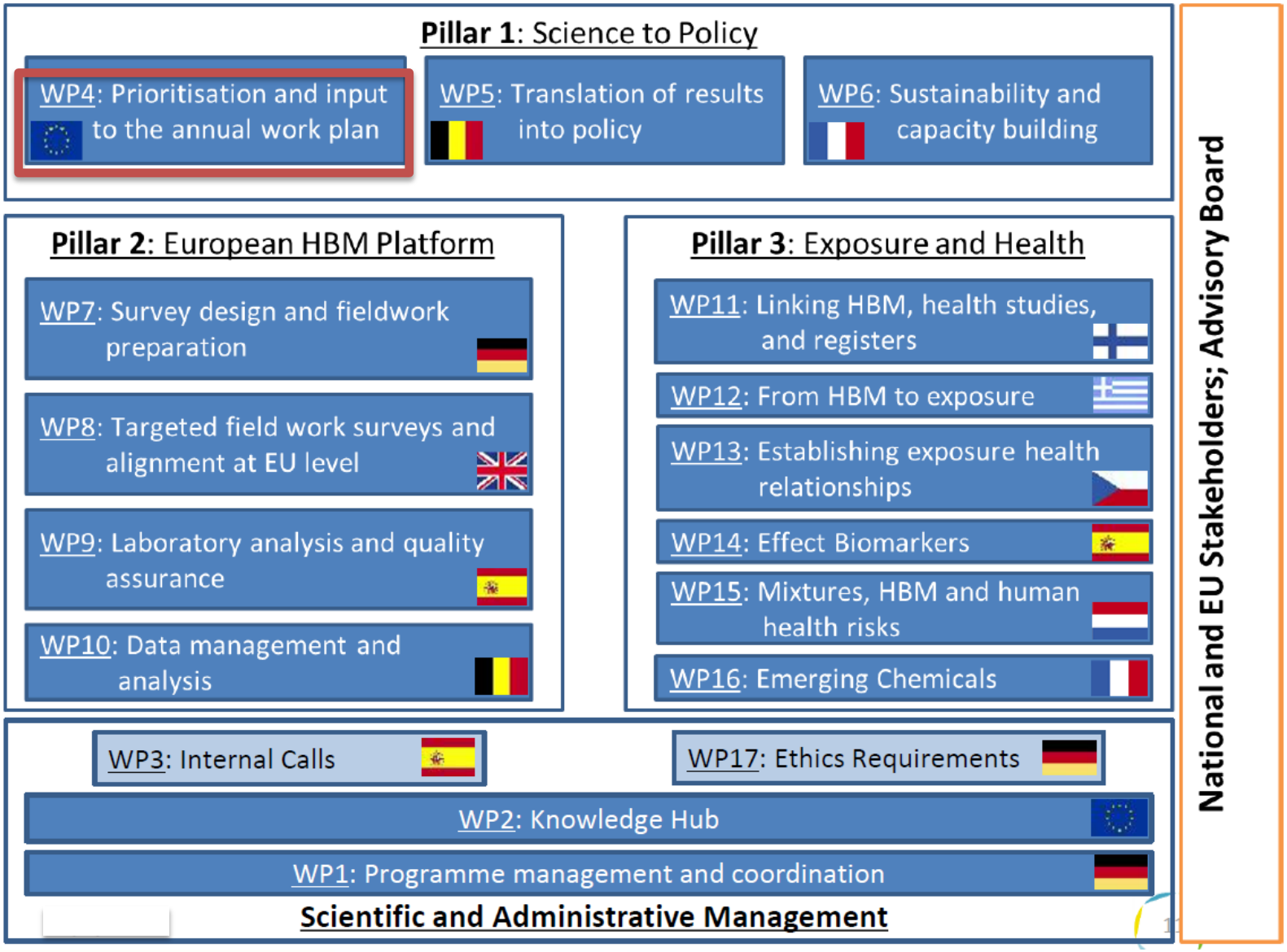
Task 2.1 ("HBM4EU Website") – *Leader: EEA, DK*

Providing details of the Portuguese National Hub to be included in the HBM4EU website.

Task 2.5 ("Training") – *Leader: RUMC - The Radboud University Medical Center, NL*

Providing lists of selected persons from the HBM4EU Portuguese organisations to be invited to participate in the a) questionnaire on training needs (QNEEDS) and b) the questionnaire on available knowledge, expertise and skills (QKES).

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP4 – "Prioritisation and input to the Annual Work Plan"

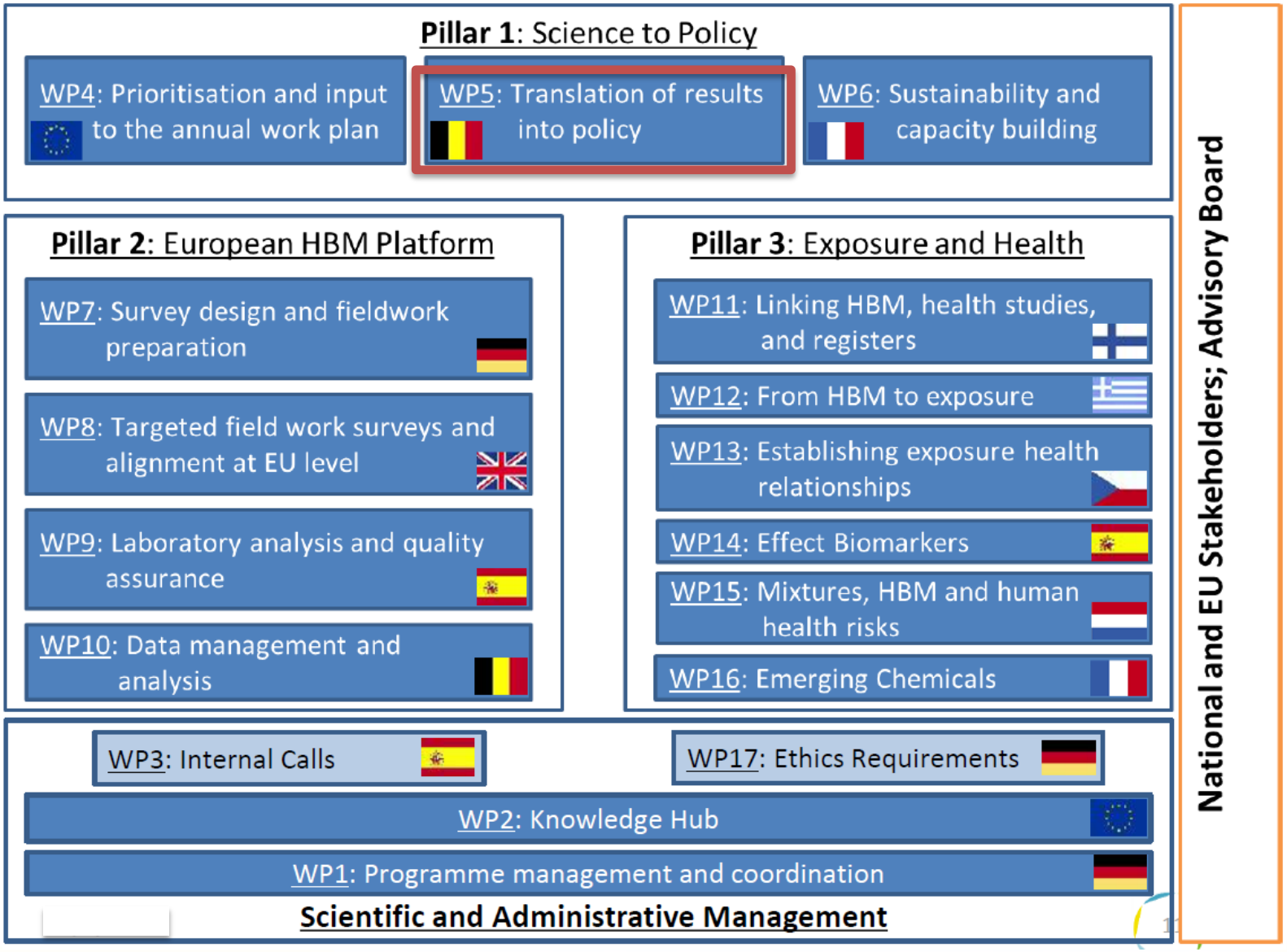
(Leader: EEA – European Environment Agency)

Task 4.1 ("Mapping the information needs of external bodies") – *Leader: EEA, DK*

Nomination of the following substances to be part of the 2nd list of HBM4EU priority substances (to be the substances of research activities from 2019 to 2021):

- Mercury
- Mycotoxins
- DINCH - *Diisononyl hexahydrophthalate* (re-nomination)
- PAHs - *Polycyclic aromatic hydrocarbons* (re-nomination with the intention to propose the study of PAHs mixtures)

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP5 – "Translation of results into policy"

(Leader: VITO – Flemish Institute for Technological Research, BE)

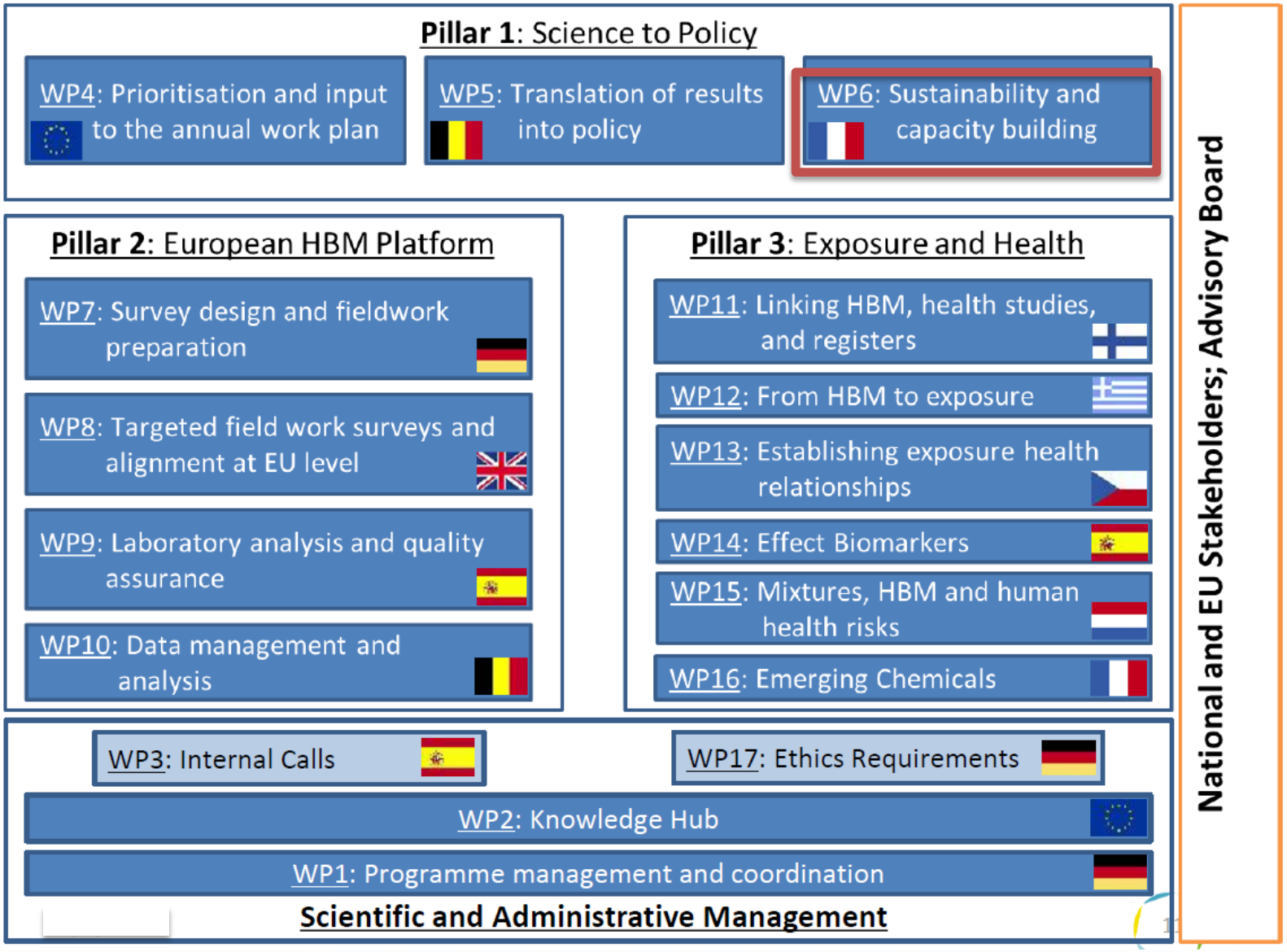
Task 5.2 ("Development and consolidation of EU level HBM health based guidance values") – *Leader: UBA - German Environment Agency, DE*

- Nomination of a phthalate expert (Teresa Borges, from DGS) to contribute to the development and consolidation of EU level HBM health based guidance values.
- Providing comments and corrections to documents on health based guidance values.

Task 5.3 ("Inclusion of HBM data in risk assessment/health impact assessment strategies") – *Leader: FIOH - Finnish Institute of Occupational Health, FI*

Dissemination of a questionnaire on regulatory risk assessment to Portuguese risk assessors working in the different legislative areas, including chemicals legislation (REACH), food safety, occupational safety, cosmetics, etc.

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP6 – "Sustainability and capacity building"

(Leader: INSERM – The French National Institute of Health and Medical Research, FR)

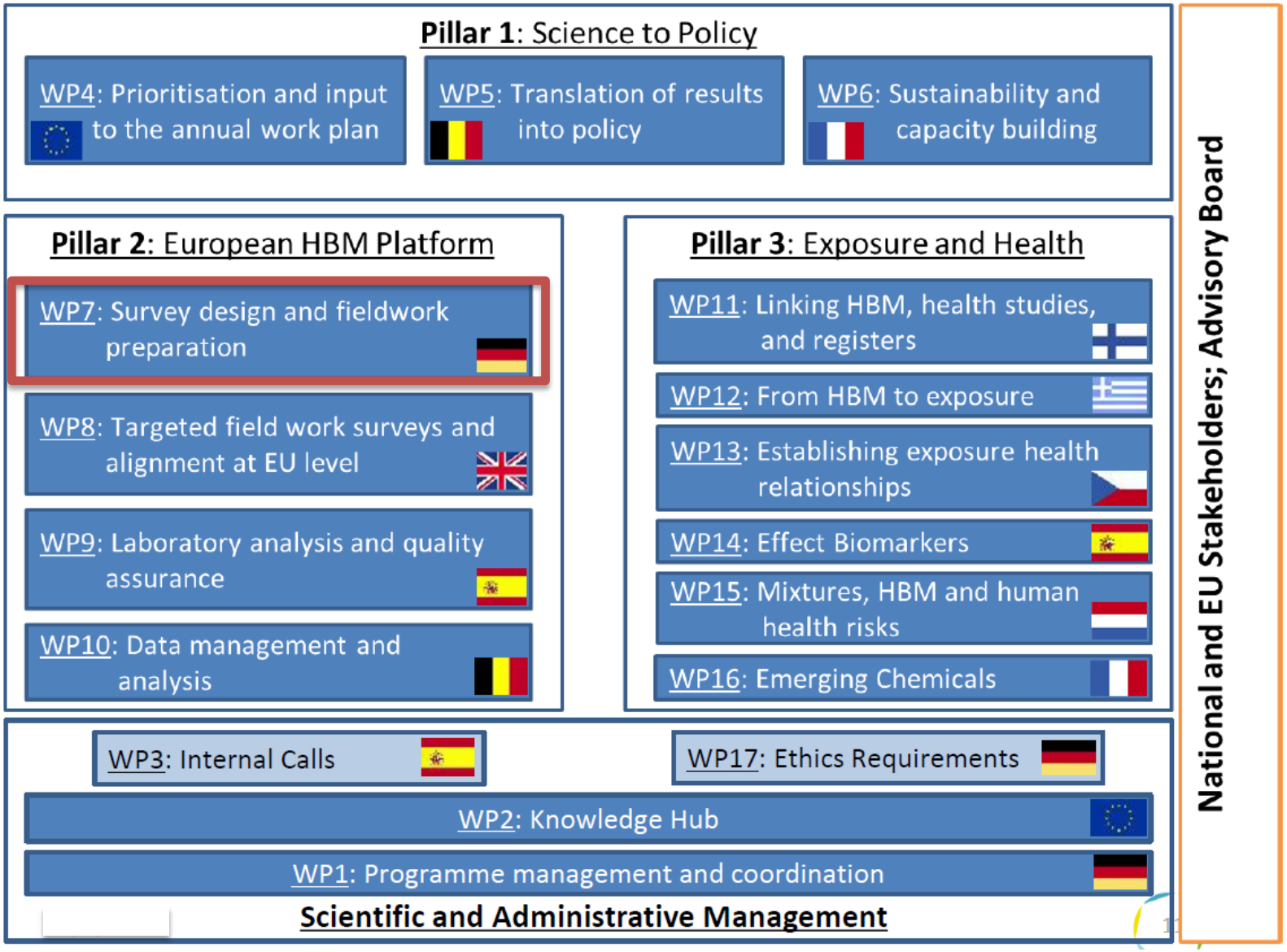
Task 6.1 ("Establishment of national framework to feed into HBM4EU")

– Leader: UK Department of Health (DH) - Public Health England

Interaction with the NHC to provide information as to the needs of the Portuguese National Hub and suggestions regarding the establishment of frameworks at national level that could support a long-term HBM4EU.

(Interaction through filling in questionnaires, teleconference and NHCP meetings).

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP7 – "Survey design and fieldwork preparation"

(Leader: UBA - German Environment Agency)

Task 7.1 ("Identification of existing data and data gaps") – *Leader: FMUL, PT*

Dissemination, among the Portuguese HBM4EU members, of the questionnaire developed by FMUL, to collect an inventory of the existing surveys (concluded in the last 10 years, ongoing and planned to start in the next 5 years).

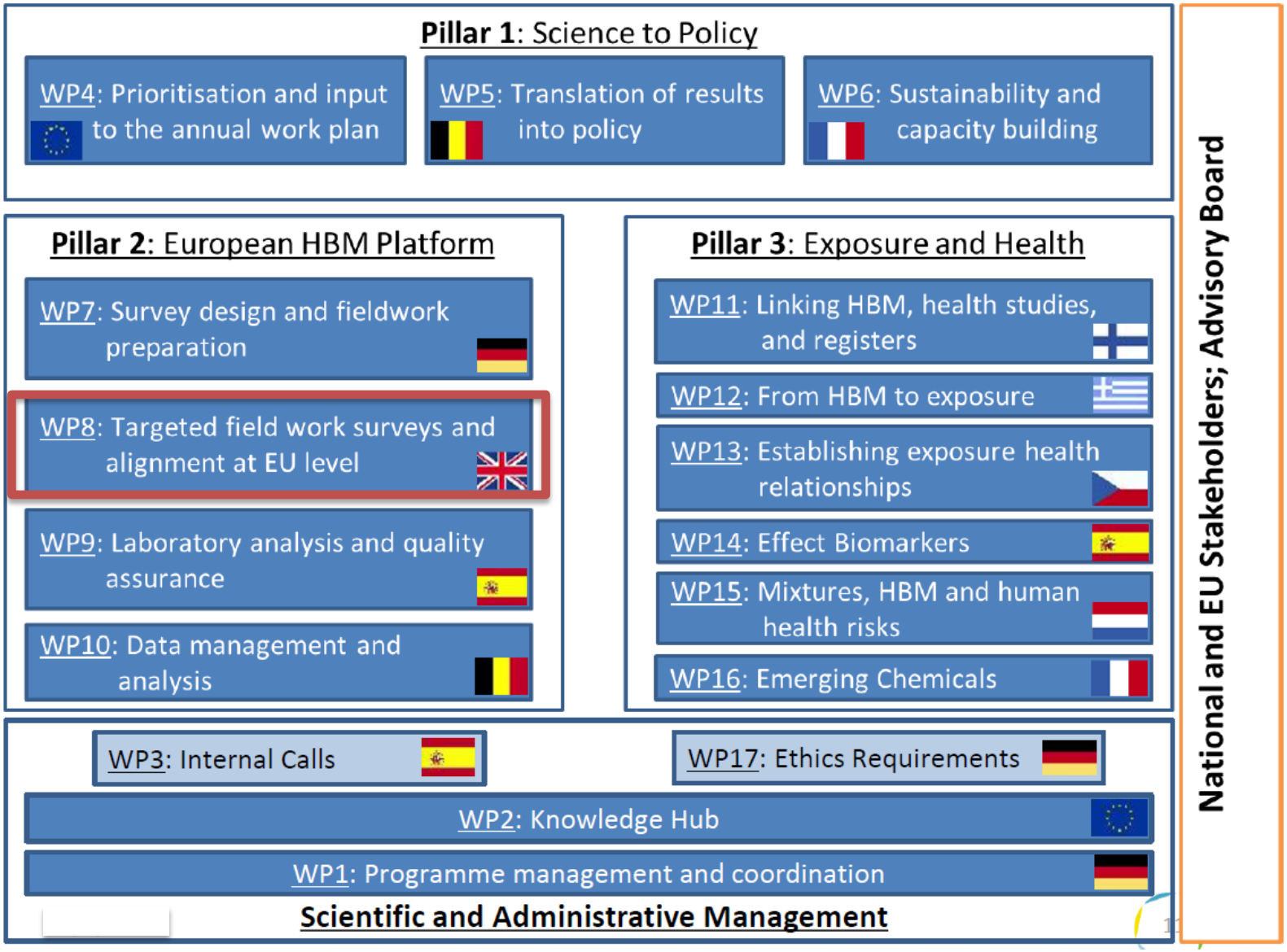
Task 7.4 ("Strategy for exchange of human samples") – *Leader: IBMT, DE*

Dissemination, among the Portuguese HBM4EU members, of a questionnaire on sample storage and sample exchange among the members of the Portuguese National Hub, in order to help identifying the most common shipping procedures of partners within the HBM4EU initiative.

Task 7.5 ("Communication with Participants") – *Leader: MOH-CY, CY*

Input in terms of communication materials for study participants used in the Portuguese HBM programs, aiming to prepare a library of "communication materials for participants" used by countries implementing national HBM programs.

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



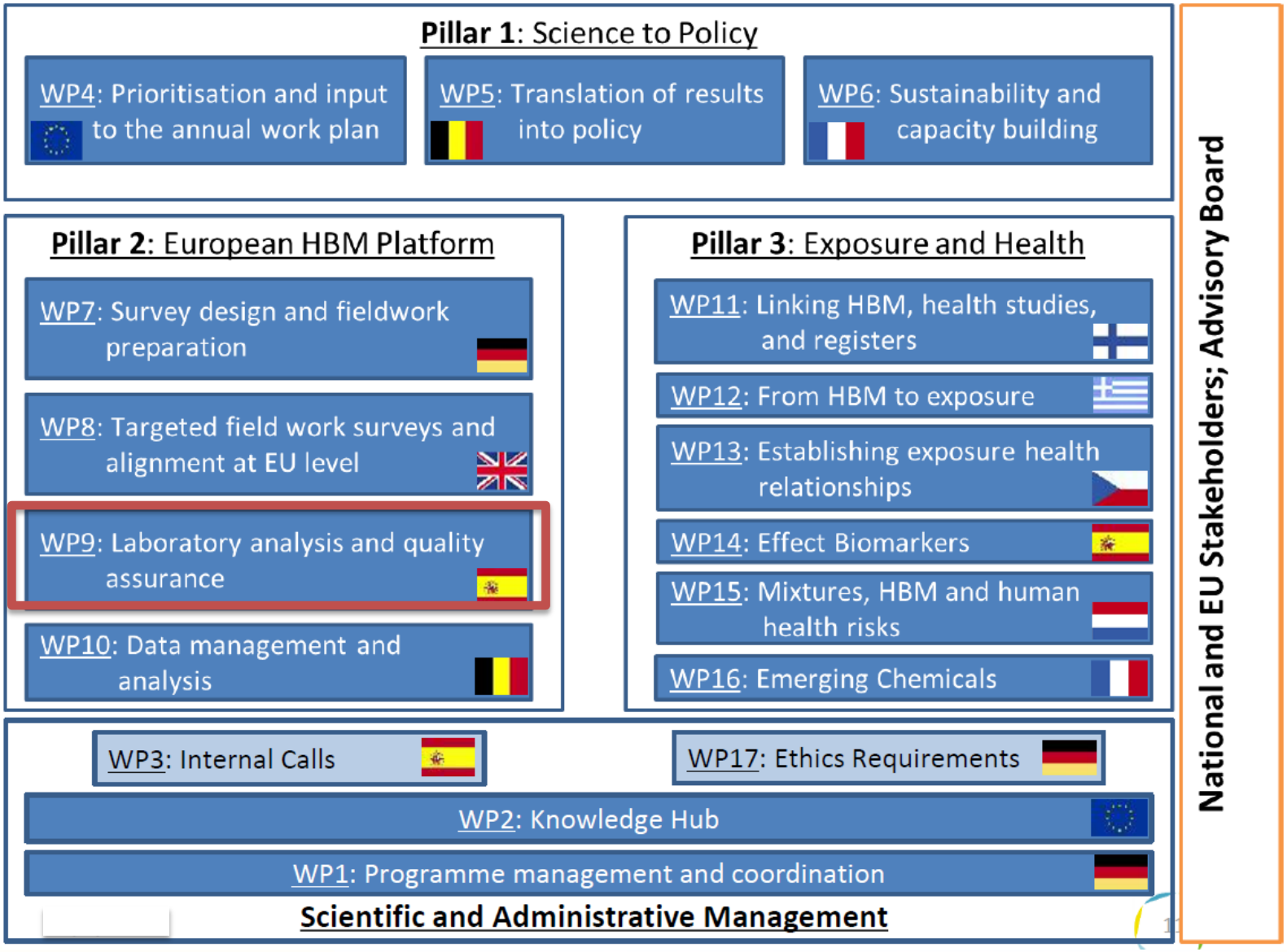
WP8 – "Targeted field work surveys and alignment at EU level "

(Leader: DH, UK)

Task 8.1 ("Alignment of national studies") – *Leader: VITO, BE*

Providing a list of Portuguese studies that have collected samples that could be used for human biomonitoring in the context of task 8.1 - Ongoing

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP9 – "Laboratory analysis and quality assurance"

(Leader: ISCIII, ES)

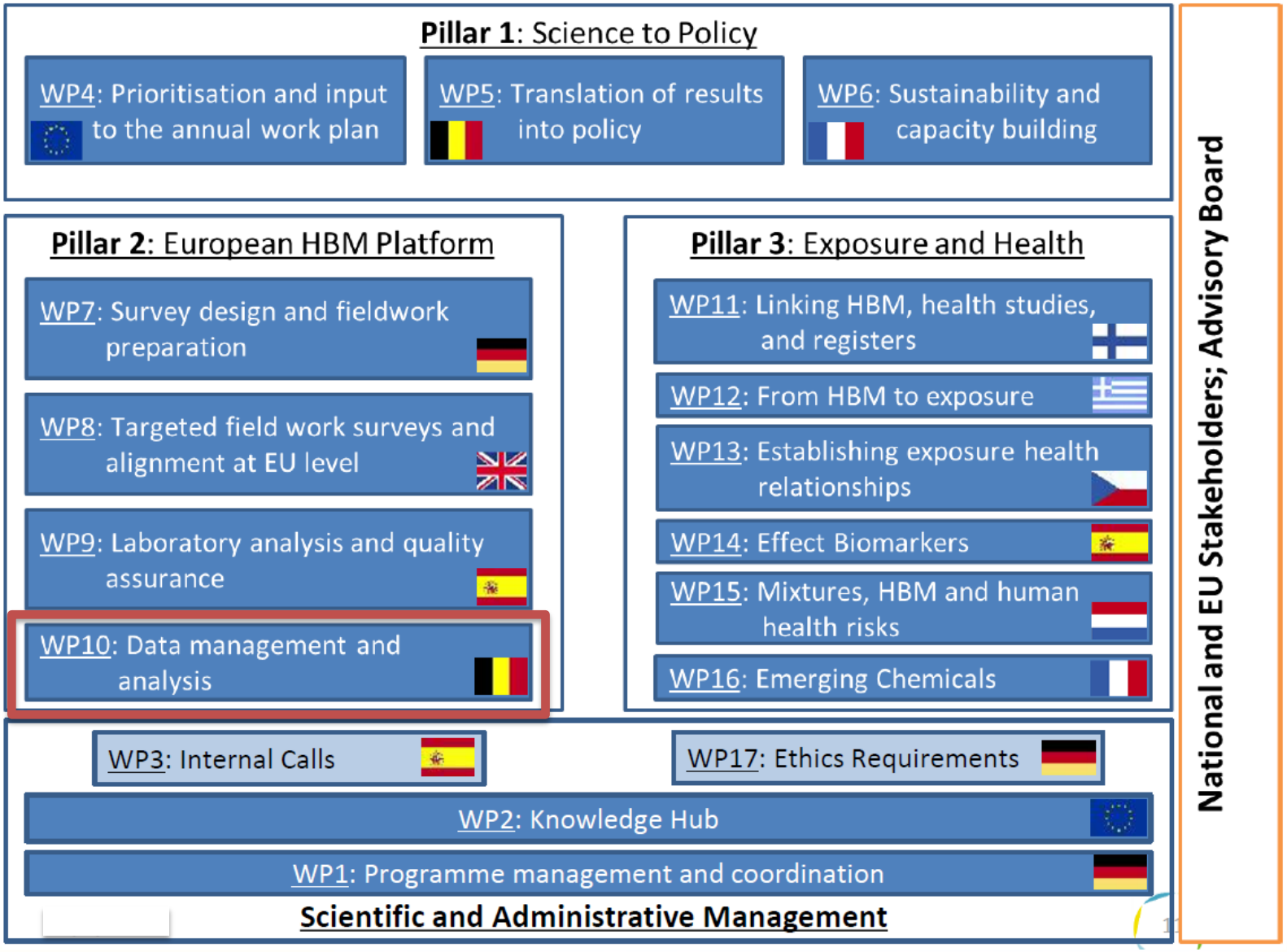
Task 9.2 ("Network of Reference HBM laboratories for performing biomarker analysis, developing new methods, and supporting the QA/QC program at EU level") – *Leader: ISCIII*

Identification and contact with Portuguese laboratories that could become integrated in the HBM4EU lab network. The identified laboratories had previous experience in one or more of the following:

1- Chemical analysis of human samples;
2- Development of new analytical methods in biological samples;
3- Organisation of ICI/EQUAS schemes with biological samples.

Among the identified Portuguese laboratories contacted by FCT, eight laboratories expressed their interest to integrate the HBM4EU lab network.

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



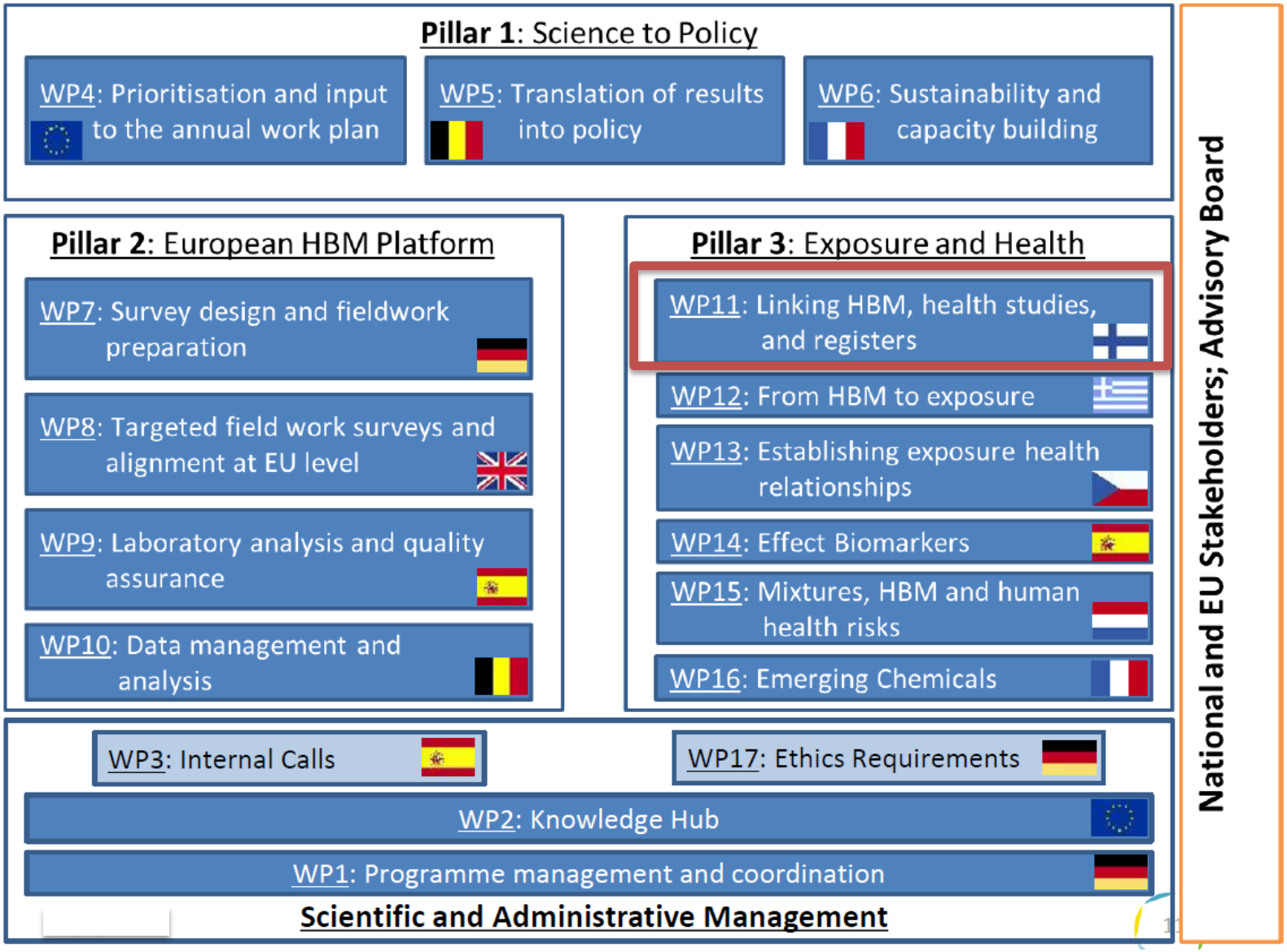
WP10 – "Data management and analysis"

(Leader: VITO, BE)

Task 10.4 ("Data analysis including the generation of European reference values") – *Leader: VITO, BE*

Identification of any interesting HBM data collections to be uploaded in the HBM4EU repository and in IPCheM - Ongoing

The Portuguese National Hub for HBM: Activities – Response to the HBM4EU requests



WP11 – "Linking HBM, health studies and registers"

(Leader: THL)

Task 11.1 ("Opportunities and obstacles for linking HBM programme and health studies") – *Leader: RegionH*

Providing contact information for health surveys/studies (excluding HBM studies) which have collected biological samples and stored them for future use, to identify the opportunities and obstacles of combining ongoing/planned health studies (health examination surveys (HES), cohort studies, dietary surveys, occupational studies, etc.) and HBM.

Task 11.5 ("Linking HBM to administrative registers") – *Leader: NIPH*

Providing the contact of people with the knowledge about linkage between administrative register information and HBM studies, in order to contribute to the update of the knowledge on availability of administrative registers and link them with HBM studies.

The Portuguese National Hub for HBM: Future Goals

- To pave the way for the creation and development of a national platform of human biomonitoring, where it could be ensured the influence of relevant national research institutions, regulators, industry and other Portuguese stakeholders.

Please fill in this questionnaire (find it in your workshop folder)

Expressão de Interesse

Nome:

Afiliação:

Email:

Área de investigação / Área profissional:

Indique por favor se tem interesse em colaborar com a *National Hub* – Portugal:

Sim ☐ **Não** ☐

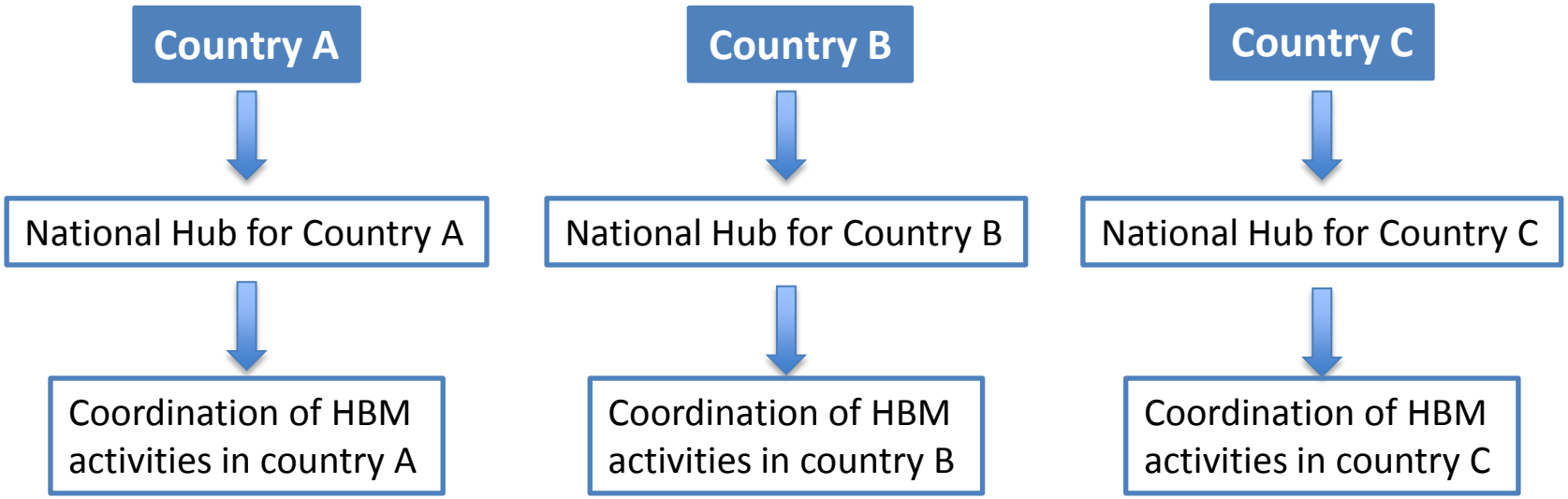
Se respondeu que sim, indique em que tipo de estrutura gostaria de colaborar:

- Conselho Consultivo da *National Hub* ☐

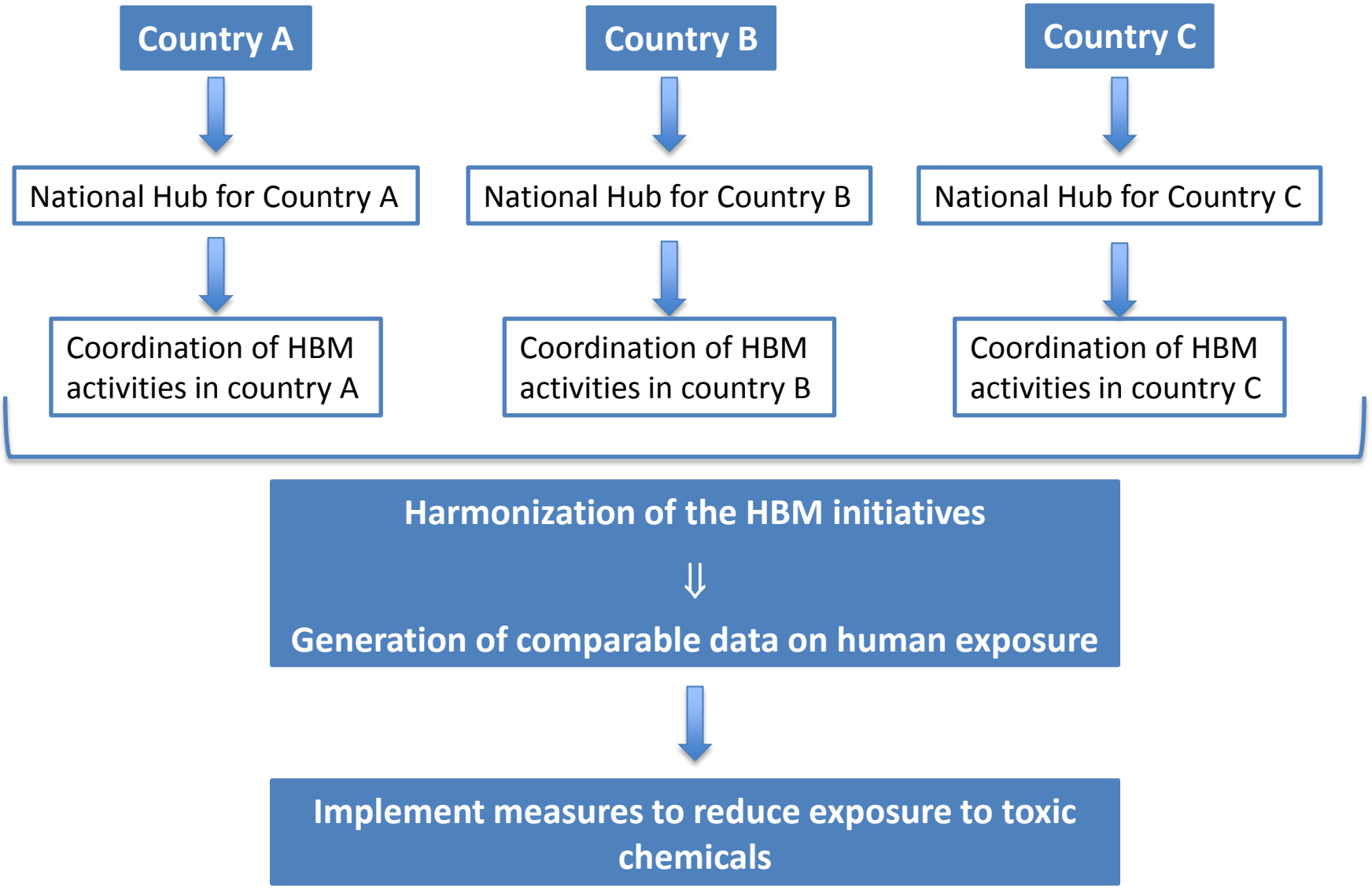
- Grupo alargado de interesse em Biomonitorização Humana ☐

- Grupo de *stakeholders* ☐

The Portuguese National Hub for HBM: Future Goals



The Portuguese National Hub for HBM: Future Goals



Fundação para a Ciência e a Tecnologia

Thank you very much for your attention!

