Exposição Humana a Micotoxinas: biomonitorização humana e contribuição para a avaliação de risco da população Europeia

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HBM4EU

science and policy for a healthy future

Seminários Ricardo Jorge

27 Junho 2022

Summary

I. The European Human Biomonitoring Initiative (HBM4EU)

- Why?
- Consortium, mission & network,
- Organization & activities.

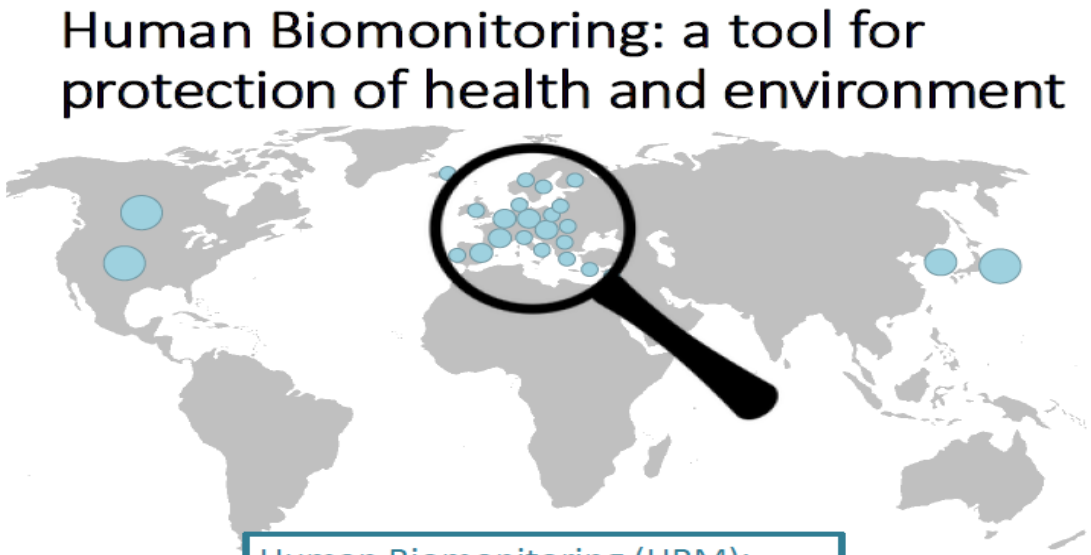
II. Mycotoxins under HBM4EU

- Impact on health,
- Prioritised substances,
- Policy-questions,

III. Main results and future perspectives

- Exposure, hazard and risk assessment
- Key messages
- Research needs and gaps

I. The HBM4EU initiative: Why?



(https://www.hbm4eu.eu/the-project/)

(Kolossa-Gerling M, HBM4EU Introduction and Progress, 4th september 2017)

I. The HBM4EU initiative: Consortium & mission

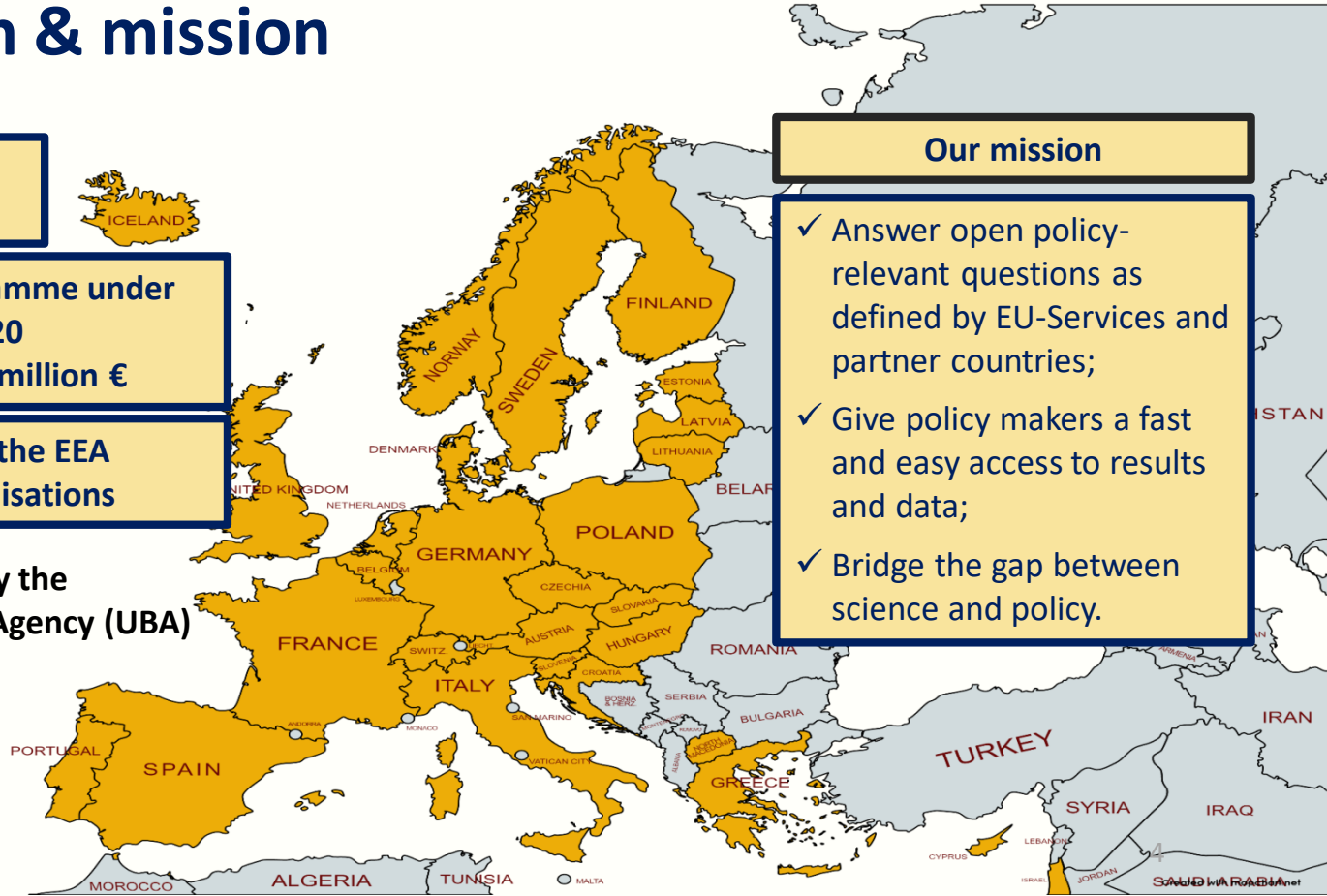
5 yrs + extension (2017-6/2022)

