Mycotoxins—Biomonitoring and Human Exposure

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Abstract: Mycotoxins are secondary metabolites produced by fungal species that commonly have a toxic effect on human and animal health. Different foodstuff can be contaminated and are considered the major source of human exposure to mycotoxins, but occupational and environmental exposure can also significantly contribute to this problem. This review aims to provide a short overview of the occurrence of toxigenic fungi and regulated mycotoxins in foods and workplaces, following the current literature and data presented in scientific papers. Biomonitoring of mycotoxins in plasma, serum, urine, and blood samples has become a common method for determining the exposure to different mycotoxins. Novel techniques are more and more precise and accurate and are aiming toward the simultaneous determination of multiple mycotoxins in one analysis. Application of liquid chromatography (LC) methodologies, coupled with tandem mass spectrometry (MS/MS) or high-resolution mass spectrometry (HRMS) has become a common and most reliable method for determining the exposure to mycotoxins. Numerous references confirm the importance of mycotoxin biomonitoring to assess the exposure for humans and animals. The objectives of this paper were to review the general approaches to biomonitoring of different mycotoxins and the occurrence of toxigenic fungi and their mycotoxins, using recent literature sources.

Keywords: mycotoxins; biomonitoring; human health; exposure

Key Contribution: This is a review of the current methods for biomonitoring human exposure to mycotoxins and the most common sources of mycotoxins contamination.

1. Overview

Food safety has become an important term for authorities and consumers. The aim is to keep the consumers safe from any harmful compounds and to ensure the producers from economical losses in case of an outbreak of contaminants in the production chain. The recommendations and the measures taken by the companies and the legal bodies are based on risk evaluations reported by food safety authorities [1]. Current regulations are established on scientific opinions given by eminent institutions such as FAO/WHO Joint Expert Committee on Food Additives of the United Nations (JECFA) and the European Food Safety Authority (EFSA). This includes the involvement of AOAC International (Association of Official Analytical Chemists) and the European Standardization Committee (CEN) who are obligated to monitor and implement the requirements for adequate sampling and analytical methods [2]. The important stages of risk evaluation studies are to identify and characterize contaminants and to evaluate the exposure to certain hazardous materials [2–4]. This often means the implementation of long-term monitoring of the occurrence of concerning substances in food. Food contaminants consist of different compounds. But this review will be limited to the most common contaminants—mycotoxins (single or mixed) and other toxins produced by various fungal species [1], some of which belong to the genus Aspergillus, Penicillium, Fusarium, and Alternaria [5]. Mycotoxins and general...
exposure to their effect have become a major concern for the scientific and popular community. Mycotoxins are a big group of compounds, with a range of chemical structures and toxicological properties [6]. The most common mycotoxins included in legislation belong to several types: aflatoxins (AFs) and ochratoxins (OT’), fumonisins (FBs), trichothecenes and zearalenone (ZEA), patulin (PAT), and citrinin (CIT) [7]. The main food groups affected by fungal metabolites are different cereals, dried fruits, nuts, coffee, and spices [5]. Well-developed strategies including contamination control measures and improvements in processing technologies are efficient in mycotoxins prevention but despite these efforts, up to 80% of food still ends up contaminated by mycotoxins [8,9] and it has been estimated that cca. 25% of cereals worldwide are contaminated with mycotoxins [8]. Reduction of mycotoxins contamination via food processing (higher temperatures or high pressure) is minimal and allows them to linger in food items. Destruction in the gastrointestinal tract is also minimal. This is why they can act in such a harmful way and affect human and animal health. Their pronounced influence on the global economy is also tremendously important [10].

To regulate human exposure to food contaminants, especially mycotoxins, human biomonitoring (HBM) emerged as a recognized, efficient, and cost-effective method [11]. By applying HBM, it is possible to track exposure points and set minimum and maximum exposure limits. The research possibilities of HBM application can be used to understand the population range values and identify consumer groups and individuals or groups (e.g., geographically). This aims to detect higher exposures and also to confirm the regional and temporal variability for trends within a population [12]. To conduct valid research, several set-points regarding HBM need to be addressed. It is very important to provide a sufficiently sensitive and validated analytical method to obtain accurate measurements of a biomarker that correlates with the external dose [12]. The most commonly used biological material for HBM is urine, plasma, or blood. Urine is, however, preferred in field studies due to the noninvasive sampling method. This generally helps to gain higher acceptance by study participants [13]. The suitability of the biomarker or matrix greatly depends on the toxicokinetic profile of the studied compound. Detailed knowledge of the compounds’ toxicokinetics, such as general metabolism properties and excretion timeline, is necessary to translate the existence of HBM biomarker data into daily intake estimates [12].