NHCP contact:
rita.cavaleiro@fct.pt

HBM4EU science and policy for a healthy future

1ST WORKSHOP ON HUMAN BIOMONITORING IN PORTUGAL (1ST HBM-PT)

The role of Metabolomics and Adductomics in Human Biomonitoring

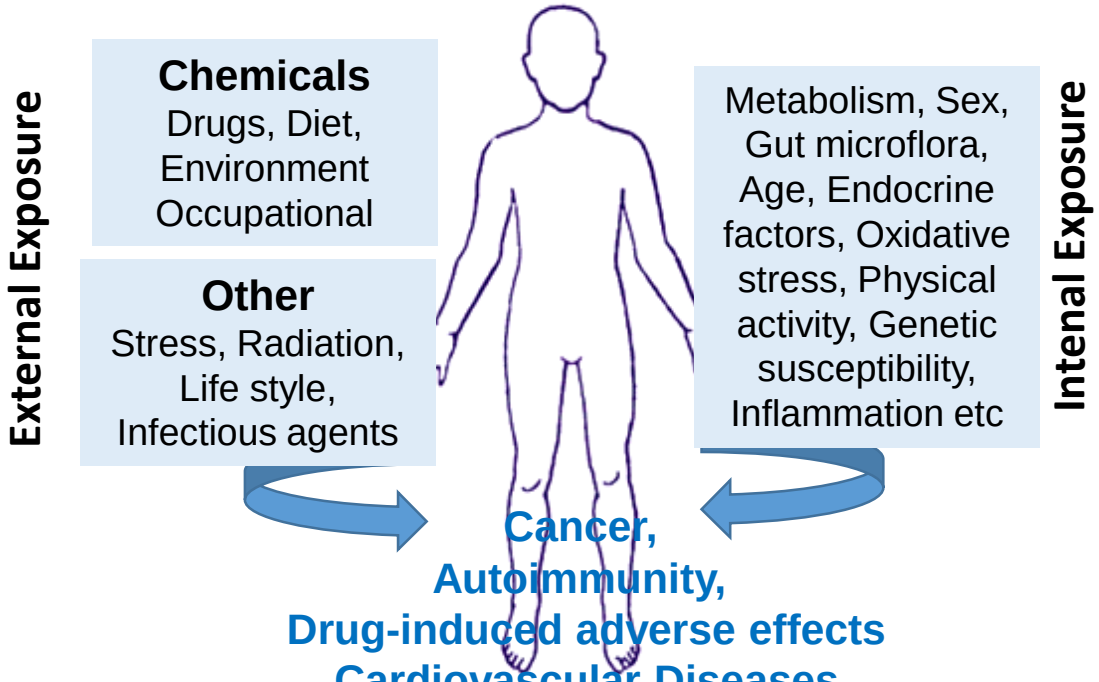
Alexandra M. M. Antunes

alexandra.antunes@tecnico.ulisboa.pt
http://alexandraantunes.weebly.com/

TÉCNICO LISBOA

CQE Química Estrutural CENTRO DE QUÍMICA ESTRUTURAL

EXPOSOME & OMICS

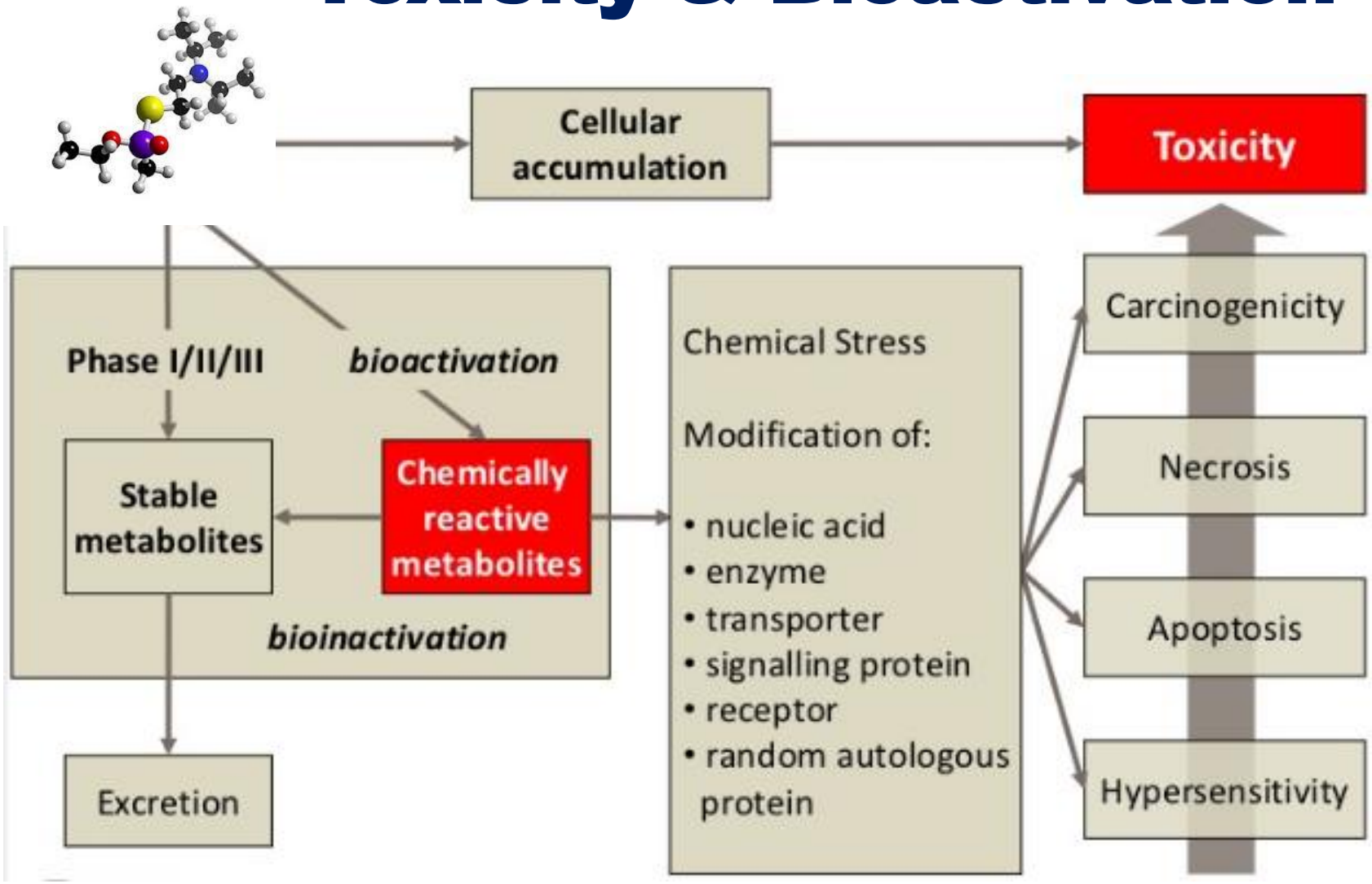


OMICS

Molecular Basis of Diseases
Biomarkers of Exposure/Diseases
Diagnosis/Prognosis Tools

Minimization of Adverse Health Outcomes

Toxicity & Bioactivation



Park *et al.* Chem.-Biol. Interac. 2011, 192, 30-33

CHEMICAL TOXICOLOGY – METABOLOMICS & ADDUCTOMICS


I. Martins


A. Godinho


N. Grilo


S. Harjivan


L. Fidalgo


R. Wanke


P. Pinheiro


Sofia Pereira

Risk assessment of drugs used in chronic therapies

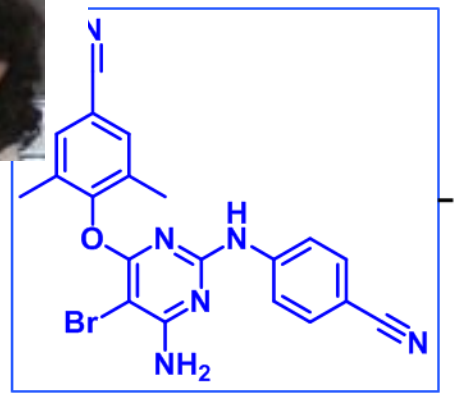
Development of early biomarkers of chemically-induced cancers

Development of diagnosis tools of diseases induced by endogenous metabolites


J. Nunes

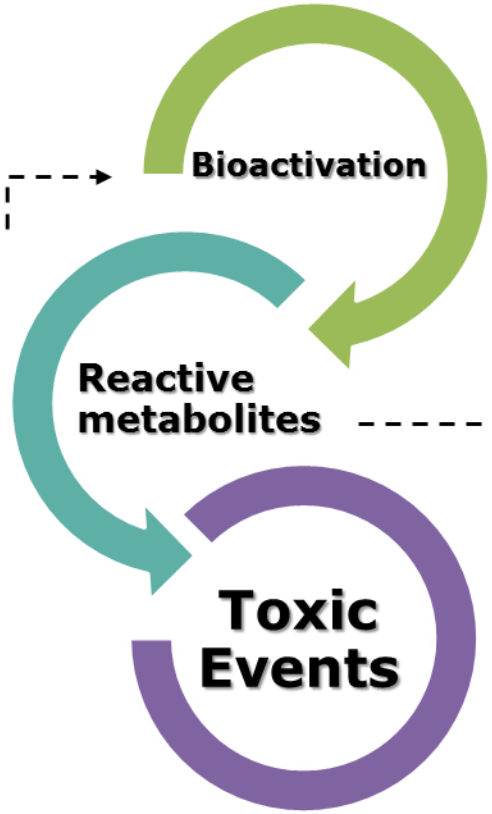

C. Charneira

Sofia Pereira



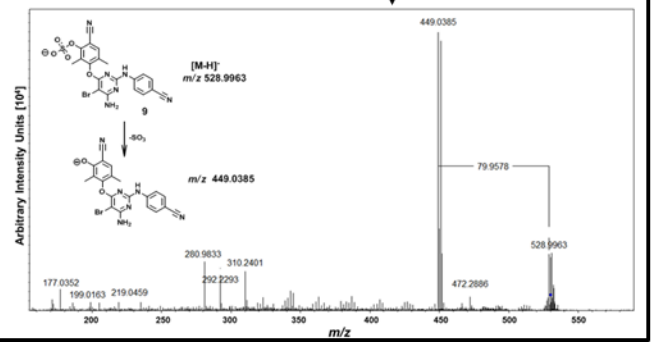
Etravirine
2nd generation NNRTI
anti-HIV Drug

Hypersensitivity



QTOF-HRMS

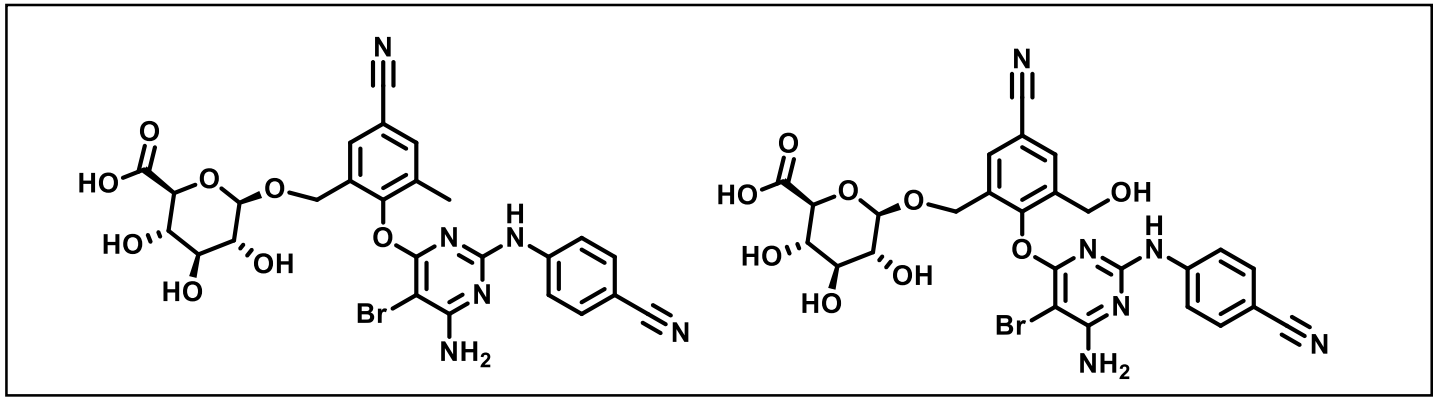
LC-HRMS/MS
Isotope Cluster Analysis
Targeted Approach

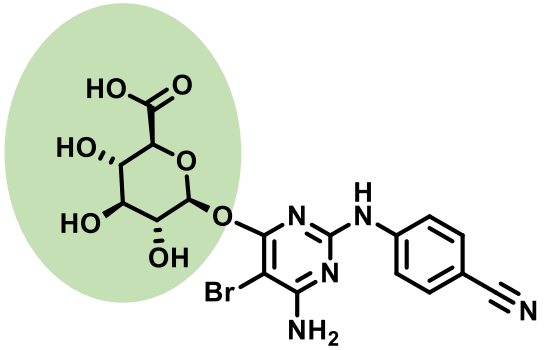


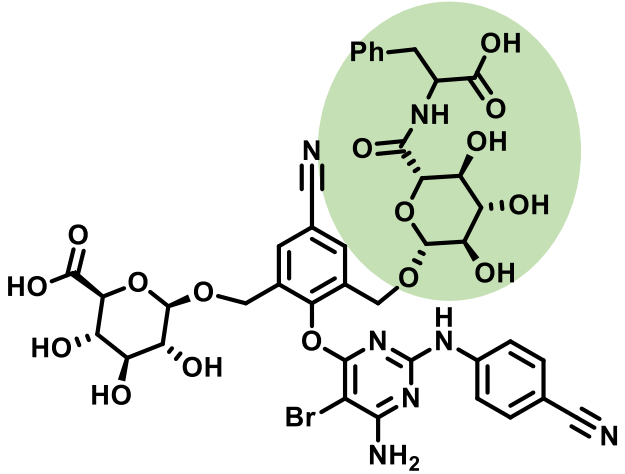
Adduct & Metabolite Profile Identification

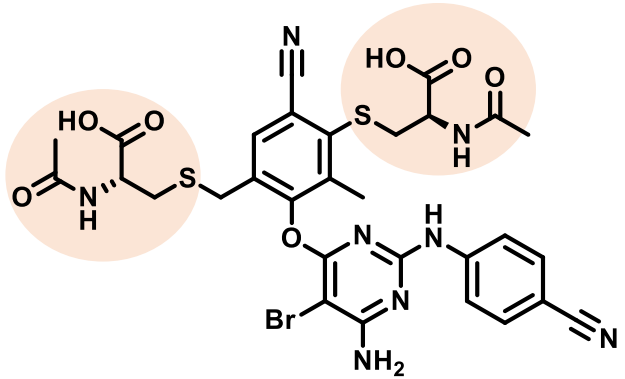
Godinho et al. Eur J Pharm Sci 119 (2018) 70–82

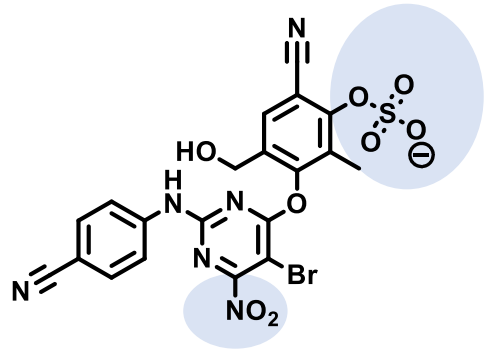
Etravirine Bioactivation to Reactive Metabolites: Identification of metabolites and adducts in the urine of patients on etravirine therapy





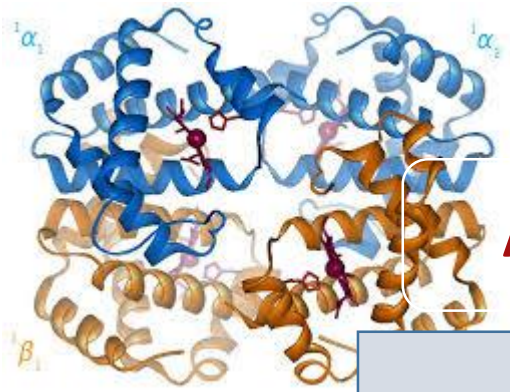




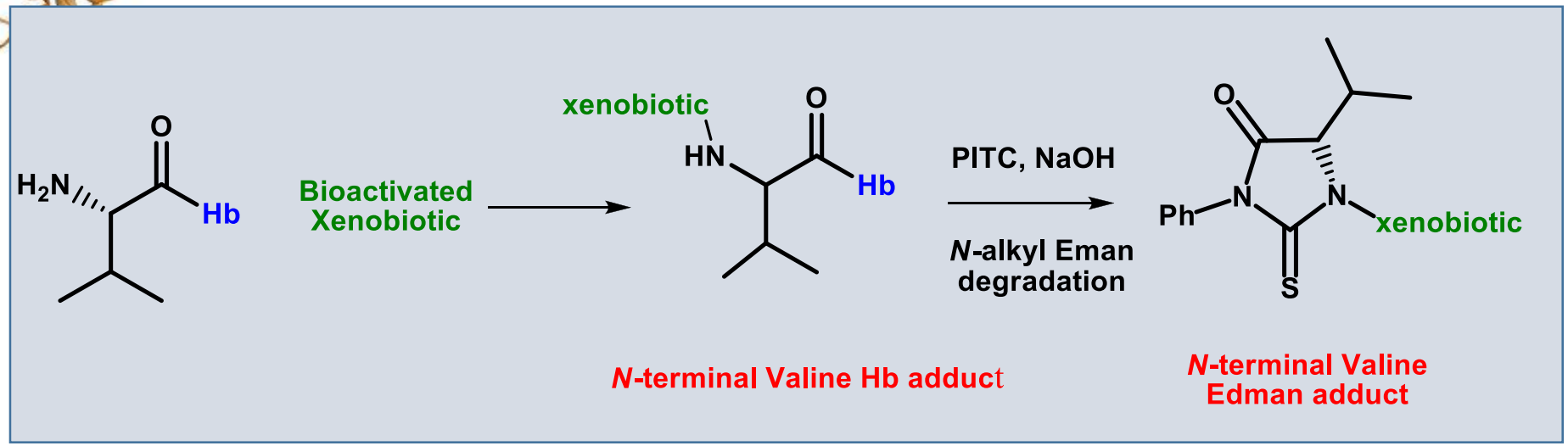


Godinho et al. Eur J Pharm Sci 119 (2018) 70–82

Adductomics Tools: Covalent adducts formed with model proteins



Adducts Formed with *N*-terminal Valine of Hemoglobin (Hb)



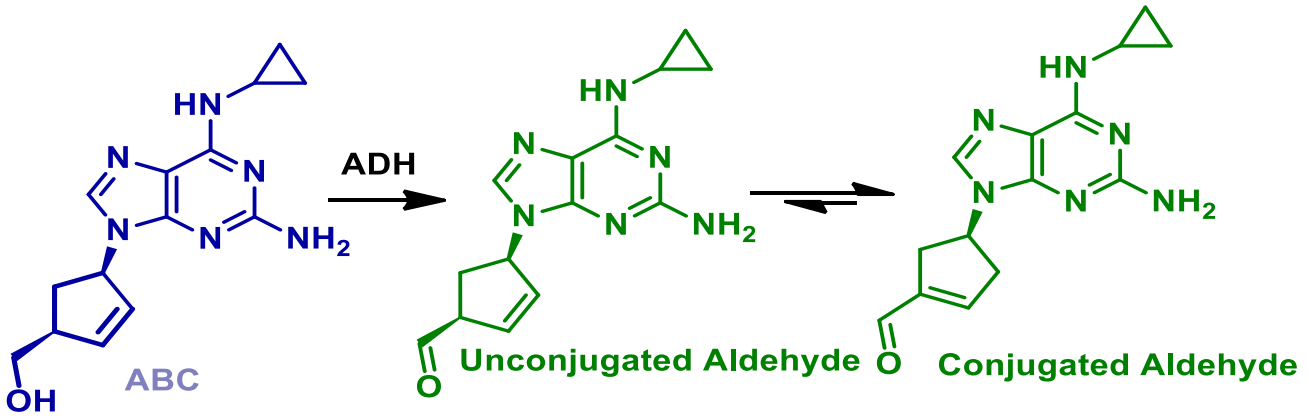
Synthesis of drug metabolite, & adduct standards

Abacavir (ABC) Bioactivation to Aldehyde Reactive Metabolites

Catarina Charneira

Nucleoside Analogue Reverse Transcriptase Inhibitor (NRTI)

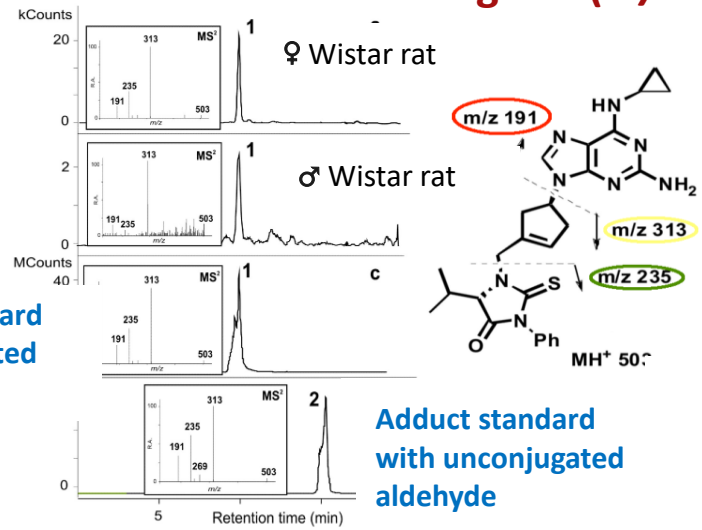
Cardiotoxicity



Biomonitoring

tification of abacavir-adducts *in vivo*: *Wistar* rats and HIV patients

LC-ESI-MS/MS (m/z 503)
Extracted ion-chromatogram (*m/z* 313)



Adduct standard with conjugated aldehyde

Adduct standard with unconjugated aldehyde

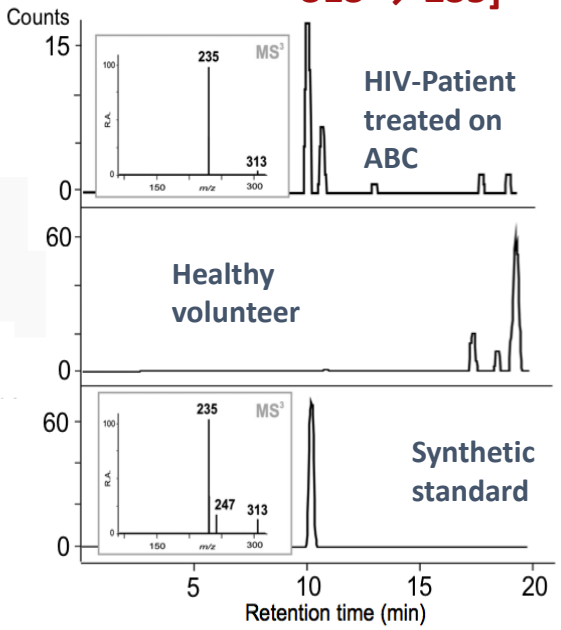
Unequivocal evidence that:

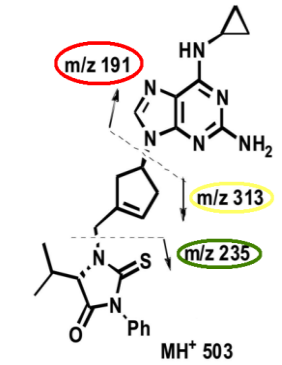
✓Abacavir is bioactivated into reactive (aldehydes) derivatives *in vivo*

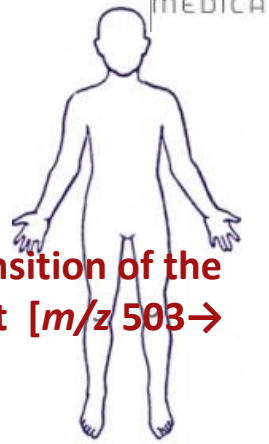
✓The conjugated aldehyde is the reactive metabolite that subsists long enough in man to react with biomacromolecules.

Charneira *et al. Br. J. Pharmacol.*, 2012, 167, 1353–1361
Charneira *et al. Toxicol. Lett.*, 2013, 219, 59-64

LC-ESI-MS/MS of the MS³ transition of the abacavir-valine *Edman* adduct [*m/z* 503→ 313 → 235]





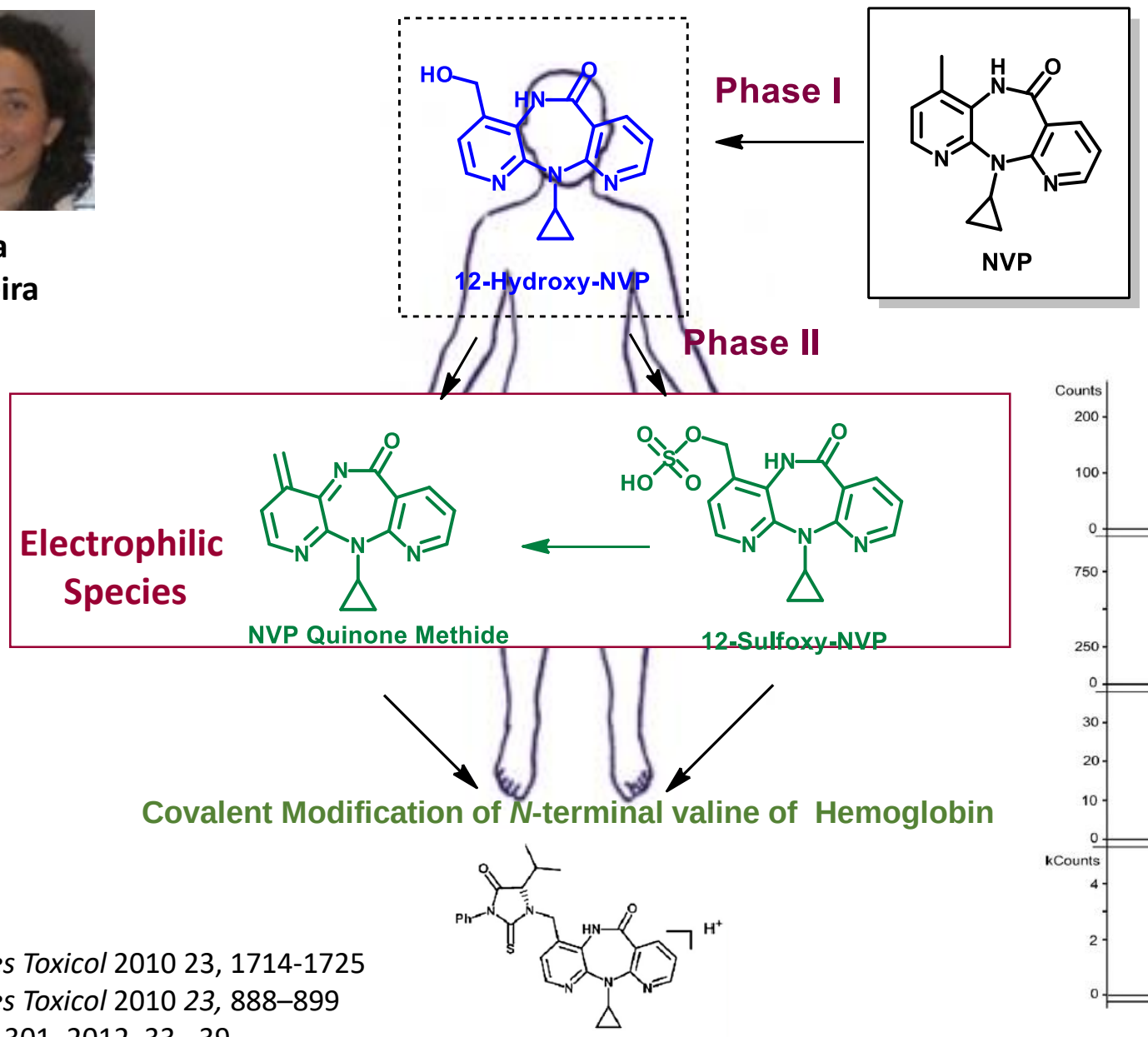


Sofia Pereira

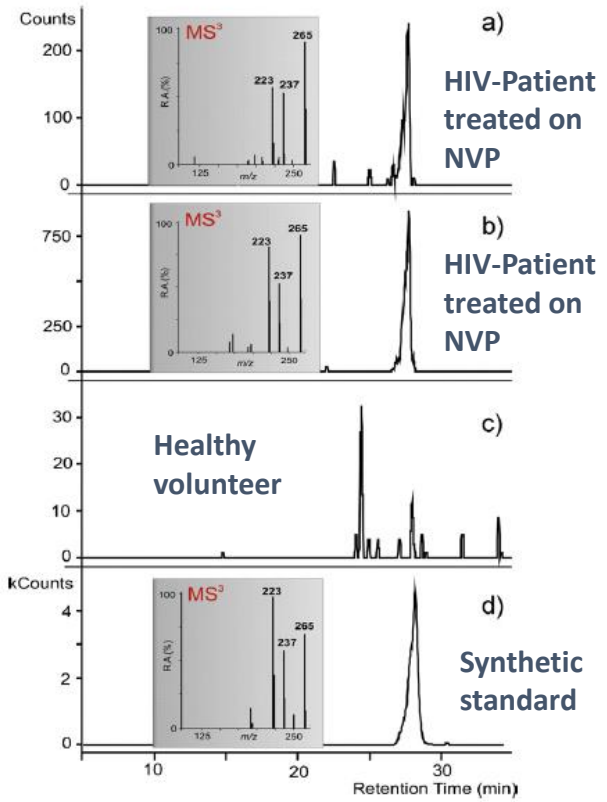
Emília Monteiro

Nevirapine Bioactivation

Sofia
Pereira

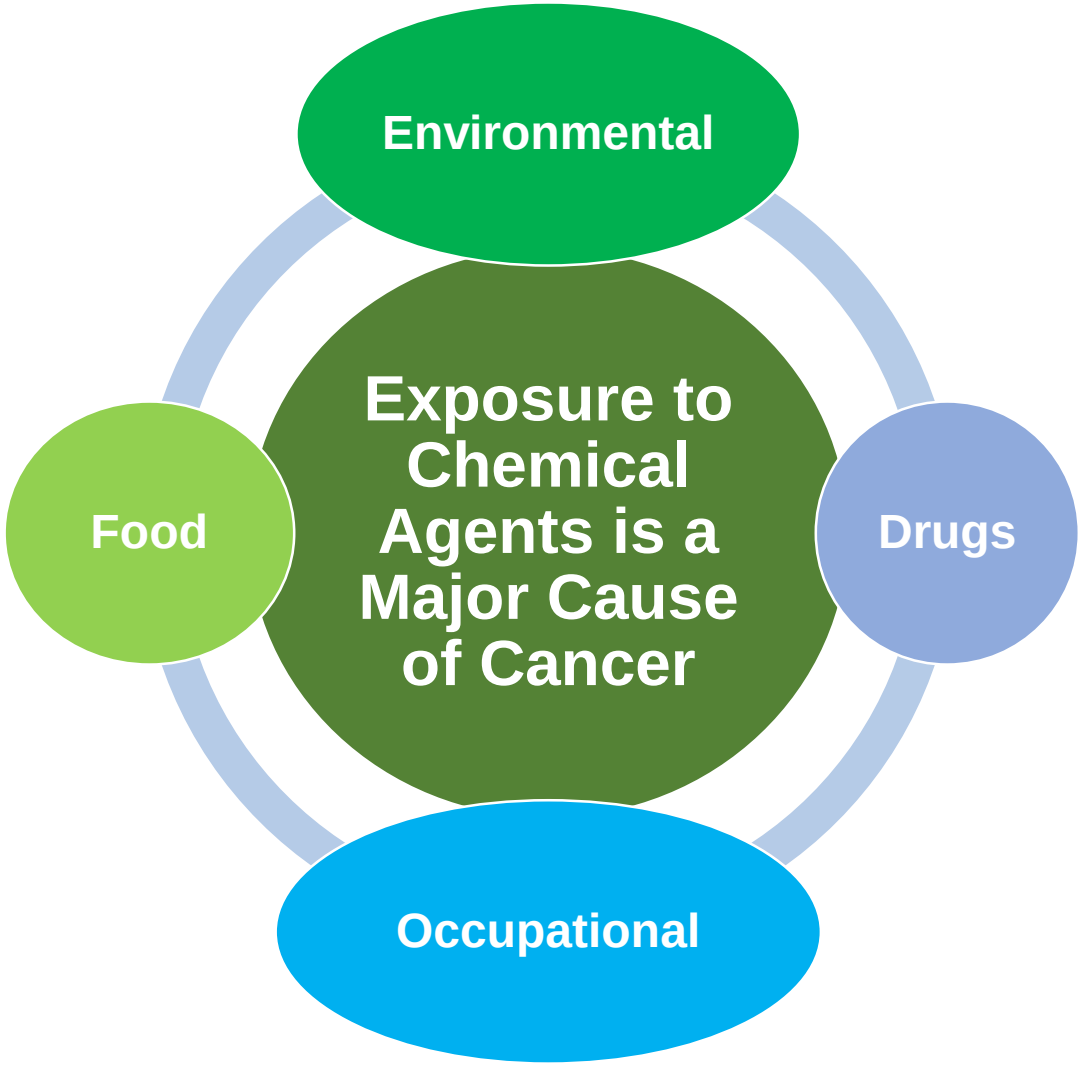


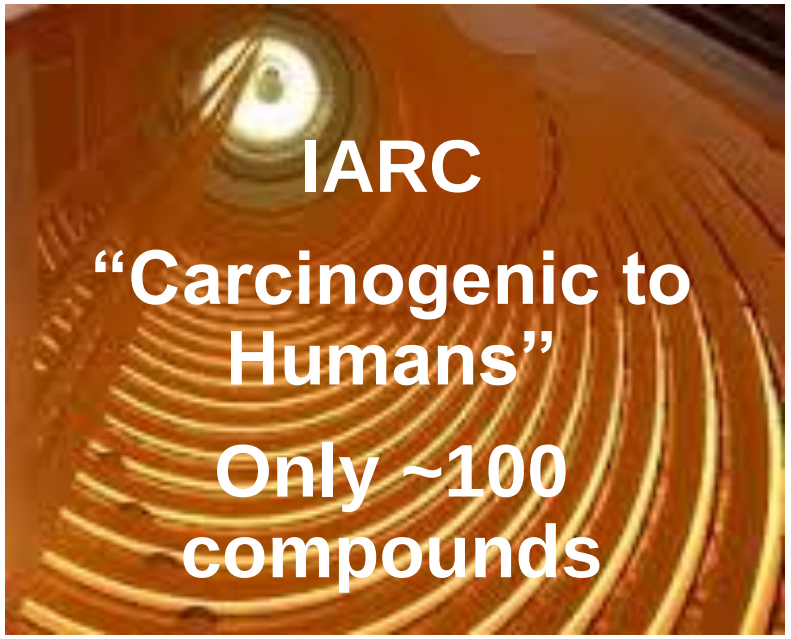
- ✓Anti HIV-drug (NNRTI)
- ✓Most used antiretroviral in developing countries
- ✓Associated with hepatotoxicity and skin rash



Antunes et al. *Chem Res Toxicol* 2010 23, 1714-1725
Antunes et al. *Chem Res Toxicol* 2010 *23,* 888–899
Caixas et al. Toxicology 301, 2012, 33– 39

ADDUCTOMICS: Development of new Biomarkers of Chemical Carcinogenesis

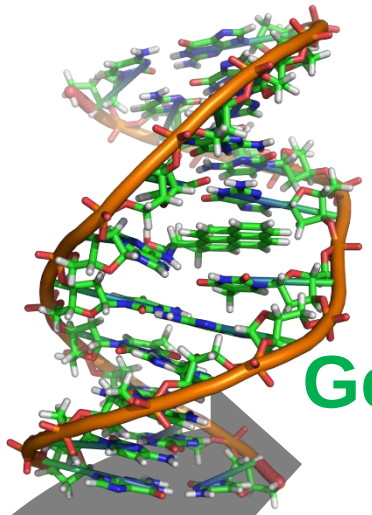




International Agency for Research on Cancer (IARC)