European Joint Programme under Horizon 2020
Total budget: ~ 74 million €

30 countries and the EEA
120 Partner organisations

Coordinated by the German Environment Agency (UBA)

(kindly shared by Marike Kolossa-Ghering, 5th Consortium Meeting, 21-22 Set 2021, Berlin)

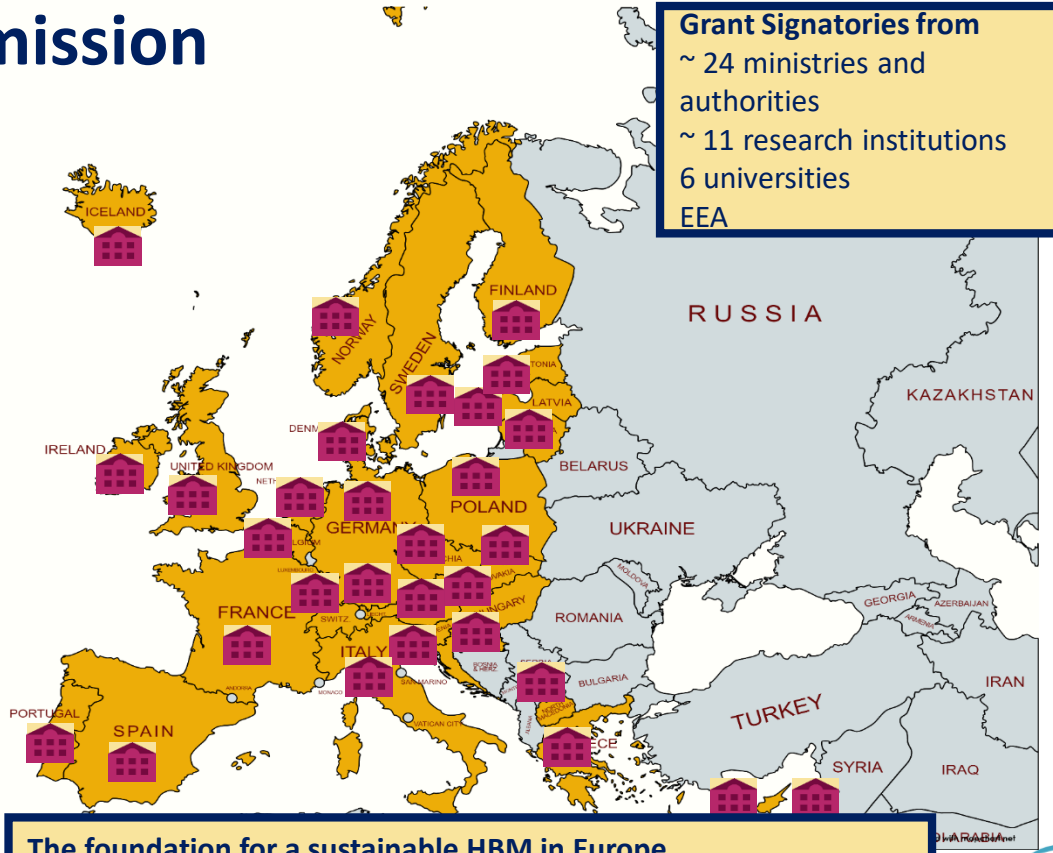


Our mission

- ✓ 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.

