Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Additional data regarding UK specific mycotoxin biomonitoring data

Background

1. A preliminary scoping paper regarding the potential risks from aggregated dietary exposure to mycotoxins (TOX/2020/34)[1] was presented to the COT in July 2020. Following discussions, the Committee requested for the Secretariat to perform a literature search on the availability of biomonitoring data for multiple mycotoxin exposures specific to the United Kingdom (UK) population. This data will help to put into perspective whether the UK population are exposed to low, medium or high levels of multiple mycotoxins. The primary route of exposure from mycotoxins is from the diet, however, inhalation exposure could also occur, especially in occupational settings (*e.g.* during grain sorting processes).

2. This paper will introduce the importance of biomonitoring data in exposure assessments, the available biomonitoring database platforms, ongoing European level surveys and studies, as well as the requested additional data described above.

Introduction

3. Biological monitoring utilises biomarkers[2] to represent or estimate the internal exposure as a result of inhalation, ingestion or dermal exposure to a chemical, and as such, biomarkers are indicators of exposure, effect, and/or susceptibility. There are three major categories of biomarkers: biomarkers of exposure (utilised in risk prediction), of response and of susceptibility (utilised in screening, diagnosis and monitoring of disease progression). The selection of a biomarker is an important process as it is affected by several factors including; inter-variability in absorption, pharmacokinetics[3], and toxicodynamics[4] (Mayeux, 2004).

4. Typically, exposure assessments to any dietary contaminant is based on intakes from food (or feed), otherwise known as the external exposure or

[1] TOX/2020/34 available on the COT website.
[2] A biomarker is a naturally occurring molecule, gene, or characteristic by which a particular pathophysiological or physical process, disease *etc.* can be identified.
[3] Pharmacokinetics describes the movement of the drug around the body. It involves the study of the rates of absorption, distribution, metabolism and excretion of a drug and its metabolites.
[4] Toxicodynamics describes the interaction of a chemical with its biological target and resulting biological effect.

oral dose. However, the bioaccessibility[5] and bioavailability[6] of the contaminant determines the internal exposure. The general advantages and disadvantages of biomarkers are shown in *Table 1*. Perhaps the most important to note is that a biomarker estimates the actual internal dose of the exposure.

Table 1– lists the advantages and disadvantages of biomarkers (reproduced from Mayeux, R. (2004)).

Advantages	**Disadvantages**
Objective assessment	Timing is critical for sample collection
Precision of measurement	Expensive (cost for analyses)
Reliable; validity can be established	Storage (longevity of samples)
Less biased than questionnaires	Laboratory errors
Disease mechanisms often studied	Normal range difficult to establish (variability)
Homogeneity of risk or disease	Ethical responsibility

5. Mycotoxins can be classified as short-lived chemicals that can only be effectively measured if the individual is undergoing continuous or continual exposures or if the timing of exposure(s) is known. Mycotoxin biomarkers have been defined as the compounds themselves (*e.g.* parent compounds and/or a metabolite) or as a result of interaction with target molecules (*e.g.* DNA or protein adducts) (Marín *et al*., 2018).

6. The most common biological samples used for quantifying exposure or effect are; urine, serum, blood and milk. However, for some toxins, other biological matrixes such as faeces or hair may be more appropriate. Urinary excretion mainly represents recent mycotoxin intake, whereas measurements in plasma/serum are more likely to represent long-term exposure.

7. The main analytical methods employed to perform biomarker analyses are based on either chromatography (*e.g.* liquid chromatography; LC) or immunochemistry (*e.g.* enzyme-linked immunosorbent assay; ELISA).

8. Arce-López *et al*., (2020) recently completed a review on human biomonitoring (HBM) of mycotoxins in blood, plasma and serum from 2015-2020 (n=164/2,388 references). This review confirmed two approaches to evaluating human exposure to mycotoxins. Firstly, the analyses of occurrence of toxins in food commodities and then combining this data with information on food consumption (external exposure) and the second involving biomonitoring a biomarker in a biological sample (internal exposure).

[5] Bioaccessibility describes events that take place during food digestion for transformation into potentially bio-accessible material, the absorption/assimilation through epithelial tissue and pre-systemic metabolism.
[6] Bioavailability describes the fraction of bio-accessible material which is likely to reach the systemic circulation.

9. The authors noted that the current analytical trend was to simultaneously detect multiple mycotoxins in a single run with a view to save time and financial resources. The forefront of analytical methods includes LC coupled with tandem mass spectroscopy (LC-MS/MS) and high-resolution mass spectrometry (HRMS) which have proven to be useful for multi-mycotoxin biomonitoring (90% of all articles reviewed). The mass analysers that were frequently used were triple quadrupole and quadrupole-ion trap, at 50% and 30%, respectively (of reviewed studies). Whilst single mycotoxin monitoring employs ionisation sources from electrospray ionization and atmospheric pressure chemical ionization.

10. They further noted that it must be kept in mind that biological samples are complex and may interfere in analyte retention, reduce purification, recovery and method sensitivity and producing matrix effects when MS detectors are utilised.

11. In this review, it was observed that the aflatoxin B_1-lysine and OTA in plasma and serum levels were the most widely studied biomarkers of mycotoxin exposure within the last 5 years. Other sub-types of AFs (B_1, B_2, G_1, G_2 and M_1), as well as CIT and ZEA have also been analysed but to a lesser extent. During this review, the authors could not find any studies relating to T-2 and HT-2 toxin biomarkers.

12. The authors concluded that HBM of mycotoxin biomarkers is considered a good approach to obtain data that could assist in determining human exposure, assess risks and identify relationships between diseases and mycotoxins. Limitations were also identified such as, the lack of harmonised approaches for the development of validated analytical methods, and the overlooked presence of modified mycotoxins. It was recommended that the methods should have affordable standards, reference materials and setting of guidelines for the validation of analytical methods.

Search strategy

13. The following search strategies were combined to identify literature relevant to the study of multi-mycotoxin biomarker analyses within the UK population. PubMed, Science Direct, Google Scholar, Scopus and Zenodo databases were searched using single words or combinations of terms as described in Annex A1.

14. The Information Platform for Chemical Monitoring (IPCheM) platform, available from the European Commission's Science Hub[7] was also mined for any relevant UK biomonitoring data.

European human biomonitoring initiatives

[7] The IPCheM platform is available in the European Commission website.

Consortium to Perform Human Biomonitoring on a European Scale (COPHES)

15. The earliest initiative was built up by the COPHES in 2009, which was funded by the European Union's Seventh Framework Programme. It involved European scientists and stakeholders from 35 institutions in 27 countries. COPHES developed harmonised protocols allowing the collection of comparable HBM data throughout Europe. Its twin project, the feasibility study DEMOCOPHES, was launched in 2010. The study measured biomarkers for mercury, cadmium, phthalates, bisphenol A, as well as environmental tobacco smoke in human hair and urine from ~120 mother-child pairs in the 17 participating countries (UK included), in total of ~4,000 samples.