RATIONAL

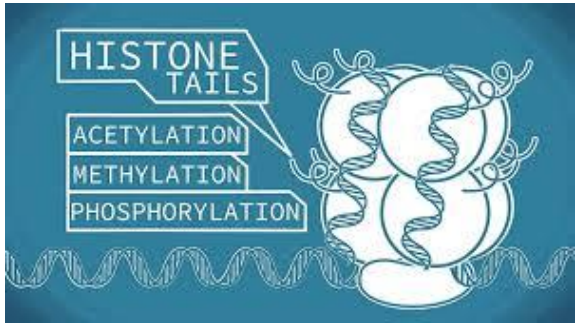
LRI Innovative Science Award 2014



Genetics

Exposure to Chemical Carcinogens

Covalent modification of histones by carcinogens



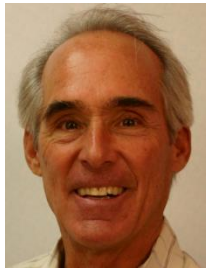
Epigenetics: The Key Mediator

Early compound-specific biomarkers of exposure to carcinogens

Fisher 344 Rats
Exposed to Furan

- Rodent non-genotoxic carcinogen
- Food contaminant

IARC: “possibly carcinogenic to humans” (Group 2B)
NTP: “reasonably anticipated to be a human carcinogen”



Fred Beland

Igor Pogribny

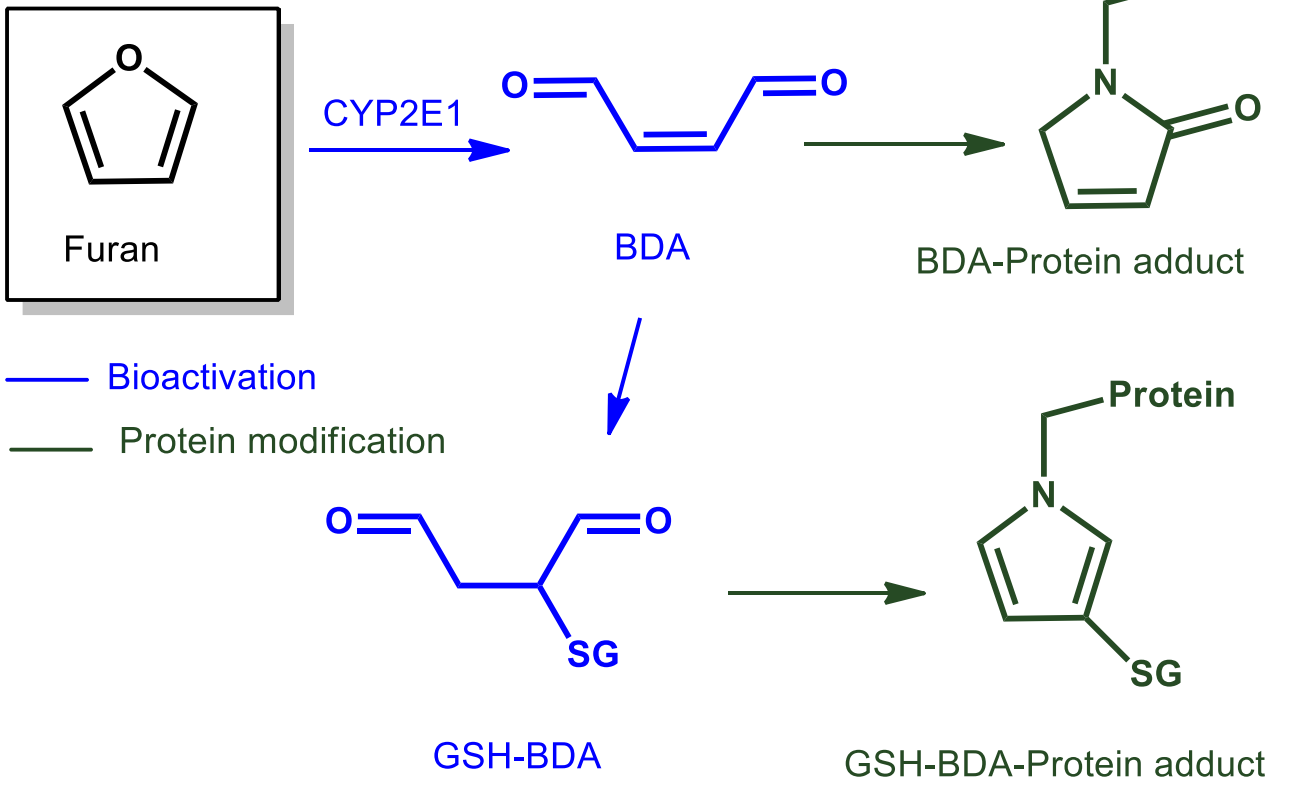
Aline de Conti

Food and Drug Administration
NCTR
National Center for Toxicological Research

In Vivo

Epigenetic Changes

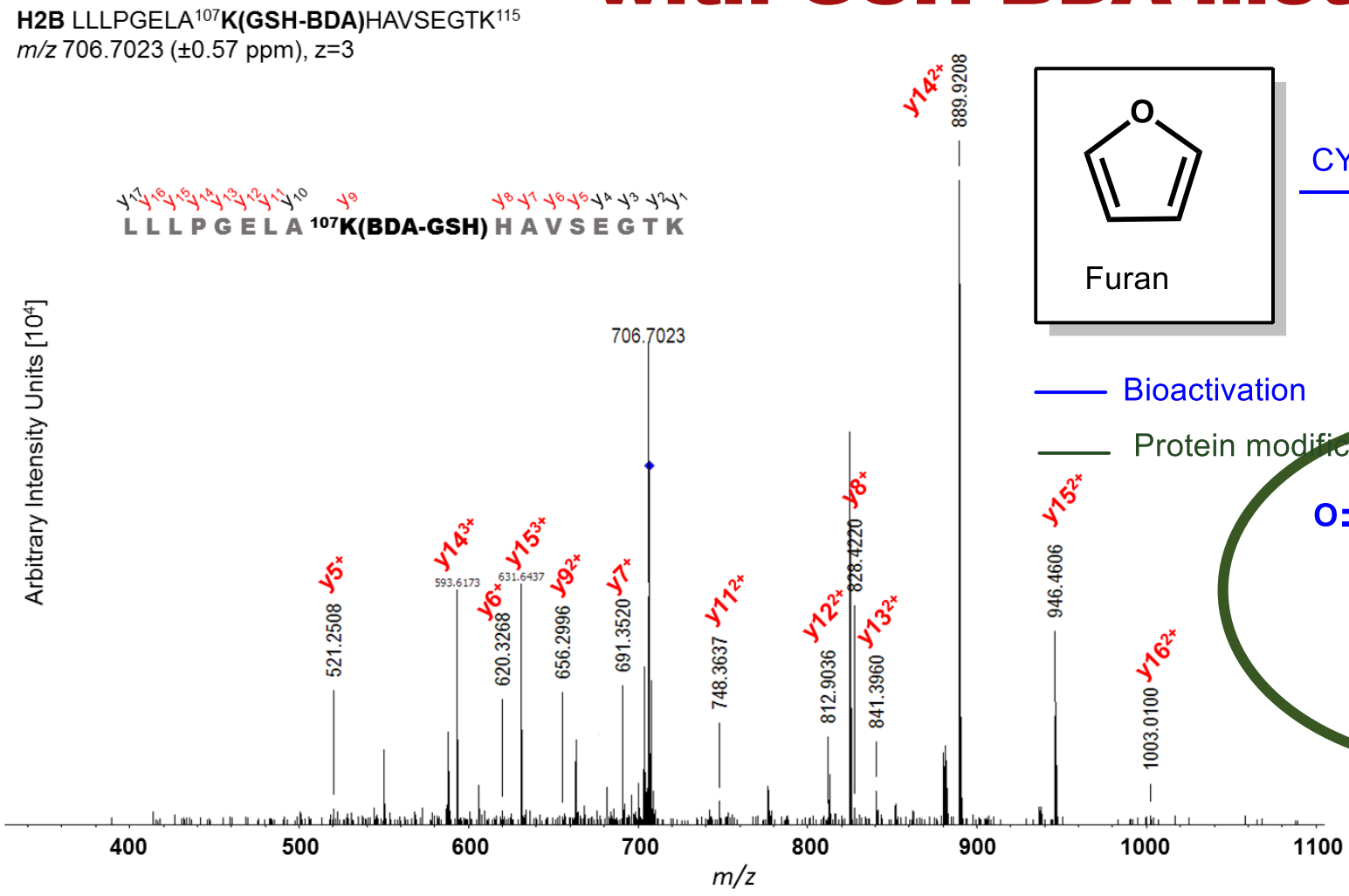
Fisher 344 Rats Exposed to Furan

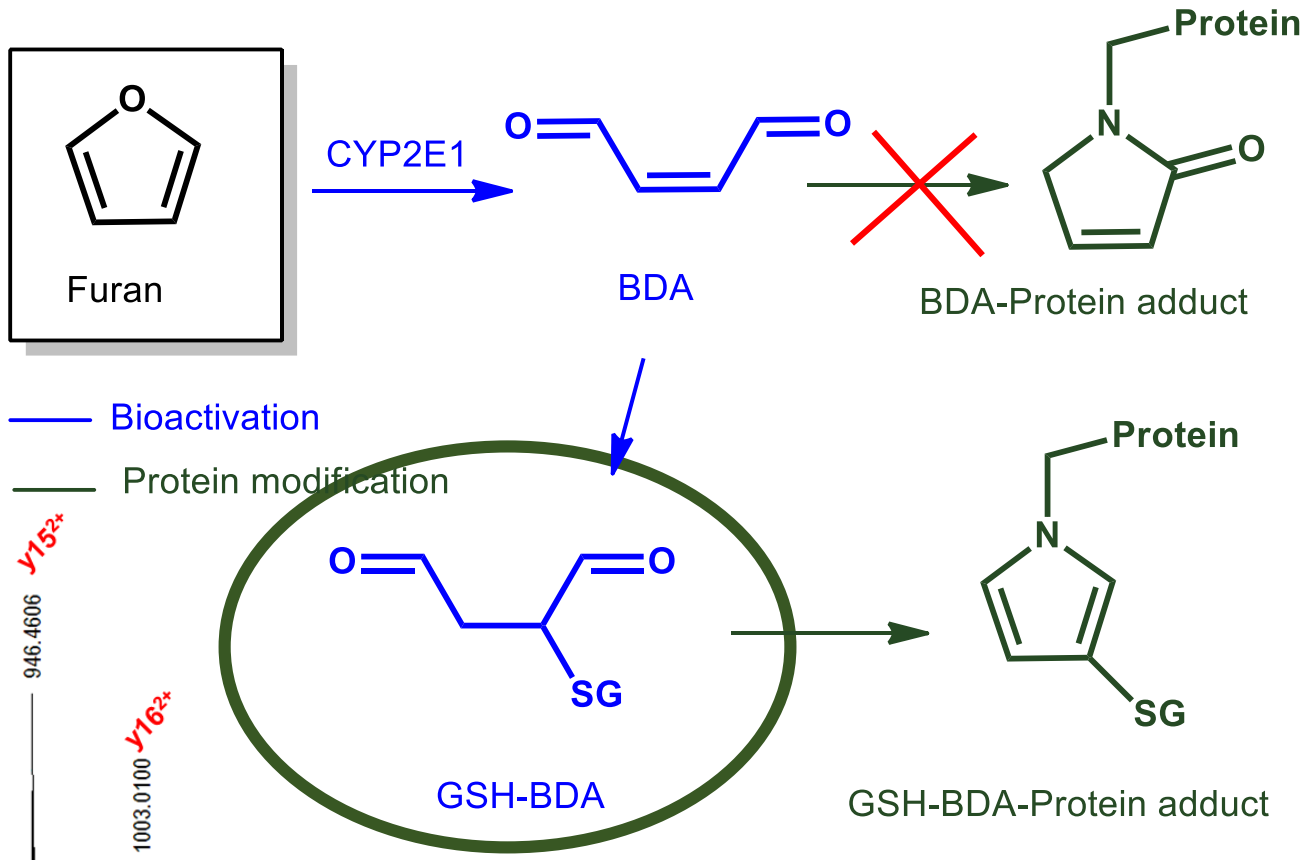


Can Histones be Covalently Modified by Non-Genotoxic Carcinogens?

Philips *et al.,* Chem. Res. Toxicol. 2014, 27, 129−135.

Lysine 107 of histone 2B covalently modified with GSH-BDA metabolite





Reactive Metabolite

Nunes et al. Toxicol Lett, 2016, 264, 106-113.

In Vivo

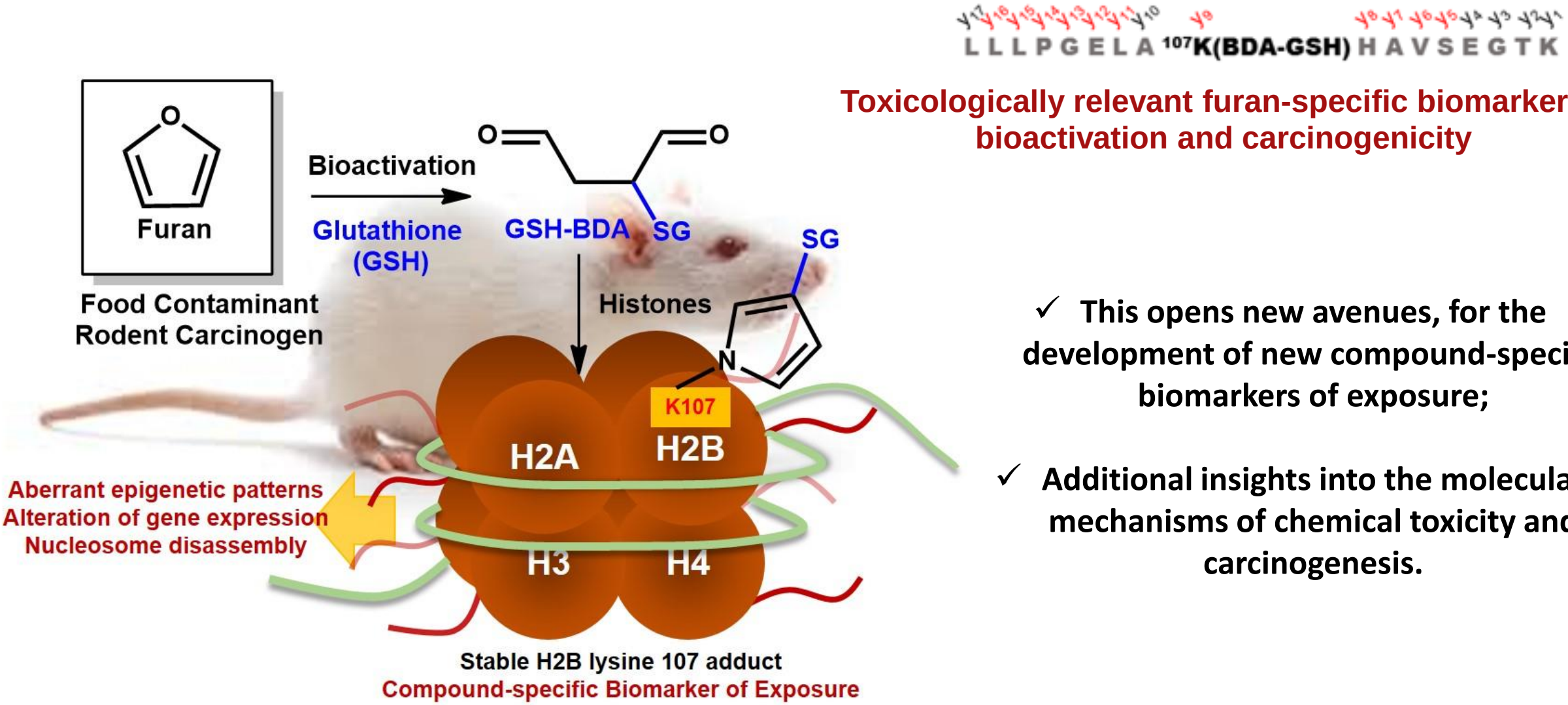
Fisher 344 Rats Exposed to Furan

Epigenetic modifications

Dose	0 mg/kg (bw/day)			0.92 mg/kg (bw/day)			2 mg/kg (bw/day)			4.4 mg/kg (bw/day)		
Length (days)	90	180	360	90	180	360	90	180	360	90	180	360
Replicates												

This covalent modification preceded the identification of altered epigenetic profiles, suggesting that it may take place at the early stages of furan-induced carcinogenesis.

Nunes et al. Toxicol Lett, 2016, 264, 106-113.



Toxicologically relevant furan-specific biomarker of bioactivation and carcinogenicity

- ✓ **This opens new avenues, for the development of new compound-specific biomarkers of exposure;**
- ✓ **Additional insights into the molecular mechanisms of chemical toxicity and carcinogenesis.**

Nunes et al. Toxicol Lett, 2016, 264, 106-113.

Metabolomics & Adductomics: devolpment of diseases diagnosis tools

External exposome

CAR

AhR

PxR

Transcriptional regulators of metabolizing enzymes

Altered metabolism of endogenous metabolites & xenobiotics

Disease

LUPUS: Autoimmune disease difficult to diagnose

Clarify LUPUS

A TEST FOR LUPUS-SPECIFIC DIAGNOSIS

- ✓ **Lupus-specific biomarker**
- ✓ **Accurate and Sensitive**

Earlier Detection
Saves & Improves lives

PATIENT BENEFITS

- ❑ **Earlier Lupus diagnosis**
- ❑ Earlier Treatment
- ❑ Live longer
- ❑ Better Life quality

HOSPITALS AND CLINICS

- ❑ Reduced healthcare costs

CLARIFY ANALYTICAL

Clarify LUPUS

João Rodrigues

HELPING LUPUS PATIENTS TO EXTEND THEIR LIVES AND IMPROVE THEIR QUALITY OF LIFE

http://www.clarifyanalytical.com

alexandra.antunes@clarifyanalytical.pt
joao.rodrigues@clarifyanalytical.pt

TÉCNICO LISBOA

CQE Química Estrutural CENTRO DE QUÍMICA ESTRUTURAL

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA E DO ENSINO SUPERIOR

M. Matilde Marques

M. Conceição Oliveira

Cristina Jacob

€€€€
PTDC/QUI-QUI/113910/2009
PTDC/SAU-TOX/111663/2009
RECI/QEQ-MED/0330/2012
PEstOE/QUI/UI0100/2013
IF/01091/2013/CP1163/CT0001
UID/QUI/00100/2013

POPH PROGRAMA OPERACIONAL POTENCIAL HUMANO

IF INVESTIGADOR FCT

SEVENTH FRAMEWORK PROGRAMME

PRIME-XS

LRI Long-Range Research Initiative

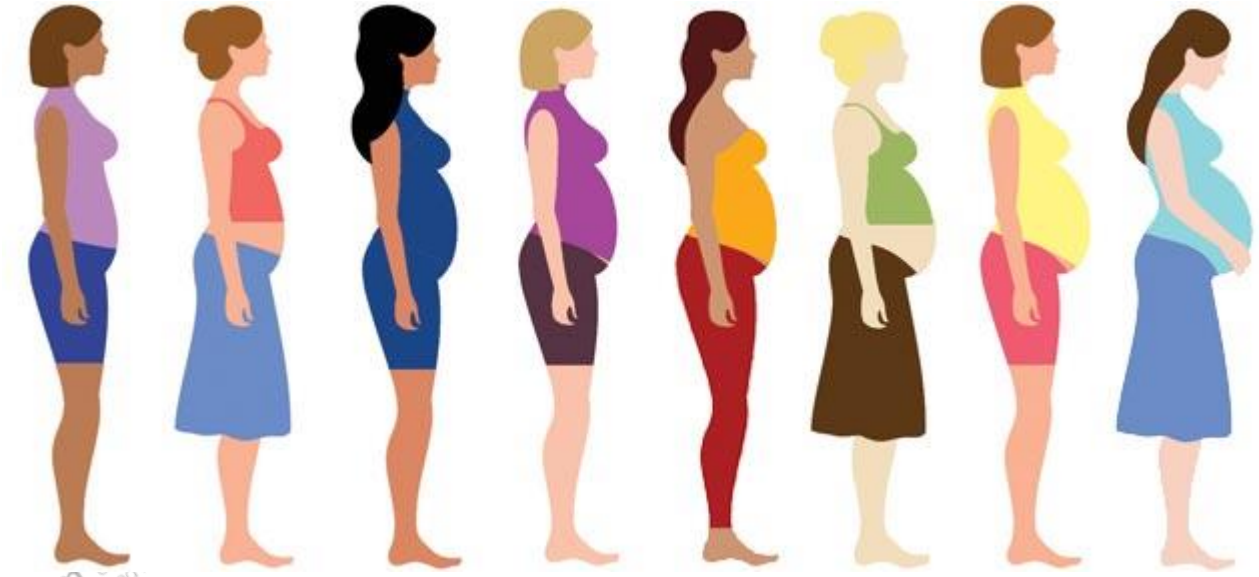
cefic

LRI Innovative Science Award 2014

PTNMR

RNE

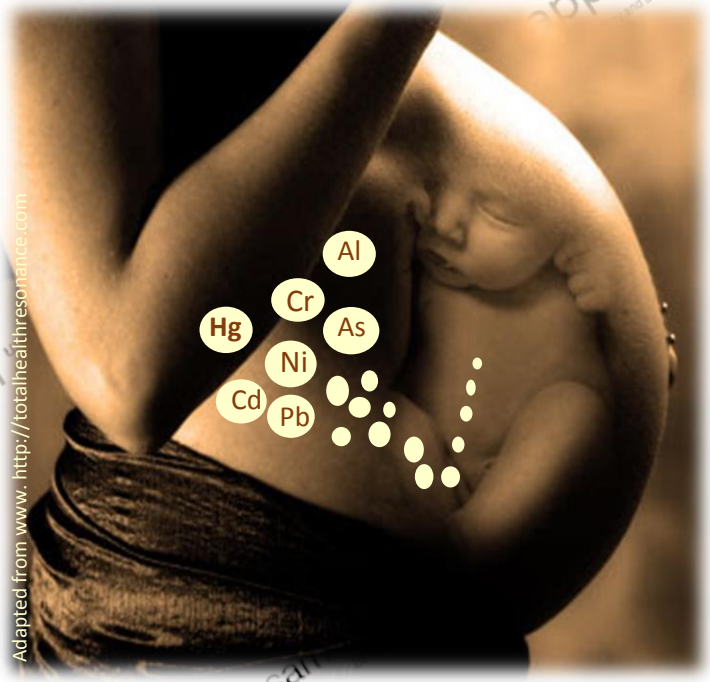
Maternal and pre-natal exposure to harmful substances in Aveiro region



Susana Loureiro and Marta S Monteiro

sloureiro@ua.pt; mmonteiro@ua.pt

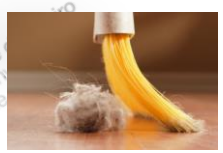
Pre-natal exposure to Potentially Harmful Substances



Adapted from www. http://totalhealthresonance.com

- A sensitive window in human development
- Impairment of the central nervous system at an higher extent than in adults (e.g. Al, Hg)
- Low birth weights, delayed growth, craniofacial malformations, impaired cognitive and psychomotor development
- Epidemiological studies assessing accumulation and potential maternal transfer of PHSs to fetus are crucial to assess human risk

monitoring of potential harmful substances @ Aveiro district - Estarreja



- **Sediments** and **soils**[1]
- **Accumulation** of metallic elements in **edible** parts of **vegetables** grown/ consumed in this area and in fish from ria de Aveiro[2,3]
- **Cu and Mn** contents in the toenail clippings are more elevated in children than in adults[4]
- **Mn** levels in toenails were associated with house dust Mn contents[4]
- **In house dust**: Al, Zn, Cu, Pb, Mn, Ba, Ni, Cr, Sn, V and As[5]
- **Hg accumulation in hair and placenta** of parturient from the Aveiro district[6]

[1]Rodrigues et al. 2010; [2]Mieiro et al. 2012; [3]Inácio et al. 2014; [4]Reis et al. 2015; [5]Plumejeaud et al., 2016; [6]Alves et al. 2017

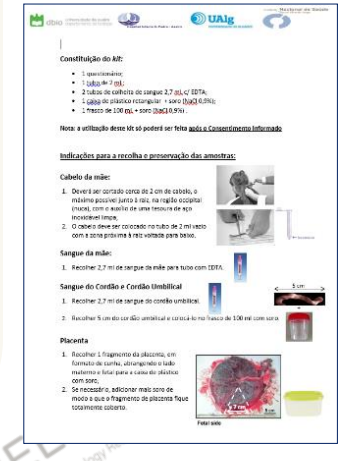
Objectives

- to assess **maternal and fetal exposure to PHSs in Aveiro** region using non-invasive biological matrices;
- to investigate the potential **influence variables** (**sociodemographic factors, eating and smoking habits and lifestyle**) which contribute to exposure to PHSs during pregnancy;
- to investigate **how PHSs levels are distributed along the Aveiro district**;
- to explore possible **effects of PHSs exposure** in placental system.

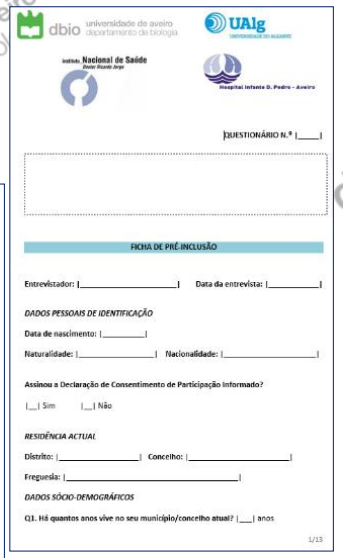
Study population & Sampling

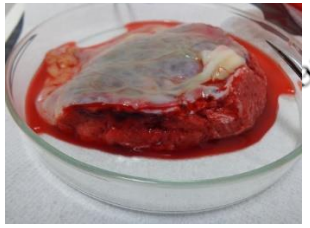
- **Cross-sectional study: 50 mother-newborn pairs** resident in Aveiro district (informed consent; Ethics Committee of HIDP (Aveiro) approval)
- Collection dates: **October 2014 - April 2015**
- **Questionnaires (lifestyle, eating and smoking habits, newborn anthropometry, etc) + kits** with material to collect and store the samples were given to the Hospital team (HIDP, Aveiro)
- Preparation and preservation of biological material at Dbio/UA for PHSs quantification and biochemical analysis

Kit

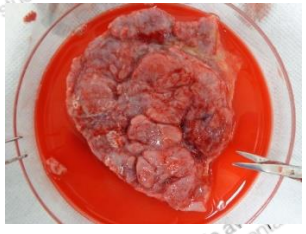


questionnaire





Fetal surface of placenta (chorionic plate) + amniotic membrane



Maternal surface of placenta (decidua basalis)

Umbilical cord

Maternal blood

Maternal hair

Biomarkers of exposure - PHEs in placenta & hair

- **Placental samples** were freeze-dried for 72 h and then homogeneized (stored at -20ºC);
- **Hair samples** were washed with acetone and water MiliQ and dried overnight at 35ºC.

- Determination of 16 elements by **ICP-MS***:

As, **Al, Cr, Cd, Ni, Pb, Mn,** Zn, Cu, Rb, Se, Sr, P, Ca, Mg, Fe;

- **Total mercury *+** determination by **AAS** after thermal decomposition of the sample using the Advanced Mercury Analyser (AMA-254, LECO).

PAHs types quantified by **fixed wavelength fluorescence:**

- Low Molecular Weight PAHs

Naphthalene equivalents (290/335 nm)

Phenanthrene equivalents (259/380 nm)

- High Molecular Weight PAHs

Pyrene equivalents (341/383 nm)

BaP equivalents (380/430 nm)

*Perfomed by Dr. **Pedro Coelho** & Profª Dra **Eduarda Pereira;** DQ & CESAM, UA

Reference materials: ERM - BB184 (bovine muscle)* and ERM-DB001 (human hair)+.

Biomarkers of effect in placenta

Biological matrix

Placenta

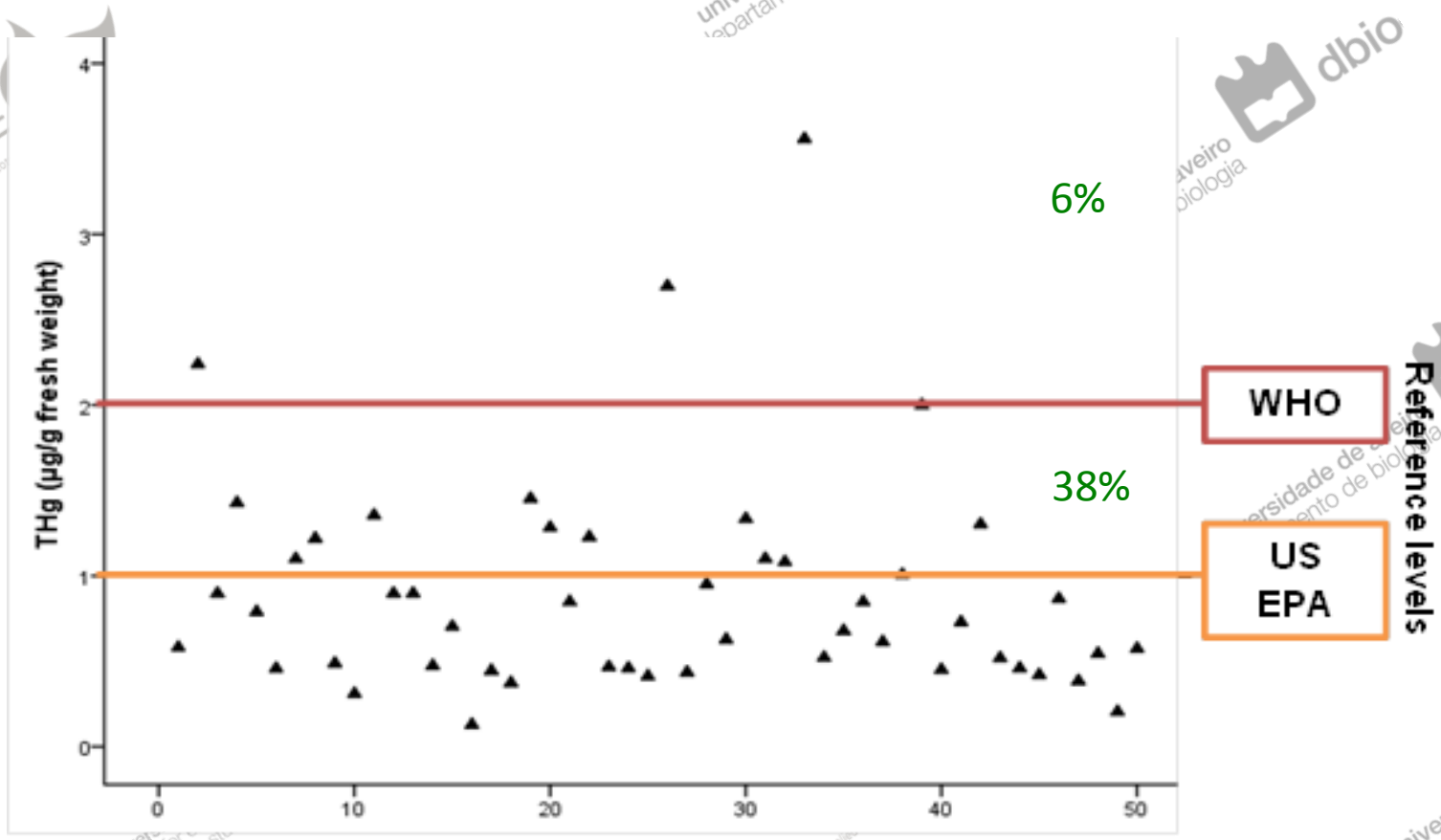
Biochemical biomarker analysis

Thermo Multiskan Spectrum microplate reader (version 2.4.4)

Biomarkers of effects:

- **Oxidative stress**
  - alterations in oxidative stress enzymes (e.g. CAT, GST)
  - glutathione (GSH) levels
  - lipid peroxidation (LPO) – oxidative damage
- **Neurotoxicity** - cholinesterase (ChE) inhibition
- **Epigenetic modifications** – DNA methylation

Total Hg in maternal hair



- THg average of 0.9 µg g^{-1}, which is very close to the limit established by US EPA (1 µg g^{-1});
- These results were similar to a recent study performed in south of Portugal;
- Favorable Concentration to Teratogenic effects: 10 µg g^{-1}

Placental Samples

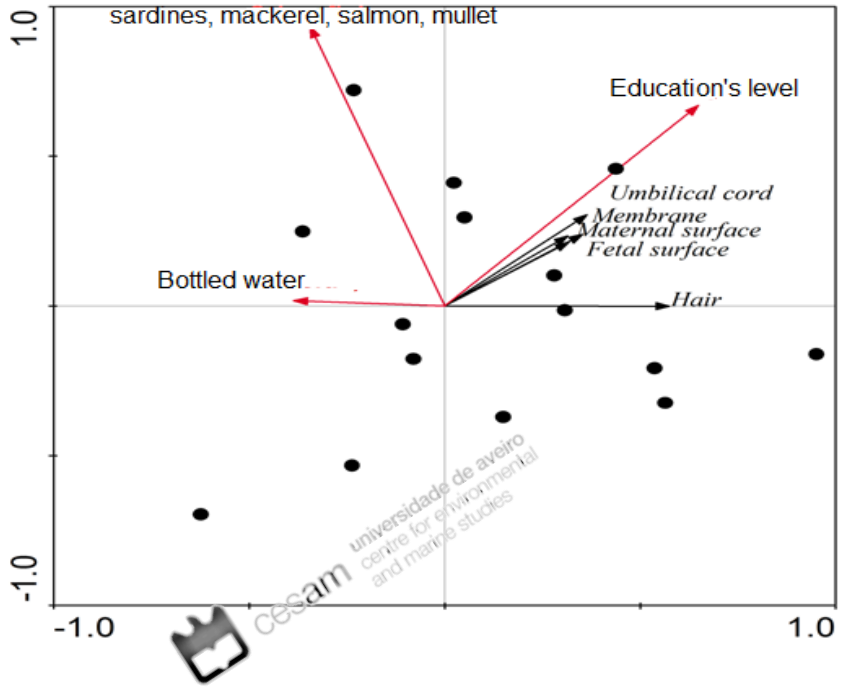
	Mean	Median	SD	Minimum	Maximum
Decidua basalis	32.84	27.55	18.34	3.0	84.10
Chorionic plate	30.18	26.80	[illegible]1	2.7	84.10
Amniotic membrane	**42.35**	**33.65**	**29.07**	**6.0**	**134.10**
Umbilical cord	30.67	27.30	16.67	3.6	76.3

units expressed by ng g^{-1} dry weight; SD: standard deviation

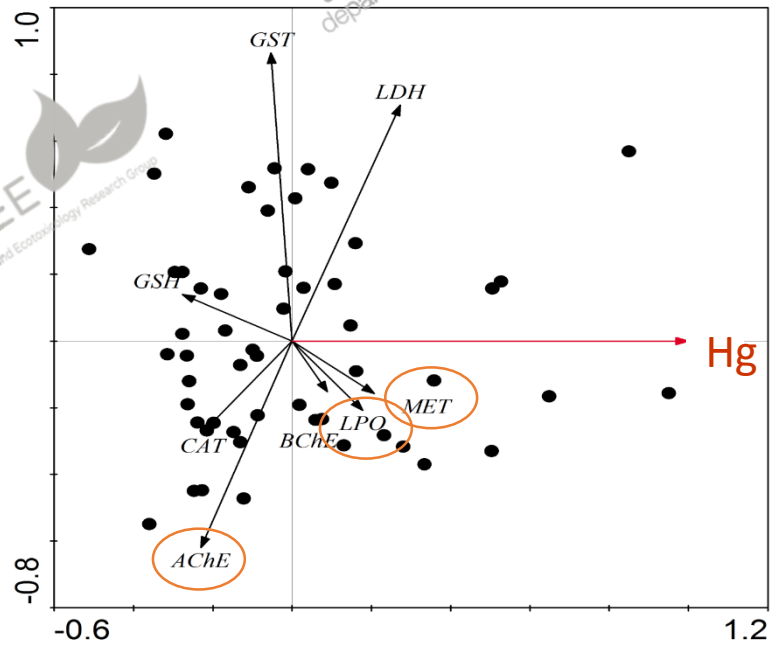
- A strong relationship ***(p<0.001)*** was found between Hg levels obtained in maternal hair, cord and placental tissues; higher levels found in the amniotic membrane;
- Our results were **lower than placental Hg levels found in Belgium, Italy, Germany and Denmark**; **higher** than for the **Czech Republic**; and similar to **Spain.**

Biplots based on Redundancy Analysis (RDA)

All matrices



Placental Samples



- Hg affects neurotransmission biomarkers, induces oxidative stress and DNA methylation

PHEs levels in placenta

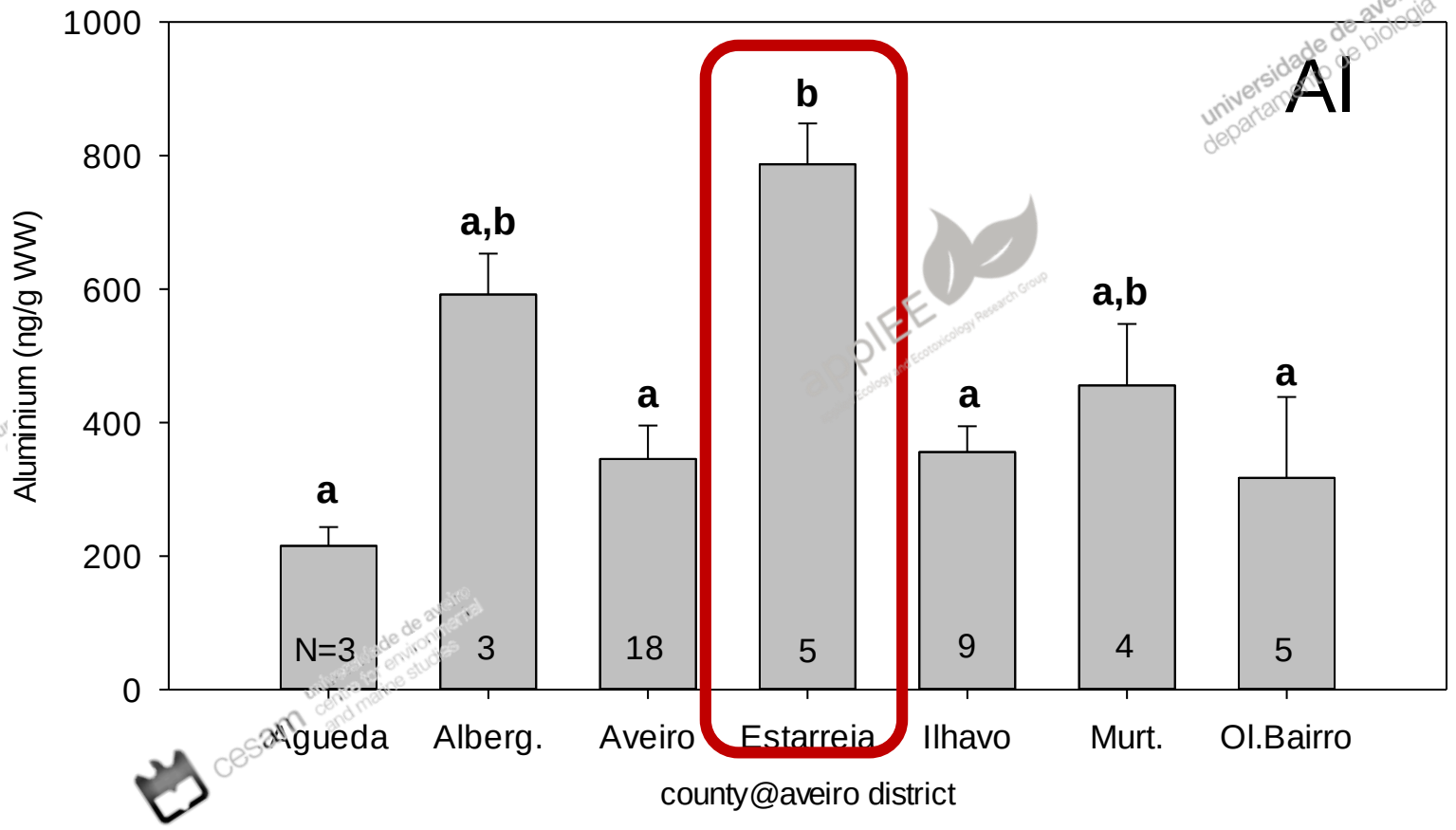
	Present study @ Aveiro					Other studies			
ng g^{-1}	Mean	SD	Min	Max	N	Algarve, PT[1]	Review[2] (1976-2000)	Review[3] 1976-2011	USA[4, 5]
Al	400	220	80	940	49	-	250	-	560
Cr	65.7	59.7	20.2	293.2	49	42 ± 11	-	-	-
Ni	64.1	79.7	11.0	315.0	30	65 ± 47	36 (9-62)	-	-
Mn	74.7	20.3	42.6	171.4	49	-	-	-	73.9 ± 39.4
Cd	4.9	1.7	2.3	10.5	49	0.005±0.004	4 (1.5–6)	1.2-53	3.5 ± 2.4
Pb	13.2	36.4	3.7	255.8	47	39 ± 6	34 (5-60)	1.18-300	2.3 ± 3.7

PHEs levels in ng g^{-1} wet weight (WW); N – number of replicates above limit of detection (LOD)

- In general, levels are within the range values obtained for placenta in other studies worldwide;
- No levels regulated for placenta (as a matrix of exposure)

[1]Serafim et al. (2012); [2]Iyengar & Rapp (2001); [3]Esteban-Vasallo (2012); [4]Kruger et al. (2010) [5]Pushon et al. (2016)

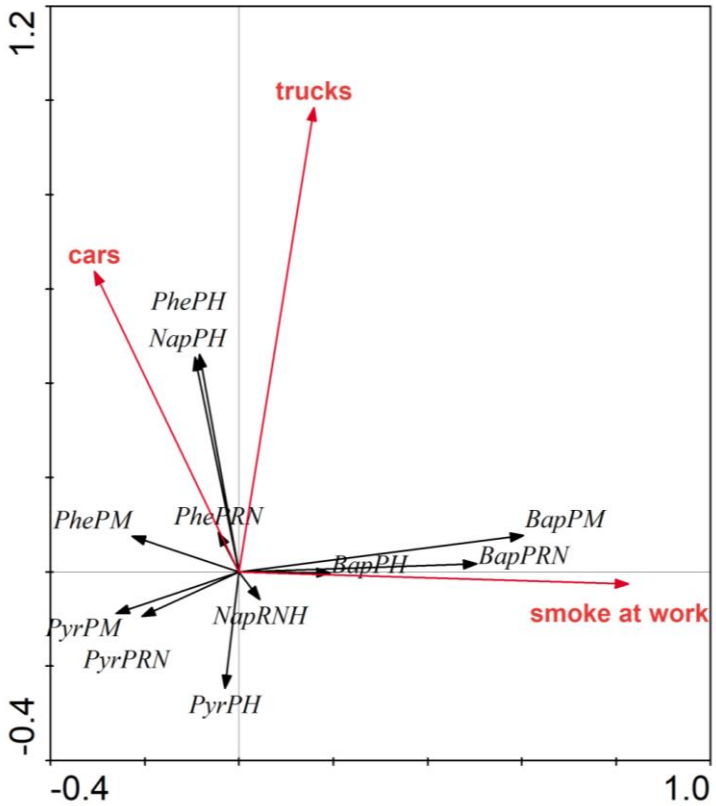
Distribution of Al levels along the Aveiro district



Al – element also found at high level in house dust @ Estarreja (Plumejeaud, et al. 2016)

Lifestyle and smoking habits influence in placenta PAHs levels

Placental and blood samples



Biplots based on redundancy analysis (RDA)

variables:

- tobacco smoke at work
  (F=3.055; p=0.0460) **(BaP)**
- residence nearby traffic roads
  - with trucks, rural areas (F=2.446; p=0.0280)
    (PAHs low mol weight)
  - with cars (F=2.302; p=0.0320) **(Naph, Phen)**

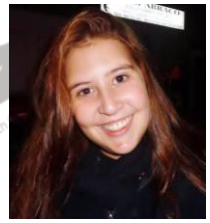
Percentage of PAHs variation explained by this variables : 15.2%

Main conclusions and remarks

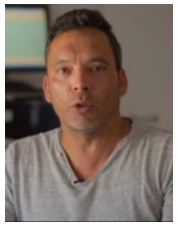
- First biomonitoring study concerning pre-natal exposure to PHSs in the Aveiro region;
- Higher levels of Hg detected in hair and in the amniotic membrane → understand its role in the placental-fetal accumulation of Hg, further research should be done with a larger sample size as well as Hg speciation;
- Living in rural areas and eating canned vegetables were associated with higher burdens of different elements (Al, Ni, Cr, Mn, Cd) in placenta;
- Further studies should be performed, particularly in Estarreja, where higher burdens of some of these elements were found (e.g. Hg, Al, Mn) – number of samples; other matrices (e.g. umbilical cord blood);
- Portugal still has limited information about intrauterine exposure to environmental contaminants. Further research should be done in order to prevent fetal exposure to harmful substances and their potential effects.
- Pregnant woman are aware of PHS exposure, but awareness only starts after pregnancy announcement!