I. The HBM4EU initiative: Consortium & mission

National Hubs –
a strong partnership
in all partner countries
- Review national needs
- Feedback from and into HBM4EU
- Strengthen national coordination

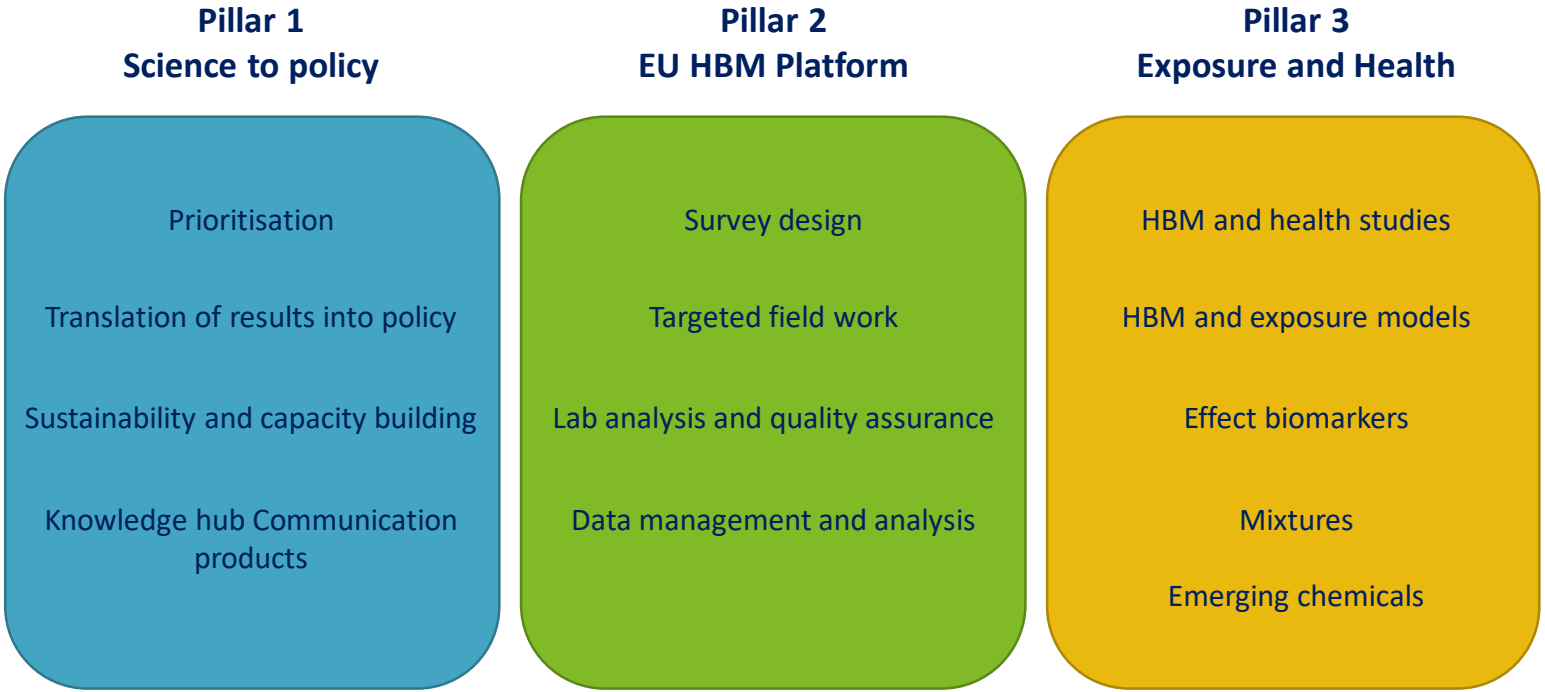


Grant Signatories from
~ 24 ministries and authorities
~ 11 research institutions
6 universities
EEA

(kindly shared by Marike Kolossa-Ghering, 5th Consortium Meeting, 21-22 Set 2021, Berlin)

The foundation for a sustainable HBM in Europe
→ To further improve the EU Chemicals policy

I. The HBM4EU initiative: organisation & activities



(kindly shared by Marike Kolossa-Gehring, 5th Consortium Meeting, 21-22 Set 2021, Berlin)

I. The HBM4EU initiative: Prioritized substances

The selection of **substances to be the subject of research activities under HBM4EU** represents a critical step towards achieving of HBM4EU objectives.

The first list of HBM4EU priority substances includes (2017-18):

- Aniline family
- Bisphenols
- Cadmium and chromium VI
- Chemical mixtures
- Emerging substances
- Flame retardants
- Polycyclic Aromatic Hydrocarbons
- Per-/poly-fluorinated compounds
- Phthalates and Hexamoll® DINCH

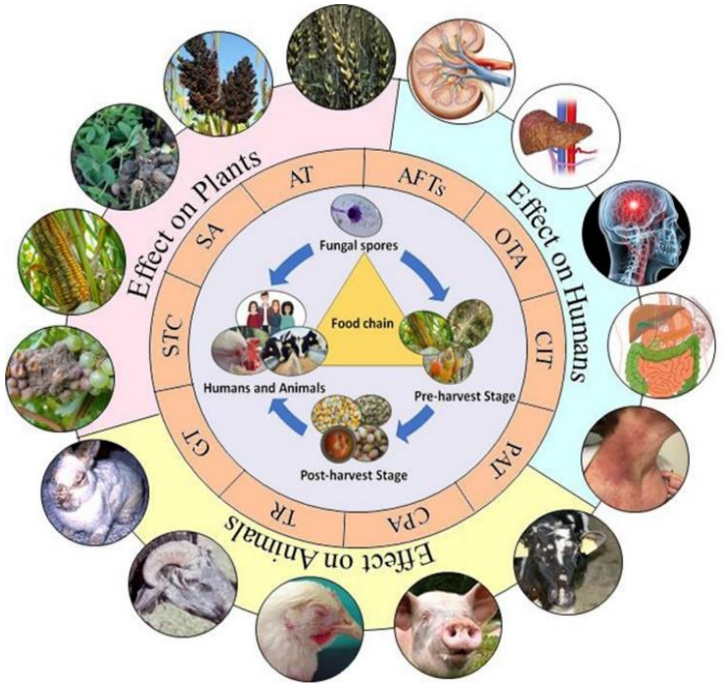
The second list of HBM4EU priority substances includes (2019-20):