Exposure to mycotoxins does not always have to be related to food consumption. There are studies [14–22] that explored the occurrence of mycotoxins in working or living environments and the results showed that exposure to mycotoxins can be related to these places too. This will be further discussed in Section 2.

2. Exposure

2.1. Food

The occurrence and co-occurrence of different mycotoxins are common in available foodstuffs. Tables 1 and 2 contain basic information on the most relevant mycotoxins and fungi detected in different foodstuffs and environments. Exposure via food is practically inevitable since fungi can withstand different conditions that would normally be harmful to other microorganisms. The additional threat is that fungi produce mycotoxins when found in unfavorable conditions and mycotoxins also can “survive” the hostile environmental conditions during food processing, such as higher temperatures and high pressures.

Dietary exposure to mycotoxins and chronic dietary exposure to a combination of mycotoxins is something that occurs daily [23]. As can be seen from Table 1, mycotoxins can be found in many types of food. Many reviews and original articles deal with worldwide exposure to mycotoxins [3,5,22–26].

The toxicological effects of different mycotoxins are reported in many in vivo studies. Descriptions of mycotoxicoses such as gastrointestinal problems, genotoxicity, estrogenicity, and even death can be found in numerous scientific reports [23,27–29].
Table 1. The general overview of the most common mycotoxins that can be found in different foods.

| Food                  | Mycotoxin(s)                                                                 | Source       |
|-----------------------|-----------------------------------------------------------------------------|--------------|
| Pistachio             | Aflatoxins B1, B2, G1, G2                                                   | [30,31]      |
| Peanuts               | Aflatoxins B1, B2, G1, G2                                                   | [30,31]      |
| Almonds               | Aflatoxins B1, B2, G1, G2                                                   | [30,31]      |
| Dried figs            | Aflatoxins B1, B2, G1, G2                                                   | [31]         |
| Cereals               | Aflatoxins B1, B2, G1, G2                                                   | [30,32–34]   |
| Barley                | Aflatoxins B1, B2, G1, G2                                                   | [30,33]      |
| Malt                  | Aflatoxins B1, B2, G1, G2                                                   | [24,30,35]   |
| Wheat flour           | Aflatoxins B1, B2, G1, G2                                                   | [30]         |
| Cereal porridge       | Aflatoxins B1, B2, G1, G2                                                   | [30]         |
| Breakfast cereals     | Aflatoxins B1, B2, G1, G2                                                   | [36]         |
| Cornflakes and corn-based foods | Fumonisins, Beauvericin                                                  | [37,38]      |
| Rice                  | Total aflatoxins, Aflatoxin B1, Ochratoxin A, Beauvericin                   | [39–41]      |
| Baby food Baby fruit foods | Aflatoxins B1, B2, G1, G2                                                   | [30,42]      |
| Breast milk           | Aflatoxin M1, Beauvericin, Dihydricitrinone, Alternariol monomethyl ether  | [25,43,44]   |
| Dried milk            | Aflatoxins B1, B2, G1, G2                                                   | [30]         |
| Milk                  | Aflatoxin M1                                                                | [30,43,45]   |
| Milk porridge         | Aflatoxin M1                                                                | [30]         |
| Cheese                | Aflatoxin M1                                                                | [46]         |
| Yoghurt               | Aflatoxin M1                                                                | [31]         |
| Fruit drink           | Patulin                                                                     | [30]         |
| Fruit foodstuffs       | Patulin                                                                     | [30]         |
| Pork meat             | Ochratoxin A                                                                | [47]         |
| Pork hams             | Ochratoxin A                                                                | [47]         |
From Table 1 it is visible that the most common mycotoxins are DON (deoxynivalenol), patulin, OTA and B (ochratoxin A and B), and AFs (aflatoxins). They can be found in everyday foods that are consumed all over the world. Mycotoxins can also be found in water, as confirmed by several studies. Special attention is paid toward the regulation of mycotoxins found in baby foods. Infants are susceptible to developing difficulties when in contact with these kinds of contaminants. To reduce the risk of developing health problems, many of the stated mycotoxins are regulated by the European legislative but many of them are still treated as emerging issues and their effect on human health is not yet well-described.