Research team


Ana Catarina Alves


Marta Fraga


Ana Luísa Machado


Carlos Gravato


Amadeu Soares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ohm ESTARREJA

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MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR Portugal

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HBM4EU

science and policy
for a healthy future

Prioritisation Strategy in HBM4EU

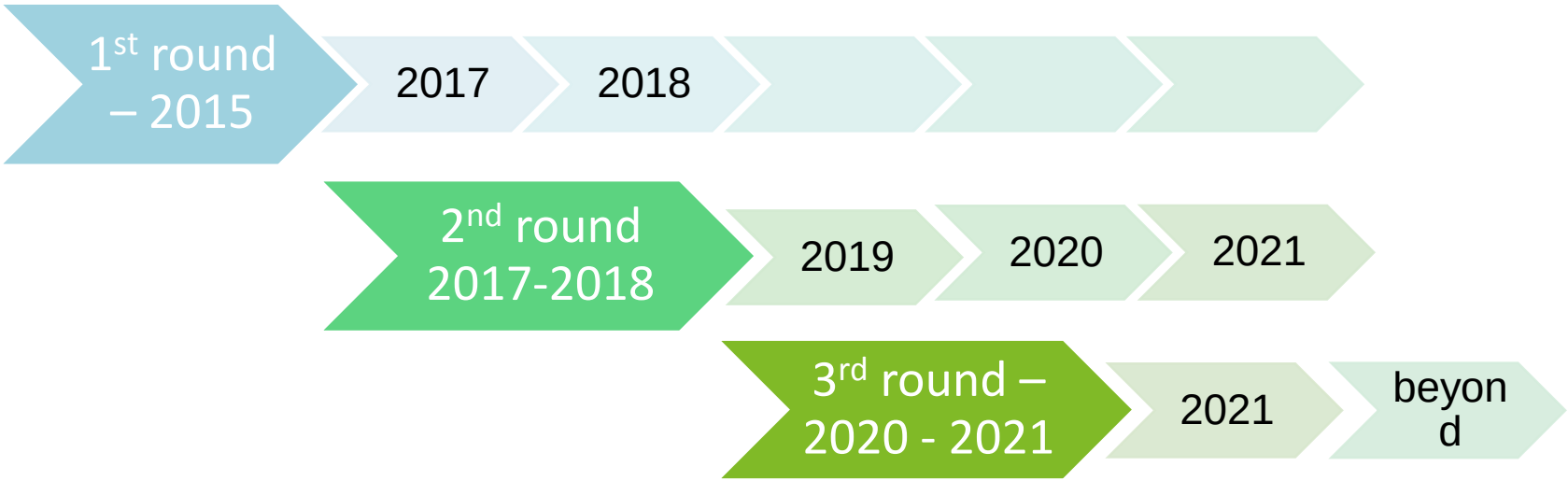
Joana Lobo Vicente

European Environment Agency

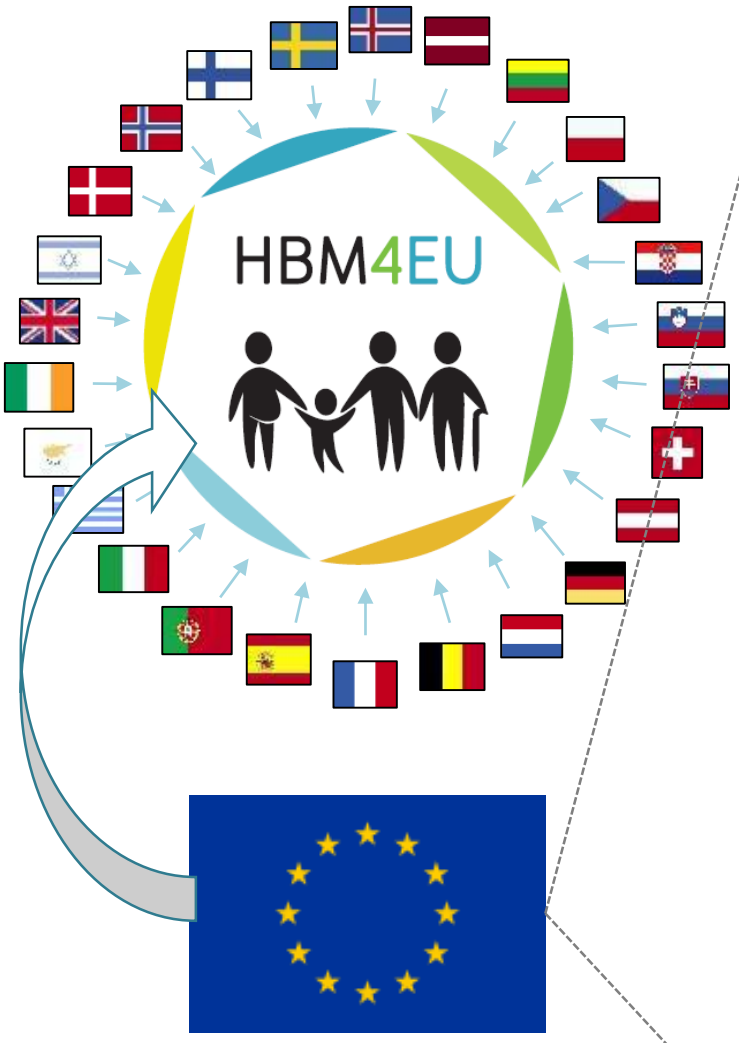
Objectives of HBM4EU

- Data on exposure is **missing.**
- Bridge the **science-policy gap.**
- Answer **policy relevant questions.**
- Track the **efficacy of existing policies.**
- Enhance **chemical risk assessment.**
- Generate evidence on **human exposure to chemicals.**
- Understand **impacts on health**
- Make **evidence available** through the **knowledge hub**
- Make **human biomonitoring** data available via **IPChem**

How we select chemicals: Three rounds of prioritisation



Prioritisation process



EU level

ENV
chemicals legislation (e.g. REACH), air/water pollution, noise

EMPL
worker safety, exposure to chemicals

RTD R&I
framework programme

SANTE
food contaminant, pesticides, biocides, EDs

GROW
product safety, cosmetics, REACH

JRC
scientific and technical support

ECHA
REACH regulation

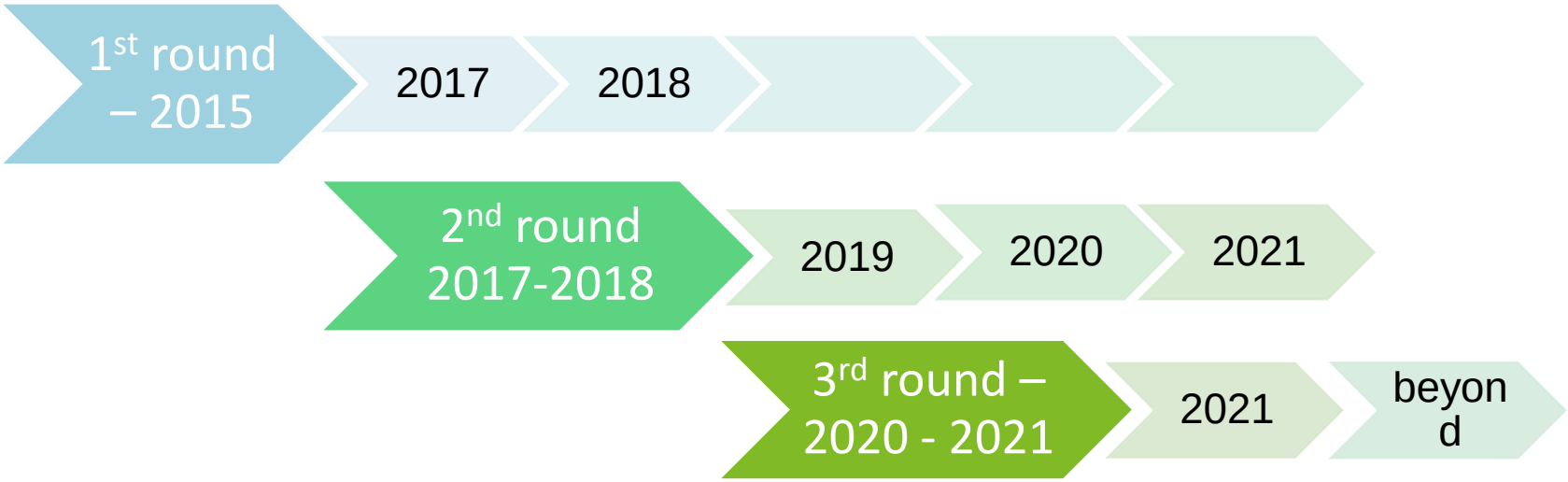
EEA
environment data, information, assessment

EFSA
risk assessment for food and feed

1st list of priority substances

Substance	Exposure routes	Policy relevance
Phthalates and DINCH	Consumer products	REACH, Chemical Agents Directive
Poly/per-fluorinated compounds	Consumer products, via environment, diet	REACH, Stockholm Convention, Chemical Agents Directive, Food Contact Materials
Bisphenol A, S and F	Consumer products, diet	REACH, Chemical Agents Directive
Brominated and organophosphate flame retardants	Consumer products	REACH, Stockholm Convention, Chemical Agents Directive
Poly aromatic hydrocarbons	Urban air	NEC Directive, Long Range Transboundary Air Pollution Convention, Chemical Agents Directive, REACH
Cadmium and chromium VI	Occupational exposure, environmental exposure, diet, smoking (Ca)	REACH, Chemical Agents Directive, Water Framework Directive, Drinking Water Directive
Aniline derivatives	Occupational exposure	REACH authorisation list, Chemical Agents Directive,
Mixtures	Multiple exposure routes	2012 Communication on combination effects, risk assessment of mixtures
Emerging substances	Multiple exposure routes	Forthcoming non toxic environment strategy

2nd round of prioritisation



The process builds on:

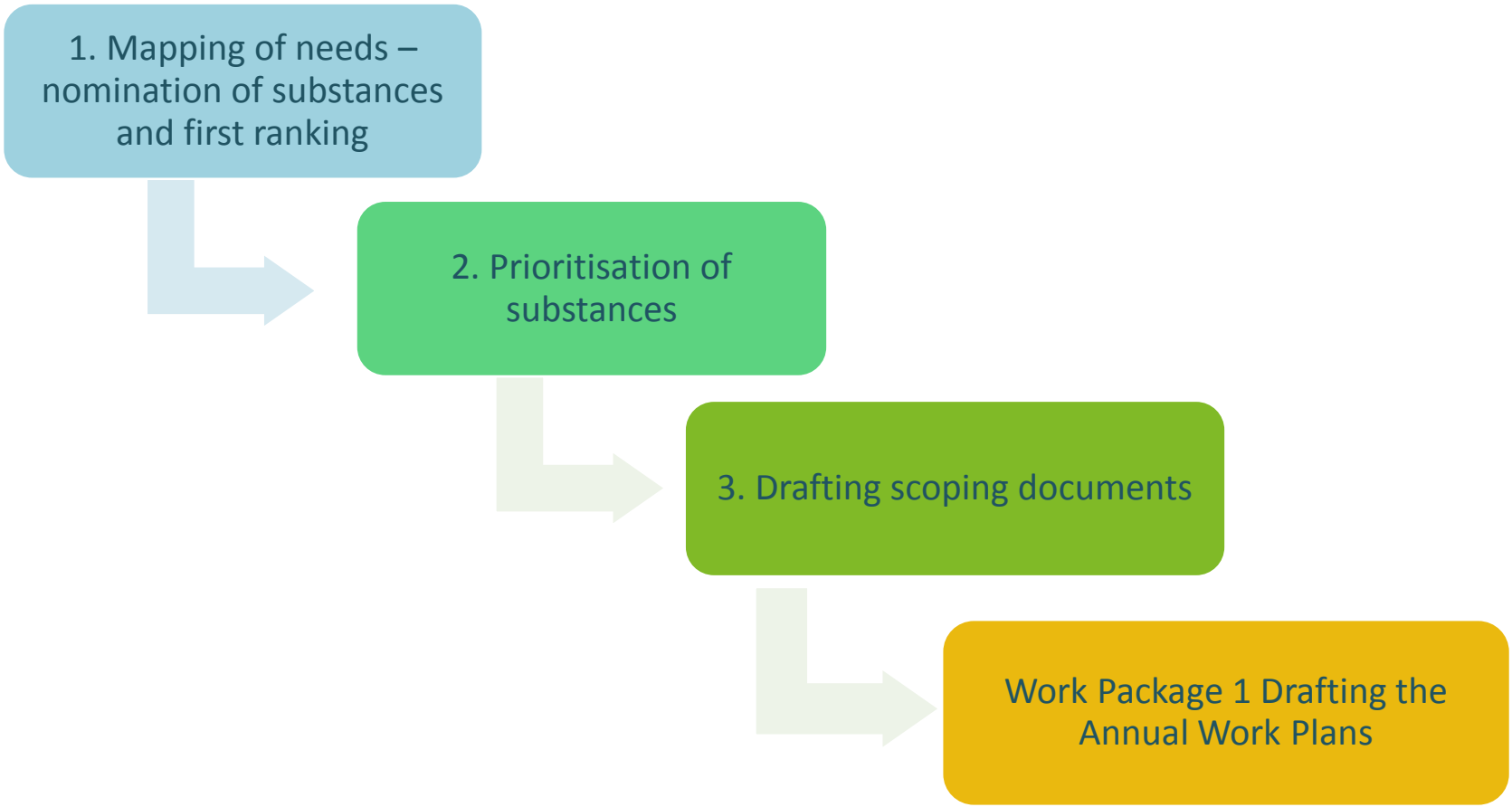
- Experience with 1st round
- Review of existing methods
- Discussions with partners
- Consultation with Management Board, EU Policy Board, National Hubs and Stakeholder Forum

The criteria

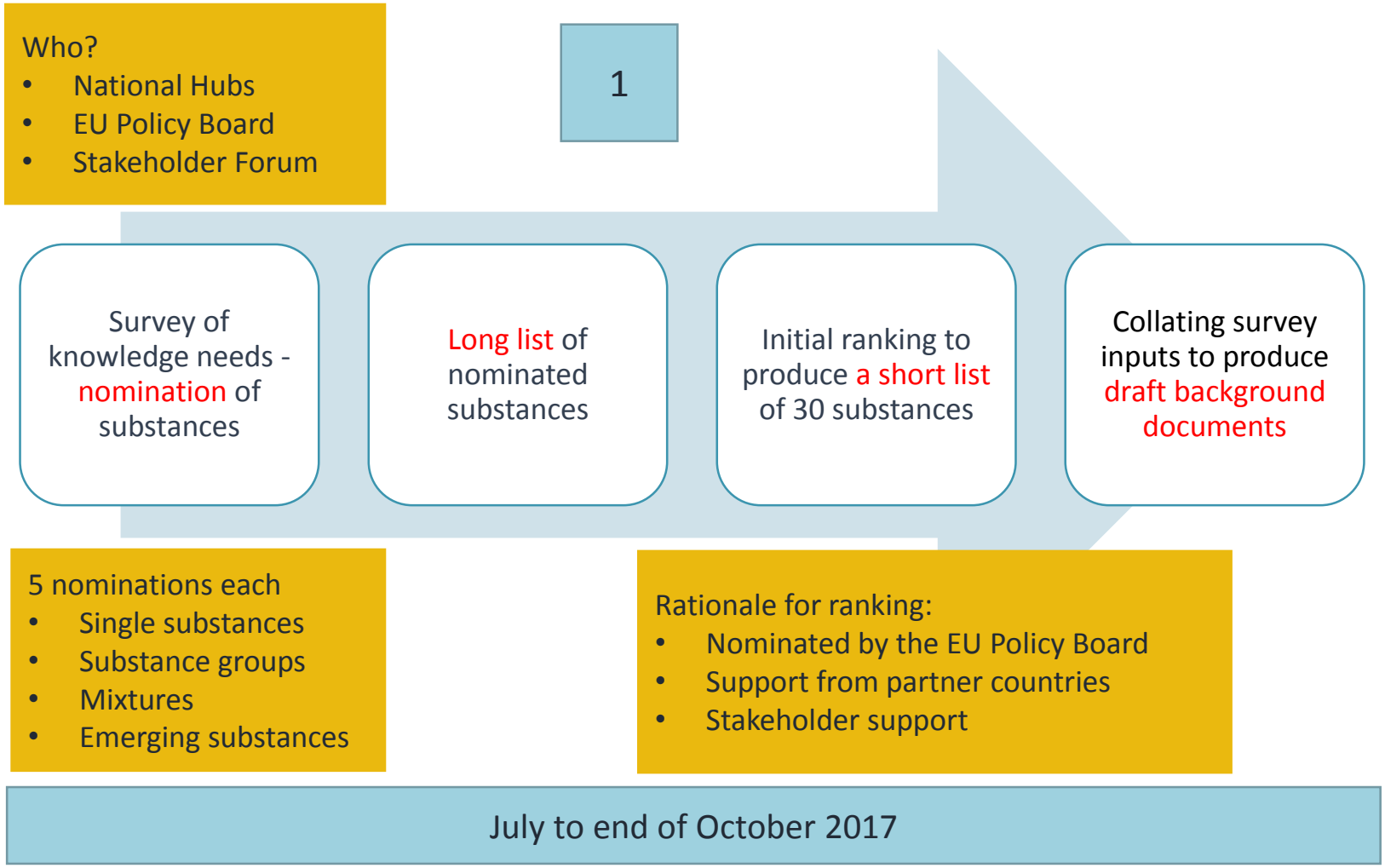
New knowledge

Hazard properties	• Hazard classifications • Other classifications – REACH substance of very high concern • Persistence, bioaccumulative and toxic
Exposure characteristics	• Media of exposure, sources • Exposure routes, prevalence, vulnerable groups • Is human biomonitoring data available?
Regulatory status	• Covered by EU legislation? • Relevant legislation at national level? • Toxicity reference values? Biomonitoring guidance values?
Public concern	• Evidence of public concern?
Technical feasibility	• Are biomarkers available? • Analytical methods?

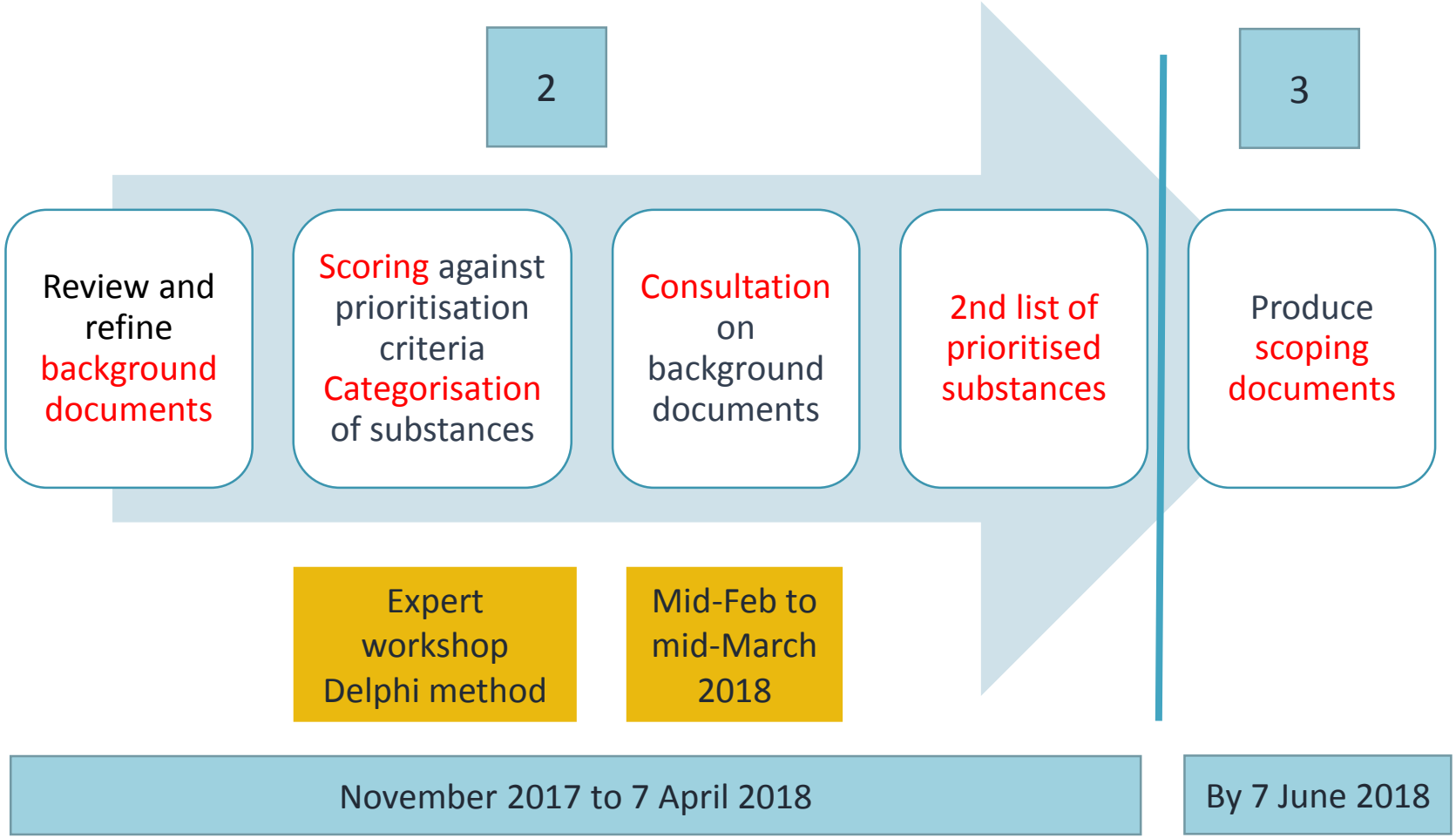
The process


1. Mapping of needs – nomination of substances and first ranking
2. Prioritisation of substances
3. Drafting scoping documents
Work Package 1 Drafting the Annual Work Plans

Mapping knowledge needs



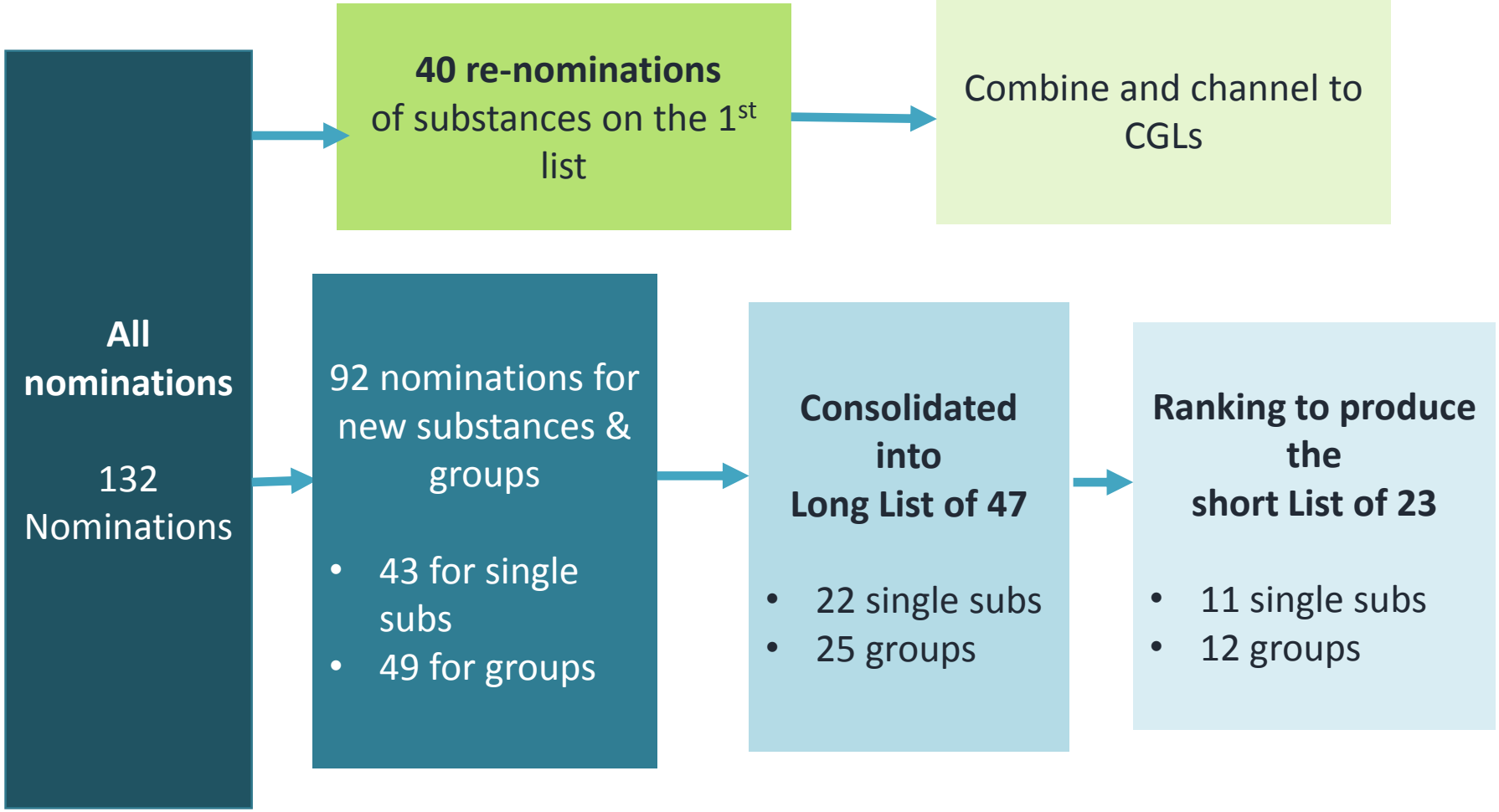
Prioritising substances



2nd priority list of substances survey - Sep. 2017

Role	Responses
Total	132 responses
Countries	24 countries
Stakeholder Forum	3 members
EU Policy Board	5 members

Process


All nominations
132 Nominations
40 re-nominations of substances on the 1st list
Combine and channel to CGLs
92 nominations for new substances & groups
• 43 for single subs
• 49 for groups
Consolidated into Long List of 47
• 22 single subs
• 25 groups
Ranking to produce the short List of 23
• 11 single subs
• 12 groups

*

Rationale for creating the short list

Aiming for consensus:

- Nominated by the EU Policy Board, SF and countries – 2
- Nominated by the EU Policy Board and countries – 10
- Nominated by one/more countries and a stakeholder – 3
- Nominated just by the EU Policy Board – 7
- Nominated by just more than 1 country – 1

Short List

Substance type	Substances/groups
Pesticides and biocides	Pesticides authorised in the EU, pyrethroids, glyphosate, POE-tallowamine, chlorpyrifos, dimethoate, fipronil, DEET
Metals	Mercury, arsenic, lead
Industrial chemicals	Aprotic solvents, diisocyanates, BHT, phenolic benzotriazoles, QACs, UV filters, substituted phenylenediamines , siloxanes
Food contaminants	Mycotoxins, including DON and fumonisin B, acrylamide, perchlorate
Nanomaterials	Nanomaterials

Scoring methodology applied to the (groups of) substances

1) **Weighting** the prioritisation criteria according to their relative importance for prioritising substances within HBM4EU

    - **hazard properties**
    - **exposure characteristics**
    - **public concern**

2) **Scoring** the substances/groups of substances against each criterion

3) **Calculating a global score** for each substance: sum of weighting score for criterion x score against criterion

Categorisation of substances

Category A - HBM data are sufficient to provide an overall picture of exposure levels across Europe, and interpretation of biomonitoring results in terms of health risks is possible.

Category B - HBM data exists, but not sufficiently to have a clear picture across Europe.

Category C - HBM data scarcely or do not exists. Efforts to develop an analytical method to obtain relevant HBM results are needed.

Category D - toxicological concern exists but HBM data are not available.

Category E - not yet identified as of toxicological concern and for which no HBM data are available. To be addressed under work package 16 on emerging substances.

The regulatory status of the substance and the technical feasibility of human biomonitoring were taken in consideration in categorising substances

The table below provides the ranking of substances and substance groups based on their global score against the criteria hazard, exposure and public concern.

Substances shaded in blue are to be monitored under the multi-annual Community control programme for 2018, 2019 and 2020, see Commission Implementing Regulation (EU) 2017/660.

Rank	Name	Hazard score	Exposure score	Public concern score	Global score	Category
1	Arsenic inorganic compounds	27.2	38	9	74.2	B
2	Lead (Group: Lead & its compound)	25.3	36	9	70.3	A
3	Acrylamide	23.2	36.8	5.4	65.4	B
4	Aflatoxin B1 (Group: Mycotoxins)	30.8	27.2	5.4	63.4	B
5	Chlorpyrifos	13.3	29.2	20	62.5	B
6	Pyrethroids	17.2	27.2	18	62.4	B
7	Dimethoate	12.8	31.2	18	62	C
8	Permethrin (Group: Pyrethroids)	14	28	18	60	B
9	Mercury (Group: Mercury & its organic compounds)	18.8	30	10.8	59.6	A
10	Glyphosate	13.2	32	12.8	58	C
11	BP-3 (Group: UV filters-Benzophenones)	15.2	30.8	9	55	B
12	DDAC (Group: QACs)	9.2	32.8	12.8	54.8	C
13	4,4-MDI, 2,4-TDI & 2,6-TDI (Group: Diisocyanate)	18.8	28	7.2	54	C
14	Nano Titane dioxide (Group: Nanos)	16	26.8	10.8	53.6	D
15	Deoxynivalenol (Group: Mycotoxins)	18	28	5.4	51.4	C
16	Methylmercury (Group: Mercury & its organic compounds)	18.7	22.7	9	50.4	B
17	D4 (Cyclic Siloxanes)	5.6	33.2	11	49.8	C
18	N,N-dimethylformamide (DMF) (Group: Reprotoxic aprotic solvents)	16	30	3.6	49.6	B
19	Nano Silver (Group: Nanos)	14	26	9	49	D
20	BHT	14	32.8	1.8	48.6	C
21	Fipronil	16.8	25.2	3.6	45.6	C
22	Perchlorate	13.2	30	1.8	45	C
23	1-methyl-2-pyrrolidone (NMP) (Group: Reprotoxic aprotic solvents)	12	27.2	3.6	42.8	B
24	Fumonisin B1 (Group: Mycotoxins)	17.2	20	5.4	42.6	C
25	BENPAT (Group: Substituted phenylenediamines)	15.2	25.2	0	40.4	D
26	UV-328 (Group: Phenolic benzotriazoles)	10.4	26.8	1.8	39	C
27	Carbon nanotube (CNTs) (Group: Nanos)	10.8	18	9	37.8	D
28	POE-tallowamine	12	20	3.6	35.6	C
29	N,N-diethyl-m-toluamide (DEET)	6.8	25.2	0	32	C

The process so far….

July-Oct 2017

- Survey for the nomination of substances and groups
- Consolidated survey responses to produce background documents
- Produced long list of all nominations
- Produced the short list of nominations and draft background documents

Nov 2018

- Anses, UBA and VITO revised background documents
- Workshop on prioritisation: substances were scored against the prioritization criteria

Feb 2018

- EEA and DG RTD held bi-laterals with DG Santé and EFSA and with ECHA to discuss priorities
- ANSES, VITO and UBA workshop on ranking of substances

Mid Feb – Mid March 2018

- The Stakeholder Forum, National Hub Contact Points and EU Policy Board were given an opportunity to comment on the background documents and scoring
- EEA consolidated feedback

March – April 2018

- Joint meeting of the EU Policy Board and the HBM4EU Management Board, 5/6 March 2018
- 2nd List of HBM4EU Priority Substances
- Send to Governing Board for comments and approval

2nd list of priority substances

Substance
Acrylamide
Aprotic solvents
Arsenic
Diisocyanates
Lead
Mercury
Mycotoxins
Pesticides, including pyrethroids
UV filters - benzophenones

Acknowledgements

ANSES, France

UBA, Germany

VITO, Belgium

Stakeholder Forum

NHCP

European Environment Agency

Thank you

Joana Lobo Vicente

European Environment Agency

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HBM4EU

science and policy
for a healthy future

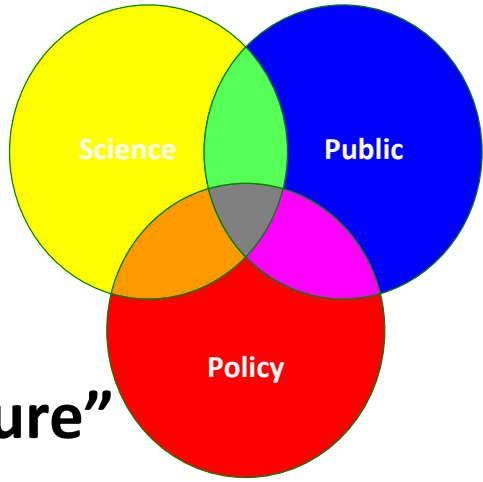
Human Biomonitoring and Risk Assessment of chemical Mixtures

Erik Lebret

RIVM National Institute of Public Health and the Environment

IRAS Institute of Risk Assessment Sciences, Utrecht University

Mixtures; A mystifying concept?