- Acrylamide
- Aprotic solvents
- Arsenic
- Diisocyanates
- Lead
- Mercury
- **Mycotoxins (DON & FB_1) - *CGL* PT, *scoping document***
- Pesticides
- Benzophenones

Deliverable 4.2 Scoping documents on HBM4EU priority substances for 2018, June 2017
Deliverable 4.5 Second list of HBM4EU priority substances and Chemical Substance Group Leaders for 2019-2021
Deliverable 4.8 Third list of HBM4EU priority substances, 2021

II. Mycotoxins under HBM4EU: impact on human health

- Mycotoxins are NATURAL TOXINS produced by fungi that contaminate agricultural crops, particularly CEREALS, although they also appear in FRUITS, VEGETABLES and ANIMAL PRODUCTS (meat, dairy, eggs).
- Humans (and animals) are mainly exposed though the consumption of contaminated FOOD and FEED. Occupational exposure can also contribute to human exposure.
- Mycotoxins can cause ACUTE EFFECTS, but the major concern is with CHRONIC EFFECTS impacting human health: e.g. HEPATOTOXICITY, NEPHROTOXICITY IMMUNOTOXICITY, REPROTOXICITY, TERATOGENICITY, GENOTOXICITY and CARCINOGENICITY.



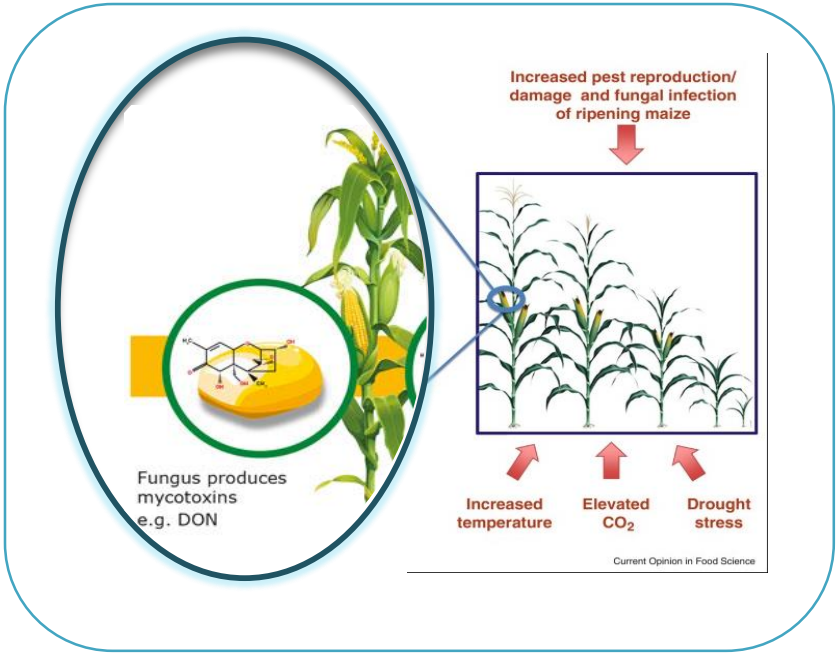
Navale et al., 2021. Toxicol Reports, 8: 2008

(IARC 2012; Wu et al, 2014; Eskola et al, 2020, Battilani et al, 2016; Viegas et al., 2018)

II. Mycotoxins under HBM4EU: impact on human health

Climate change: impact on mycotoxins production and human exposure

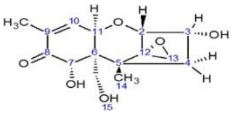
- With the CLIMATE CHANGE scenario, some fungal species might shift their geographical distribution in response to global warming, leading to CHANGES IN THE PATTERN OF MYCOTOXIN OCCURRENCE.
- It is predicted that due to climate change, zones with a relatively low occurrence of FUSARIUM will become prone to the occurrence of the fungus and FORMATION OF TOXINS (WHO, 2018).
- HUMAN EXPOSURE to MYCOTOXINS is predicted to increase in the future.



Medina et al., 2015. Current Opinion in Food Science, 5:99
https://www2.biomin.net/es/blog-posts/61-of-those-polled-had-a-mycotoxin-issue-in-the-past-year/

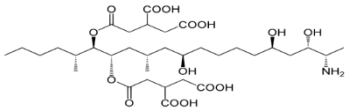
II. Mycotoxins under HBM4EU
Prioritised substances

DON



https://mycotoxinsite.com/fumonisins-do-we-know-the-risks/?lang=en

FB_1



Health outcomes

Iimmunotoxic & reprotoxic

Inadequate evidence for carcinogenicity (IARC group 3).

MoA

› Potent inhibitor of protein synthesis and stimulates the pro-inflammatory response leading to oxidative stress generation.

Regulation

› Tolerable daily intake (TDI) = 1 µg / Kg bw per day, based on reduced body weight gain in mice.

Additional health concern

› The estimated mean chronic dietary exposure is above the group-TDI in infants, toddlers and other children, and at high exposure also in adolescents and adults, indicating a potential health concern (EFSA, 2017).

