HBM4EU science and policy for a healthy future

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HBM4EU

POLICY BRIEF

JUNE 2022

European Human Biomonitoring Initiative

Mycotoxins

This policy brief summarizes HBM4EU's results, the adverse human health effects of mycotoxins, their main exposure pathways for humans, and how human biomonitoring of mycotoxins could be of value in the development of EU policy.

Mycotoxins are toxic compounds that are naturally produced by a variety of fungal species or moulds. They can enter the food chain when these moulds infect crops and end up in foodstuffs, particularly cereals, cereal-based products, fruits and nuts. Mycotoxins can also enter the food chain via animal-products such as offal and dairy and eggs from animals that were fed mycotoxin-contaminated feed.

KEY MESSAGES

- An inventory of biomarkers for DON and FB_1 was developed in HBM4EU.
- HBM4EU Aligned Studies[1] (2014-2021) have generated data for DON in 6 countries.
- HBM4EU has assessed how the European population is exposed to mycotoxins, exploring regional differences and identifying vulnerable groups, to inform the development of targeted measures to reduce mycotoxin exposure.
- The HBM4EU Aligned Study conducted to evaluate EU-population exposure to DON and the comparison with the HBM-GV defined in the scope of HBM4EU allowed to conclude that the European population is exposed to DON and that a fraction of this population is, to some extent, exposed to levels that might represent a potential health concern.
- Efforts have been made to identify the key events that determine the long-term health effects from low-dose continuous exposure to the target mycotoxins and the most reliable and meaningful effect biomarkers for single and combined effects.
- Vulnerable groups that may be exposed to harmful levels of mycotoxins include pregnant women, babies, infants and workers in the agricultural and food production sectors.
- Climate change is expected to increase the prevalence of warm and humid climate conditions in Europe that favour fungal growth and is likely to result in an increase in the production of mycotoxins, increasing the risk of human exposure.

BACKGROUND: HBM4EU

The European Human Biomonitoring Initiative, HBM4EU, running from 2017 to June 2022, is a joint effort of 28 countries, the European Environment Agency and the European Commission, and co-funded under Horizon 2020. The main aim of the initiative is to coordinate and advance human biomonitoring in Europe. HBM4EU has provided a wealth of improved evidence of the actual exposure of citizens to chemicals and their possible health effects. Human biomonitoring allows us to measure our exposure to chemicals by measuring either the substances themselves, their metabolites or markers of subsequent health effects in body fluids or tissues. Information on human exposure can be linked to data on sources and epidemiological surveys to inform research, prevention, and policy with the objective of addressing knowledge gaps and promoting innovative approaches. If you would like to read more about the project itself, please visit the HBM4EU website.

1 The HBM4EU Aligned Studies are a survey aimed at collecting HBM samples and data as harmonised as possible from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread.

HBM4EU RESULTS

In order to further support current and future HBM studies, HBM4EU has produced a variety of publicly available groundwork materials for a harmonised approach to study planning and conduct in Europe. Relevant studies were identified for DON (deoxynivalenol) and fumonisin B_1 (FB_1) after a literature review. These were used to elaborate a risk assessment plan for EU exposure and to prepare a research protocol on human exposure and geographic variation.

An inventory of biomarkers for DON and FB_1 was developed, as well as harmonised analytical methods and certified reference materials. On top of that, a human biomonitoring guidance value (HBM-GV) for DON for the general population has been developed. DON measurement in urine has been selected as the biomarker for exposure assessment as part of the work for the HBM4EU Aligned Studies.

For DON, a toxicokinetic model in humans has already been established. A report will be done to elaborate further on the possible mechanism for FB_1 adverse health effects in humans.

A putative adverse outcome pathway (AOP) for FB_1 with the adverse outcome of neural tube defects, which is associated with chronic exposure in humans, has also been addressed (van den Brand et al. 2022).

HBM4EU also laid the foundations for a European HBM Network to monitor human exposure to priority chemicals, including mycotoxins.