16. The final deliverables from this 3-year effort were substantiated through a final report[8] and a shortened version of the technical report[9]. In brief, it was reported that a coordinated and harmonised approach to HBM in Europe is possible, and the collected results were comparable across Europe. In addition, the results showed variation between countries, indicating that there are differences in exposures across Europe. The understanding of influencing factors will aid to evidence-based policy decisions. Several stakeholder workshops were further organised and the basis of an HBM framework in Europe was proposed to include three core pillars:

- An European Union (EU) HBM suggestion and coordination platform for guidance and decision making;
- A selection procedure for the identification and prioritisation of substance and method development linked to existing EU law and upcoming threats and;
- An HBM implementation and enforcement network embedded in Member States.

Human Early-Life Exposome (HELIX)

17. HELIX was set-up in 2013 and ended in 2017[10]. The project aimed to implement tools and methods (biomarkers, omics-based approaches, remote sensing and GIS-based spatial methods, personal exposure devices, statistical tools for combined exposures, and burden of disease methodologies), to characterise early-life exposure to a wide range of chemical and physical environmental factors and associate these with data on major child health outcomes (including growth and obesity, neurodevelopment, respiratory health), and thus developing an "early-life exposome" approach.

18. In terms of the UK cohort, these were recorded by Wright *et al*., (2013) involving ~11,400 mother-child pairings that were enrolled in 2007-2010, the project was called Born in Bradford (BiB), UK. The BiB is a longitudinal multi-

[8] The COPHES final report is available at the EU HBM website.
[9] The COPHES brief technical report is available at the EU HBM website.
[10] Further information on the HELIX project is available on the CORDIS EUROPA website.

ethnic birth cohort study that aimed to examine the impact of environmental, psychological and genetic factors on maternal and child health and wellbeing[11].

19. Based on the reported findings, the biomonitoring of mycotoxins for this cohort was not included in the scope (Yang & Chew, 2019), however, the study provides great insights on various factors that influence the early life of children.

European Union Human Biomonitoring (HBM4EU)

20. A more recent initiative; HBM4EU was set-up in 2017 to coordinate and advance HBM in Europe[12]. It is a joint effort of 28 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020[13]. The project lasts for 5 years (running to the end of 2021), the key objectives are:

- Harmonising procedures for HBM across the 28 participating countries, to provide policy makers with comparable data on human internal exposure to chemicals and mixtures of chemicals at EU level;
- Linking data on internal exposure to chemicals to aggregate external exposure and identifying exposure pathways and upstream sources;
- Generating scientific evidence on the causal links between human exposure to chemicals and health outcomes;
- Providing the most relevant tools to detect emerging chemicals and to identify the chemical mixtures of highest concern;
- Adapting chemical risk assessment methodologies to use human biomonitoring data and account for the contribution of multiple external exposure pathways to the total chemical body burden and;
- Feeding information on exposure pathways into the design of targeted policy measures to reduce exposure.

21. The above objectives were organised into work packages under three pillars: Science to Policy, European HBM Platform and Exposure and Health. The strategy for the prioritisation of substances under HBM4EU was developed in 2017[14] and a short-list of nominated substances and substance groups was published. The current HBM4EU priority substance groups include phthalates and Hexamoll ® DINCH, bisphenols, per-/polyfluorinated compounds, flame retardants, cadmium and chromium VI, poly-aromatic hydrocarbons, aniline family, chemical mixtures and emerging substances.

[11] Further information on the findings of the BiB study is available on the BiB NHS website.
[12] A pdf file for a brief informative guide for HBM4EU is available on the HBM4U website.
[13] Horizon 2020 is the biggest EU Research and Innovation programme. Further information available on the European Commission website.
[14] Further information of this process can be found in the HBM4EU website.

22. The second list of HBM4EU priority substances includes: acrylamide, aprotic solvents, arsenic, diisocyanates, lead, mercury, mycotoxins, pesticides[15] and UV filters (benzophenones) (Ougier *et al*., 2018). The rationale and progress of mycotoxin biomonitoring within the HBM4EU initiative is briefly summarised in the following paragraphs.

23. The main rationale for the inclusion of mycotoxins involve concerns over effects of long term, intermittent exposure to low quantities of carcinogens as some mycotoxins are known hepatotoxicants. The cumulative exposure to various mycotoxins should also further be investigated, in response to changes of temperature (as a result of climate change), which is predicted to increase the *Fusarium* spp.

24. AFB_1 (CAS No. 1162-65-8), DON (CAS No. 51481-10-8), and FB_1 (CAS No. 116355-83-0) ranked 4th, 5th and 21st on the prioritisation list. It was noted that HBM data for AFB1 are available, however, they were not sufficient in providing a clear picture of the exposure pattern across Europe. As for DON and FB_1, scarcely any HBM data exists.

25. The initial project proposal agreed by the HBM4EU Management Board and EU Policy Board for mycotoxins were collecting and sharing HBM data across the HBM4EU member state countries *via* the IPCheM platform, in order to draw up the exposure profile of the general population and to further include DON and possibly fumonisins in a general population HBM survey to assess the dietary exposure to these mycotoxins.

26. Schoeters *et al*., (2019) produced a deliverable report on scoping documents for the second-round priority substances. The responsible authors for mycotoxins (Chapter 11)[16] are Paula Alvito, Susana Viegas and Maria João Silva which were involved in the Portuguese project entitled 'MYCOMIX; Exploring the toxic effects of mixtures of mycotoxins in infant food and potential health impact', as introduced and summarised in TOX/2020/34[17].

27. Within this report, it was highlighted that HBM efforts would focus on DON and FB_1. The in-depth rationale for DON was due to the lack of clarity for the following three hazards:

- Hepatotoxicity - Peng *et al*., (2016) (abstract only) performed a review on the reported hepatotoxic effects of DON in humans and animals, and concluded that a full and systematic discussion of the hepatotoxicity of DON is still lacking;

- Reproductive toxicity – DON is suspected to be toxic for reproduction and has the ability to cross the human placental barrier (Nielsen *et al*.,

[15] The pesticide group is expected to include: chlorpyrifos, dimethoate, pyrethroids, glyphosate and POE-tallowamine and fipronil.
[16] Chapter 11 is described from page 122 on the HBM4EU deliverable report available on the HBM4EU website.
[17] The MYCOMIX project are described from paragraphs 65-78 in TOX/2020/34 available on the COT website.