› Immunotoxic, hepatoxic, and nephrotoxic.

› Possible carcinogen to humans (IARC group 2B), associated with oesophageal cancer.

› Inhibition of ceramide synthases, key enzymes in sphingolipid metabolism.

› Suspect mutagen (structural alerts).

› TDI = 1 µg / Kg bw per day (EFSA CONTAM Panel, 2018) considering a BMDL10 = 0.1 mg / Kg bw per day for megalocytic hepatocytes in mice.

› Apart from its chronic effects, a wider dissemination of *Fusarium* fungi will increase human (and animal) exposure and the prevalence of related health outcomes.

II. Mycotoxins under HBM4EU: Policy-questions: exposure

- Are there validated and harmonised **ANALYTICAL METHODS** to assess the target mycotoxins exposure?
- What are the current **EXPOSURE LEVELS** of the European population to DON and FB_1?
- Does the exposure to mycotoxins differ among different **POPULATION GROUPS**? Which are the main **FACTORS** related with these differences (age, gender, settings, geographic localisation)?
- Are there **TOXICOKINETIC** data for both mycotoxins and which are the limitations?

II. Mycotoxins under HBM4EU: Policy-questions: hazard

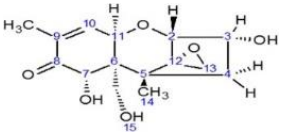
- Which are the **KEY EVENTS** that determine the long-term health effects to the target mycotoxins?
- Which are the **EFFECT BIOMARKERS** for prioritized mycotoxins?

III. Mycotoxins under HBM4EU: Policy-questions: risk

- Is it possible to set a **HBM GUIDANCE VALUE** (HBM-GV) for mycotoxins?
- Is the **RISK** associated with human exposure to these mycotoxins characterized?
- Research **NEEDS AND GAPS**?

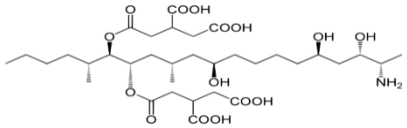
III. Mycotoxins under HBM4EU: Main results: exposure

DON



- total DON (tDON) in urine selected as exposure biomarker to assess exposure to DON and its derivatives (3/15-acetyl-DON, DON-3G).
- Four EU LABORATORIES QUALIFIED for tDON analysis (LC-MS/MS used by 3 laboratories; LC-HR-MS/MS by 1 lab).
- A physiologically-based TOXICOKINETIC MODEL developed (Van den Brand et al, 2021; doi: 10.3390/toxins13100675)
- EU POPULATION EXPOSURE TO DON assessed.

FB_1

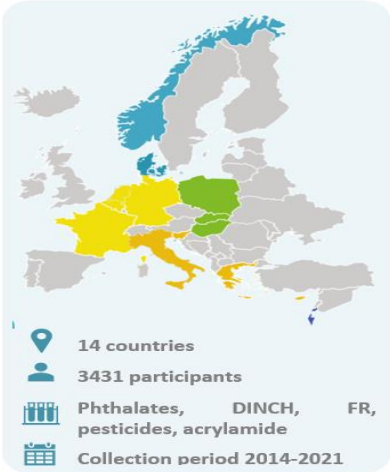


- Methods to measure FB_1 in urine are difficult to implement:
- Low urinary recovery and high inter-individual variability in absorption and excretion
- Limited HBM data for the EU population due to lack of reliable exposure biomarkers. No data obtained under the aligned studies.
- No toxicokinetic model for FB_1 in humans has been developed yet.

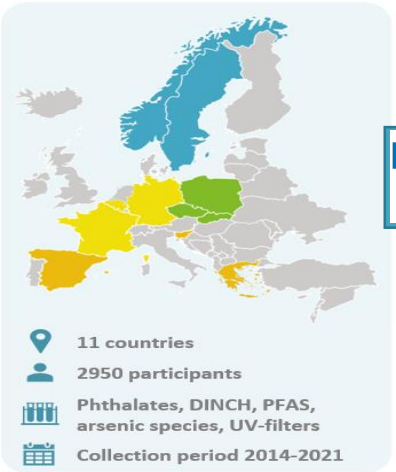
III. Mycotoxins under HBM4EU: Exposure - Aligned studies

What are the current exposure levels for the HBM4EU prioritised substances?
Comparison with guidance values? Geographical variability?
Exposure determinants? Exposure effects asssociations?

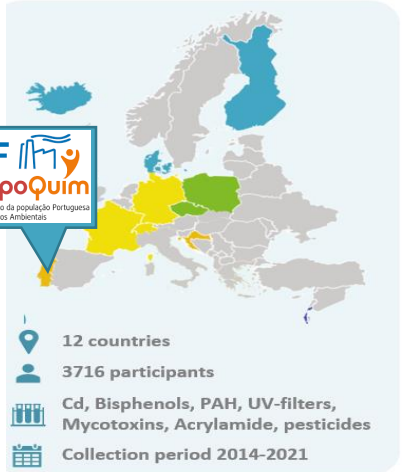
Children 6-11 years



Teenagers 12-19 years



Adults 20-39 years



Northern Europe | Eastern Europe | Southern Europe | Western Europe

(kindly shared by Eva Govarts, HBM4EU Final Conference, 27-28 April 2022)