Besides the sites in which mycotoxins or fungi can reside, a novel approach to the study of mycotoxin exposure was described by Assunção et al. [60]. They published a review about the influence of climatic changes on aflatoxin exposure and overall human health issues related to these mycotoxins in Portugal. Global warming could result in higher numbers of hepatocellular carcinoma related to aflatoxins, as certain forecasts have predicted that aflatoxin contamination in European crops could become a food safety issue within the next 100 years. Battilani et al. [61] identified cereals and maize as crops susceptible to contamination due to climate change. Higher levels of mycotoxins detected in breakfast cereals have already confirmed the effect of climate change in this respect on cereal-based foods [60,61]. This shows that global warming affects fungal metabolism, and that when such fungi encounter unfavorable conditions (warmer temperatures, drought, stress), they produce more mycotoxins.

2.2. Environment

As mentioned before, biomonitoring means not only a follow up on mycotoxin intake via food, but active monitoring of possible exposure through inhalation, from the environment. To investigate something like this, it is immensely important to implement a suitable analysis method. The most common source of bodily fluids for mycotoxin detection is urine [62]. The presence of mycotoxins in a certain environment, such as working or living, and repeated exposure to contamination can pose a serious threat to human health. It is immensely important to provide the appropriate working safety equipment and conditions for exposed workers. In the following sections, the emphasis will be put on different sources of mycotoxin contamination, the most common mycotoxins, and exposure potential.
Table 2. The most habitual fungi in different environments.

| Fungi                        | Environment   | Fungal Domicile          | Source |
|------------------------------|---------------|--------------------------|--------|
| Aspergillus spp., Eurotium spp., Cladosporium spp., Penicillium spp. | Apartments | Air                      | [63]   |
| Penicillium spp., Aspergillus spp., Cladosporium spp. | Basements    | Air                      |        |
| C. herbarum, D. macrocarpa, P. crustosum, A. puulaauensis, P. italicum, P. waksmani, R. stolonifera | Library or archive | Air Surfaces              |        |
| Aspergillus spp., Cladosporium spp., Penicillium spp., Rhizopus spp., Trichoderma spp. | Passenger vehicles | Filter or air-conditioning system | [65]   |

Although these studies did not measure mycotoxins it is important to know the fungal microbiome surrounding us. It is proven that these fungi synthesize mycotoxins and therefore a possibility of mycotoxin contamination in the human body is not to be taken lightly.

2.3. Occupational Exposure to Mycotoxins

Exposure can be related to workplaces, especially in the field of agriculture (farms) and the food industry (mills, bakeries) [15,17,62,64,66,67]. Working environments with poor ventilation, inappropriate protective clothing, and equipment [68,69] expose workers to a higher risk of contamination. The accurate risk assessment of mycotoxins in agricultural-related workers is an important tool in ensuring the health of workers. Exposure to mycotoxins in working environments relies on the same methods of assessment, measuring their residual levels (or specific metabolites) as biomarkers in biological fluids including blood and urine [62,70]. In such cases, it is important to analyze and compare the urine from potentially exposed subjects and those who are nonoccupationally exposed (i.e., a control group) [62].

However, according to Föllmann et al. [62], the measured biomarkers in urine samples from the two groups, control (with dietary intake only) and the mill workers, showed dominantly dietary mycotoxin exposure, concluding that inhalational exposure of mill workers, is presumably very low. Nevertheless, the possibility of contamination still exists and attention should be paid to preserve the health of workers whenever possible.

3. Mycotoxins, Biomarkers, and Matrix Analysis

Mycotoxins that can be harmful to humans are included in the legislation of many countries. And, as can be seen from Table 1, these are the most detected mycotoxins in marketed foods. Some of them are not as common but are very toxic and thus included in the legislation. Aflatoxins, ochratoxin A, zearalenone, deoxynivalenol, fumonisins, and the methods of their detection and biomonitoring are well described by [21]. Some of it will be conveyed in this section.

Combining information from web source [5,71] mycotoxin biomarkers can be detected using three approaches:
• direct-or exposure-based biomarkers are specific; standardized analytical methods (optimized and validated), mainly for parent compounds, because not many metabolites are available as reference substances.

• Indirect—indirect (or biomarkers of effect) are generally non-specific and represent structural or functional alterations produced in the body under exposure to certain drugs or toxins.

• Non-targeted—the determination of unknown mycotoxin derivatives.