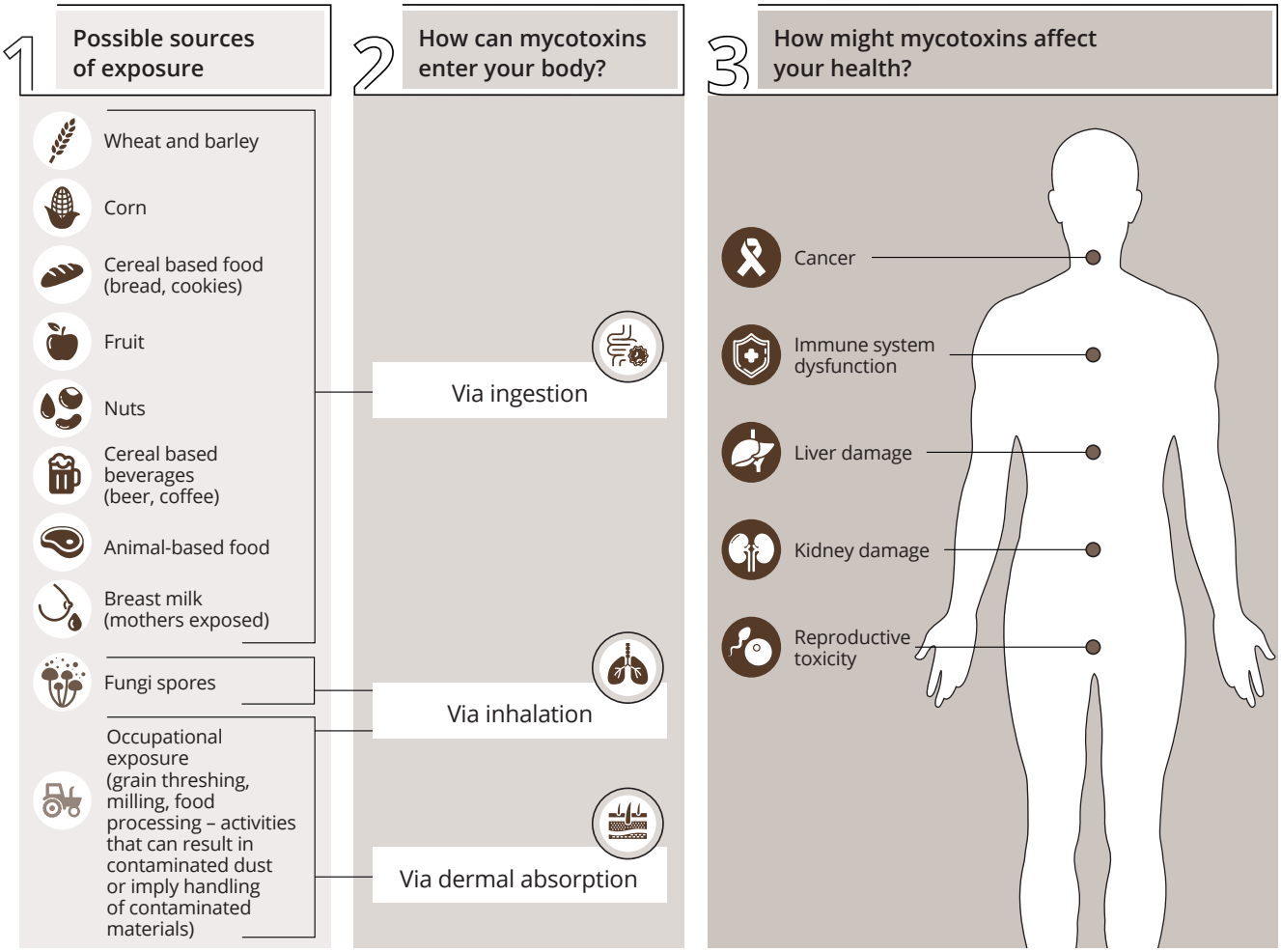
EXPOSURE & HEALTH EFFECTS

An overview of the main sources of exposure (environmental, occupational, consumer) and exposure pathways can be found in Figure 1.