No common widely shared definition of "mixture"

- To regulators: combination of substances falling under their regulatory context and jurisdiction
- To scientists: generically, any combination of substances circulating simultaneously in the body, depending on their scientific discipline
- To public: involuntary exposures and archetypical scare and suspicion that single-substance risk assessment aren't telling the whole story, depending on their core beliefs and worldviews

es in HBM

- Any combination of chemical substances or their metabolites, circulating in the human body at a given time

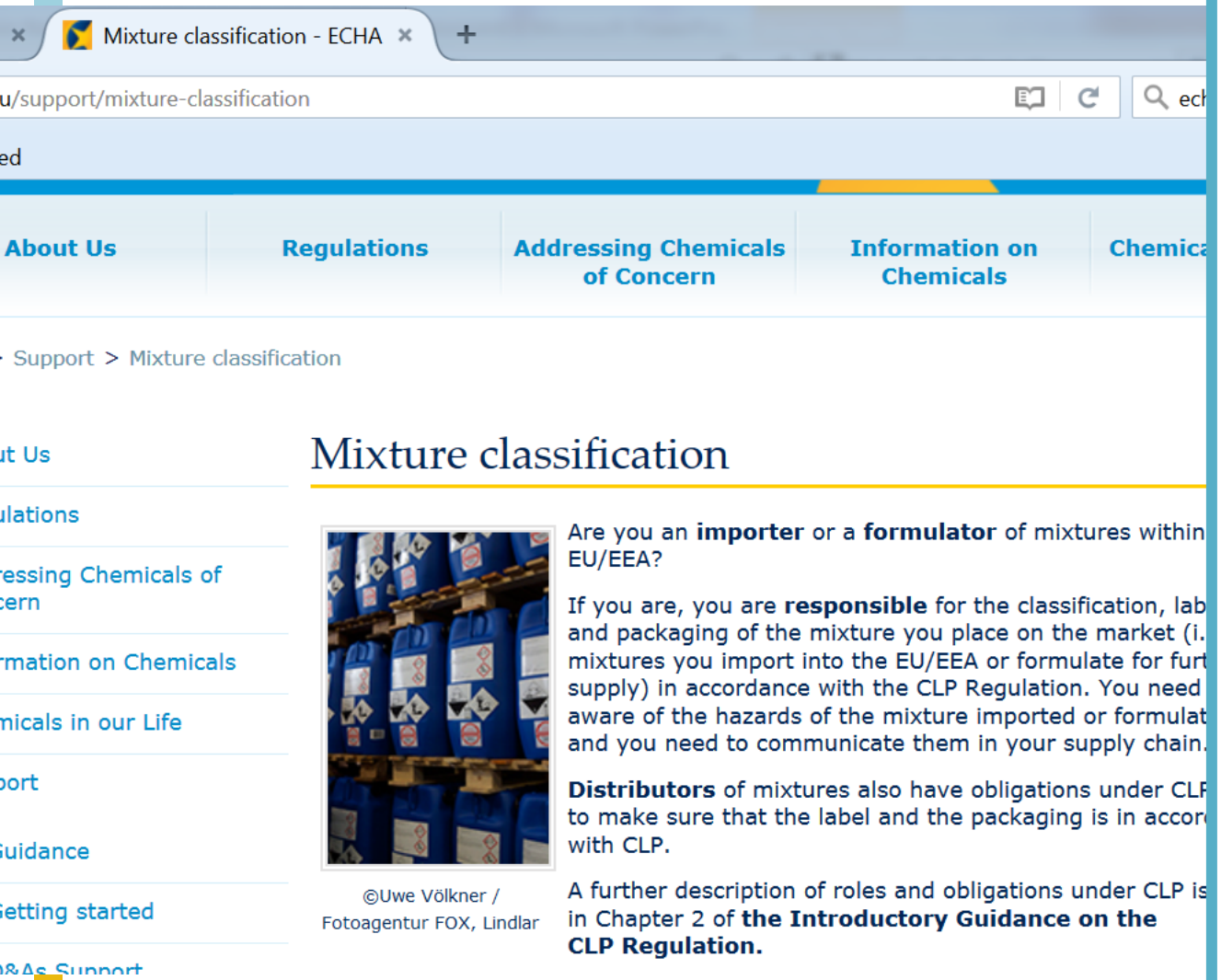
- Stemming from:
  - Joint simultaneous exposure from a single common source across single exposure routes
  - Joint simultaneous exposure from multiple different sources, possibly through different exposure routes and pathways
  - Past protracted or repeated exposure from multiple sources across multiple pathways

tions thereof

CEFIC report 2016. REACH Practical Guide on Safe Use Information for Mixtures under REACH

Stakeholders, intentional mixtures

From ECHA website and from CEFIC report



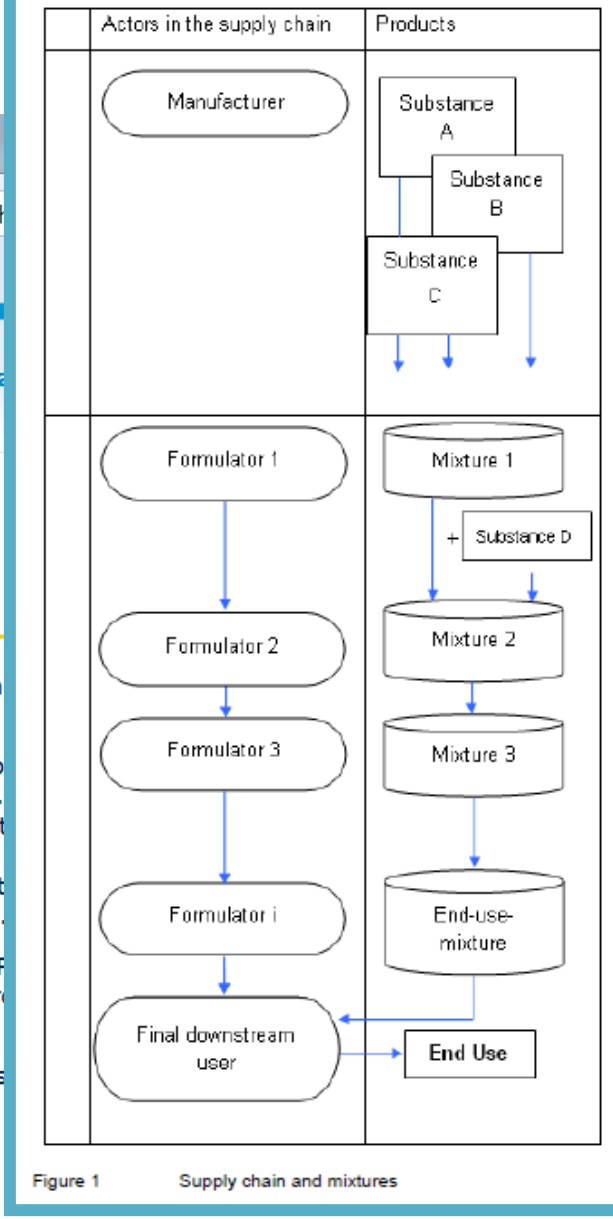
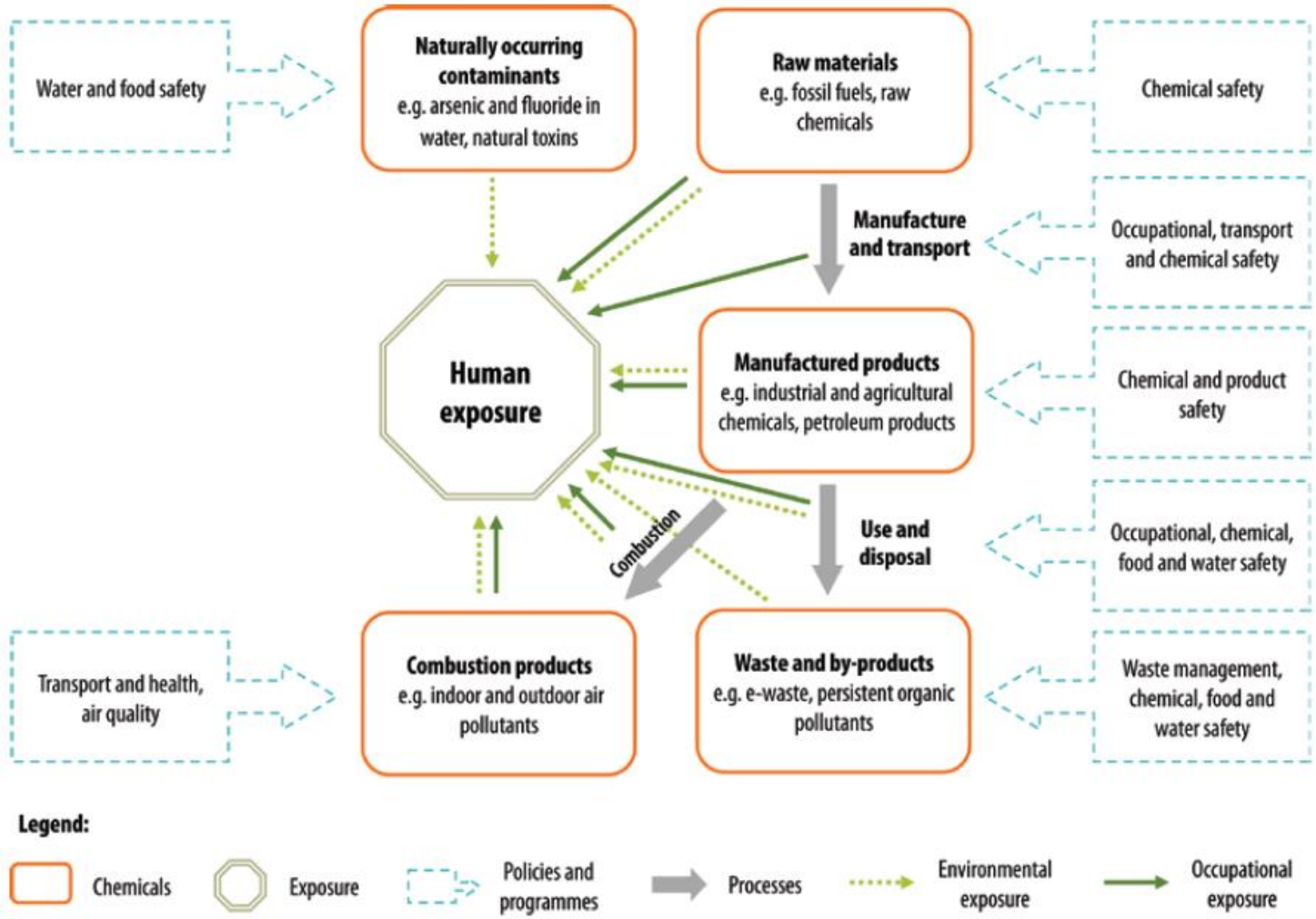


Figure 1 Supply chain and mixtures



Source: Knowns and unknowns on burden of disease due to chemicals: A systematic review, Prüss-Ustün et al (2011).

What mixtures are we talking about?

- Essentially, all the priority substances of HBM4EU are classes of mixtures by themselves; they can be grouped by:
  - Chemical family, e.g. phtalates, metals and PAH's
  - Application, e.g. plasticisers, flame retardants, pesticides, food additives, medication, recreational drugs
  - Supposed joint working mechanism of effect, e.g. endocrine disruptors
- These groups overlap and are not mutually exclusive

Challenge for Mixtures

"We encourage the consortium to start addressing identification of chemical mixtures to which humans are exposed and develop concrete activities, across all three pillars, which would be carried out in the second half of the project. The pre-defined mixtures of substances having common mode of action could frame the initial perspective on this topic."

Overarching objective

To improve the efficacy of HBM to inform science, policy/regulatory actions and societal debate with respect to dealing with mixtures

Some underlying questions:

- What is the information need of regulatory bodies and stakeholders?
- What are common HBM mixture patterns in the European population?
- Can we identify hotspots or risk groups with high mixture exposures?
- Which sources & pathways contribute most to HBM mixture values?
- Which effect markers can we use to assess health risks of mixtures?
- What action perspectives are available to reduce mixture levels?

More specific objectives

- Develop summary indicators to describe the exposure and body burdens of mixtures with an emphasis on defining priority mixtures and drivers of mixture toxicity
- Re-evaluate existing HBM mixture data to identify real-life exposure patterns to mixtures
- Collect new HBM mixture data in selected European countries
- Further develop and apply practical approaches to assess the potential health risks and impacts of mixtures
- Inform policy makers, stakeholders and the public at large about mixture exposures, possible health risks and action perspectives

Main tasks

15.1 Analysis of mixture HBM datasets

Existing datasets from the HBM4EU repository

15.2 Joint Survey

Measuring body burdens to pesticides mixtures in 3-5 countries

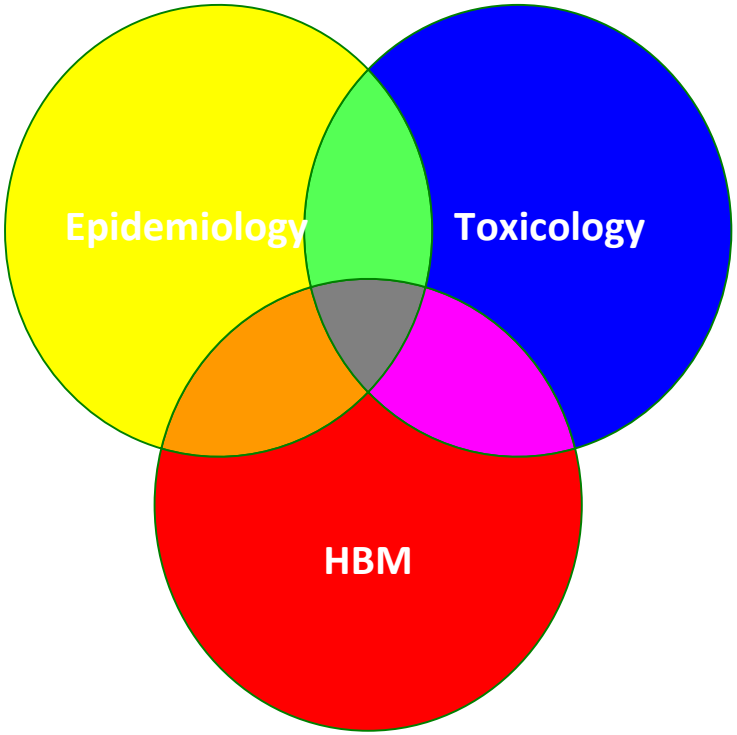
15.3 Case studies on health effects

Proof of concept

HBM4EU

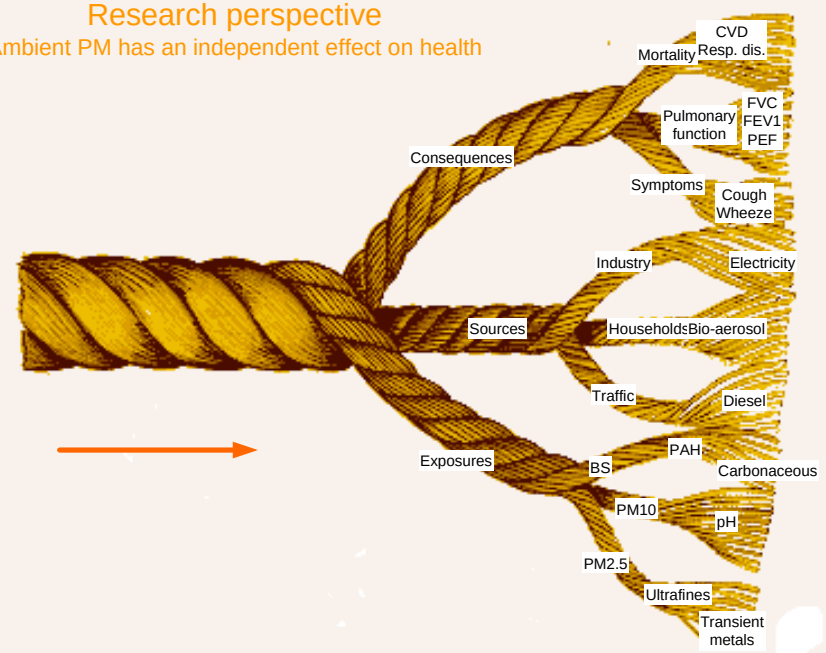
- After Greet Schoeters' introduction of HBM4EU, everyone is sufficiently informed about the nature and objectives of the EJP

- Nevertheless:



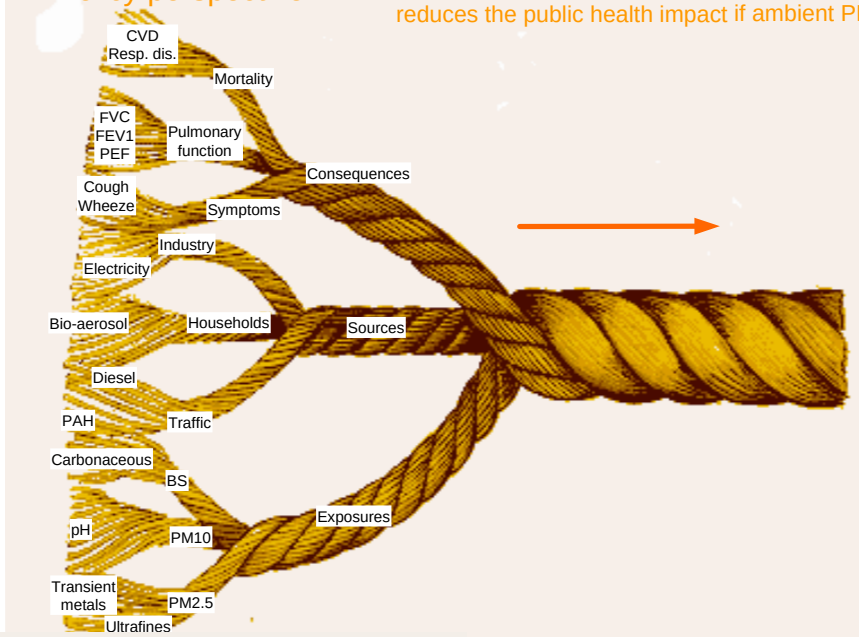
Research perspective

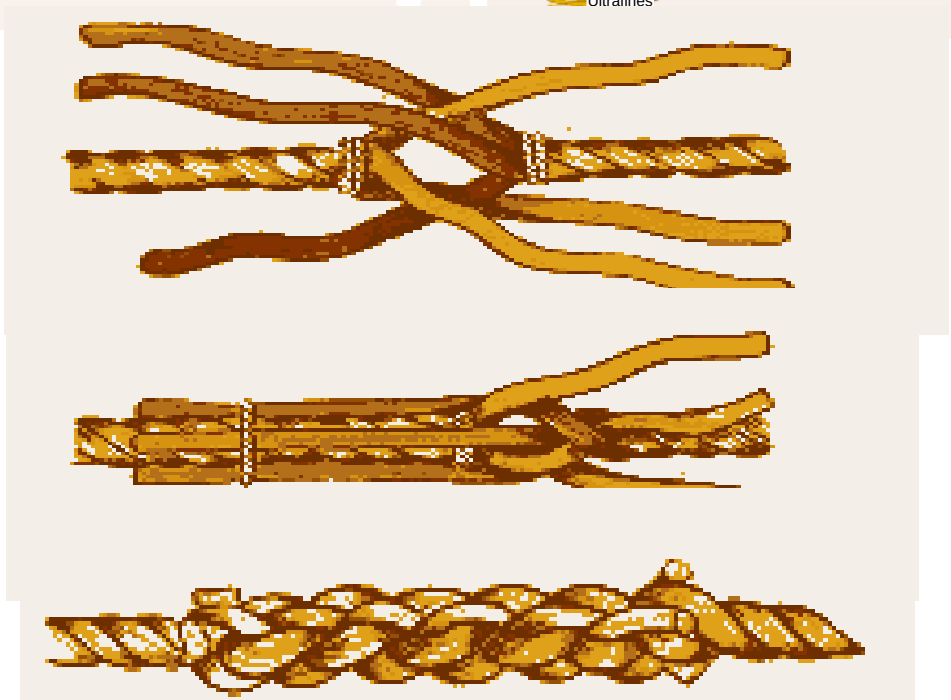
Ambient PM has an independent effect on health



Policy perspective

A strong ,effective, efficient and coherent policy reduces the public health impact if ambient PM





Challenges

- Define Action Perspectives across silos, for policy makers, regulators and stake holders
  - MoA trading?
- Communication with the public about risks of mixtures
- Or “how to connect the (virtual) system world of research and regulation of mixtures with the real world?”

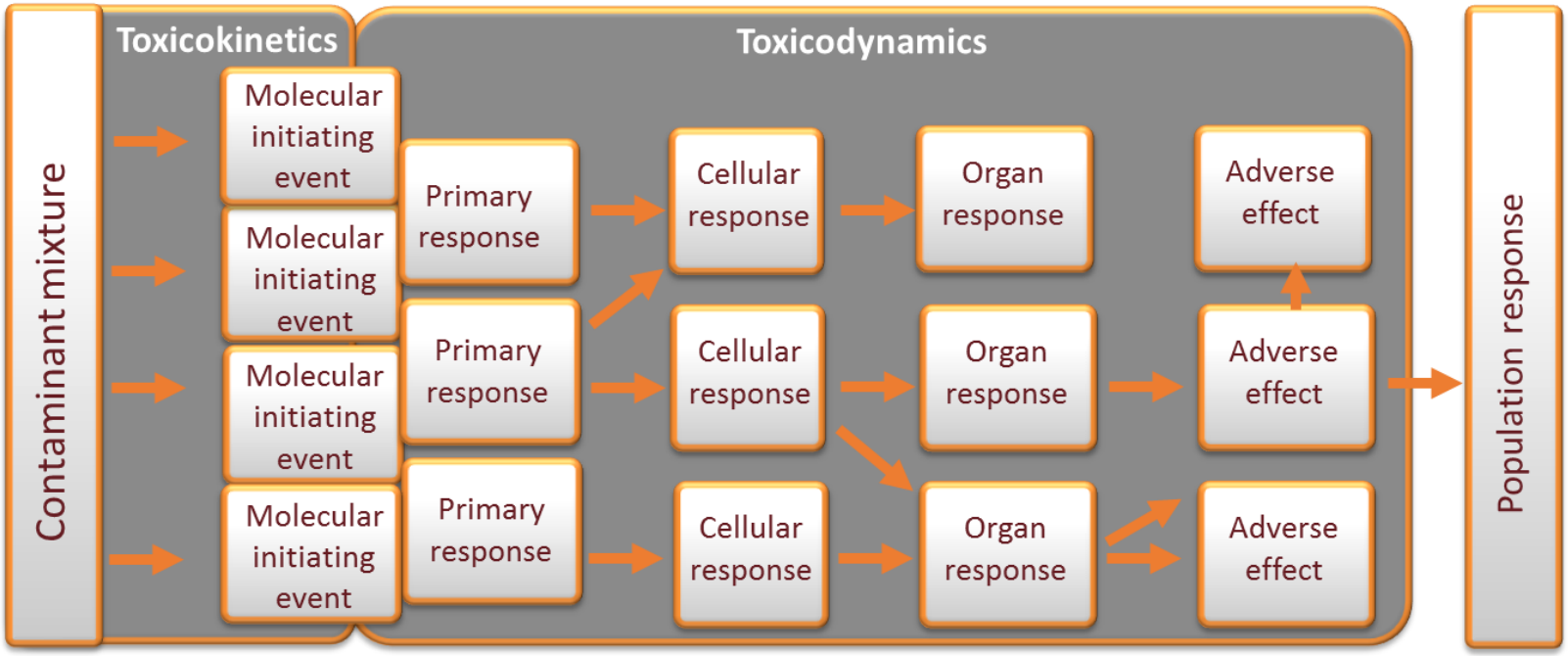
Mental models in social sciences on risk

- **Mental models** are psychological representations of real, hypothetical, or imaginary situations. (http://mentalmodels.princeton.edu/about/what-are-mental-models/)

- A **mental model** is an explanation of someone's thought process about how something works in the real world. It is a representation of the surrounding world, the relationships between its various parts and a person's intuitive perception about his or her own acts and their consequences. Mental models can help shape behaviour and set an approach to solving problems (akin to a personal algorithm) and doing tasks. https://en.wikipedia.org/wiki/Mental_model)

Mental models in r.a. of mixtures

Source unknown; happy to add proper reference



Bioanalytical tools in mixture impact assessment

Effect-based tools

- *Similar action*
- *Dissimilar action*
- *Interaction indicators*

Results: Lay mental models (interviews)

- Little knowledge on EMF technology:

  "It is a mystery to me. You don't see it …. Waves through the air?"

- EMF is perceived as a potential danger:

  "I've read somewhere that some people have sleeping problems, there are even people who say it can cause cancer."

- But most people have no serious concerns:

  "When I read about it, I sometimes think "gee" but yes, I usually forget it very quick"

- Little knowledge of and trust in risk management:

  "If they (i.e. the government) *are doing anything than perhaps it is just on paper, they should enforce the rules but I wonder if that is the case"*

Some statements to (dis)agree with

- I think we should try to avoid any chemicals from entering our body
- I can limit my exposure and body burden to chemicals by personal lifestyle choices (diet, use of consumer products, cosmetics)
- Most citizens are aware that a lot of different chemicals are circulating in their body
- Given our modern lifestyle it is unavoidable that we are exposed to different chemicals that enter our body
- The human body - by nature - is sensitive to small changes which can bring it to collapse; it cannot handle mixtures well
- Mixture risk assessment has become so complex that we cannot explain it to lay people

Identification of mixture health effects: Lisbon Workshop 9-10th May 2018

Some outcomes

- Different concepts of mixtures between experimental toxicologists and epidemiologist
  - Tox: focus on simultaneous exposure
  - Epi: simultaneous + repeated & protracted exposures
- Consensus about approaches and indicators in tox
- More exploratory approaches in epi
- Interesting, open and dynamic exchange of views
- Eight potential case studies presented and discussed

Two main ‘ pipelines’ for case studies

- Case studies proposed primarily from:
  - Concern about health effects, e.g. neurodevelopmental effects
  - Concern about chemicals, e.g. combination of metals, where each metal already has too small Margin of Exposure
- Consider common (epi-tox) topics to allow triangulation across domains
- Allow more methodological issues, e.g. effect of ‘ measurement error’ and exposure misclassification

Currently considered case studies

- Expand the HI approach for neurodevelopmental toxicity beyond flame retardants to include other neuro dev chemicals; use outcomes to guide epi studies on existing cohorts
- Develop study on nephrotoxicity of metals Cd, Hg, Pb ; use outcomes to guide epi studies on existing cohorts
- Develop case study on anti-adrogenic effects of multiple priority substances; use outcomes to guide epi studies on existing cohorts
- Cr, PAH's (and nickel and asbestos) lung carcinogenicity in occupational exposures
- Exposure errors & misclassification, what are implications for mixture data and ability to detect interaction effects of mixtures in population studies; guidance for a repeat measurements design and strengthen interpretation of results

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Thank you.

WWW.HBM4EU.EU

erik.lebret@rivm.nl

Questions?

Universiteit Utrecht

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

Human Biomonitoring and Public Health

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Human Biomonitoring and Public Health

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The relevance

The difficulties

The challenges

[The Logistics & The Science & The Policies]

Human Biomonitoring and Public Health

The relevance

The difficulties

The challenges

A quality assurance program is being installed to generate comparable human biomonitoring data from biobanked samples or from new surveys and studies that are planned in line with protocols that are generated in HBM4EU

[The Logistics & The Science & The Policies]

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Co-incineração

Responder

MNI
07 julho 2000

topo

Co-incineração suspensa

Co-incineração suspensa até conclusão de relatório médico
O projecto de lei de Os Verdes, que suspende a co-incineração em território nacional, foi ontem aprovado em votação final global por todas as bancadas da oposição e por quatro deputados do PS/Coimbra.
Na sequência desta aprovação, o ministro do Ambiente José Sócrates considerou que o processo de co-incineração fica agora dependente do relatório a elaborar por um grupo de trabalho médico que vai analisar o impacto na saúde pública dos processos de queima de resíduos industriais perigosos, e que só deverá estar concluído dentro de três meses.
Fonte: lusa.pt

citar

www.lemonde.fr/planete/article/2017/11/26/glyphosate-revelations-sur-les-failles-de-l-expertise-eu

INTERNATIONAL | POLITIQUE | SOCIÉTÉ | ÉCO | CULTURE | IDÉES | PLANÈTE | SPORT | SCIENCES

Planète

PLANÈTE | COP22 | One Planet Summit | Climat | Énergies | Biodiversité | Santé-environnement | A

ÉDITION ABONNÉS

ARTICLE SÉLECTIONNÉ DANS LA MATINALE DU 26/11/2017 > Découvrir l'application

Glyphosate : révélations sur les failles de l'expertise européenne

Alors que l'Europe doit décider de sa réautorisation lundi 27 novembre, « Le Monde » relate comment les agences officielles ont blanchi l'herbicide en recopiant les évaluations fournies par Monsanto.

LE MONDE | 26.11.2017 à 20h04 • Mis à jour le 27.11.2017 à 10h23 |

Par **Stéphane Foucart** et Stéphane Horel

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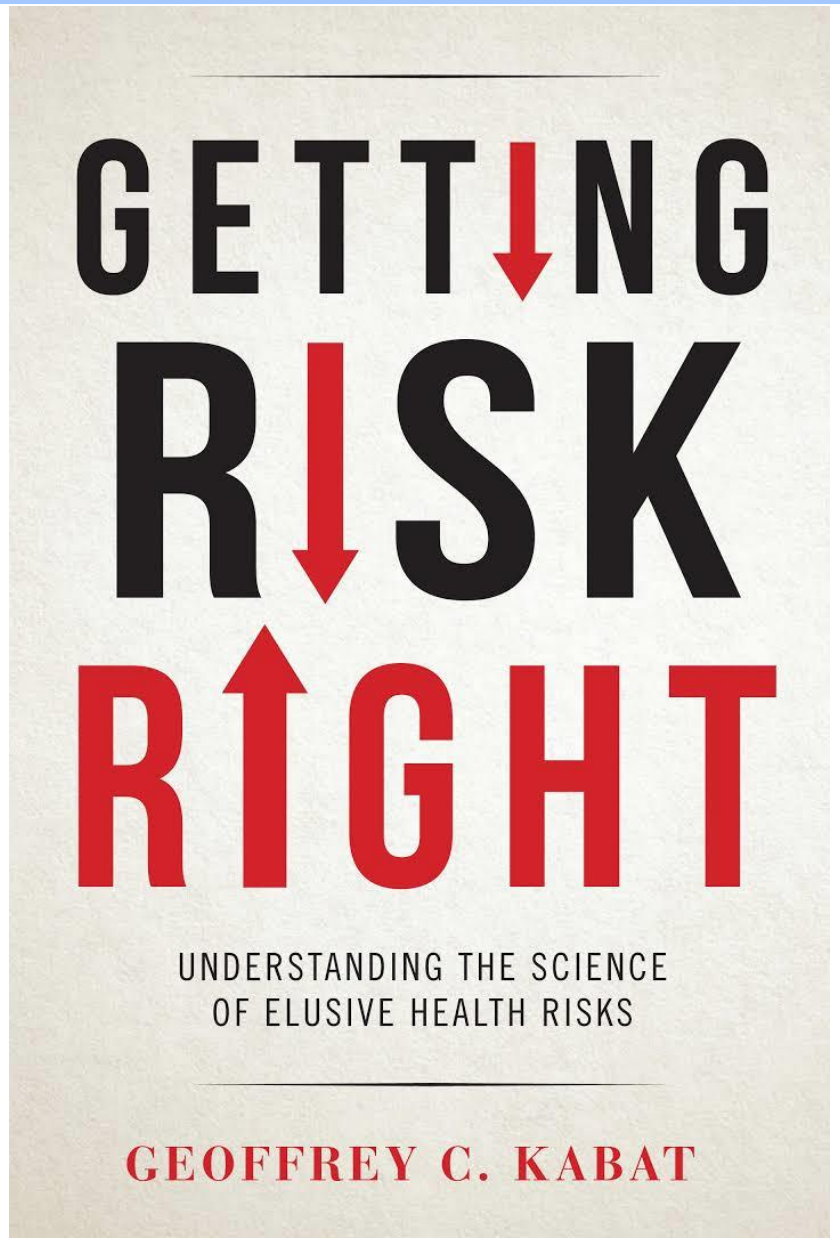

Everyone has the right to a standard of living adequate for the health and well-being of himself and his family, including food, clothing housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control.

Universal Declaration of Human Rights, 1948
Article 25 (1)

"Human height becomes greater and growth takes place more rapidly…in proportion as the country is richer, comfort more general…privation during infancy and youth less…"

René Villermé, 1829

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FPH's 12 priorities for public health action

Any government serious about creating a fairer, healthier society should have these 12 commitments at the forefront of their public health action plan:

Give every child a good start in life

1. Give all babies the best possible start in life by implementing the recommendations of the 1001 Critical Days cross-party report.
2. Help children and young people develop essential life skills and make personal, social, health and economic, and sex and relationship education a statutory duty in all schools.
3. Promote healthy, active lifestyles in children and young people by reinstating at least two hours per week of physical activity in all schools.

The role of biomarkers in biological pathways leading from SES to healthy ageing

Vineis P, Avendano-Pavon M, Barros H, et.al.The biology of inequalities in health: the LIFEPATH project. *Longitudinal and Life Course Studies 2017 Volume 8 Issue 4 Pp 417 – 439*.

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Socioeconomic differences in health have been consistently observed worldwide.
Physical health deteriorates more rapidly with age among men and women with lower socioeconomic status (SES) than among those with higher SES.
The biological processes underlying these differences are best understood by adopting a life course approach.

Ageing is a phenomenon with two broad stages across life: build-up and decline.
The **‘build-up’** stage, from conception and early intra-uterine life to late adolescence or early twenties, is characterized by rapid successions of developmentally and socially sensitive periods.
The second stage, starting in early adulthood, is a period of **'decline'** from maximum attained health to loss of function, overt disease and death.

The role of biomarkers in biological pathways leading from SES to healthy ageing

Vineis P, Avendano-Pavon M, Barros H, et al. The biology of inequalities in health: the LIFEPATH project. *Longitudinal and Life Course Studies 2017 Volume 8 Issue 4 Pp 417 – 439*.

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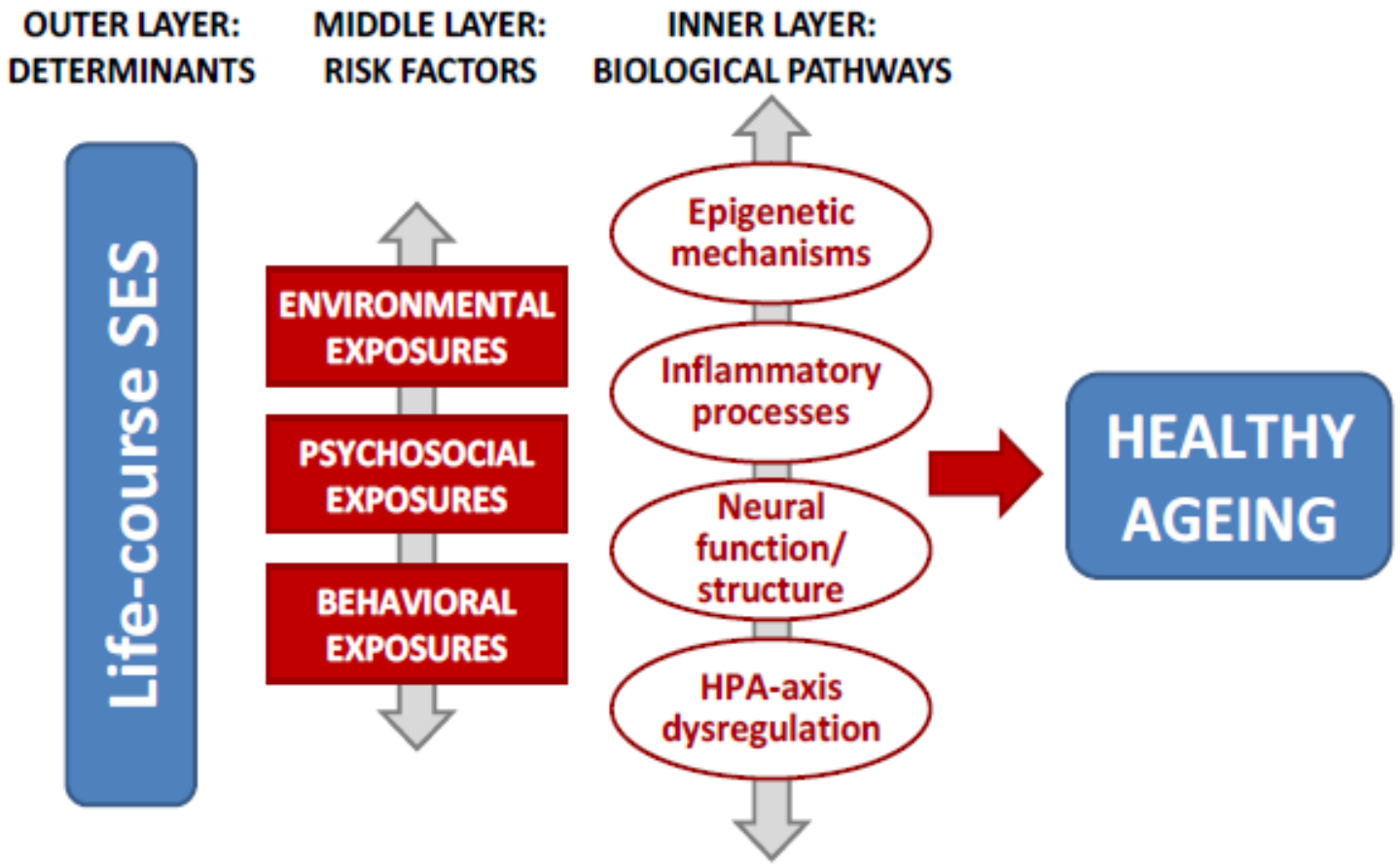

Stringhini S, CarmeliC, Jokela M, Avendaño M, Muennig P, Guida F, Ricceri F, d'Errico A, Barros H, Bochud M, Chadeau-Hyam M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. The Lancet 2017;389 (10075):1229-1237