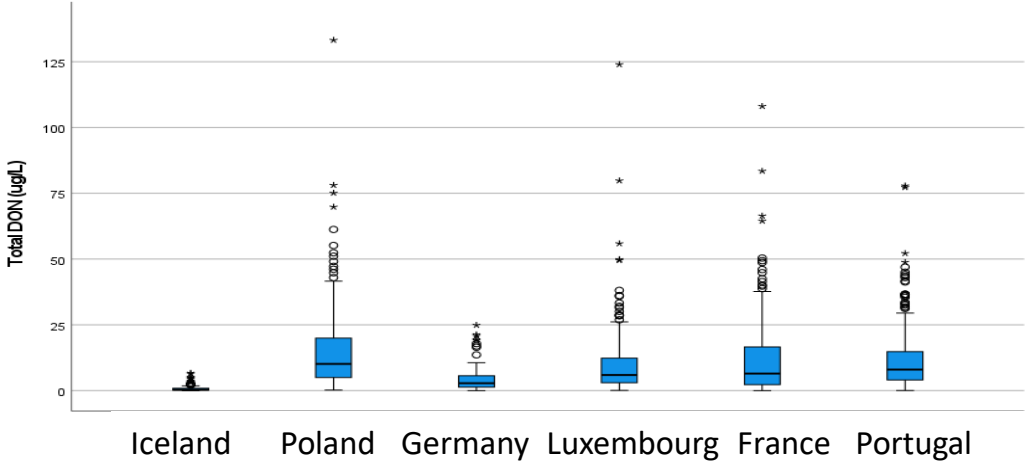
III. Mycotoxins under HBM4EU: Main results: exposure - aligned studies

DON

Total DON	
North	**East**
Iceland	Poland
South	**West**
Portugal	France
	Germany
	Luxembourg

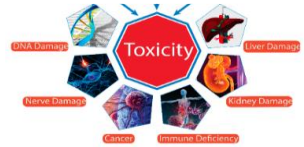
N=1270

28 – 39 years

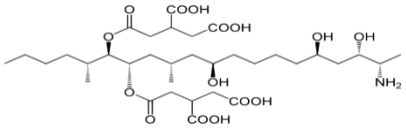


- P50 and P95 values for urinary tDON ranged between 0.41 - 10.16 µg/L and 2.10 - 33.76 µg/L respectively.
- There are highly exposed individuals with the highest percentiles of exposure found in adults from the Eastern region, followed by the Southern and Western regions. Adults' exposure to DON is low in the Northern region.
- Share of individuals with exposure levels exceeding the new HBM-GV (23 µg DON/L urine) ranged from 0.0% - 20.73%.

III. Mycotoxins under HBM4EU: Main results: hazard



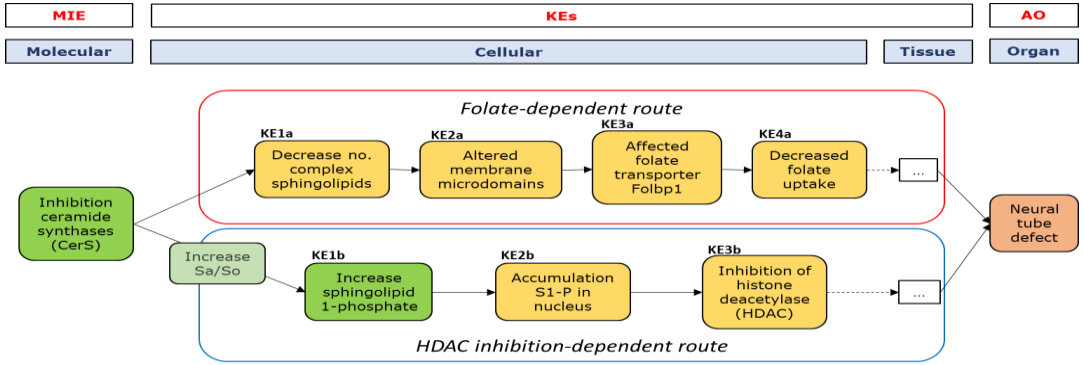
FB_1



- The ADVERSE OUTCOME PATHWAY (AOP) framework was used to collect and organize *in vitro* and *in vivo* studies on possible key events that lead to neural tube defects (NTD).

- A specific EFFECT BIOMARKER identified : sphinganine (Sa) and sphingosine (So) levels in blood or urine.

Putative AOP for CerS inhibition mediated NTD

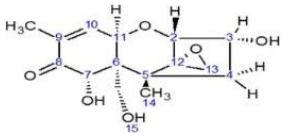


Van den Brand et al. 2022. Toxins, 14: 279

- The molecular initiating event (MIE) that may cause **NTD** in the fetuses of pregnant women after exposure to FB_1 is the **inhibition of ceramide synthase**, which causes an increase of sphingolipids in the cell.
- As sphingolipids are important for a variety of cellular processes, this event is likely also the key event that causes **hepatotoxicity and nephrotoxicity** that are observed in animal studies.