Easily accessible biological matrices (urine, serum, plasma and breast milk) are key elements in HBM. Urine samples are easily obtainable by non-invasive methods, it can contain biomarkers of different mycotoxins [13]. However, urine biomarkers are susceptible to daily variations in mycotoxin intake, demanding at least 24 h sampling. Urine volume is individual for each person so this results in changes in the concentration of excreted compounds in the samples. This discrepancy can be reduced by applying a common—but still questionable—method for adjusting the mycotoxin levels in creatinine concentrations [72,73]. Namely, it is still unclear if the mycotoxin/creatinine ratio is applicable for comparison between individuals since creatinine is influenced by many factors (muscle mass, sex, age, season, diet, etc.) [74].

Breast milk is a great point to estimate the exposure in breastfed babies to different mycotoxins, but it is used to monitor only lactating women.

Other bodily fluids, such as serum and plasma, require somewhat invasive methods and educated medical staff to be collected, but can contain higher levels of studied chemicals [75] and are often used in long-term exposure studies [76].

Some mycotoxins can end up in the blood unchanged, and some can go through different modifications while in the human (or animal) metabolic system [77–83]. To calculate the exposure to mycotoxins, the metabolized form, very often the biomarker, needs to be included in the calculation [84,85]. Examples of well-established biomarkers for follow up on mycotoxins exposure is the production of glucuronic acid conjugates from deoxynivalenol. As mentioned before, some mycotoxins are resilient to endogenous metabolism and may be detected in their original form. A good example of this is the non-polar fumonisins (FB), which show off low rates of absorption and metabolic activity [77,86–88]. Since dietary analyses are broadly utilized in assessing the intake of food contaminants in the general population, certain tools need to be employed to reduce and clarify the variance among populations. For that reason, recent reports point to an increased interest in using dietary biomarkers to detect possible analytical errors in external exposure estimates [89].

Due to the complexity of blood, plasma, and serum samples, matrix components might interfere in analyte retention. They can also affect to reducing purification, recovery, and method sensitivity when mass spectrometry (MS) detectors are used.