Some mycotoxins have been shown to exhibit carcinogenic and/or mutagenic potential in human and animal species. In particular, FB_1 highlighted the development of tumours in rodents in both kidneys and liver, with additional evidence also highlighting risks for the stomach and digestive system. Both DON and FB_1 have specific target organ toxicity affecting the liver (hepatotoxicity) and central nervous system.

Studies have shown that mycotoxins (including FB_1) can cross the placenta with concerns for health impacts on the foetus.

Figure 1. Overview of exposure sources, pathways and health effects associated with mycotoxins



INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as EFSA. These are available in the HBM4EU Science to Policy section.

The policy briefs under HBM4EU have divided the legislative context into four categories: regulations i) on chemicals; ii) the environment; iii) consumer products and iv) occupational exposure.

In the chemical context, there is no specific legislation on mycotoxins, and DON and FB_1 are not registered under REACH and formally have no known commercial use. However, some voluntary classifications have been provided under CLP.

For the environment, the Commission recommendation 2006/576/EC sets out recommendations for advisory levels of mycotoxins in products intended for animal feed.

For consumer products, Regulation EU 1881/2006 establishes maximum permissible limits for AFB_1, OTA, DON, FB_1 in specific food products. This includes lower thresholds for products intended for infants and young children. Under the Codex Committee on contaminants in food, farmers need to continuously assess the risk from mycotoxins to both crops and animals. Commission recommendation 2012/154/EU requires the monitoring of presence for ergot alkaloids in feed and food. Regulation EC 401/2006 provides sampling plans according to nine different groups of commodities considering mycotoxins.

In terms of occupational legislation, mycotoxins are covered indirectly by existing legislation (Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work). Generally, mycotoxins are not recognised as a risk factor present in workplaces due to the lack of information and therefore there is currently no occupational exposure limit available.

POLICY QUESTIONS

The answers below are summarised. For more details, please consult the substance report available on the dedicated substance page of the HBM4EU website.

1 Are there validated and harmonised analytical methods to assess the target mycotoxins exposure?

There is a validated method to measure total DON in urine that has been chosen as a biomarker of exposure to DON and its derivatives. Given that FB_1 is mainly excreted in faeces and not in urine, this has impaired the development of reliable analytical methods to measure FB_1 exposure.

2 What are the current exposure levels of the European population to DON and FB1? Are there exposure data for other mycotoxins?

New data for tDON is currently available from the HBM4EU Aligned Study focused on adults. The data was collected between 2014 and 2021 across six sampling sites in Europe (Iceland, Poland, France, Germany, Portugal and Luxembourg) representing 1270 individuals. P50 and P95 of urinary tDON concentrations are in the range of 0.39-9.05 µg/g crt and 2.38-39.18 µg/g crt respectively. The share of individuals with exposure levels exceeding the BE-value of 23 µg/L ranges from 0.0%-20.73%.

Concerning FB_1, new data was not obtained due to the limitations related to the selection of a reliable exposure biomarker.

In conclusion, urinary HBM data on total DON obtained from a literature search and from the HBM4EU Aligned Studies confirm that the European population is exposed to DON and that a fraction of this population is, to some extent, exposed to levels that represent a potential health concern.

3 Does the exposure to mycotoxins differ among different population groups? What are the main factors related to these differences (age, gender, settings, geographic localisation)?

From a literature search, children and pregnant women are the most at risk. The Eastern region was not represented in the current assessment. Additionally, it is important to emphasize that some studies from the literature search reported a statistically significant difference between workers and control groups, confirming that the occupational environment can increase the exposure to DON.

4 Is there a time trend in human exposure to mycotoxins across Europe? Which are the identifiable factors associated with these trends (regulation related with food safety, climate change, others)?

The risk assessment performed using the exposure data obtained from the HBM4EU Aligned Studies indicates that a part of the adult population from Poland and, to some extent, from Luxembourg, France and Portugal is at high risk, which raises a potential health concern.

The current HBM data from the HBM4EU aligned studies set a baseline that will allow for future data comparison and time trend analysis.

5 Is the risk associated to human exposure to these mycotoxins characterised?

The HBM-GV derived for DON allowed to assess the risk of DON based on exposure biomarkers data for the first time.