III. Mycotoxins under HBM4EU: Main results on risk

DON

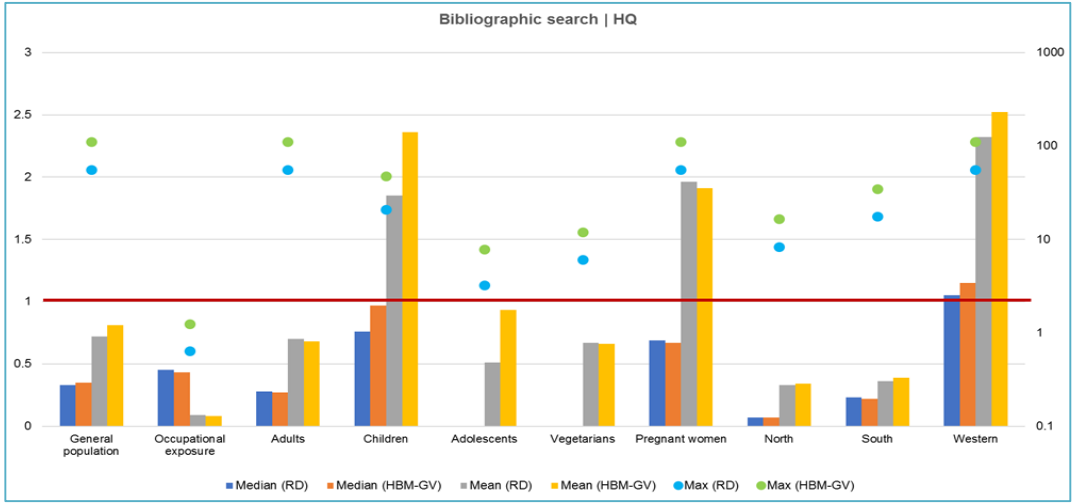


- A **HBM-GV** was derived - Total DON: 0.69 µg DON/kg bw/total 24h ≈ 23 µg DON/L urine (CI: 5-33 µg/L).

- EXPOSURE TO DON IN THE EU POPULATION IS GENERALIZED, affecting different age groups.
- CHILDREN AND PREGNANT WOMEN are at the highest risk.
- The risk of ADULTS FROM THE WESTERN REGION raises a potential health concern.
- OCCUPATIONAL EXPOSURE exists.

Risk characterization through hazard quotient (HQ*) calculation using data from literature

(reverse dosimetry and direct comparison with HBM-GV)

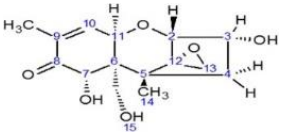


Y-axis = median and mean HQ; Secondary Y-axis = maximum HQ (logarithmic scale); (RD) – using reverse dosimetry value; (HBM-GV) – using human biomonitoring guidance value as the reference value

*Hazard Quotient (HQ) = Exposure Concentration/Reference Concentration

III. Mycotoxins under HBM4EU: Main results on risk

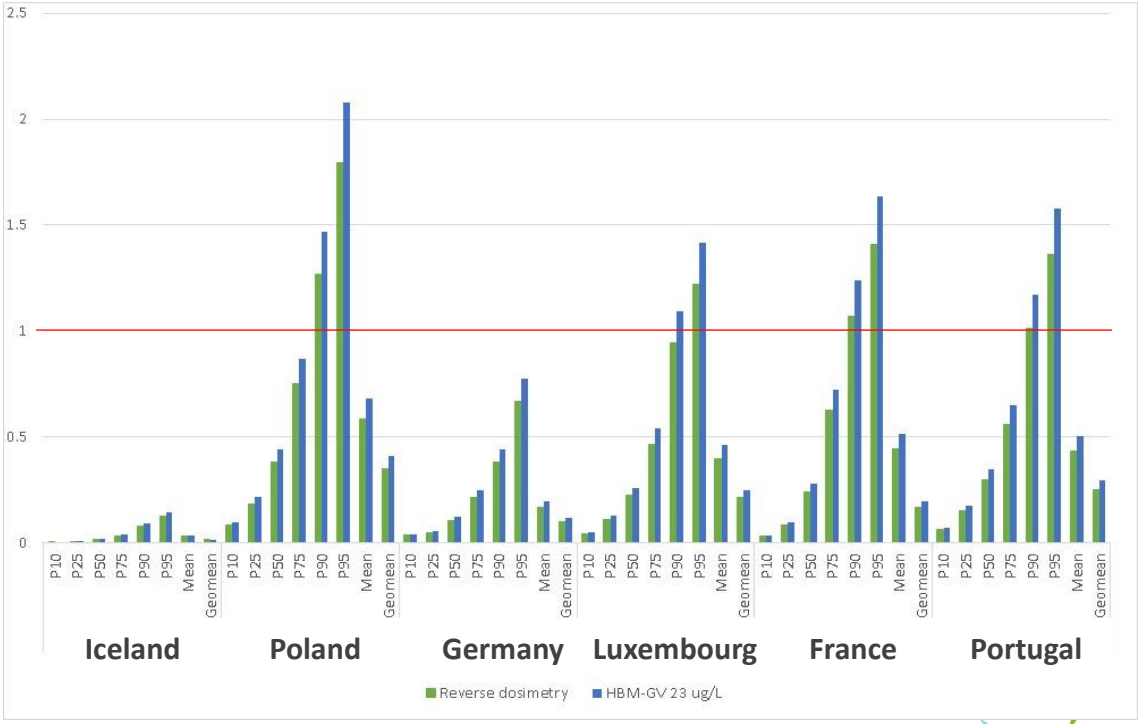
DON



- The risk calculated for adults from Poland and, to some extent, from Luxembourg, France and Portugal is high and raises a POTENTIAL HEALTH CONCERN.
- The results obtained using reverse dosimetry or comparison with HBM-GV for HQ calculation are similar, with the use of HBM-GV presenting consistently higher values.