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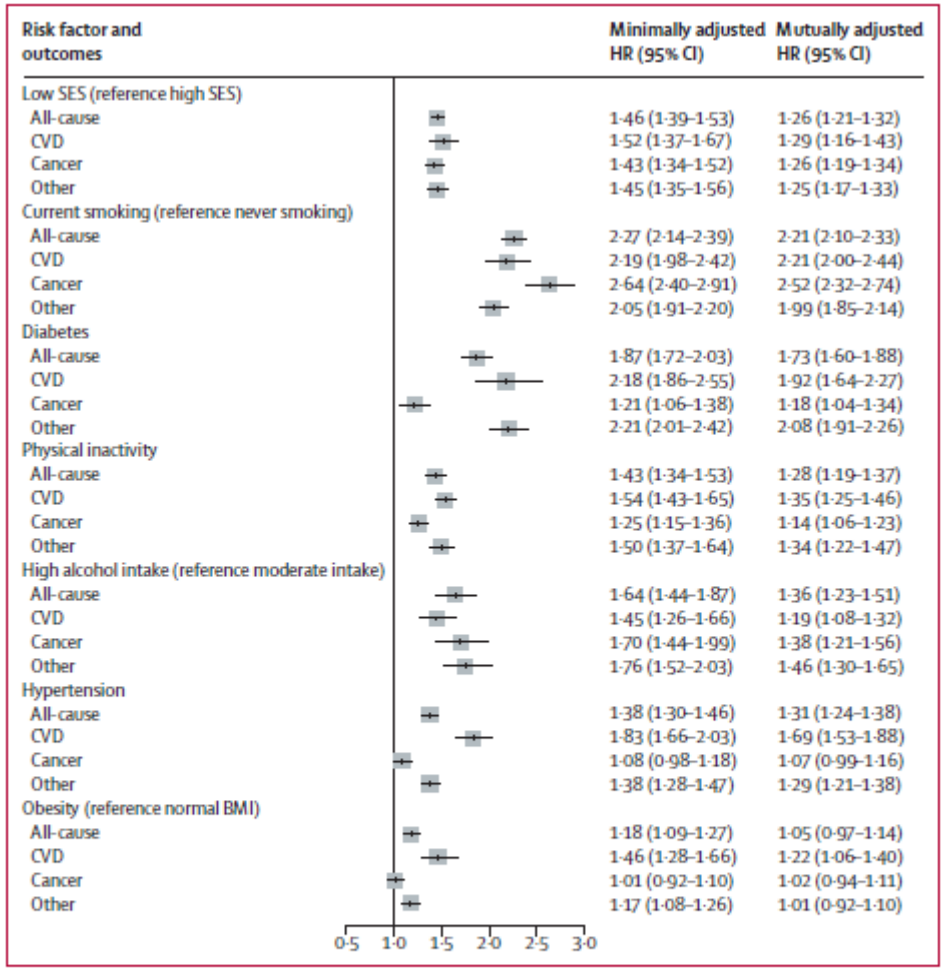
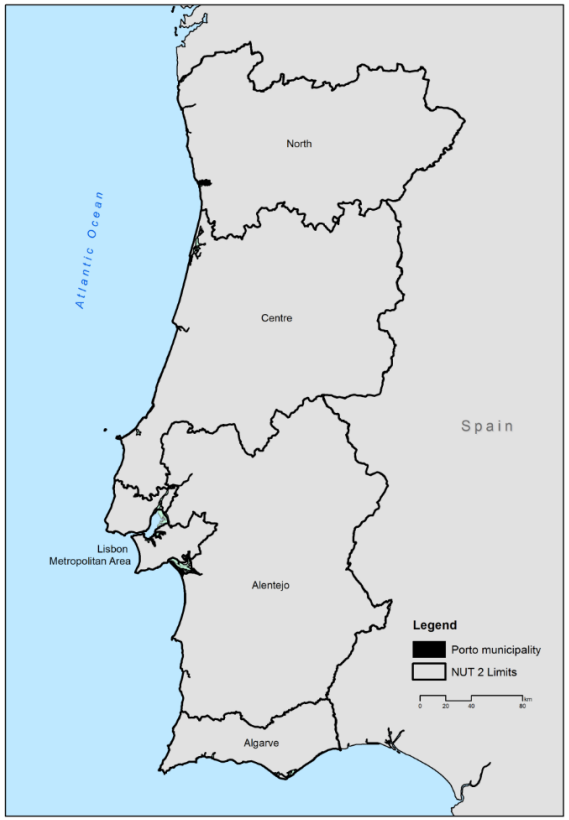
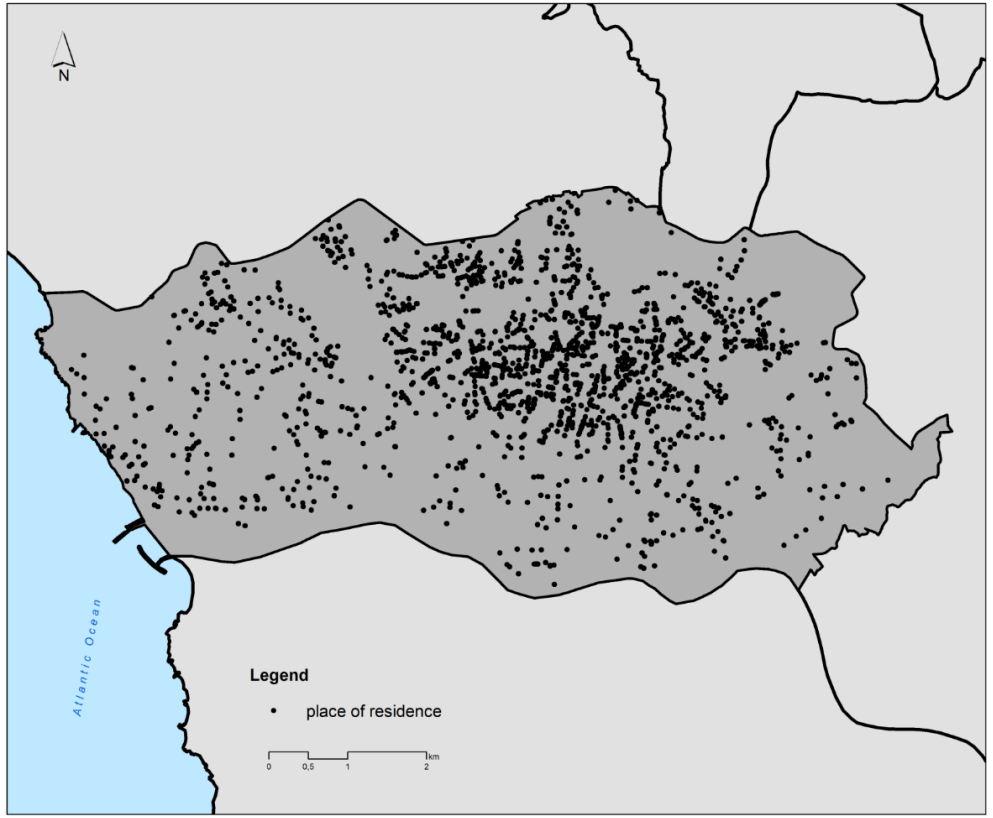


***Figure 4*: Pooled hazard ratios of socioeconomic status and 25 × 25 risk factors for all-cause mortality and cause-specific mortality**

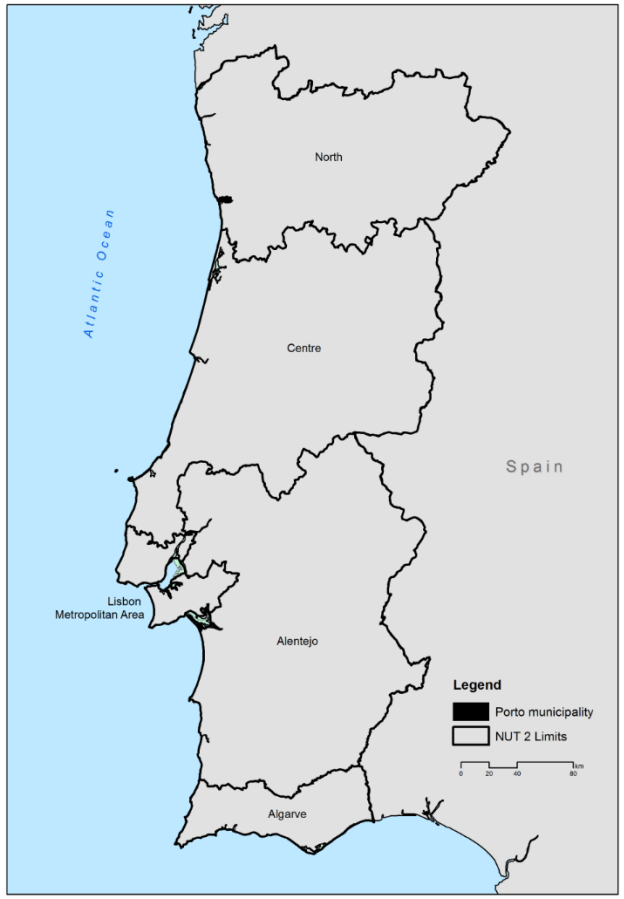
The minimally adjusted models were only adjusted for sex, age, and race or ethnicity; in the mutually adjusted models, SES and the 25 × 25 risk factors are mutually adjusted. BMI=body-mass index. CVD=cardiovascular disease. SES=socioeconomic status.

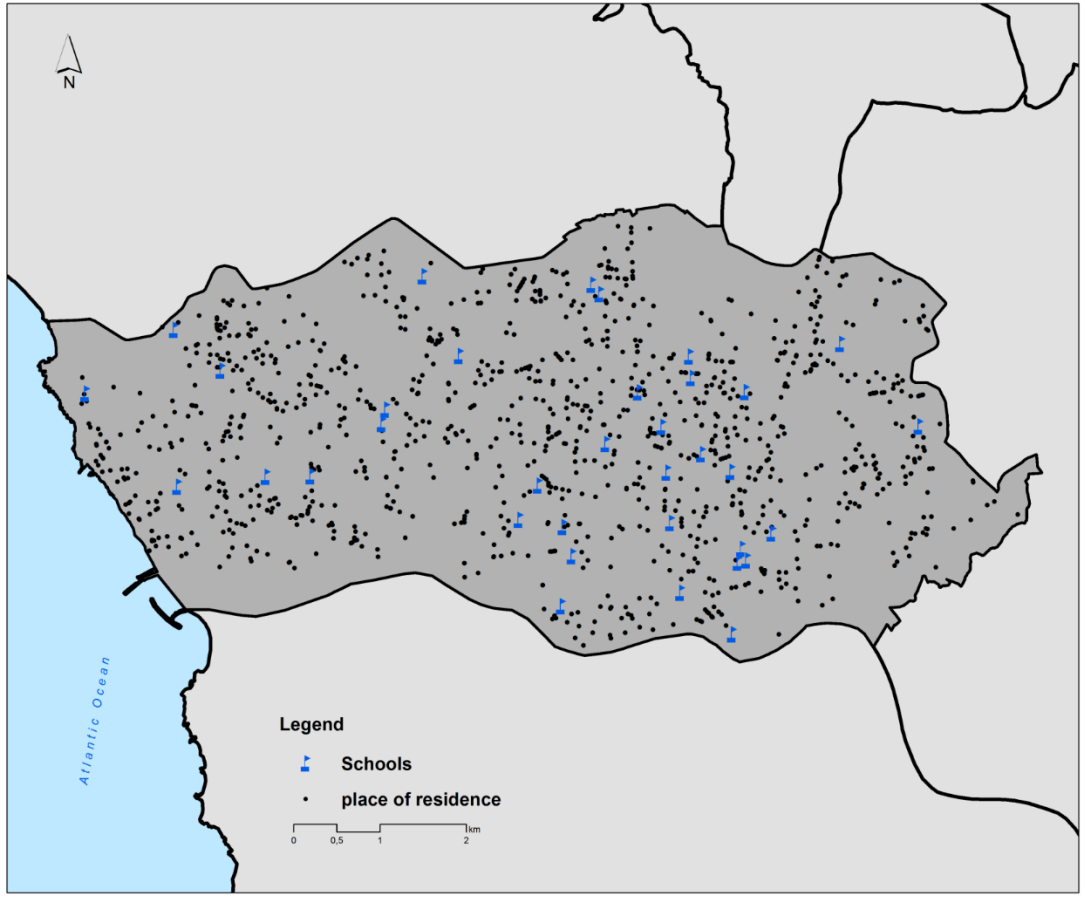
EPIPorto (n=2500; 1995-8)





EPITeen (n=2500; born in 1990, followed since 2003)





2499 participants

(763 new)

Birth Cohorts in Europe

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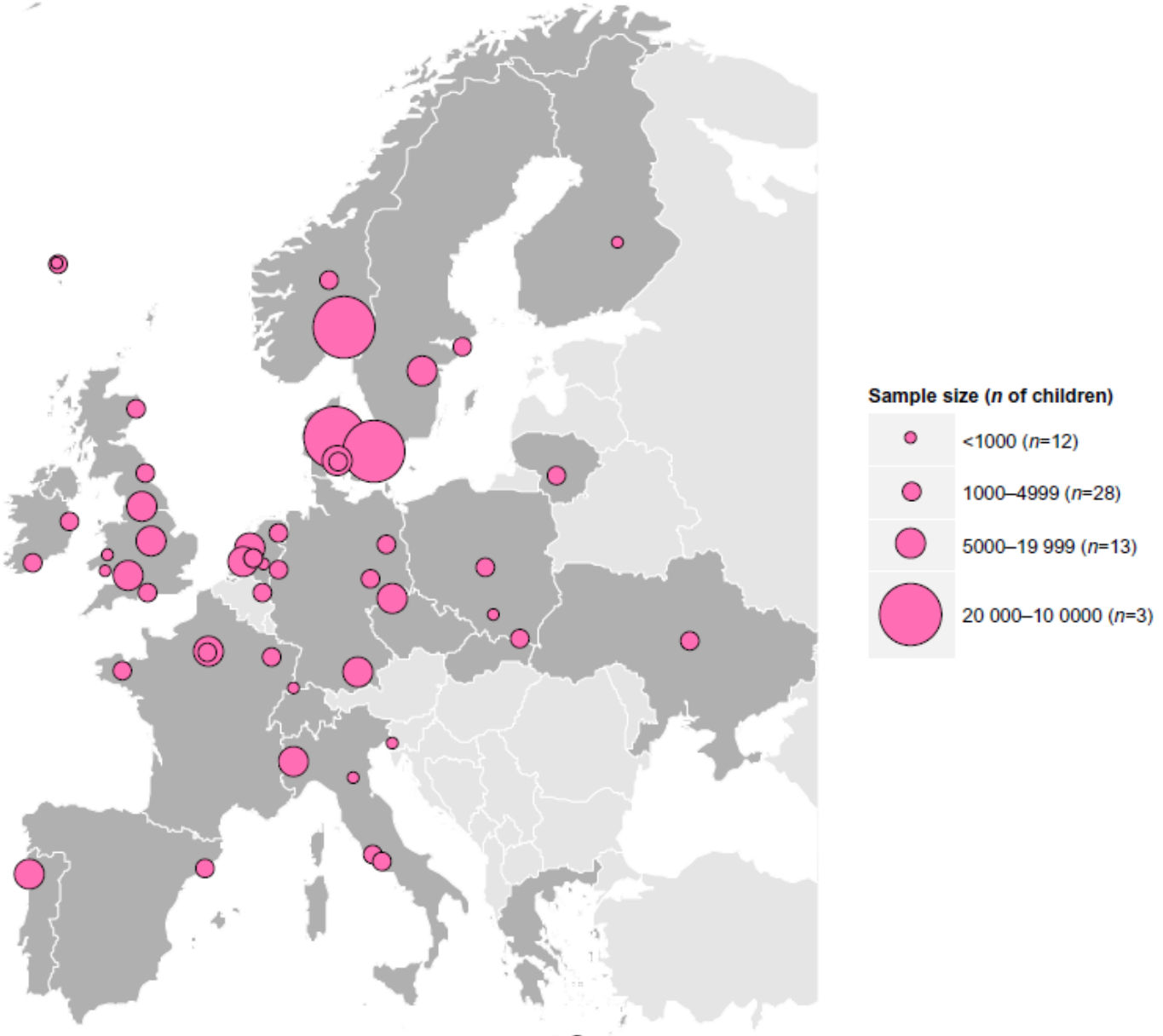

www.geracao21.com

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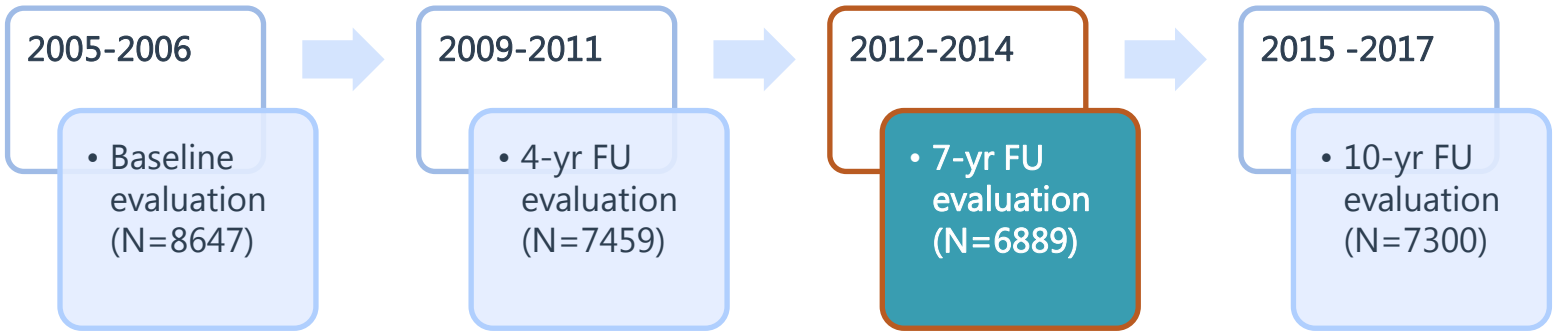
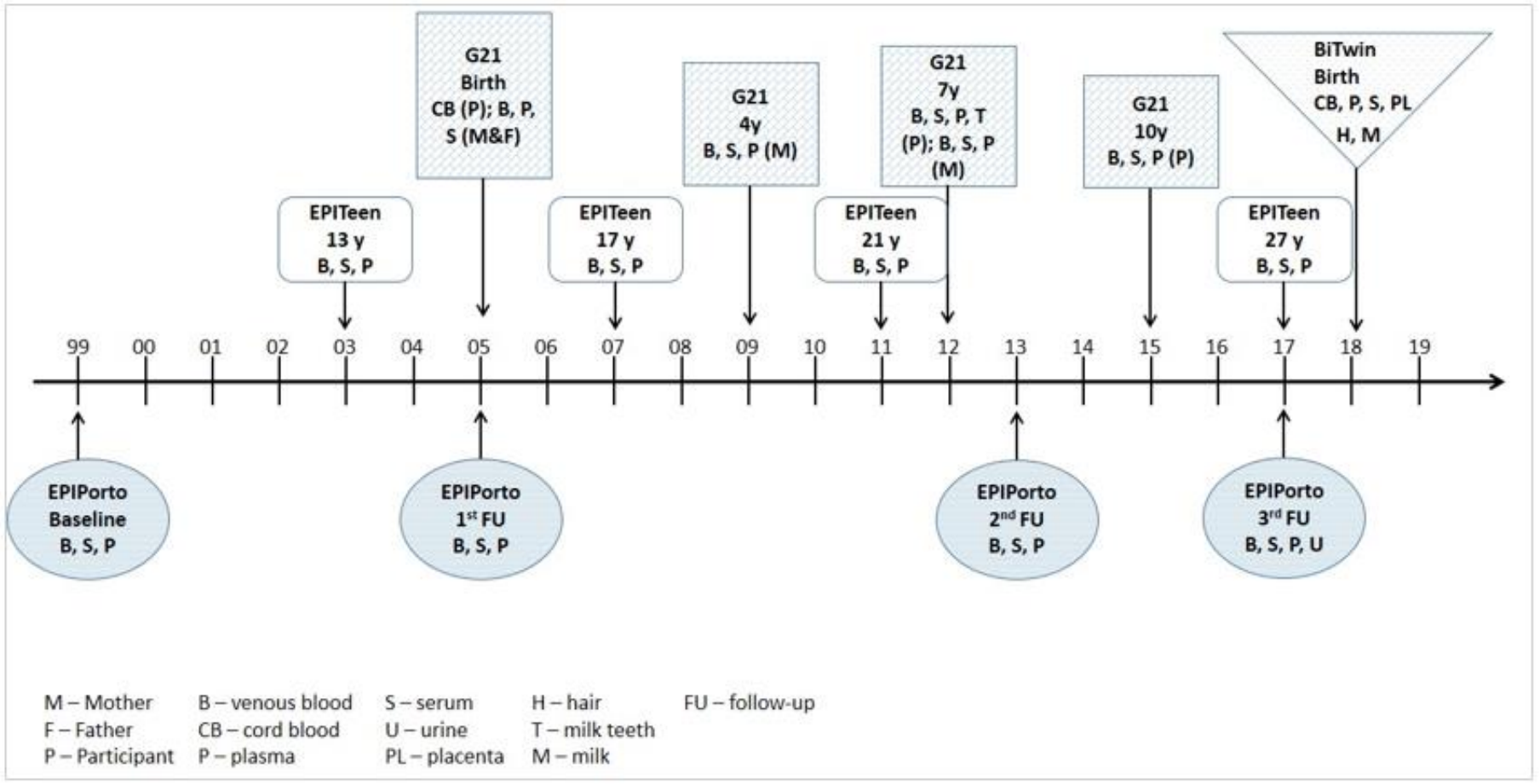

2005-2006
• Baseline evaluation (N=8647)
2009-2011
• 4-yr FU evaluation (N=7459)
2012-2014
• 7-yr FU evaluation (N=6889)
2015 -2017
• 10-yr FU evaluation (N=7300)

Biobank (n> 200,000 samples



Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev. 2005;14:1847–50.
Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. Toxicol Sci. 2014;137:1–2.

Exposome:

"the totality of environmental exposures encountered from birth to death"

"cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, behavior, diet, and endogenous processes"

Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev. 2005;14:1847–50.
Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. Toxicol Sci. 2014;137:1–2.

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Exposome:

The exposome is a highly interdisciplinary holistic approach that intersects environmental exposure monitoring with modern technologies such as genomics and metabolomics. It is a valuable science particularly important for understanding how environmental factors affect children’s health and later-life outcomes.

Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev. 2005;14:1847–50.
Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. Toxicol Sci. 2014;137:1–2.

From EXPOSURE to OUCOME

The epic task of attempting to analyze all exposures that an individual may encounter over their lifespan and connect those to biological impact

Simple or Simplistic thinking?

ISIS System Dynamics Model for Tobacco Control

Natl. Cancer Inst. (NCI). 2007.Greater than the Sum: Systems Thinking in Tobacco Control

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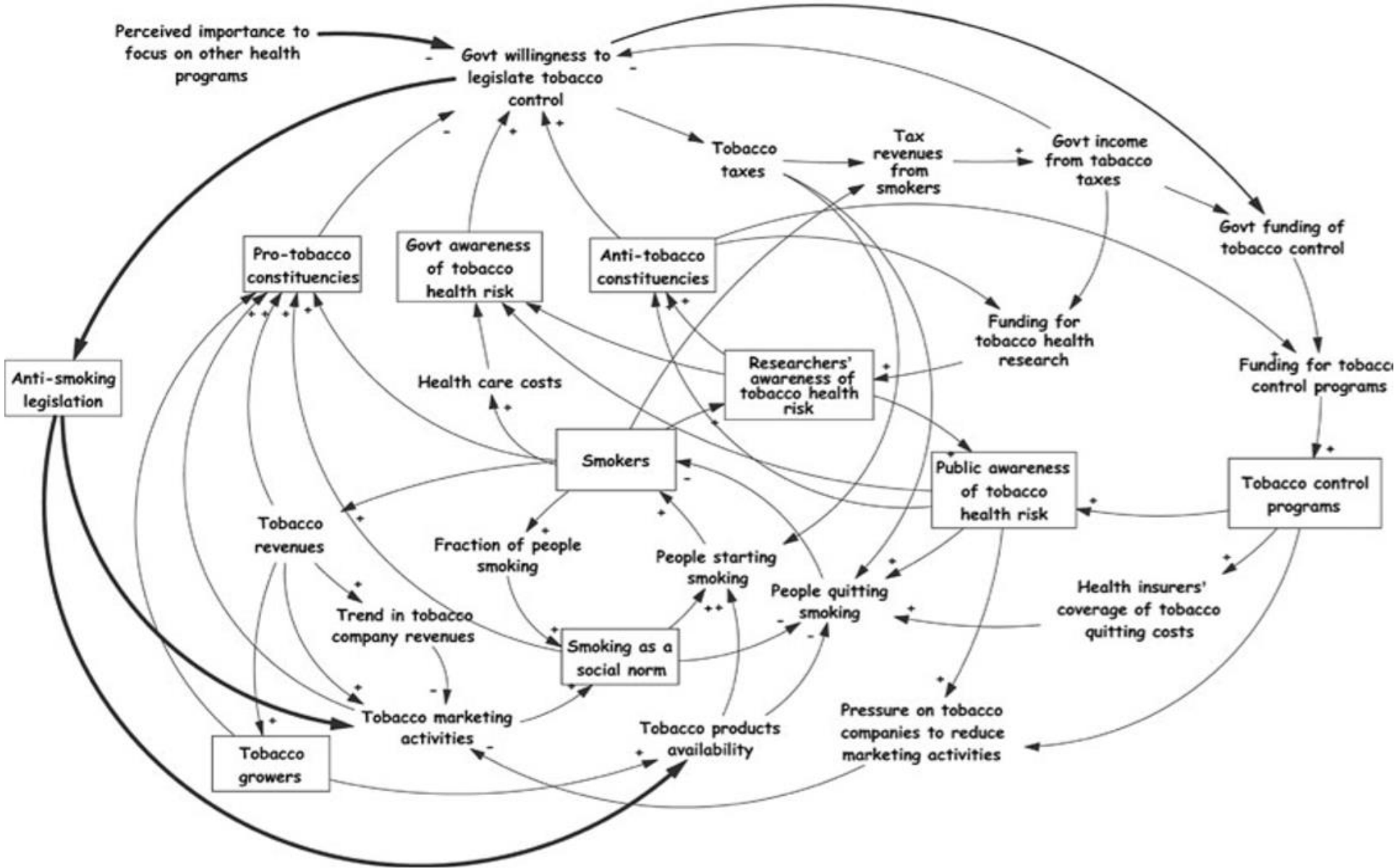

Dennis KK, Marder E, Balshaw DM, Cui Y, Lynes MA, Patti GJ, Rappaport SM, Shaughnessy DT, Vrijheid M, Barr DB. Biomonitoring in the era of the exposome.
Environ Health Perspect. 2016;125:502–10.

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Biomonitoring

Exploring cumulative exposure history requires a hybrid of traditional (targeted) and exposomic (untargeted) biomonitoring approaches and utilizing advantages of both methods.

Dennis KK, Auerbach SS, Balshaw DM, Cui Y, Fallin MD, Smith MT, Spira A, Sumner S, Miller GW.
The importance of the biological impact of exposure to the concept of the exposome.
Environ Health Perspect. 2016;124:1504–10.

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Biological response and impact

External and internal exposures interact to alter biological processes and trigger production of new chemical intermediates.
Exposomic technologies can link exposures to these downstream effects.

Stingone JA, Buck Louis GM, Nakayama SF, Vermeulen RC, Kwok RK, Cui Y, Balshaw DM, Teitelbaum SL. Toward greater implementation of the exposome research paradigm within environmental epidemiology. Annu Rev Public Health. 2017;38:315–27.

Epidemiology

The exposome is a complement to environmental epidemiology. Untargeted analyses can generate findings that need to be investigated using hypothesis-driven approaches central to epidemiology.
Merging data across cohorts with different life stages enables characterization of the exposome across the life course.

Manrai AK, Cui Y, Bushel PR, Hall M, Karakitsios S, Mattingly CJ, Ritchie M, Schmitt C, Sarigiannis DA, Thomas DC, et al. Informatics and data analytics to support exposome-based discovery for public health. Annu Rev Public Health. 2017;38:279–94.

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Data Science

Exposomic approaches generate extensive data to be stored, managed, analyzed, integrated, and shared. Development of community based data standards and ontologies is critical.

After using an EWAS-like approach to find exposure factors putatively correlated with telomere length, it was investigated how the exposure factors potentially influence changes in
gene expression using publicly available data from the Gene Expression Omnibus [Patel CJ, Manrai AK, Corona E, Kohane IS. Systematic correlation of environmental exposure and physiological and self-reported behavior factors with leukocyte telomere length. Int J Epidemiol. 2017;46:44–56.].

Exposures must influence changes in biological function if causal, and gene expression investigations are among the important approaches to decipher causal routes to disease.

The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data

Causal inference is a core task of science. However, authors and editors often refrain from explicitly acknowledging the causal goal of research projects; they refer to causal effect estimates as associational estimates.

This commentary argues that using the term "causal" is necessary to improve the quality of observational research.

Specifically, being explicit about the causal objective of a study reduces ambiguity in the scientific question, errors in the data analysis, and excesses in the interpretation of the results. (*Am J Public Health*. 2018;108:616–619. doi:10.2105/AJPH.2018.304337)

Miguel A. Hernán, MD, DrPH

See also Galea and Vaughan, p. 602; Begg and March, p. 620; Ahern, p. 621; Chiolero, p. 622; Glymour and Hamad, p. 623; Jones and Schooling, p. 624; and Hernán, p. 625.

You know the story:

> Dear author: Your observational study cannot prove causation. Please replace all references to causal effects by references to associations.

Many journal editors request authors to avoid causal language,[1] and many observational researchers, trained in a scientific environment that frowns upon causality claims, spontaneously refrain from mentioning the C-word ("causal") in their work. As a result, "causal effect" and terms with similar meaning ("impact," "benefit," etc.) are routinely avoided in scientific publications that describe nonrandomized studies. Instead, we see terms like "association" and others that

Confusion then ensues at the most basic levels of the scientific process and, inevitably, errors are made.

We need to stop treating "causal" as a dirty word that respectable investigators do not say in public or put in print. It is true that observational studies cannot definitely prove causation, but this statement misses the point, as discussed in this commentary.

OF COURSE "ASSOCIATION IS NOT CAUSATION"

Suppose we want to know

glass of red wine per day versus no alcohol drinking. For simplicity, disregard measurement error and random variability—that is, suppose the 0.8 comes from a very large population so that the 95% confidence interval around it is tiny.

The risk ratio of 0.8 is a measure of the association between wine intake and heart disease. Strictly speaking, it means that drinkers of one glass of wine have, on average, a 20% lower risk of heart disease than individuals who do not drink. The risk ratio of 0.8 does not imply that drinking a glass of wine every day lowers the risk of heart disease by 20%. It is possible that the

Barros H. Epidemiologic practice and conduct guidelines: a new kid on the block.
J Clin Epidemiol. 2018;38:279.

Decency should be everybody's concern: in scientific research or in daily activities which seek to apply scientific methods and principles of epidemiology to understand and to transform the health reality of individuals or especially of populations.

Most often these tasks are accomplished by following already-tested protocols, lists of known paths, or by applying survey methods that fit the art of health professions.

However, in other cases, in the face of unexpected emergent phenomena or genuinely unknown threats, practitioners take up with their training as, or become, scientists, and the need to follow responsible practices becomes even more evident, to ensure that also epidemiology first does no harm.

… what happens when science is hijacked by people who use the power and the prestige of science to scare the public, work the media, and press health agencies to pile on the bandwagon and fund work that stands little chance of advancing our knowledge about the complex process involved in normal development and disease.

Geoffrey C. Kabat
Getting risk right: Understanding the Science of Elusive Health Risks. New York: Columbia University Press, 2017.

1st Workshop on Human Biomonitoring in Portugal (1st HBM-PT)

"Bridging Chemical Exposure to Human Health"

11 May 2018, Lisbon, Portugal
Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P. (INSA)

The quest for biomarkers of effect in human biomonitoring studies

António Sebastião Rodrigues

Centre for Toxicogenomics and Human Health (ToxOmics)
Genetics, Oncology and Human Toxicology
NOVA Medical School | Faculdade de Ciências Médicas

sebastiao.rodrigues@nms.unl.pt

Definitions

Biomarker: a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body.

WHO, 2006.

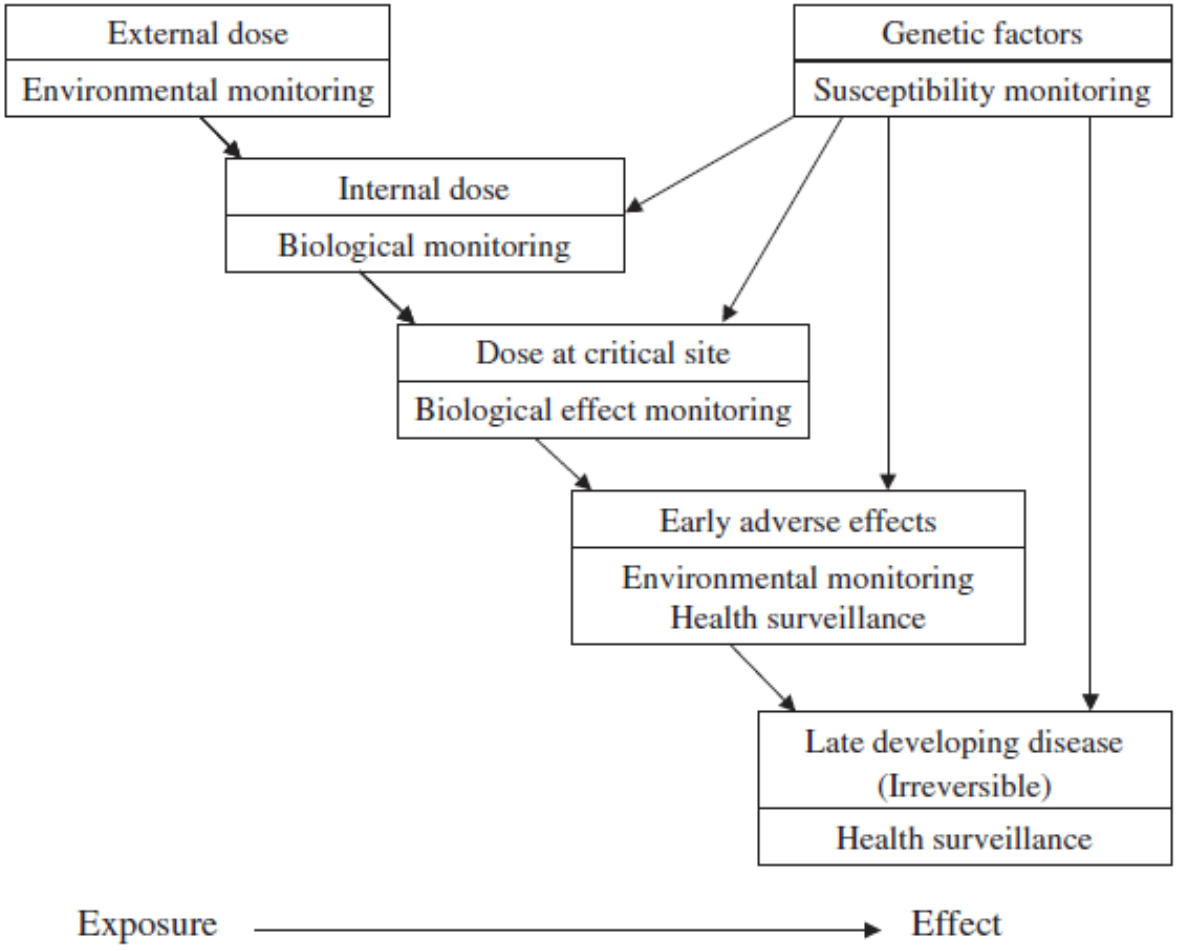
Environmental monitoring: the measurement of a contaminant's concentration in a medium (e.g., air, soil, water, or food).

Agency for Toxic Substances & Disease Registry.

Human biomonitoring: the direct measurement of people's exposure to toxic substances in the environment by measuring the substances or their metabolites in human specimens, such as blood or urine.

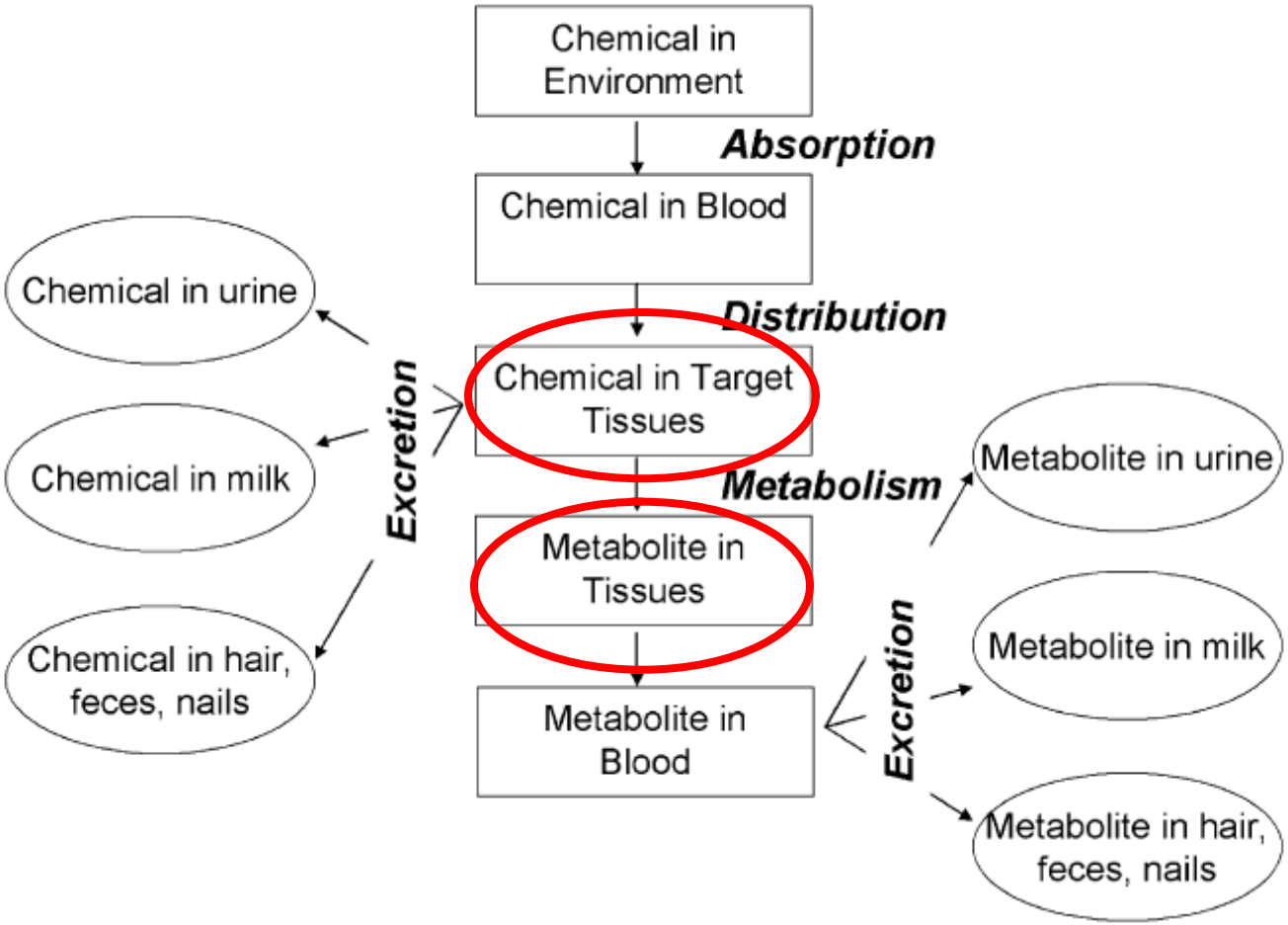
Centers for Disease Control and Prevention.

Levels and methodologies used in the biological monitoring of genotoxicity.