2011). Furthermore, teratogenic effects have also been observed in animals (Yu *et al*., 2017) and;

- Immunotoxicity – DON acts as a potent inhibitor of protein synthesis and stimulates the pro-inflammatory response (Sundheim *et al*., 2017).

28. The hazard characterisation for FB_1 were as those discussed in the European Food Safety Authority (EFSA) Scientific Opinion published in 2018. FB1 is classified as possibly carcinogenic to humans, with repeated exposure leading to hepato- and nephrotoxicity, it is able to induce the formation of hepato- and nephrocarcinomas. Additionally, it induces the production of oxidative stress, and is clastogenic[18] to mammalian cells. The mode of action for FB_1 is its inhibition of ceramide synthases, which are key enzymes in sphingolipid metabolism.

29. For reference, the health-based guidance values (HBGV) for DON and FB_1 is a tolerable daily intake (TDI) of 1 µg/kg bw (EFSA, 2017) (EFSA, 2018).

30. DON and FB1 were further reported to be the most common mycotoxins found in food commodities from January to March 2018, based on results of the BIOMIN Mycotoxin Survey[19]. Updated results for Europe in January-March 2020, showed that corn in Southern Europe shows high prevalence of fumonisins with 99%, the average was considered high at 1,568 ppb. Whilst in Central Europe, corn shows 82% abundance of DON at an average of 903 ppb (BIOMIN, 2020a). *Table 2* provides a mycotoxin prevalence breakdown for Central, Eastern, Northern and Southern Europe. An overview of European results is provided in *Table 3*.

31. Co-contamination analysis was carried out for all collected samples (n=5,241) from 59 countries; 67% were detected to contain more than 1 mycotoxin, 22% with one mycotoxin and 11% were below the limit of detection (Note that the number of mycotoxins per sample is based on samples tested for 3 or more mycotoxins). Multiple mycotoxin occurrence was reported using Biomin Spectrum 380® (LC-MS/MS based mycotoxin detection service from BIOMIN)[20]. Approximately 30% of samples (n=196) were detected to have 20-29 metabolites, with an average of 36 mycotoxins and metabolites per sample, 9.9 out of 10 samples were contaminated with *Fusarium* toxins, and 99% contained 10 or more mycotoxins and metabolites (BIOMIN, 2020b).

[18] A clastogen is a mutagenic agent that induces breaks in chromosomes, which results in sections of the chromosomes being deleted, added or rearranged.
[19] The BIOMIN Mycotoxin Survey constitutes the longest running and most comprehensive survey of its kind. The survey results provide insights on the incidence of the six major mycotoxins (AFs, ZEN, DON, FUM, T-2 and OTA) in the agricultural commodities used for livestock feed in order to identify the potential risk posed to livestock animal production. Further information available on the BIOMIN website.
[20] Further information regarding the BIOMIN Spectrum 380® is available on the BIOMIN website.

Table 2 - the BIOMIN Mycotoxin Survey Central, Eastern, Northern and Southern Europe results on prevalence of mycotoxins in animal feed (%) for January to March 2020 (reproduced from BIOMIN, 2020b).

Mycotoxin	AF	ZEN	DON	T-2	FUM	OTA
Central Europe	6	54	72	32	64	10
Eastern Europe	3	41	35	45	39	30
Northern Europe	0	39	56	11	10	11
Southern Europe	13	44	47	15	93	8

Abbreviations: AF = Aflatoxins; ZEN = Zearalenone; DON = Deoxynivalenol; T-2 = T-2 toxin; FUM = Fumonisins; OTA = Ochratoxin-A.

Table 3 - lists the BIOMIN Mycotoxin Survey European results for January to March 2020 (total number of samples = 1,441) (reproduced from BIOMIN, 2020b).

Mycotoxin	AF	ZEN	DON	T-2	FUM	OTA
Number of samples tested	756	1,182	1,430	886	959	752
% of contaminated samples	5	49	59	33	58	18
% of samples above the risk threshold	4	13	38	5	19	3
Average of positive samples (ppb)	6	59	595	32	660	15
Median of positive samples (ppb)	3	21	250	13	158	3
Maximum of positive samples (ppb)	33	1,149	11,875	898	8,285	560

Abbreviations: AF = Aflatoxins; ZEN = Zearalenone; DON = Deoxynivalenol; T-2 = T-2 toxin; FUM = Fumonisins; OTA = Ochratoxin-A.

32. Advances in biomarker research has allowed the determination of DON and its metabolites in urine, primarily DON-glucuronides, by single or multiple biomarker methods. The following DON-biomarkers of exposures in urine have been widely accepted including; DON-15-glucuronide, the sum of DON-glucuronides, or total DON (sum of free DON + DON-glucuronides post-deconjugation). DON-3- glucoside, a modified form of DON, has a similar excretion profile as DON with DON-15- glucuronide being the most abundant metabolite (Vidal *et al*., 2018). An emerging novel human metabolite, DON-3-sulfate and potential biomarker was reported in urine samples obtained from pregnant women in Croatia (Warth *et al*., 2016).

33. An issue with DON biomarker urinary analysis is that commercial sources for DON-glucuronide standards are scarce and no certified reference materials are available (EFSA, 2017).

34. Exposure to fumonisins can also be evaluated using urinary biomarkers. FB_1 and its hydrolysed form have been suggested as direct biomarkers of exposure, however, fumonisins have poor urinary excretion rates – as such, there is a requirement for compensation in utilising high

sensitivity analytical procedures, where sample preparation and purification are extensive (EFSA, 2018).

35. COT Members are directed to Chapter 4 (pp. 10) of the scoping paper prepared by Alvito *et al*., (2019)[21] where 10 policy-related questions were listed to act as a steer on the scope of the work. This documentation further identifies the current available knowledge, and further research to be undertaken to address the identified knowledge gaps for each question (*Tables 4 - 7*).

36. In brief, there are numerous factors that need to be considered when attempting to integrate biomarker data for exposure assessment – and thus the following risk assessment. These factors include: the validation and harmonisation of analytical methods to assess mycotoxin exposure biomarkers, a greater understanding of the current exposure levels of the European population to multiple mycotoxins and whether this differs for each Member State *etc.*

37. At this stage, several work packages and streams are still ongoing for the mycotoxin HBM4EU project and conclusions cannot be yet made.

[21] The HBM4EU mycotoxin scoping document is available on the HBM4EU website.

Table 4 presents policy questions relating to human biomonitoring of mycotoxins, the available knowledge, data gaps, and future activities (reproduced from Alvito *et al*., 2019).