Namorado et al. Current exposure of the European adult population to mycotoxins: results from the HBM4EU Aligned Studies (in preparation)

Risk characterization through hazard quotient (HQ) calculation
using data from HBM4EU aligned studies
(reverse dosimetry and direct comparison with HBM-GV)



III. Mycotoxins under HBM4EU: Key messages

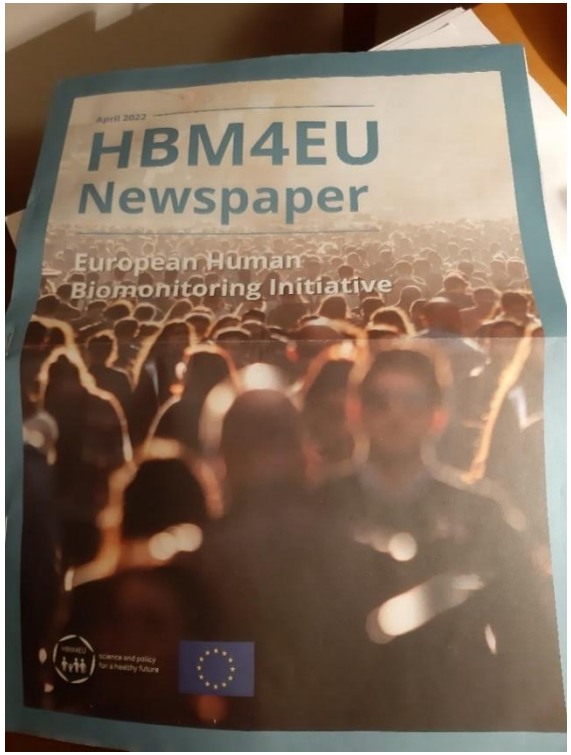
New and harmonized HBM data obtained from 1270 adults under the HBM4EU aligned studies for DON show European population exposure to this mycotoxin.

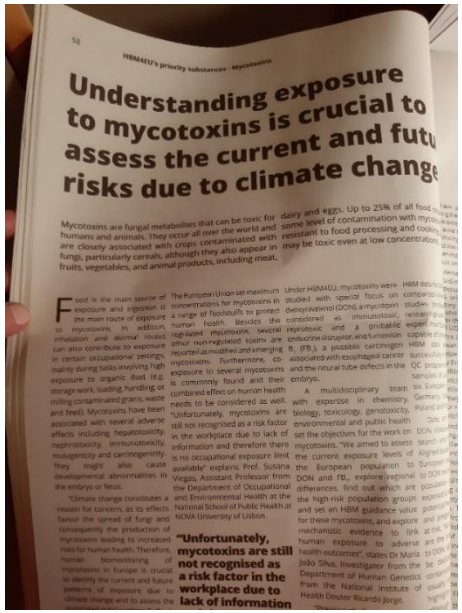
Exposure to DON for the population of some European region might represent a potential health concern, particularly for children and pregnant women; some workplace environments also contribute to the exposure.

A human biomonitoring guidance value (HBM-GV) for the general population was derived for DON and can be used to compare the actual exposure data and assess the associated risk.

Mechanistic data from various *in vitro* and *in vivo* studies support the possibility that FB_1 exposure during pregnancy may result in foetal neural tube defects.

Understanding the exposure to mycotoxins is crucial to assess the current and future risks due to climate change.



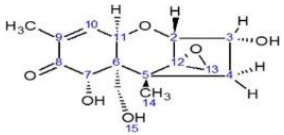


https://www.hbm4eu.eu/citizens-corner/watch-our-videos/

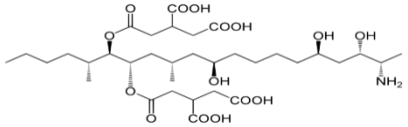
https://www.hbm4eu.eu/wp-content/uploads/2022/05/HBM4EU-Newspaper.pdf

III. Mycotoxins under HBM4EU: needs and gaps

DON

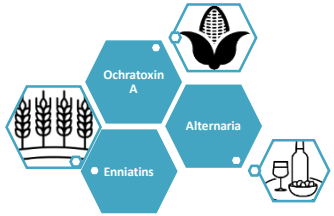


FB_1



- Further development of TOXICOKINETIC MODELS.
- More research on AOPs for relevant health outcomes.
- Research on novel EFFECT BIOMARKERS.

DATA FOR OTHER MYCOTOXINS and MYCOTOXINS MIXTURES



- Identification of harmonised and reliable EXPOSURE BIOMARKERS (FB_1 and other fumonisins).
- ANALYTICAL STANDARDS AND REFERENCE MATERIALS.
- HBM DATA WITH EU COVERAGE (enabling time and/or geographical trends analyses and follow up of climate changes impact).
- Data on VULNERABLE POPULATION SUBGROUPS.
- Development of TOXICOKINETIC MODELS.
- Determination of HBM-GV.
- AOP DEVELOPMENT for other relevant health outcomes.
- Research on novel EFFECT BIOMARKERS.

Thanks to all colleagues who greatly contributed to the work on mycotoxins…

CGL








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

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MASARYKOVA UNIVERZITA


…and thank you for your attention!

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