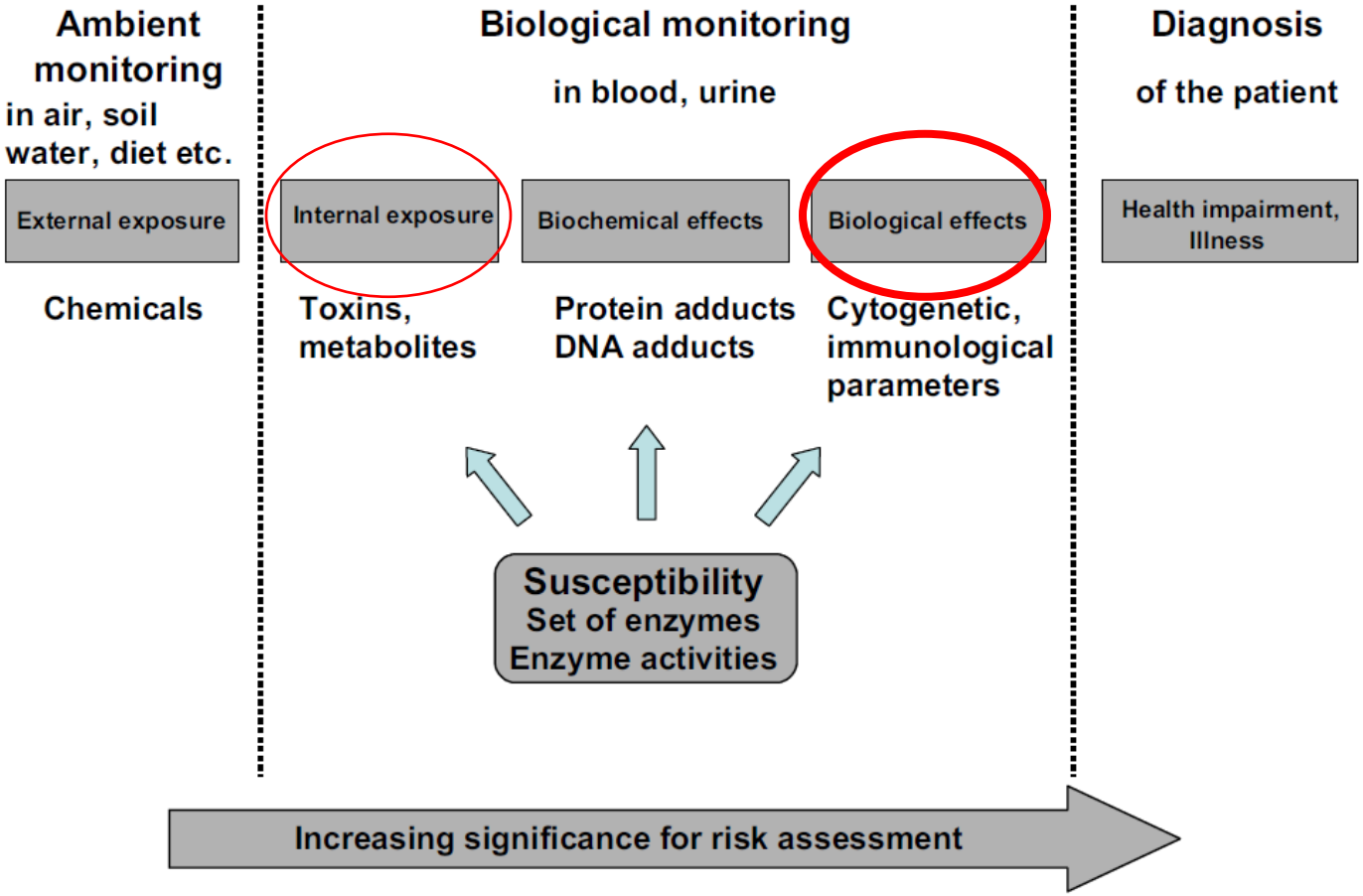
Rodrigues, A. S., et al., Radiation Protection Dosimetry, 115(1-4), 455-460, (2005).

Human Biomonitoring and Biomarkers



Hays, Regulatory Toxicology and Pharmacology 47 (2007) 96–109

Human Biomonitoring and Biomarkers



Angerer, Ewers and Wilhelm (2007) International Journal of Hygiene and Environmental Health, Volume 210, Issues 3–4, 201–228

Strengths and Limitations of Human Biomonitoring

Strengths

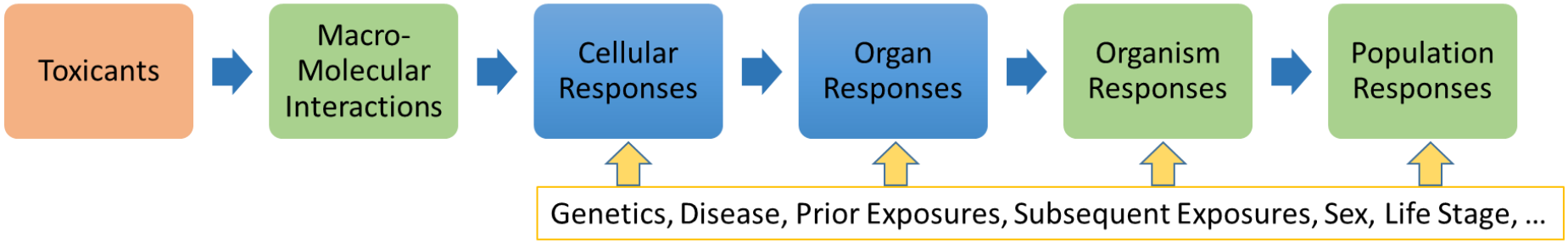
- Which substances are absorbed by the human body (all routes)
- Exposure levels
- Which group are more exposed
- Trends in exposure
- Establish reference ranges
- Is it feasible to reduce exposure levels?
- Regulations

Limitations

- No information about the source of an exposure
- Time of exposure? Accumulation of exposure from many sources and routes over a period of time
- What effect does exposure have on human health?

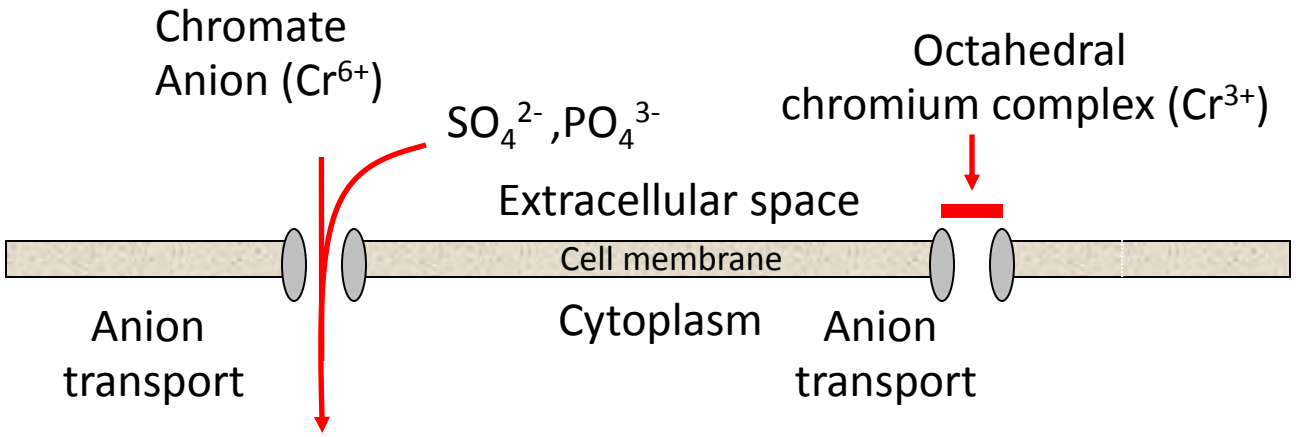
Strengths and Limitations of Human Biomonitoring

Adverse Outcome Pathways (AOP)



Stephen Edwards
U.S. Environmental Protection Agency
Integrated Systems Toxicology Division

Example 1



Cr^{6+} reduction to Cr^{3+} by Glutathione, cysteine, ascorbate, cytochrome P450, etc

Reactive intermediates
ROS

Slow uptake by passive difusion and endocytosis

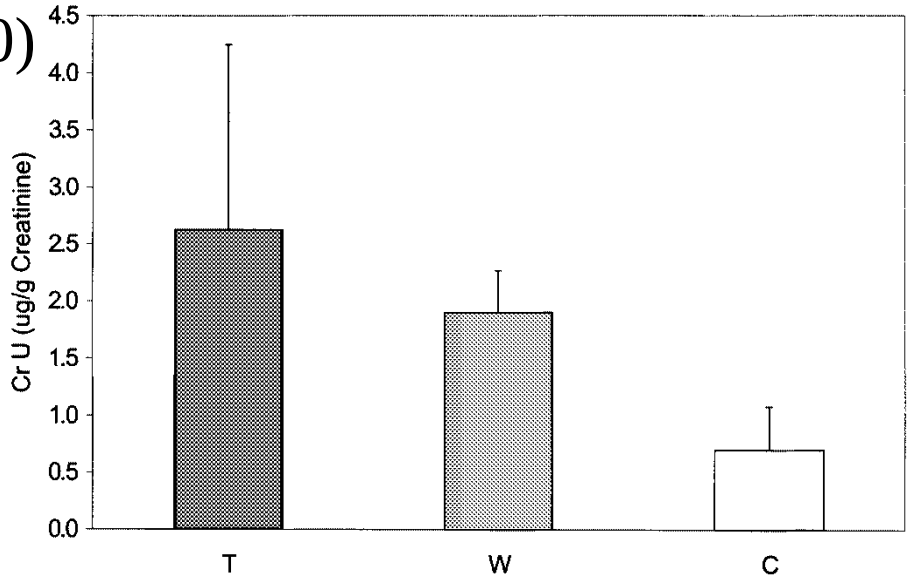
Chronic toxicity: DNA –protein crosslinks, strand breaks, DNA-chromium adducts. Carcinogenic, mutagenic and teratogenic effects

Acute toxic effects: necrosis and cell death

Example 1

Urinary chromium

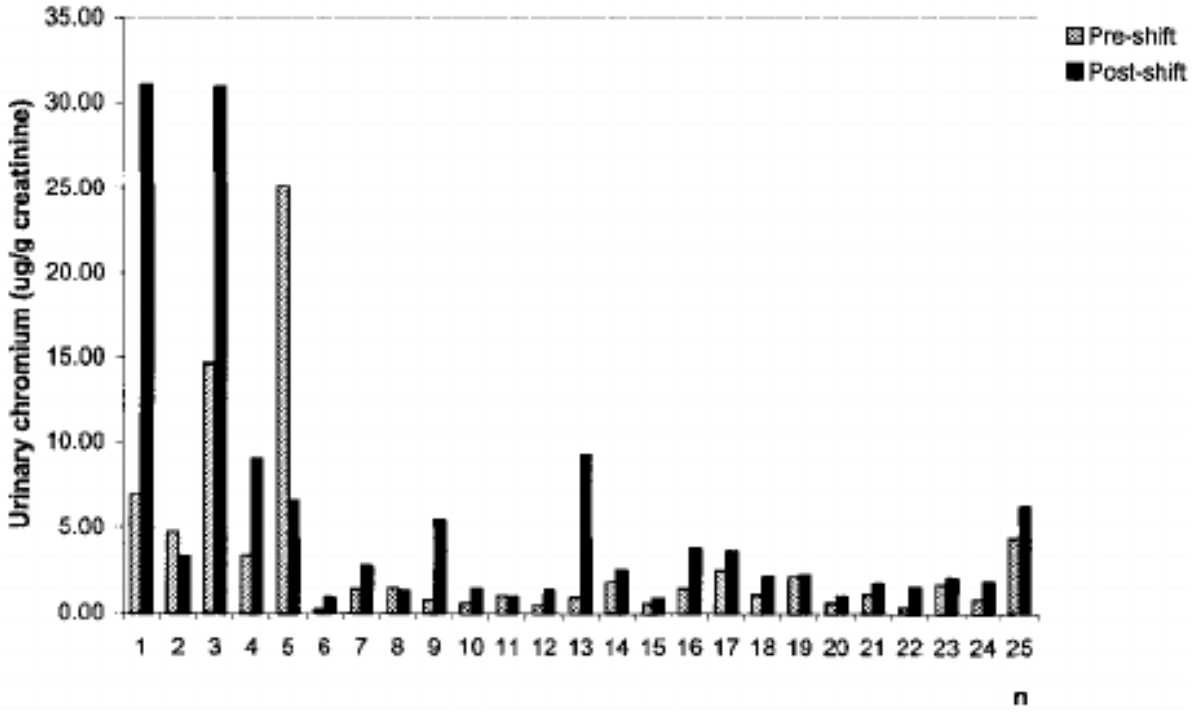
T – tanners (n=33)
W - welders (n=5)
C - controls (n=20)



Medeiros, M., et al., Mutagenesis, 18,19-24 (2003)
Goulart, M., et al., Mutagenesis, 20(5), 311-315, (2005).
Medeiros, M. G., et al., *Nato Science Series*, *351*, 132-141, (2003).

Example 1

Urinary chromium



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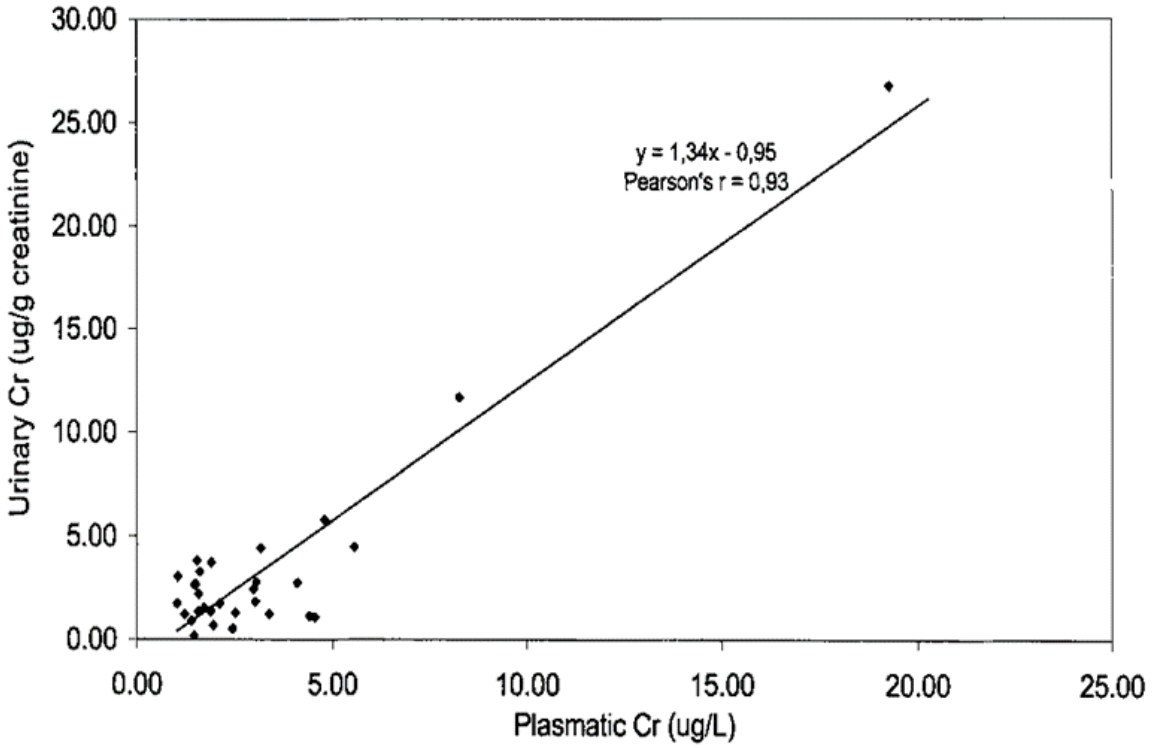
Goulart, M., et al., Mutagenesis, 20(5), 311-315, (2005).
Medeiros, M. G., et al., *Nato Science Series*, *351*, 132-141, (2003).

Human Biomonitoring and Biomarkers

Example 1



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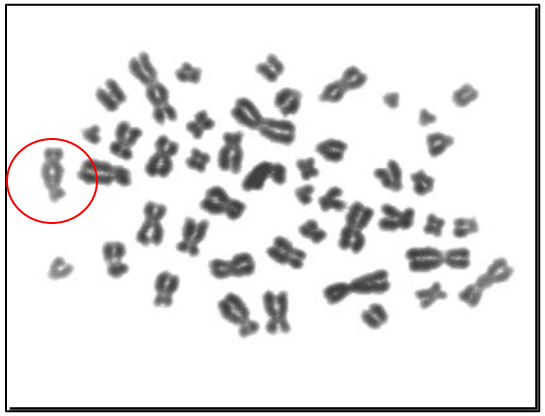
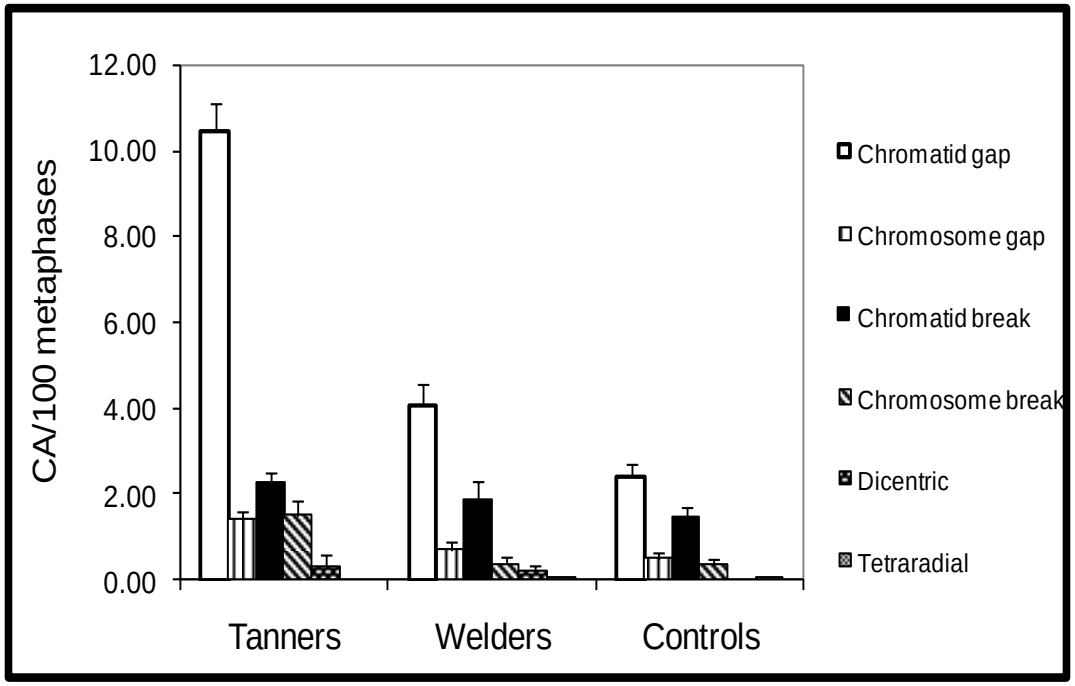
Goulart, M., et al., Mutagenesis, 20(5), 311-315, (2005).
Medeiros, M. G., et al., *Nato Science Series*, *351*, 132-141, (2003).

Example 1

Chromosomal Aberrations in peripheral lymphocytes

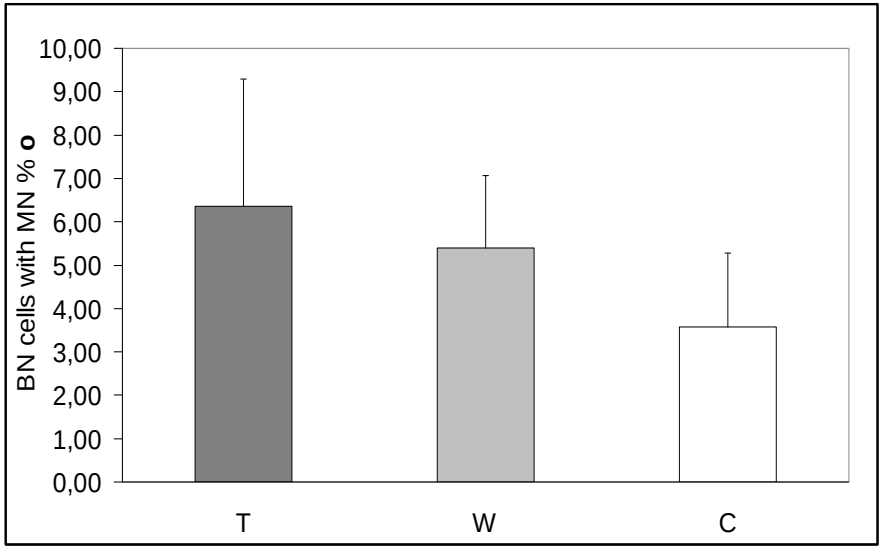


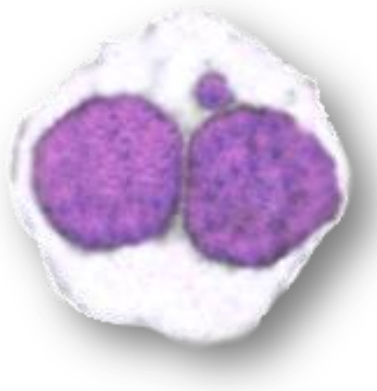


Medeiros, M., et al., Mutagenesis, 18,19-24 (2003)
Goulart, M., et al., Mutagenesis, 20(5), 311-315, (2005).

Example 1

Micronuclei in peripheral lymphocytes

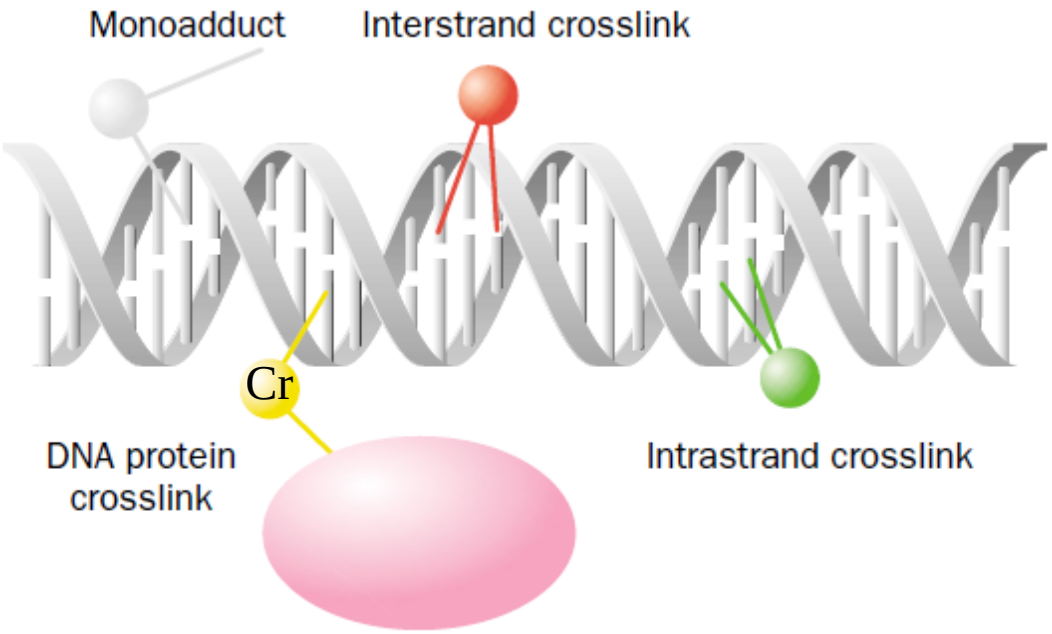




Medeiros, M., et al., Mutagenesis, 18,19-24 (2003)
Goulart, M., et al., Mutagenesis, 20(5), 311-315, (2005).

Example 1

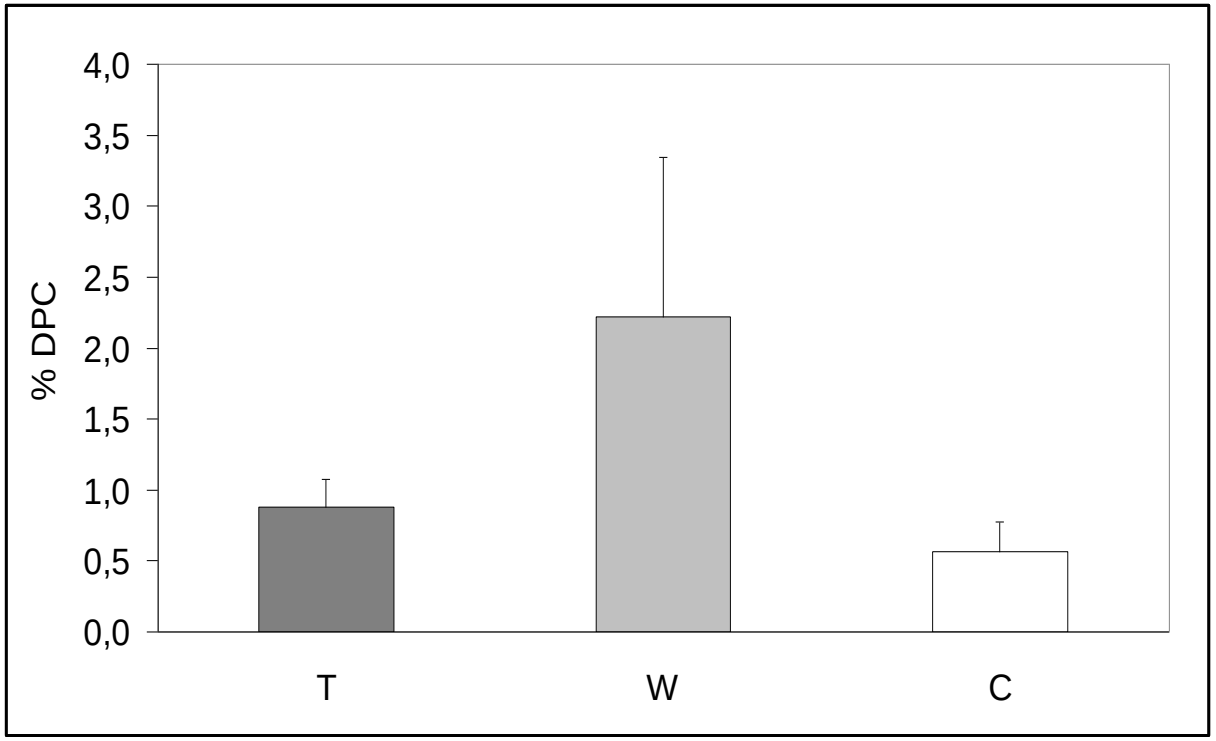
DNA-protein crosslinks in peripheral lymphocytes



McHugh Lancet Oncol 2001; 2,483–90 2001

Example 1

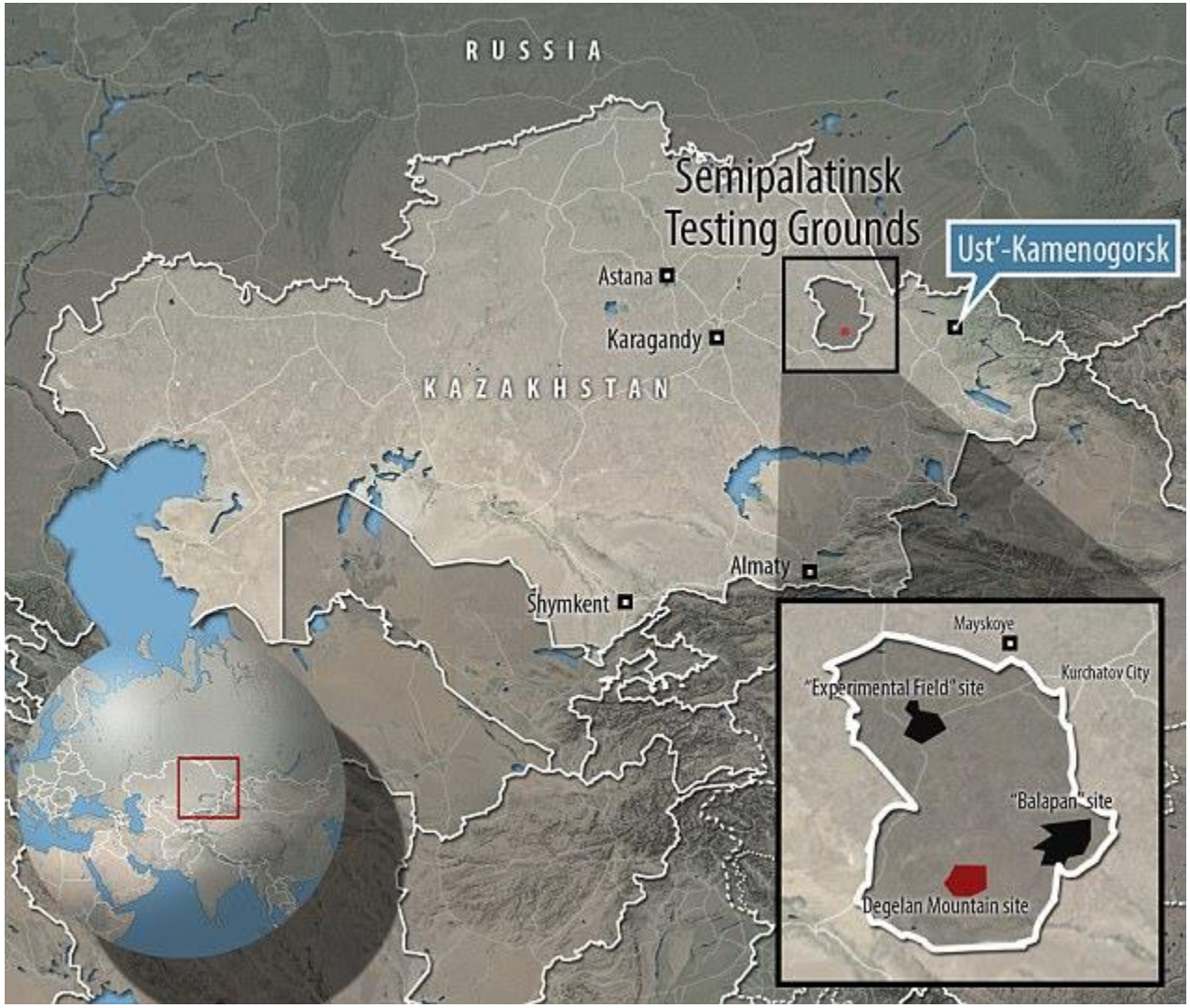
DNA-protein crosslinks in peripheral lymphocytes



Medeiros, M., et al., Mutagenesis, 18,19-24 (2003)
Goulart, M., et al., Mutagenesis, 20(5), 311-315, (2005).

Example 2

Kazakhstan



http://www.dailymail.co.uk/sciencetech/article-4346408

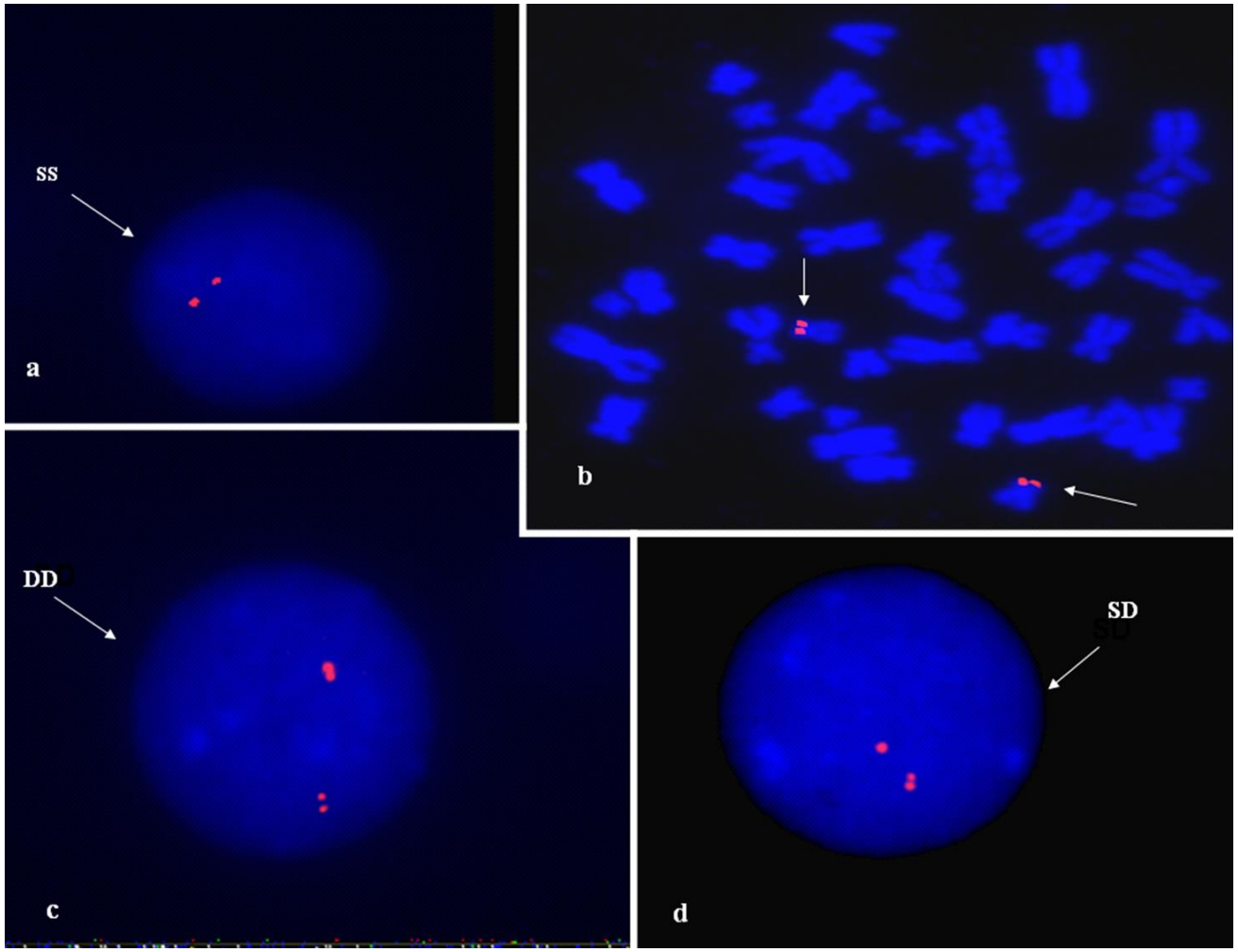
Example 2

Tumour sites with increased mortality rate in Ust-Kamenogorsk compared to Almaty (per 100,000 inhabitants, 2000)

Organs	Ust-Kamenogorsk	Almaty (control area)
Mouth and throat	4.1	2.4
Stomach	34.0	14.3
Colon	13.0	2.8
Rectum	11.4	3.6
Lung	44.2	16.4
Breast	14.3	7.2
Ovary	5.4	2.7
Prostate	3.8	1.7
Lymphoma	5.0	1.7
Leukemia	5.0	2.2

Example 2

Asynchronous replication in peripheral lymphocytes



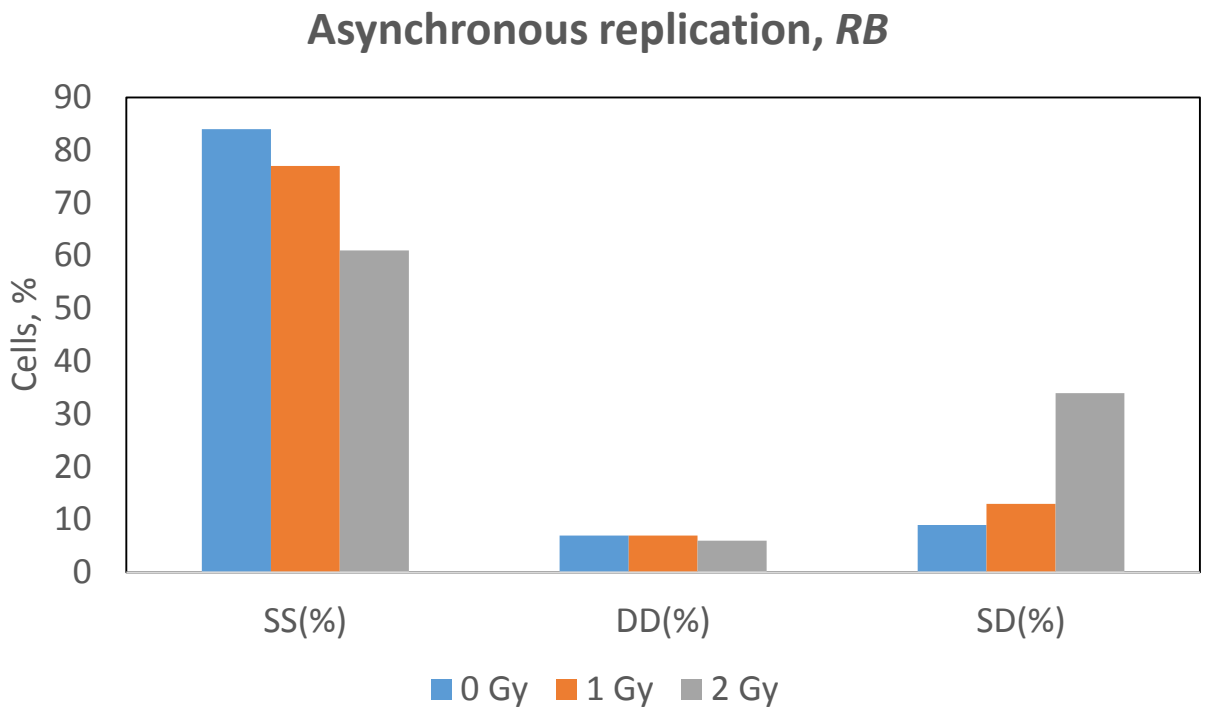
(SS)- two single signals
(DD)-two double signals
(SD)-one singlet, one doublet

Brás, A., et al., Oncology reports, 19(2), 369-375 (2008).

Brás et al. 2008, Oncol Reports

Example 2

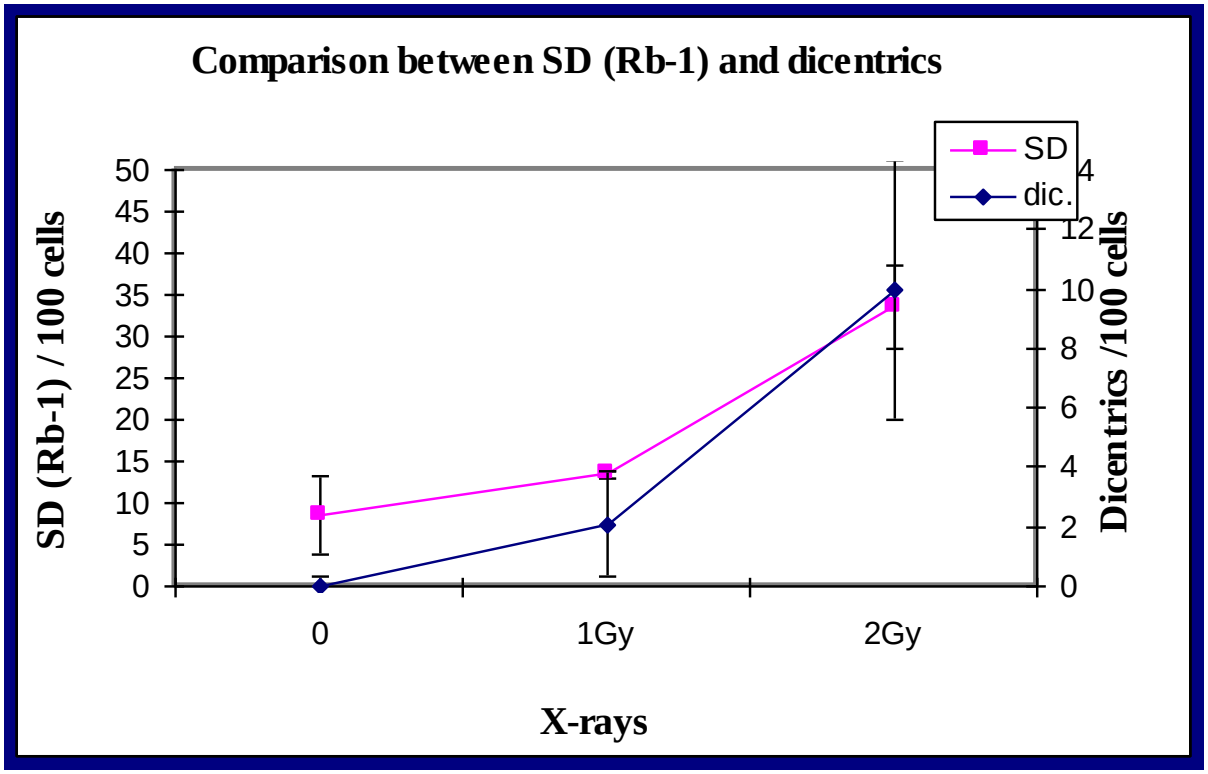
Human lymphocytes exposed *in vitro* to ionizing radiation



Brás, A., et al., Oncology reports, 19(2), 369-375 (2008).