Policy question	**Available knowledge**	**Knowledge gaps and activities needed**
Are there validated and harmonised analytical methods to assess mycotoxin exposure biomarkers?	Analytical methods for DON and its glucuronides as well as FB1–4 are mainly based on mass spectroscopy, however, commercial sources for DON glucuronide standards are scarce and no certified reference materials are available for urinary DON biomarkers Only FB1–3 are available on the market as calibrant solutions, while FB4 can be purchased as purified powder. Except for HFB1, analytical standards for modified forms are not commercially available.	Gaps: Current analytical methods, harmonized methods, reference materials, proficiency tests, expert laboratories. Activities (x7): 1. Identify across Europe the analytical capacity for determination of multiple biomarkers of exposure, availability of reference materials and standards; best biomarkers, matrices and methods. 2. Promote training and harmonization on analysis of selected mycotoxins biomarkers including an inter-laboratorial assay. 3. Identify expert laboratories to conduct the inter-laboratorial trial. 4. Elaboration of SOP for trial assay. 5. Extension of qualified laboratories by introduction of HBM specialised laboratories. 6. Identify quality assurance requirements. 7. Identify needs and gaps.
What are the current exposure levels of the European population to DON and FB1? Are there exposure data for other mycotoxins?	Wide exposure to mycotoxins have been reported mainly through food commodities. Additional studies also report exposure by inhalation in occupational settings. DON (total DON) and FB1 were detected in the urine of the general population in United Kingdom, France, Sweden, Italy, Croatia, Austria, Belgium, Germany as well as in occupational settings (although in a lower extent).	Gaps: Current data on mycotoxin exposure from EU countries for general population (different population groups including vulnerable populations as children, special diet, pregnant women) and workers. Activities (x4): 1. Perform an inventory survey on FB1 data before initiation of a large-scale survey and monitoring activities to evaluate the percentage of left-censored date available. 2. Create a database for mycotoxin exposure using HBM data from different EU countries (gathered by national hubs) including mycotoxin identification, population group and ages, routes of exposure and HBM data. Collect, harmonize, compare data from different population groups available and evaluate. 3. Integrate into IPChem. 4. Identify needs and gaps.

Table 5 presents policy questions relating to human biomonitoring of mycotoxins, the available knowledge, data gaps, and future activities (reproduced from Alvito *et al*., 2019).

Policy question	**Available knowledge**	**Knowledge gaps and activities needed**
Does the exposure to mycotoxins differ among countries and different population groups? Which are the main factors related with these differences (*e.g.* age, gender, settings, geographic localization, season/year *etc*)?	Females and males show different excretion patterns, and human exposure to DON also shows some geographical differences. Occupational exposure revealed exposure associated with professional activity.	Gaps: Current risk groups related to age, gender, diet, occupational setting, location, in EU. Activities (x4): 1.Identify risk groups, including highly exposed, vulnerable and hotspots in Europe. 2. Statistical analysis. 3. Identify significant differences between analysed groups. 4. Identify needs and gaps.
Is there a time trend in human exposure to mycotoxins across Europe? Which are the identifiable factors associated with these trends (*e.g.* regulation related with food safety, climate change, others)?	More than half of all worldwide agricultural samples contain DON and FUM (BIOMIN surveys). A total of 72,011 results of DON and its metabolites in food were obtained from 27 reporting countries and were related to samples collected between 2007 and 2014 (EFSA, 2017).	Gaps: Analysis of trends on HBM mycotoxin exposure. Activities (x4): 1.Identify possible temporal and geographic trends related to HBM mycotoxin exposure taking seasonal variation into account. 2. Evaluate significant differences. 3. Identify possible reasons for the differences founded. 4. Identify needs and gaps.
Are there exposure models and toxicokinetics data for mycotoxins and which are their limitations?	DON and its metabolite DON-3-glucoside were absorbed, distributed, metabolized and rapidly excreted through urine as shown in a human intervention study. Animal studies indicate that FB1 is poorly absorbed from the gastrointestinal tract (less than 4% of the dose), rapidly cleared from the blood (with half-lives of less than 4 h) by the biliary route, and excreted with the faeces (usually more than 90% of the dose).	Gaps: Exposure models and toxicokinetics in humans. Activities (x3): 1. Explore the possibility of applying the previously developed toxicokinetic models to DON and FB1. 2. Determine exposure levels from HBM databases and available literature through reverse dosimetry models. 3. Identify needs and gaps

Table 6 presents policy questions relating to human biomonitoring of mycotoxins, the available knowledge, data gaps, and future activities (reproduced from Alvito *et al*., 2019).

Policy question	**Available knowledge**	**Knowledge gaps and activities needed**
Is the risk associated with human exposure to these mycotoxins characterized? Are there health impact assessment studies? Is it possible to set a HBGV for mycotoxins in biological samples?	The estimated mean chronic dietary exposure was above the group-TDI in infants, toddlers and other children, and at high exposure also in adolescents and adults, indicating a potential health concern. Little if any work has been done in estimating the burden of human disease caused by exposure to the dietary mycotoxins. The only studies available are related to aflatoxin B1 (Wu *et al*., 2014; Assunçao *et al*., 2018).	Gaps: Risk characterisation and health impact assessment. Activities (x5): 1. Identify available estimates of human exposure via biomarkers. 2. Collect toxicological data. 3. If possible, establish HBGV values for mycotoxins in biological samples. 4. From risk assessment to health impact assessment: trying to derive the consequences of human exposure to mycotoxins using epidemiological data (*e.g*. incidence of disease, age of onset of disease and its evolution) and data gathered on human exposure studies (*e.g*. DALY). 5. Identify needs and gaps.
Does the aggregate exposure to mycotoxins/other food contaminants contribute to combined effects? What are the knowledge gaps for risk assessment?	Co-occurrence of DON or FB1 and other mycotoxins has been widely reported and human aggregated exposure to mycotoxins and other food contaminants is likely to occur.	Gaps: Lack of an inventory of exposure to DON or FB1 and other mycotoxins/other food contaminants in EU and potential interactive effects Activities (x4): 1. Identify main mycotoxin/other food contaminants mixtures. from available HBM data (biomarkers and routes of exposure). 2. Compare available HBM mixtures data over EU countries, look for significant differences and trends. 3. Assess common endpoints, determine whether the additive model is adequate to describe mycotoxins/other food contaminants combined effects; assess if this is dependent of mode of action or the target organ toxicity. 4. Identify needs and gaps.

Abbreviations: HBGV = Health-based guidance value; TDI = Tolerable daily intake; DALY = Disability-adjusted life year; DON = Deoxynivalenol; FB1 = Fumonisin B1; EU = European Union; HBM = Human biomonitoring.