The risk assessment performed using published data and a mass balance approach showed that exposure to DON in the European population is widespread, affecting different age groups of the population. Children and pregnant women, which are traditionally considered vulnerable population groups, presented the highest risk groups according to data from the literature survey. The children group deserves particular attention considering the associated vulnerability and the potential long-term consequences that are difficult to predict.

The risk assessment performed using results from the HBM4EU aligned studies conducted in the adult population, as referred above, showed that the highest percentiles of exposure (P90 and P95) represented a potential health concern for the population from Poland and, to a certain extent from Luxembourg, France and Portugal, since the hazard quotient determined is above one. However, the mean and median levels of exposure were considered as not representing a concern for health. The risk is low for populations from Iceland and Germany.

Results obtained from the HBM4EU aligned studies conducted in Iceland and Germany revealed that exposure to DON does not represent a health concern there.

6 Are there exposure models and toxicokinetics data for mycotoxins and what are their limitations?

Kinetic models for DON in humans are available but not for FB_1. A dedicated model for DON was developed within HBM4EU. Based on the available HBM data, median intake levels for DON are in the range of 1 µg/kgbw/d, which is the Acceptable Daily Intake by the Joint FAO/WHO Expert Committee on Food Additives. It has to be noted that maximum intake levels of DON have a large variability with maximum levels in the EU population reaching close to 100 µg/kg bw/d.

Regarding FB_1, future efforts should be undertaken to increase the knowledge on their toxicokinetics and, consequently, contribute to a better human risk assessment. Other mycotoxins PBPK models available include zearalenone and its metabolites.

7 Is it possible to set HBM guidance values for mycotoxins?

A provisional HBM-GV_{GenPop} (general population) was derived for DON that should be considered as an orientation value. The value was set to 23 µg DON/L urine for 24 h sample (CI: 5-33 µg/L) corresponding to an intake of 1 mg total DON/kg bw/total 24h.

8 What are the key events that determine the long-term health effects from continuous low-dose exposure to the target mycotoxins?

Neural tube defects in the foetuses of pregnant women after chronic exposure to FB_1 may come from the inhibition of ceramide synthase, which affects sphingolipid metabolism in the cell. As sphingolipids are important for a variety of cellular processes, this event is likely to start the chain of events that cause neural tube defects. It is also likely to be implicated in hepatotoxicity and nephrotoxicity that are observed in animal studies.

For DON, the binding of DON to ribosomes may be considered as the molecular initiating event, which can subsequently activate mitogen-activated protein kinases (MAPK). This key event may result, via multiple routes, in DON-induced reduced body weight gain.

9 What are the most reliable and informative AOP- based effect biomarkers for prioritised mycotoxins?

Combining toxicological information on FB_1 with AOPs (in vitro) and data from human studies allowed to identify the measurement of sphinganine (Sa) and sphingosine (So) and Sa/So ratio in urine as potential effect biomarkers associated with fumonisin B_1 exposure, which can also be linked to the neural tube defects.

Other works have pointed to some methodological approaches, e.g. gene expression or gene methylation analyses that deserve to be further explored in order to discover novel effect biomarkers.

No relevant long-term health effects were yet identified after chronic exposure to DON in humans. Likewise, no informative effect biomarker was identified for DON.

KNOWLEDGE GAPS

HBM4EU has helped identify a number of specific data gaps that need to be filled to give policy makers relevant and strategic data in order to establish appropriate regulations and improve chemical risk management.

The main gaps identified are:

- validation and harmonisation of analytical methods for mycotoxins,
- availability of standards and reference materials,
- update of HBM exposure data to perform a more accurate RA and risk characterisation as well as to trying to identify time trends and possible relation with climate change (since exposure to some mycotoxins is expected to increase in Europe due to changes in climatic parameters),
- determination of HBM GV and reference values for FB_1,
- further development of toxicokinetic models,
- further epidemiological research on novel effect biomarkers for FB_1 and validation of the existing ones; identification of effect biomarkers and AOP development for DON,
- identification, characterisation and risk assessment of mycotoxin mixtures,
- risk assessment of other mycotoxins, including unregulated mycotoxins (e.g., enniatins and Alternaria toxins).

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