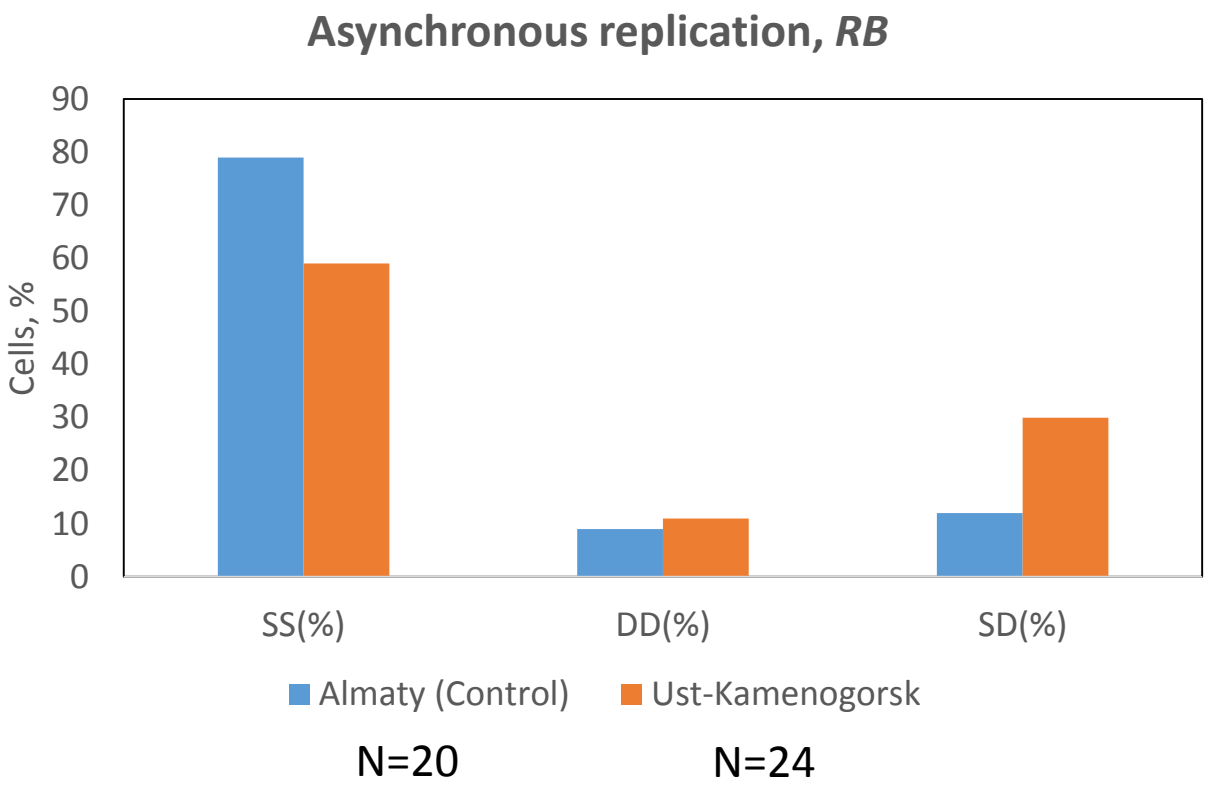
Example 2

Human lymphocytes exposed *in vitro* to ionizing radiation



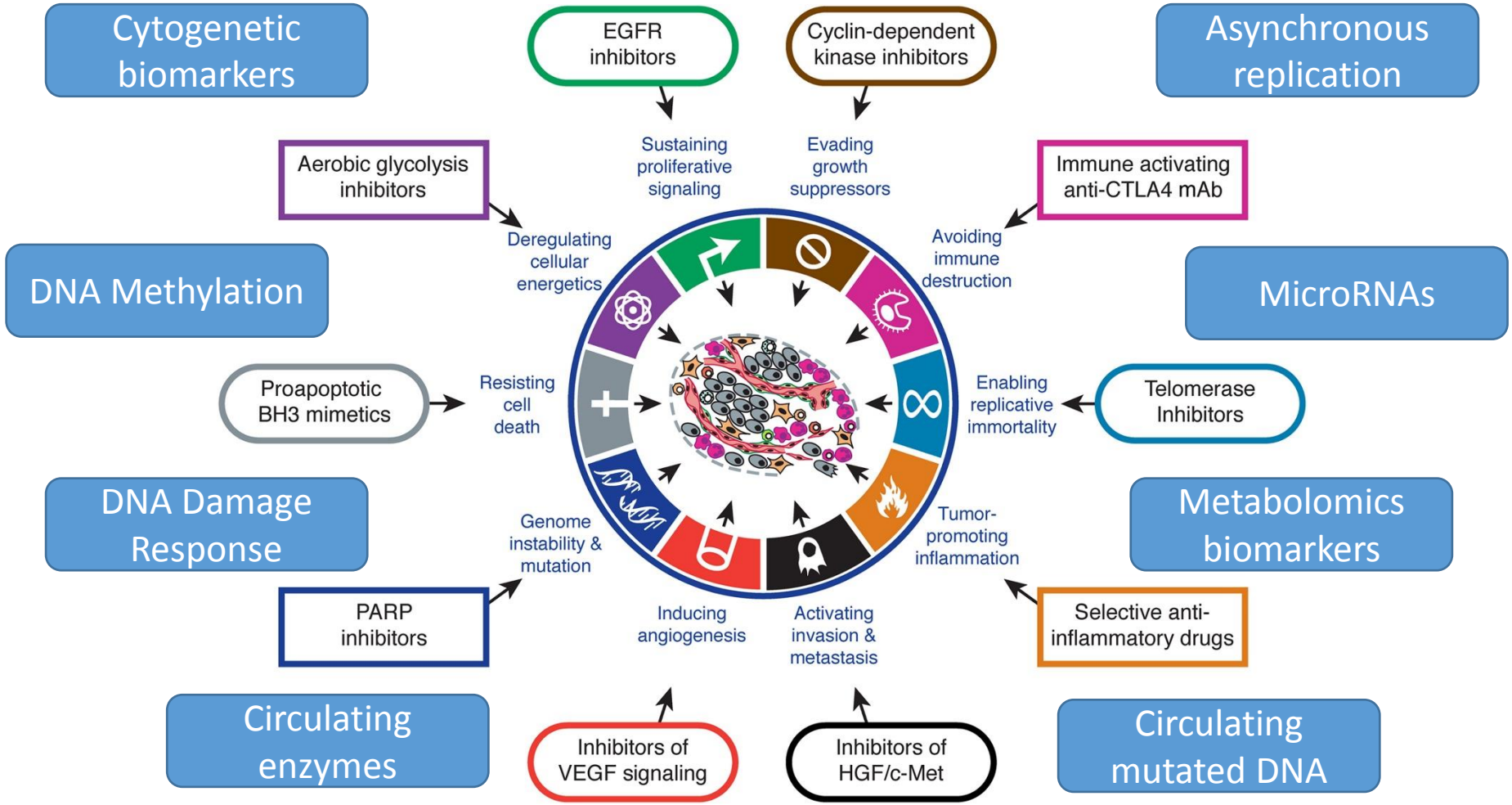
Example 2

Asynchronous replication in Human lymphocytes from study areas



Brás, A., et al., Oncology reports, 19(2), 369-375 (2008).

The Hallmarks of Cancer



Hanahan & Weinberg, Cell, 144, 5, 646-674 (2011)

SUMMARY

- Assessing exposure is critical to understand environmental illnesses - **Biomonitoring**
- Biomonitoring is able to measure integrated exposures within the human body but alone cannot explain where or how the exposure occurred or the toxic potential for that exposure – **Biomarkers of Effect**
- An integrated approach that uses all data types along the environmental disease continuum is required for a complete understanding of environmental illness - **Biomarkers of Exposure, Effect, Susceptibility – Adverse Outcome Pathways**
- Validation of Biomarkers is needed to associate exposure to potential health outcomes – **Adverse Outcome Pathways**

Thank You

Health Examination Surveys and Human Biomonitoring – the added value of combined studies

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Departamento de Epidemiologia
Instituto Nacional de Saúde Doutor Ricardo Jorge

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

Instituto_Nacional de Saúde
Doutor Ricardo Jorge

Human Biomonitoring (HBM) surveys

- **Include:**
  - Questionnaire (interviewed and/or self-administered); and
  - Collection of biological samples for the determination of internal human exposure or of exposure effects.
- **May identify particularly vulnerable or exposed subgroups.**
- **May associate body burden/reactions to health effects.**

Information on "Determinants of Health"

HBM surveys

- **Czech Environmental Health Monitoring System (EHMS)** (since 1994).
- **Flanders human biomonitoring network (FLEHS)** (since 2002).
- **Japan Environmental and Children's Study (JECS)** (since 2010).
- **Spanish monitoring programme BIOAMBIENT.ES** (2009 – 2010).
- **Programme for Italian population exposure (PROBE)** (2008 – 2011).
- **Slovenia's national HBM programme** (since 2010).

HBM projects

- **ESBIO (Expert Team to Support Biomonitoring in Europe)** (2005-2008).
- **ECNIS (Environmental Cancer Risk, Nutrition and Individual Susceptibility)** (2005-2013).
- **INTARESE (Integrated Assessment of Health Risks from Environmental Stressors)** (2005-2010).
- **PHIME (Public Health Impact of Long-Term, Low-Level Mixed Element Exposure in susceptible population strata)** (2006-2011).
- **NewGeneris (Newborns and Genotoxic Exposure Risks)** (2005-2010).
- **EnviroGenomarkers (Genomics Biomarkers of Environmental Health)** (2009-2013).
- **COPHES (Consortium to Perform Human Biomonitoring on an European Scale) and its Life pilot survey (DEMOCOPHES)** (2009-2013).
- **EXPOsOMICs** (2013-2018).
- **HELIX (The Human Early Life Exposome)** (2013-2018).
- **HEALS (Health and Environment-wide Associations based on Large Population Surveys)** (2013-2019).

Health Examination Surveys (HES)

- **Include:**
  - Questionnaire (interviewed and/or self-administered);
  - Physical measurements such as anthropometric measurements, blood pressure and functional capacity; and
  - Collection of biological samples, such as blood and urine.
- **Contents of the survey are based on needs of individual countries.**
- **Usually starts with a few core measurements and is extended in next rounds as more experience is gained.**

HES - European level initiatives

- **Feasibility of the European Health Examination Survey (FEHES) Project (2006-2008)**
  - Prepared European level guidelines and recommendations
- **European Health Examination Survey (EHES) Pilot Project**
  - 2009-2012 - Establishment of the EHES Reference Centre and EU level coordination activities
  - Preparation of the EHES Manuals
  - 2010-2011 Pilot surveys

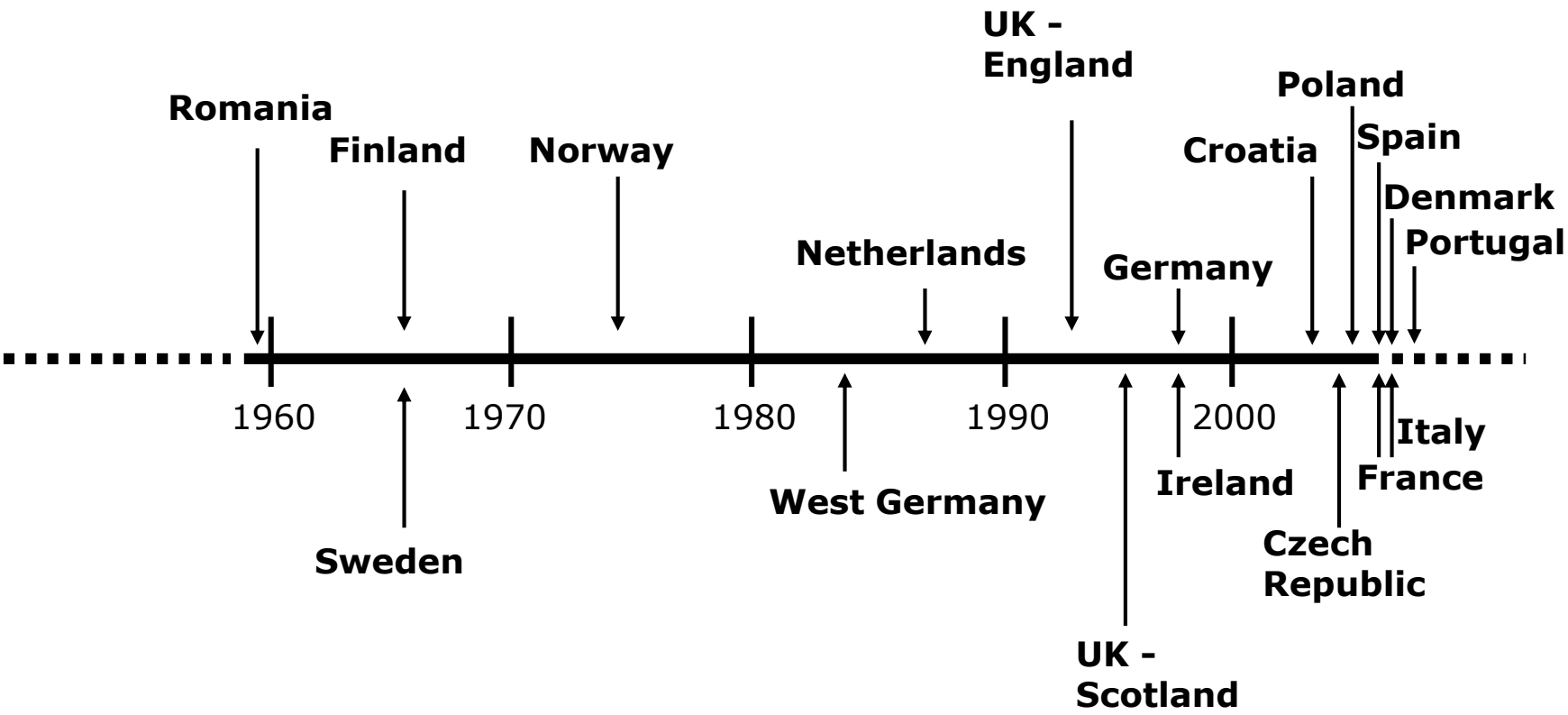
EHES
Measuring the Health of Europeans

European level initiatives

- **Initiative to set up sustainable European health information system (EU/DG SANTÉ)**
  - BRIDGE Health project http://www.bridge-health.eu)
  - bridged the best of EU projects in domains of population and health system monitoring, indicator development, health examination surveys, environment and health, population injury and disease registries, clinical and administrative health data collection systems and methods of health systems monitoring and evaluation.

BRIDGEHEALTH
BRidging Information and Data Generation for Evidence-based Health Policy and Research

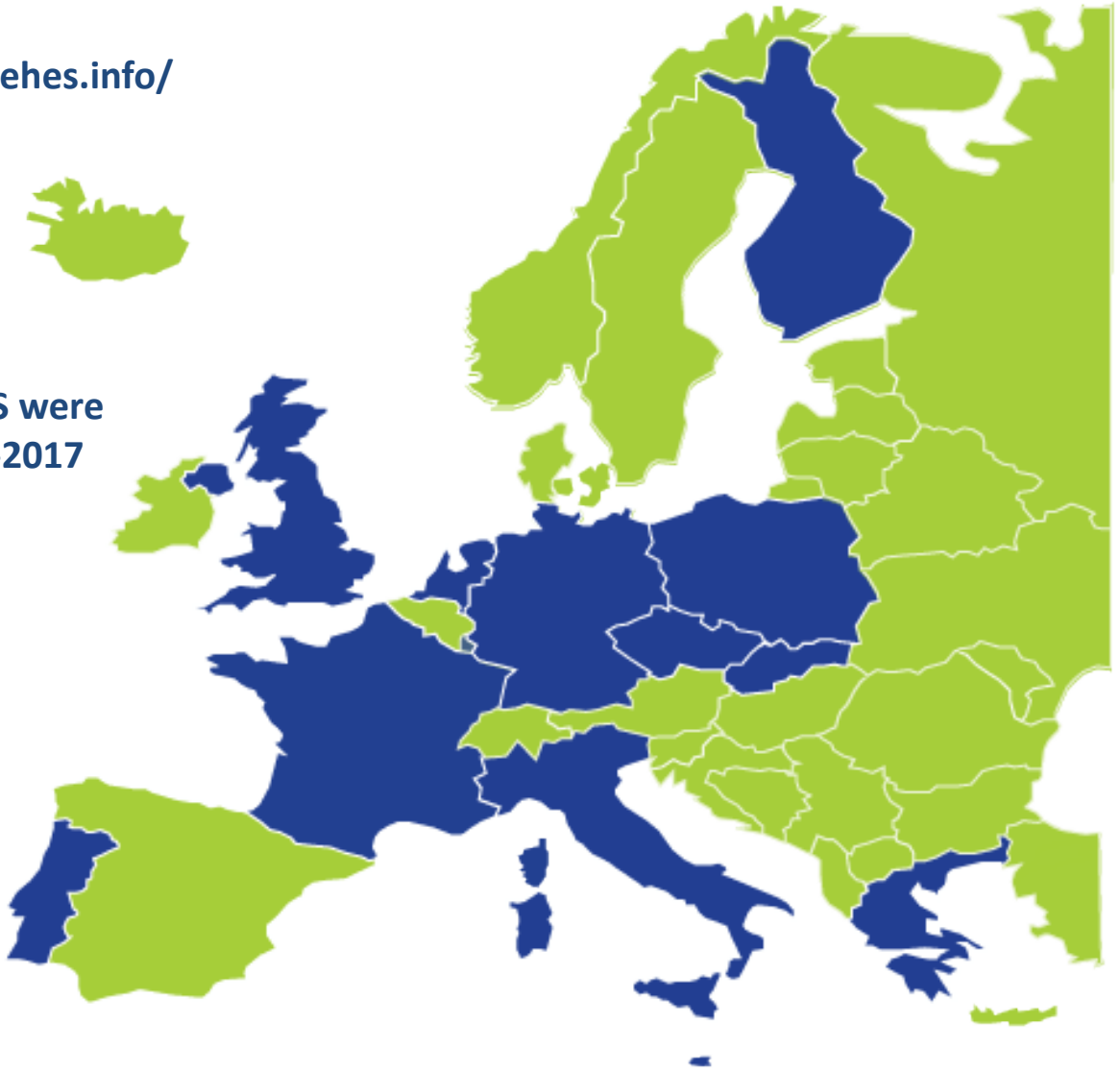
History of HES in Europe



Source: http://www.ehes.info/

HES in Europe

Source: http://www.ehes.info/



Countries were HES were developed in 2010-2017

HES in Portugal - INSEF

- **First National Health Examination Survey (INSEF)**
  - observational epidemiological, cross-sectional, population-based study designed to be representative at the regional and national level;
  - target population consisted of individuals aged between 25 and 74 years old, living in Portugal for more than 12 months, not institutionalized and able to follow the interview in Portuguese;
  - included a set of physical and biochemical measurements, in addition to an interview;
  - collected data on 4911 individuals in 2015.

INSEF
Inquérito Nacional de Saúde com Exame Físico 2013-2016

Source: www.insef.pt

Similarities between HES & HBM surveys

- Ethics and data protection issues
- Sampling
- Training
- Recruitment
- Questionnaires
- Collection of biological samples
- Quality control
- Data management/storage
- Data analysis
- Interpretation of results
- Communication

Potential synergies

- Sampling frame
- Sampling scheme
- Ethics and data protection
- Team members
- Training
- Fieldwork logistics (coordination; recruitment; data and sample collection, handling, processing and storage; sample transport)
- Quality control
- Reporting

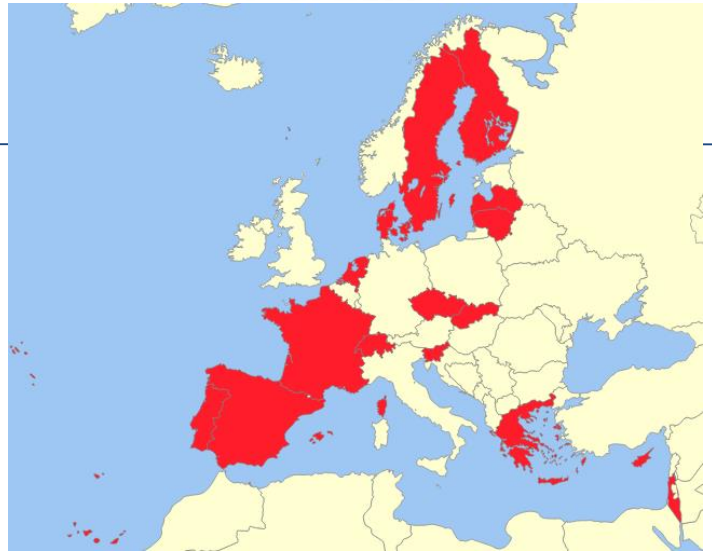
Combined HBM & HES surveys

- **U.S. National Health and Nutrition Examination Survey (NHANES)** (HES since 1960; NHANES since 1971; continuous since 1999).
- **German Environment Surveys (GerES I – VI) & German Health Interview and Examination Survey** (since 1985).
- **Korea National Health and Nutrition Examination Survey (KNHANES)** (since 1998).
- **French Nutrition and Health Survey (ENNS)** (2006-2007) and **French Health Study on Environment, Biomonitoring, Physical Activity and Nutrition (ESTEBAN)** (2014-2016).
- **Canadian Health Measures Survey (CHMS)** (since 2007).

HBM4EU
WP11 - Linking HBM, health studies and registers

- Evaluate opportunities and obstacles related to linking HBM, health surveys and administrative data sources.
- Evaluate existing biological samples from health studies which could be used to analyse HBM biomarkers.
- Provide tools for linking HBM and health studies for improved cost-benefit and knowledge on human exposure-health outcome correlations.
- Provide broader HBM and health data on the same individuals.

WP11 inventory



- 52 different surveys;
- 30 researchers;
- 16 European countries;
- Most of the studies include the collection of biological samples and storage for future use;
- Most frequently stored samples: blood, plasma, serum and DNA;
- Ethical approval for the measurements of chemicals would be possible to obtain;
- Half of the studies are longitudinal;
- Register data was only retrieved for half the studies.

Advantages

- Increased sampling size
- Use of common logistical infrastructure
- Reduced cost
- Access to detailed health and exposure data
- Possibility to study links between exposure and health related outcomes
- Reinforce public awareness and interest in HBM through health

Obstacles

- **Financial**
- **Logistic**
  - recruitment
  - higher data complexity, more samples and more results
- **Combined questionnaire**
- **Coordination between HBM/HES modules**

Recommendations

- Adequate and integrated planning including both components from the beginning;
- National prioritization;
- Pluri-annual planning.

Acknowledgements

- **Carlos Matias Dias** (INSA)
- **Baltazar Nunes** (INSA)
- **INSEF Team**
- **Hanna Tolonen** (THL, Finland)
- **Anna-Maria Andersson** (RegionH, Denmark)
- **Stine Holmboe** (RegionH, Denmark)
- **Portuguese National Hub for Human Biomonitoring** set for the **HBM4EU project**

Thank you for your attention!

The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 733032.

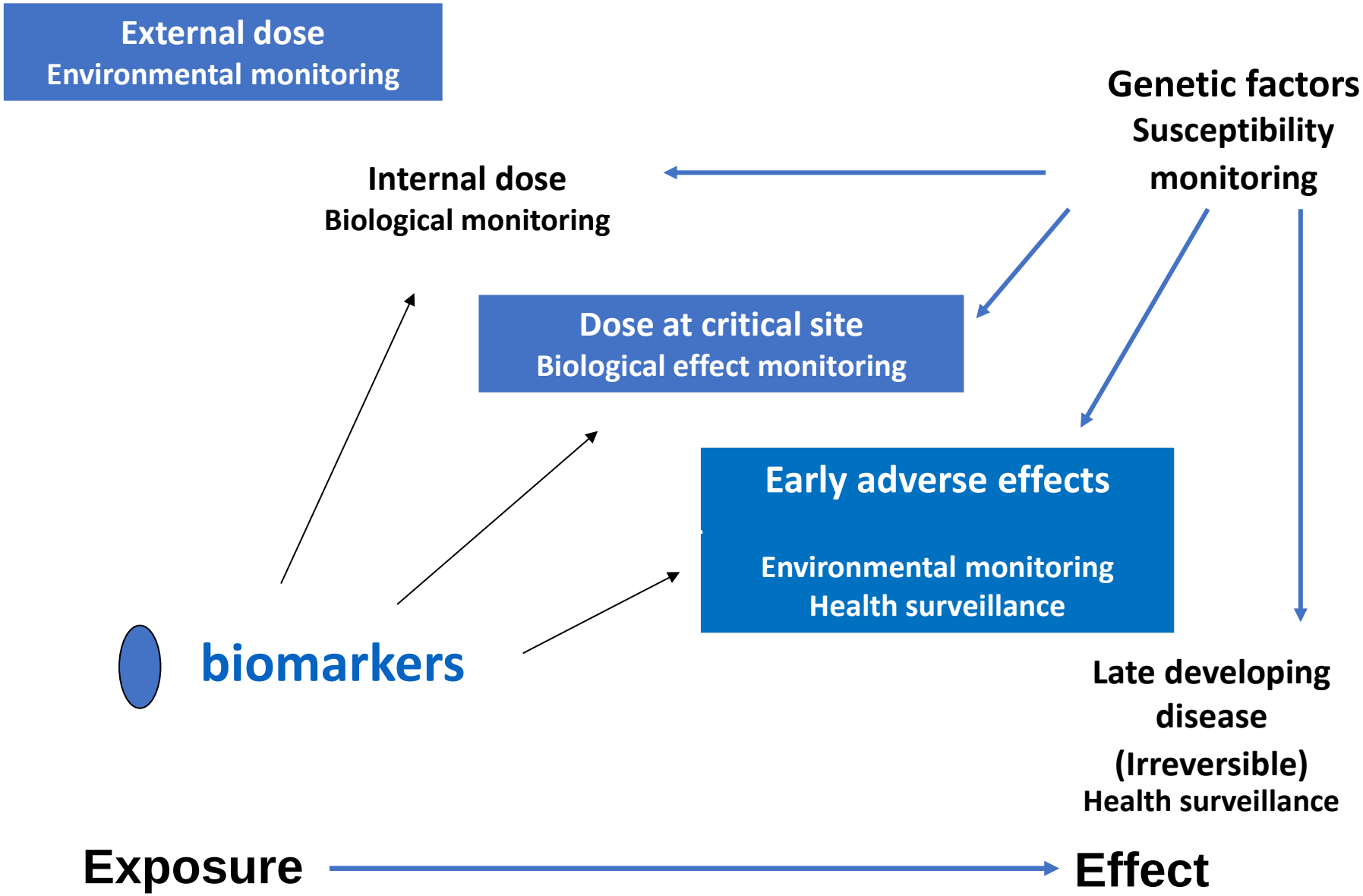
José Rueff

Nova Medical School

Universidade Nova de Lisboa

2018

Biomarkers and monitoring



Alguns trabalhos de Rueff *et al.* sobre biomonitorização

- **Chromium** (matrice: blood)
- Mutagenesis. 2005; 20(5):3 1-315.
- Mutagenesis. 2003 18(1): 19-24.
- In "Human Monitoring for Genetic Effects" IOS Press, 2003, pp.132-141
- **Acrylonitrile** (matrice: blood):
- *Mutat Res.* ; 436(3):263-283. 1999
- *Carcinogenesis.* ; 17(12):2655-2660, 1996
- *Teratog Carcinog Mutagen.;*16(4):205-218. 1996
- **Styrene** (matrices: blood, urine):
- *J Toxicol Environ Health A.*; 75(13-15): 735-746. 2012
- *Mutagenesis.* ; 25(6): 617-621..2010
- *Clin Chim Acta.* ; 399(1-2): 8-23. 2009
- *Int J Hyg Environ Health.* 211(1-2): 59-62. 2008
- *Toxicology.* 31;237(1-3): 58-64. 2007
- *Toxicology*. 15;195(2-3): 231-42. 2004
- **Iron oxide particles and mineral oils** (matrice: urine)
- . *Prog Clin Biol Res.*; 109: 443-452. 1982
- *Carcinogenesis.* ; 3(9): 1077-1079. 1982

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Direção-Geral da Saúde

1ST WORKSHOP ON HUMAN BIOMONITORING IN PORTUGAL

"Bridging Chemical Exposure to Human Health"

11 May 2018 / INSA / Lisbon - Portugal

Needs for Human Biomonitoring in Portugal: Occupational Health and Safety (OHS) setting

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Division of Environmental and Occupational Health
Directorate-General of Health
Ministry of Health - **PORTUGAL**

SAÚDE OCUPACIONAL

Introdution

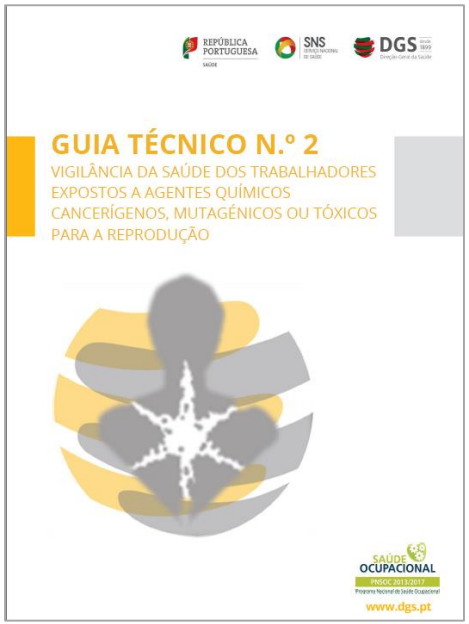
• **Law n.º 102/2009, of September 10th** (and its amendments) establishes the Legal Regime for Occupational Health and Safety (OHS):

- The employer is required to organize "Occupational Health and Safety Services" for all his workers.

- These Services aim achieving:
  - occupational risks prevention;
  - protection and promotion of workers health;
  - OHS information and workers training;
  - the improvement of healthy work environments.

- Occupational risk assessment and workers health surveillance are core activities of the OHS Services.

National Occupational Health Program



- The National Occupational Health Program has developed several **guidelines** aiming the promotion of good practices in occupational health.

- In 2017, the **Technical Guide on "Workers exposed to carcinogenic, mutagenic or toxic for reproduction (CMR) chemicals health surveillance**" was developed by a Technical Group, including several entities:

- Autoridade para as Condições do Trabalho
- Instituto Nacional de Saúde Dr. Ricardo Jorge
- Ordem dos Engenheiros
- Ordem dos Médicos
- Sociedade Portuguesa de Medicina do Trabalho
- Escola Nacional de Saúde Pública
- Faculdade de Medicina (Universidades de Lisboa e Porto)
- Faculdade de Farmácia (Universidade de Lisboa)
- Instituto Superior Técnico

COORDINATION: *Direção-Geral de Saúde*

Technical Guide

REACH
CLP

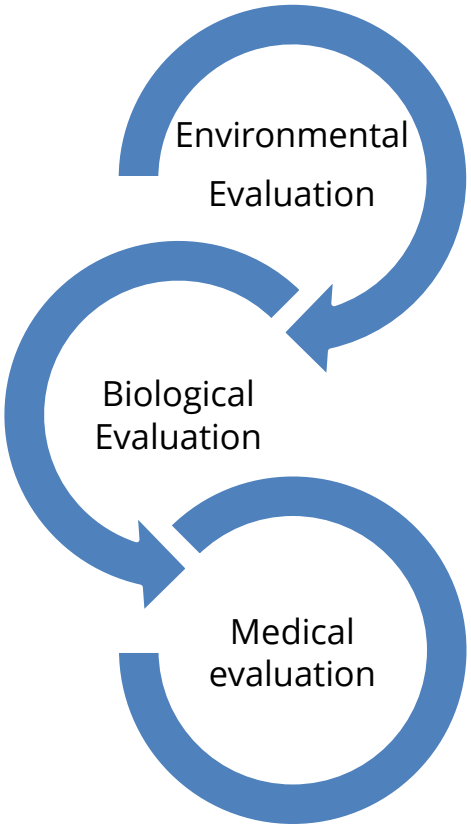
Occupational
Health and
Safety

Purpose: to identify good practices for occupational risks prevention and health surveillance of workers exposed to CMR chemical agents, aiming to be an action guideline for the OHS Services.

Highlights the legal obligation to carry out:

- Assessment of occupational risk (article 42 of Law n.º 102/2009);
- Workers health surveillance, which includes "biological surveillance whenever needed" (article 44 of Law n.º 102/2009).

Technical Guide:
Environmental, Biological and Medical evaluations



- **Environmental evaluation**: measures the external dose (quantifies the chemical agent in the workplace).
- **Biological evaluation**: measures the internal dose (quantifies the interaction between the chemical agent and the organism).

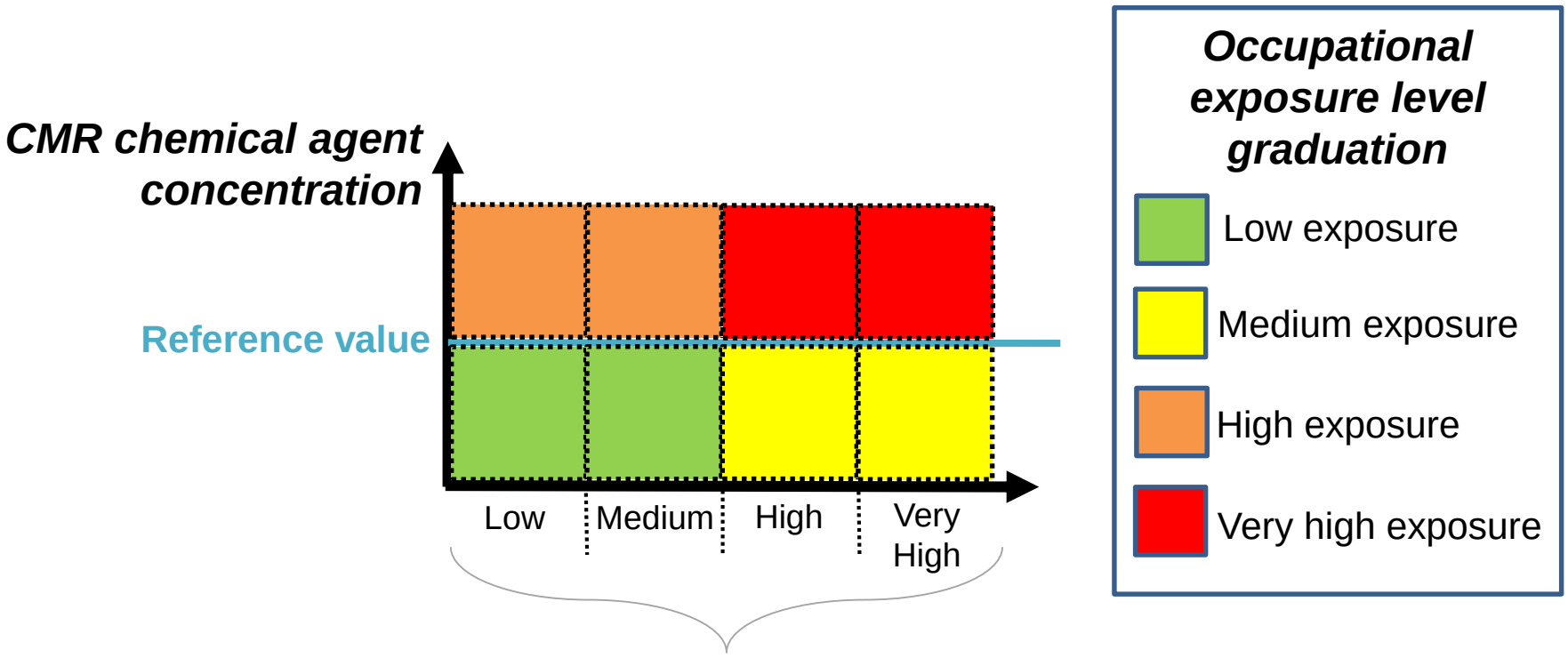
*Measurements that give **complementary** information*

- **Medical evaluation:** identifies early signs of disease and diagnoses diseases and their evolution (within the framework of a continuous health surveillance).

*Integrated evaluations to define a strategy for the **occupational risks prevention***

Technical Guide: stepwise approach

Occupational risk assessment and management (1)



Occupational Exposure Context

e.g. quantity, chemical physical properties, process conditions, frequency and duration of use

Technical Guide: stepwise approach

Occupational risk assessment and management (2)

Occupational Exposure Level	Human Health Effects: Category 2	Human Health Effects: Category 1B	Human Health Effects: Category 1A	Human Health Effects: More than one Category (1A or 1B)
Low	Low Risk	Low Risk	Medium Risk	Medium Risk
Medium	Low Risk	Medium Risk	High Risk	High Risk
High	Medium Risk	High Risk	High Risk	Very High Risk
Very High	Medium Risk	High Risk	Very High Risk	Very High Risk

→ **Individual correction factor** (decision made by occupational health doctor)

→ ***Final graduation of the occupational risk level***

→ **OHS Intervention / Preventive measures**

Technical Guide: stepwise approach

Occupational risk assessment and management (3)

Registration form

Parte A. *A preencher pelo TST/TSST*

A. 2.3.1. Foi realizada avaliação ambiental: *Sim* ☐ *Não* ☐

Justificar "*Não*":

☐ *Contexto de exposição profissional "baixo" (de acordo com o Quadro 7 do Guia Técnico da DGS)*

☐ *Avaliação ambiental será realizada em* ☐☐☐ *dias/meses*

☐ *Outra. Qual?* _____

A. 2.3.2. Avaliação(ões) efetuadas:

Parâmetro avaliado	*Valor de referência*	*Fonte do valor de referência*	*Valor medido (resultado da amostra)*	*Unidades do valor medido*	*Data da avaliação / medição*
(Acrescentar as linhas necessárias)	(...)	(...)	(...)	(...)	(...)

A. 2.3.3. Graduação do nível de exposição profissional (*vide Figura 6 do Guia Técnico da DGS*) - *Proceder à graduação preliminar:*

Exposição profissional	*Baixa*	*Média*	*Alta*	*Muito Alta*
(sinalize o resultado com cruz)	☐ (Verde)	☐ (Amarelo)	☐ (Laranja)	☐ (Vermelho)

Parte B. *A preencher pelo Médico do Trabalho*

B. 2.3.1. Foi realizada avaliação biológica: *Sim* ☐ *Não* ☐

Justificar "*Não*":

☐ *Contexto de exposição profissional "baixo" (de acordo com o Quadro 7 do Guia Técnico da DGS)*

☐ *Avaliação biológica será realizada em* ☐☐☐ *dias/meses*

☐ *Não existe bioindicador disponível*

☐ *Outra. Qual?* _____

B. 2.3.2. Avaliação(ões) efetuadas:

Parâmetro avaliado	*Observações*	*Data da avaliação / medição*
(Acrescentar as linhas necessárias)	(...)	(...)

B. 2.3.3. Graduação do nível de exposição profissional (*vide Figura 6 do Guia Técnico da DGS*) - *Proceder à graduação final:*

Exposição profissional	*Baixa*	*Média*	*Alta*	*Muito Alta*
(sinalize o resultado com cruz)	☐ (Verde)	☐ (Amarelo)	☐ (Laranja)	☐ (Vermelho)

Final considerations: *research needs*

- Availability of more (and more accurate) biological indicators (biomarkers) in Occupational Health settings.
- Selection and interpretation of biomarkers in the process of occupational risk assessment to justify / reinforce the adoption of occupational health and safety preventive measures.
- Integrated assessment of environmental, biological and medical evaluations.
- Identification of workers' genetic susceptibilities to chemical hazards and others.

Thank you for your attention!

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