Table 7 presents policy questions relating to human biomonitoring of mycotoxins, the available knowledge, data gaps, and future activities (reproduced from Alvito *et al*., 2019).

Policy question	**Available knowledge**	**Knowledge gaps and activities needed**
Which are the key events that determine the long-term health effects from low-dose continuous exposure to the target mycotoxins? Which are the health effects associated with short-term high exposure by inhalation (occupational exposure)?	DON is considered immunotoxic, reprotoxic and a probable endocrine disruptor. Limited evidence on its potential genotoxicity and carcinogenicity. It is a potent inhibitor of protein synthesis and stimulates the pro-inflammatory response leading to oxidative stress. FB1 is a liver and kidney toxicant and it is immunotoxic. It is a probable carcinogen but there are data gaps on its mutagenicity. Its adverse effects are mainly mediated by the inhibition of ceramide synthases, which are key enzymes in sphingolipid metabolism.	Gaps: Several health effects known and mechanistic data available but AOP for DON and FB1 lacking. Activities (x3): 1. Identify for DON and FB1 the health effect for which an AOP might be developed (*e.g*. immunotoxicity for DON and liver toxicity for FB1). 2. Disclose the key-events for the effects referred in 1. in order to contribute to AOPs development. 3. Identify needs and gaps.
Which are the most reliable and meaningful effect biomarkers for single and combined effects?	Some biomarkers of early biological effects have been pointed for DON (*e.g*. proinflammatory cytokines) and FB1 (*e.g.*, sphinganine-to-sphingosine ratio in blood) but further knowledge is needed.	Gaps: Limited information on available biomarkers of effects Activities (x3): 1. Identify available targeted and untargeted biomarkers of effect for the selected mycotoxins. 2. Identify biomarkers of effect related to interactive effects of mixtures. 3. Identify needs and gaps.
Are there mycotoxins beside those currently covered by the risk assessment, which could be potentially relevant concerning their (co-)occurrence and toxicological properties?	An increasing number of studies are paying attention to mixtures involving the “emerging” toxins (enniantins, beauvericin, Alternaria toxin, *etc*).	Gaps: Co-occurring forms (emergent mycotoxins) with potential toxicity and health impact that are not covered in risk assessment. Activities (x3): 1. Bibliography search. 2. Identify most relevant co-occurring forms other than those already covered, to refine human risk assessment. 3. Identify needs and gaps.

UK specific mycotoxin biomonitoring data

38. There are no UK government led HBM initiatives relating to mycotoxins, however, Public Health England (PHE) lead on the UK's participation in the HBM4EU in collaboration with the Department for Environment, Food and Rural Affairs (Defra). Through this project, a cross-government steering group was formed, with Defra acting as chair, and PHE, Environment Agency, Food Standards Agency (FSA) and the Health and Safety Executive (HSE) as its members.

39. In July 2019, the Environmental Audit Committee published its 25th Report of Session 2019-2019, Toxic Chemicals in Everyday life (HC 1805)[22], which includes recommendations that the Government establish a UK-wide human and wildlife biomonitoring programme as part of the Government's Chemical Strategy. The UK Government's response to this recommendation was that it 'recognises the importance of the issue and will continue to explore the best approach and practice in the field of human biomonitoring. This will be achieved, in line with 25 Year Environment Plan commitments, through the Chemicals Strategy, which will continue to support collaborative work on human biomonitoring and explore options for further biomonitoring programmes' (UK Parliament, 2019).

40. In the meantime, a UK Biomonitoring Network has been set-up by the HSE, following a successful meeting organised by the Interdepartmental Group on Health and Risks from Chemicals and Royal Society Toxicology group in January 2019 (HSE, 2019).

41. Despite the lack of a UK government led HBM initiative for mycotoxins, scientific interest for this has and continues to grow which has led to several publications. These will be summarised in the next following sections.

Singular mycotoxin biomarker analyses

Ochratoxin A (OTA)

42. Gilbert *et al*., (2001) assessed the dietary exposure to OTA in the UK by using a duplicate diet approach and analysis of urine and plasma samples from 50 individuals (sex ratio for females and males was undetermined; aged <30->45 years) 11 were vegetarian and 7 consumed an ethnic diet. The study period was for 30 days. Analysis involved immune-affinity column (IAC) clean-up and high-performance liquid chromatography (HPLC) determination with fluorescence detection.

43. OTA was detected in all composite diet samples, reported results ranged from 10-115 ng OTA/kg diet, (mean ~31 ng/kg; median 23.7 ng/kg) resulting in an average intake of ~0.3-3.5 ng/kg bw/day over 30 days.

[22] The Toxic Chemicals in Everyday life (HC 1805) report is available on the UK Parliament website.

44. OTA was found in all plasma samples and in 92% of urine samples (n=46/50). Plasma concentrations appeared to be dependent on age groups with higher levels observed for the 30-44 years old age group. It was hypothesised that the efficiency of OTA removal from the body decreases with age, leading to higher plasma levels.

45. In terms of the differences associated with diets, there were no significant observations associated with ethnic diets. Although, vegetarians had higher consumption of OTA; on average their plasma or urine levels were not significantly higher.

46. It was observed that the correlation between the plasma OTA concentrations and OTA consumption was not significant, however, the correlation for OTA concentrations in the urine and OTA consumption was significant (concentration expressed as the total amount excreted).

47. The authors concluded that there is a possibility in using OTA in urine as a biomarker, however, further research is needed to determine inter-individual differences.

Deoxynivalenol (DON)

48. Turner *et al*., (2011) assessed the DON metabolite profiles of 34 UK adults (n=18 females and 17 males; aged 21-59 years). Four consecutive daily morning urine samples were analysed from 22 individuals, whilst for the remaining 12, only one single sample each was analysed. All samples (n=100) were analysed for the presence of free DON, de-epoxy DON (DOM-1)[23] (which were previously analysed for the combined measure of free DON and DON-glucuronide in their 2010 study; described below) by LC-MS (post purification on IAC). It must be highlighted that these subset of samples from the Turner *et al*., (2010) had combined measure of free DON and DON-glucuronide that was > 5 ng/mL.

49. The mean concentration of the combined subset was ~18 ng/mL (range:0.5-9.3 ng/mL). Urinary DOM-1 was detected in 3% of individuals (n=1/34)., which was present at 1% of the combined urinary subset concentration for this specific individual. The authors noted that the concentration of the combined subset was significantly correlated with urinary free DON, however, this was not the case with the percentage of free DON to the combined subset. Based on this observation the authors concluded that, the level of DON exposure did not affect the metabolism to DON-glucuronide within the range observed.

50. The results further revealed that most individuals had no detectable amount of urinary DOM-1 (limit of quantification (LOQ): 0.06 ng/mL urine) and 68% did not detoxify all of the ingested DON to DON-glucuronide –

[23] De-epoxy deoxynivalenol (DOM-1) is metabolite of DON. It is formed as a result of microbial biotransformation in the intestines.

suggesting that there is inter-variability of DON susceptibility in the UK adult population.

51. Turner *et al*., (2010) performed a comparison of DON intake and urinary DON in 35 UK adults (n= 18 females and 17 males; aged between 20-50 years and all were white Caucasian, except for one from Southeast Asia) funded by the FSA and the US National Institute of Environmental Health Sciences (grant ES06052).

52. DON was assessed in first morning urine samples collected during a period of normal diet (n=8 days), a wheat-restriction intervention diet (n=4 days), and partial wheat-restriction intervention (n=4 days; bread was allowed). Food diaries were kept for 12 days by 30 individuals, 11 days by three individuals, and 10 days by two individuals (n=413 days of consumption data were collected).

53. Urinary DON was detected in ~94% of normal diet samples (n=198/210), where the geometric mean was ~10 ng DON/mg creatinine (range: not detected–70.7 ng/mg), in ~96% of partial intervention samples (n=94/98) geometric mean was ~6 ng/mg (range: not detected–28.4 ng/mg), and ~43% of full intervention samples (n=17/40) geometric mean was 0.5 ng /mg, (range not detected–3.3 ng/mg).

54. Based on the estimated mean transfer of DON to urine (~72%), the estimated mean DON intake for individuals during the consumption of their normal diet was 298 ng/kg bw/day. This exceeds the recommended TDI of 1 µg/kg bw (SCF, 2002, EFSA 2017) for 17% of individuals (n=6/35) on one or more day, and a further 13 individuals had one or more days when the estimated intake exceeded 50% of the recommended TDI.

55. A strong correlation between DON intake and the urinary biomarker was observed (adjusted R^2: 0.83) in models adjusting for age, sex and body mass index. The authors hoped that this quantitative correlation between DON exposure and urinary DON, serve to validate the use of urinary DON as an exposure biomarker.

56. Turner *et al*., (2009) assessed whether intake of cereal correlated more strongly with urinary DON, compared with the longer-term assessment of usual cereal intake from 7-day food diaries (n=255). Four timeframes for consumption were analysed: the day of the urine collection, previous 24-hours period, the day of the urine collection and previous 24-hours combined, and the 7-day average consumption of cereals.

57. Urinary DON was detected in ~100% (n=254/255) urine samples, with a mean value of 12 µg DON/day (range: not detected-66 µg DON/day). For all four timeframes, the total cereal intake was positively associated with urinary DON. Goodness of fit analyses were utilised to assess how well each timeframe explained the variation in urinary DON levels. Cereal consumption on day of the urine collection provided a better goodness of fit value (adjusted R^2: 0.22) than the 7-day average cereal consumed (adjusted R^2: 0.19),

however, the combined day and post-24 hours consumption timeframe provided the best fit (adjusted R^2: 0.27). The authors concluded that inter-individual variation in urinary DON was better explained by recent cereal intake rather than the cereal intake assessed over 7-days.

58. Turner *et al*., (2008a) utilised the UK adult National Diet and Nutrition Survey to compare 24-hours urinary DON excretion with cereal intake. 100 subjects (n total = 158 females and 142 males) aged between 19-64 years were identified for each of the following cereal consumption groups: low (n=62 f/38 m) (mean: 107 g cereal/day; range: 188-125 g), medium (n=50 f/50 m) (mean: 179 g cereal/day; range: 162-195 g) and high (n=46 f/54 m) (mean: 300 g/day; range: 276-325 g). Total urinary DON (after hydrolysis of glucuronide conjugates) was analysed in 24-hours urine samples by LC-MS (post purification on IAC).

59. The results were detection of DON in ~99% of samples (n= 296/300). Cereal intake was significantly associated with urinary DON, with geometric mean urinary levels of 6.55, 9.63 and 13.24 µg DON/day for low-, medium-, and high-intake groups, respectively.

60. Intakes of other food commodities including; wholemeal bread, white bread, 'other' bread, buns/cakes, high-fibre breakfast cereal and pasta were also investigated using multi-variable analysis. Wholemeal bread was associated with the greatest percent increase in urinary DON per unit of consumption, however, white bread contributed ~2 times more than wholemeal bread to the urinary DON levels as it was consumed in higher amounts.

61. The authors concluded that the UK adults are exposed to DON, and on the basis of the urinary levels – estimated that some individuals exceed the 2018 EFSA recommended TDI of 1 µg DON/kg bw.

62. Turner *et al*., (2008b) further investigated whether dietary wheat (bread, breakfast cereal, cakes/biscuits, pasta, potatoes, and rice) reduction decreases the level of urinary DON in UK adults. Twenty-five adult volunteers (n=16 females and 9 males; aged between 21-59 years) completed semi-weighed food diaries on days 1-2 (normal diet), and a morning urine sample was provided on day 3. On days 3-6 (intervention), individuals were restricted major sources of wheat intake following dietary guidance. Diaries where updated and completed on days 5 and 6, and a further morning urine sample was provided on day 7.

63. Urinary DON was measured following IAC clean-up and analysis by LC–MS. The recorded wheat-based food intake was shown to have good compliance during the intervention phase from a mean value of 322 g/day (range: 131-542 g/day) to 26 g/day (range: 0-159 g/day).

64. DON was detected in all 25 urine samples taken on day 3 (geometric mean 7.2 ng DON/mg creatinine) but following intervention a significant 11-fold reduction was observed (0.6 ng/mg creatinine).

65. Papageorgiou *et al*., (2018a) assessed urinary DON concentrations in 40 children (n= 20 females and 20 males; aged 3–9 years) and 39 adolescents (n= 20 females and 19 males; aged 10–17 years) in the UK (Hull, East Yorkshire). Morning urine samples were collected over two consecutive days and analysed for free DON, DON-glucuronides, DOM-1, and total DON. Analyses was carried *via* HPLC-MS/MS.

66. Total DON was detected in the urine of >95% of children and adolescents on both days, with mean concentrations of ~42 and 21 ng total DON/mg creatinine, respectively. Female children had the greatest DON levels on both days (214 and 219 ng/mg creatinine on days 1 and 2, respectively). Free DON and DON-glucuronides were detected in the majority of urine samples, whereas DOM-1 was not present in any sample (LOQ: >0.50 ng/mL urine).

67. The mean estimated dietary intake of DON was 1, 1.5, and 2 µg/kg bw/day, based on the estimated urine volume of 1, 1.5 and 2 mL/kg bw/h, respectively. For adolescents, the estimated dietary intake was 0.5, 0.6 and 1 µg/kg bw/day, based on the estimated urine volume of 0.5, 0.75, 1 mL kg bw/h, respectively. The highest food commodity that correlated to the observed urinary DON level was bread, with a mean consumption of 101 and 95 g/day in children and adolescents, respectively. Estimation of dietary DON exposure suggested that 33–63% of children (n=15-25/40) and 5–46% (n=2-18/39) of adolescents exceeded current TDI for DON.

68. Papageorgiou *et al*., (2018b) characterised urinary DON concentrations and its metabolites in 20 elderly individuals (n= 10 females and 10 males; aged ≥65 years) living in Hull, East Yorkshire, UK. Morning urinary specimens were collected over two consecutive days together with food records to assess dietary intake over a 24 hour-period prior to each urinary collection. Free DON, total DON (sum of free DON and DON-glucuronide) and DOM-1 were analysed using a validated LC-MS/MS methodology.

69. Total DON above the limit of quantification 0.25 ng/mL was detected in the urine from 90% of elderly men and women on both days. The mean total DON concentrations for elderly males were ~22 and 28 ng/mg creatinine on days 1 and 2, respectively. As for elderly females the total DON concentrations was ~22 and ~15 ng/mg creatinine on days 1 and 2, respectively. Free DON and DON-glucuronide were detected in 60-70% and 90% of total urine samples, respectively. DOM-1 was absent from all samples (LOQ: 0.50 ng/mL).

70. The estimated mean dietary intake of DON was 0.43 µg/kg bw/day (range: 0-2.33) with 10% exceeding the TDI for DON. The highest food commodity that correlated to the observed urinary DON level was bread, with a mean consumption of 101 g/d, however, the authors recognise that larger studies are required to investigate DON exposure in the elderly from different regions of the UK.

71. Wells *et al*., (2017) determined the levels of total DON and DOM-1 in urine samples using LC-MS from UK vegetarians from Hull, East Yorkshire, UK. Morning urine samples were collected over two consecutive days from 32 vegetarians (n=21 females and 11 males) and 31 non-vegetarian (n=15 females and 16 males) UK adult volunteers. The associated food consumption 24-hours prior to the sample collection was recorded.

72. Statistically significant differences between the weight of the two groups were observed. The mean weight of the female and male vegetarians was ~67 and ~73 kg, respectively. On the other hand, the weight of the female and male non-vegetarians was ~73 and ~91 kg, respectively. Urinary DOM-1 was not present on either day for both test groups.

73. Urinary DON was observed to be present in 100% of both female and male samples (n=31) for both days. The mean levels of DON in non-vegetarian group on day 1 and 2 were 3.05 and 2.98 ng free DON/mg creatinine, respectively. Most adults were within the TDI of DON (1 µg/kg bw/day; EFSA, 2018).

74. Urinary DON was present in 81% of vegetarian female samples (n=17) and increased to ~91% on day 2 (n=19). Urinary DON was present in ~78% (n=7) of vegetarian males on both days. The mean levels of DON in the vegetarian group on day 1 and 2 were 6.69 and 3.42 ng free DON/mg creatinine, respectively. These levels equate to up to 32% of UK vegetarians exceeding the recommended TDI.

75. Wells *et al*., (2016) determined the levels of total DON (free DON and DON-glucuronide) and DOM-1 in urine samples from pregnant human from Hull, East Yorkshire, UK by using LC-MS. Morning urine samples were collected over two consecutive days from 42 white Caucasian females (aged between 20-38 years; the majority of which were in the second trimester of pregnancy (n=23), others were in the first (n=2) or final trimester (n=17)) Food consumption was also recorded for the 24-hours prior to sample collection.

76. Free DON and DON-glucuronide were detected in most of the urine samples on day 1 at ~88% (n=37/42) and on day 2 at ~84% (n=35/42), whereas DOM-1 was not detected in any samples (limit of detection (LOD); 0.25 ng/mL). Of the seven food categories, bread provided the largest contributor to the daily food intake, followed by pasta, then baked goods. The only significant correlation was found between total SON on day 1 with baked goods (defined as sweet biscuits excluding fine bakery wares such as croissants and cakes).

77. Spearman's rho non-parametric test for correlation was utilised; results showed that levels of DON did not differ significantly between day 1 and day 2 urine samples, with mean values of 29.7 and 28.7 ng/mL urine, respectively. The identified limitations included: small sample size, portion sizes and only collecting the first morning urine sample.

78. The authors concluded that 50th percentile (of tested volunteers) were within acceptable and safe limits. It was also recommended that an appropriate information program given by physicians (which considers the potential mycotoxin transfer to foetus) should be collated to help orient the dietary habits of UK pregnant women.

79. Hepworth *et al*., (2012) determined DON exposure in 85 pregnant women from Bradford, UK whom where having elective caesarean sections (aged 21-44 years, n= 29 were of South Asian origin, n=53 was classified non-South Asian and n=3 could not be classified). Obtained urine samples were from the last trimester of pregnancy. The total urinary DON (free DON and DON-glucuronide) and DOM-1 and were analysed by LC/MS. Food diaries were also collected.

80. The DON urinary biomarker was detected in all samples with a geometric mean of ~10 ng DON/mg creatinine (range: 0-5-~117 ng DON/mg creatinine). Women of South Asian descent were detected to have higher concentrations of the DON biomarker in their samples at ~15 ng/mg creatinine) compared to ~9 ng DON/mg creatinine in non-South Asians. The observed difference was believed to be correlated with higher white bread consumption by the South Asian group (mean intake: 154 g/day compared to 58 g/day in non-South Asian women). DOM-1 was not detected in any samples (LOQ: 0.06 ng/mL urine).

Multi-mycotoxin biomarker analyses

81. At the time of review, one reference for multi-mycotoxins exposure assessment in the UK population using urinary biomarkers was identified.

82. Gratz *et al*., (2020) carried out a pilot survey on multi-mycotoxin exposure assessment in 21 UK children (n=9 females and 12 males; aged between 2-6 years) using urinary biomarkers. Spot urines (n=21) were analysed for the presence of six regulated mycotoxins DON, OTA, ZEN, T-2 toxin, HT-2 toxin and AFB_1, and their important metabolites DOM-1, NIV, α-ZEN, β-ZEN and AFM_1) using LC-MS/MS.

83. Urine samples were observed to contain mean levels of DON, NIV, OTA, and ZEN at 13, 0.36, 0.05, and 0.09 ng/mL, respectively. DON, ZEN, OTA, NIV, DOM-1, α-ZEN, β-ZEN, HT-2 and T-2 toxins was observed in 100% (n=21), 100% (n=21), 95% (n=20/21), 81% (n=17/21), 14% (n=3/21), 9% (n=2/21), 5% (n=1/21) and 5% (n=21), respectively. AFs were below the LOD of 0.003 ng.

84. Mean total dietary intakes were estimated for DON, ZEN and OTA these resulted in values of ~27, 2.2 and 1.39 µg/day, respectively. This suggests that children were frequently exposure to levels exceeding the TDI for 52% of DON and 95% of OTA cases. Thus, the authors concluded that UK children are exposed to multiple mycotoxins through their habitual diet.

Summary of UK specific mycotoxin biomonitoring

85. To summarise, there is currently no UK Government led HBM programme for mycotoxins. Available literature seems to focus on estimating DON exposures from using total DON (free DON and DON-glucuronides) in urinary samples as biomarkers in the UK population. The presence of DOM-1, a metabolite that is formed by microbiota metabolism in urine is rarely reported suggesting that its it may not be a suitable an exposure biomarker for DON.

86. From the reviewed studies, a proportion of the UK population (adults, children, adolescents, pregnant women, elderly and vegetarians) the TDI for DON was exceeded.

87. At the time of review, only one report by Gratz *et al*., (2020) performed multi-mycotoxin biomarker analyses. In this pilot study, UK children (n=21) were estimated to frequently exceed the TDI for 52% of DON and 95% of OTA cases.

Further considerations

88. As discussed in the introduction, the advancement and availability of detection techniques and equipment has progressed the development of biomarkers of exposure to some mycotoxins (FB_1 and DON). Understanding the toxicokinetics of mycotoxin metabolites and their availability in different biological samples (*e.g.* OTA has the potential to be transferred to breastmilk) and how they may correlate to the exposure still needs further investigation. Furthermore, there is a need for the development of biomarkers of exposure for the detection of masked mycotoxins.

89. There are also three main limitations associated with multi-biomarker monitoring (Marín *et al*., 2018):

- Biological fluids contain extremely low analyte concentrations following dietary exposure, as such sample preparation is crucial to obtain acceptable LODs;
- There is a great chemical diversity of analytes and makes this clean-up methodologies challenging (*e.g.* polar compounds like glucuronides);
- Careful optimisation needs to be carried out to overcome matrix effects and interfering matrix peaks, eluents, the chromatographic gradient, and the dilution factor;
- The co-elution of matrix components is said to have a negative influence the accuracy of quantitative methods through ion suppression or enhancement in the ion source and;
- In general, there is a lack of authentic reference standards and certified reference materials.

90. Marín *et al*., (2018) suggested a major research gap which is the potential concurrent exposure of mycotoxins with other environmental

chemicals that may exhibit some interactive activity and/or exert a biological function converging in the same molecular pathways.

Summary and conclusions

91. A biomarker is a biological measure (of *e.g.* parent toxins, protein or DNA adducts, glucuronide conjugates measured in urine or plasma/serum) which is correlated with the quantity of xenobiotic ingested. The validation of biomarker requires demonstration of assay robustness, understanding between the correlation of intake and observed biomarker levels, and their stability in stored biological samples.

92. Urinary samples are typically utilised for estimating mycotoxin exposure and the main analytical methods employed to perform biomarker analyses are based on either chromatography (*e.g.* LC) or immunochemistry (*e.g.* ELISA). As for multi-biomarker analyses, LC-MS/MS systems are commonly utilised.

93. There are is a number of European HBM initiatives the main being COPHES/DEMOCOPHES, HELIX, HBM4U, however, there is currently no UK Government led HBM programme for mycotoxins.

94. Available literature seems to focus on estimating DON exposures in the UK population. From the reviewed studies, a proportion of the UK population (adults, children, adolescents, pregnant women, elderly and vegetarians) the TDI for DON was exceeded.

95. Limited data was found for UK multi-mycotoxin biomarker studies. One pilot study in UK children (n=21) by Gratz *et al*., (2020) observed exceedances in the TDI for 52% of DON and 95% of OTA cases.

96. Further considerations should be kept in mind including the processes involved in validation of biomarkers, the further need for development of biomarkers for masked mycotoxins and the limitations/challenges associated with multi-biomarker analysis.

Secretariat
September 2020

Abbreviations

15-AcDON	15-acetyldeoxynivalenol
3-AcDON	3-acetyldeoxynivalenol
AFs	Aflatoxins
AOP	Adverse outcome pathway
BiB	Born in Bradford
CIT	Citrinin
COPHES	Consortium to Perform Human Biomonitoring on a European Scale
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CPA	Cyclopiazonic acid
DAS	4,15-diacetoxyscirpenol
DALY	Disability-adjusted life year
Defra	Department for Environment, Food and Rural Affairs
DEMOCOPHES	Trial phase (Demo) Consortium to Perform Human Biomonitoring on a European Scale
DNA	Deoxyribonucleic acid
DOM-1	De-epoxy deoxynivalenol
DON	Deoxynivalenol
EFSA	European Food Safety Authority
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FB1	Fumonisin B1
FB2	Fumonisin B2
FSA	Food Standards Agency
FUM	Fumonisins
Fus-X	Fusarenon-X
HBGV	Health-based guidance value
HBM	Human biomonitoring
HBM4EU	European Union Human Biomonitoring
HELIX	Human Early-Life Exposome
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSE	Health and Safety Executive
IAC	Immune-affinity column
IPCheM	Information Platform for Chemical Monitoring
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography with tandem mass spectroscopy
LOD	Limit of detection
LOQ	Limit of quantification
MoA	Mode of Action
MON	Moniliformin
NEO	Neosolaniol
NIV	Nivalenol
OTA	Ochratoxin A
PAT	Patulin
PHE	Public Health England
STC	Sterigmatocystin

SOP	Standard operating procedure
TDI	Tolerable daily intake
UK	United Kingdom
ZEN	Zearalenone
α-ZEN	α-zearalenone
β-ZEN	β-zearalenone

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Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Additional data regarding UK specific mycotoxin biomonitoring data and mode of action toxicity mechanisms for single mycotoxins

Details of literature search carried out by the Secretariat at the Food Standards Agency (FSA)

Relevant literature was obtained from various scientific databases as described in paragraphs 14-16 of the main discussion paper. The search terms utilised are listed below. The literature searches were performed by the Secretariat at the FSA, with a limit of publication date ranging from default to current.

Search terms

“United Kingdom” &

Aggregate mycotoxin exposure
Biomonitoring
Breastmilk
Co-exposure of mycotoxins
Combined mycotoxin exposure
Human biomonitoring
Multi-biomarker study/approach
Multi-mycotoxin study/analysis
Mycotoxins

Secretariat
September 2020