Table 3 shows the most common and efficient methods for the determination of different mycotoxins or their biomarkers. Depending on the mycotoxin, extraction methods vary (IAC—immunoaffinity columns, SPE—solid phase extraction, LLE—liquid-liquid extraction, QuEChERS®—quick, easy, cheap, effective, rugged, and safe, etc.), but some methods include a practical dilute-shoot or Filter-shoot preparation which makes the analysis more simple. Sample volumes also differ (10–0.1 mL), depending on the method. Detailed information can be found in an extensive review by Escrivá et al. [90].
| Mycotoxins          | Matrix          | Detection Technique                  | Source |
|---------------------|-----------------|--------------------------------------|--------|
| OTA                 | Serum           | ELISA                                | [91–99]|
|                     |                 | CE-LIF (CE/laser-induced FD)         |        |
|                     |                 | HPLC-FD                              |        |
|                     |                 | HPLC-FD LC-ESI-MS/MS                |        |
| AFB1                | Serum           | ELISA                                | [70]   |
| OTA, OTα            | Serum           | HPLC-FD                              | [34]   |
| OTA                 | Urine           | HPLC-FD                              | [100–102]|
|                     |                 | HPLC-ESI-MS/MS                      |        |
| AFB1-N7-Gua         | Urine           | HPLC-ESI-MS/MS                      | [104]  |
| DON-GlcA            | Urine           | HPLC-FD                              | [105]  |
| STG                 | Urine           | LC-MS/MS                             | [106]  |
| DON, DOM-1          | Urine           | LC-MS/MS                             | [107]  |
| DON, DON-GlcAs      | Urine           | LC-MS/MS                             | [108]  |
| DON, DOM-1, DON-1-G, DON-G1, DON-G2 | Urine | HPLC-APCI-MS/MS                      | [109]  |
| FB1, FB2            | Urine           | HPLC-ESI-MS/MS                      | [110]  |
| ZON, α-ZOL, β-ZOL, ZAN, α-ZAL, β-ZAL | Urine | HPLC-EC                              | [111]  |
| CIT, HO-CIT         | Urine           | LC-MS/MS                             | [112,113]|
| DON, DOM-1          | Urine           | LC-MS/MS                             | [114,115]|
| OTA, OTA-GlcA, OTA-sulfates | Urine | LC-MS/MS                             | [116]  |
| AFM1, FB1, FB2, OTA, OTα | Urine | HPLC-ESI-MS/MS                      | [117]  |
| AFB1, AFB2, AFG1, AFG2, OTA, DON, ZON, FB1, FB2, T-2, HT-2 | Urine | LC-QTRAP-MS/MS                      | [118]  |
| AFM1, OTA, DON, DOM-1, α-ZOL, β-ZOL, FB1 | Urine | HPLC-Qtrap-MS/MS                    | [119]  |
| DON, NEO, AFB1, AFM1, HT-2, HT2, OTA, OTα, ZON, α-ZOL, β-ZOL, FB1 | Urine | LC-MS/MS                             | [120]  |
| DON, OTA, FB1, AFB1, ZON, T-2, HT-2, AFB1, CIT, DOM, DON-2-GlcA, ZON-14-GlcA, α-ZOL, β-ZOL, 4-OH-OTA, OTα, AFM1, AFB1-N7-Gua | Urine | LC-MS/MS                             | [121]  |
| DON, DON-3-GlcA, DON-15-GlcA, DOM-1, NIV, T-2, HT-2, ZON, ZON-14-O-GlcA, α-ZOL, β-ZOL, FB1, FB2, OTA, AFM1 | Urine | HPLC-ESI-MS/MS                      | [122]  |
| DON, DON-3-GlcA, DON-15-GlcA, ZEN, ZEN-14-GlcA. | Urine | LC-MS/MS                             | [123]  |
| DON, DOM-1, AFM1, FB1, ZON, α-ZOL, β-ZOL, OTA | Urine | UPLC-MS/MS LC-Qtrap MS/MS UPLC-API 5000 MS/MS | [124]  |
| AFM1, OTA, FB1, DON, DON-GlcAs, FB2, DOM-1, ZON, ZON-14-GlcA, α-ZOL, β-ZOL, T-2, HT-2, NIV | Urine | LC-MS/MS                             | [125]  |
| AFB1, AFB2, AFG1, AFG2, AFB1-N7-gua, AFM1, CIT, DON, DON-3-GlcA, DOM-1, FB1, HFB1, OTA, OTα, 4-OH-OTA, T-2, HT-2, ZON, ZON-14-GlcA, α-ZOL, β-ZOL | Urine | LC-MS/MS                             | [126,127] |
| Mycotoxins | Matrix | Detection Technique | Source |
|-----------|--------|---------------------|--------|
| AFB1, AFB2, AFG1, AFG2, AFM1, CIT, OH-CIT, DON, DON-3-GlcA, DON-15-GlcA, DOM-1, DOM-1-3-GlcA, 3-ADON, 3-ADON-15-GlcA, 15-ADON, 15-ADON-3-GlcA, DAS, FB1, FB2, FB3, FUS-X, OTA, OTα, T-2, HT-2, ZON, ZON-14-GlcA, α-ZOL, β-ZOL-7-GlcA, α-ZOL-14-GlcA, β-ZOL-14-GlcA. | | | |
| AFB1, DAS, FusX, 3-AcDON, 15-AcDON, α-ZEL, β-ZEL, OTα, DOM-1, FB1, FB2, FB3, DON, ZEN, T2, HT2, DON-3-GlcA, DOM-GlcA, ZEN-14-GlcA, β-ZEL-7-GlcA, β-ZEL-14-GlcA, α-ZEL-7-GlcA, α-ZEL-14-GlcA, 15-AcDON-3-GlcA, 3-AcDON-15-GlcA, OTA, CIT and AFM1 | Urine | LC-MS/MS | [128] |
| DON, DON-3-GlcA, T-2, HT-2, HT-2-4-GlcA, FB1, AFB1, AFB2, AFG1, AFG2, AFM1, ZON, ZAN, α-ZOL, β-ZOL, ZON-14-GlcA, ZAN-14-GlcA, α-ZOL-14-GlcA, β-ZOL-14-GlcA, OTA, OTα, ENN B, DH-CIT | Urine | LC-MS/MS | [129] |
| DON, DON-3-GlcA, T-2, HT-2, HT-2-4-GlcA, FB1, AFB1, AFB2, AFG1, AFG2, AFM1, ZON, ZAN, α-ZOL, β-ZOL, ZON-14-GlcA, ZAN-14-GlcA, α-ZOL-14-GlcA, β-ZOL-14-GlcA, OTA, OTα, ENN B, DH-CIT | Urine | LC-MS/MS | [130] |
| DOM-1, DON, 3-ADON, FUS-X, DAS, NIV, NEO, HT-2, T-2, ZON, α-ZOL, β-ZOL, ZAN, α-ZAL, β-ZAL | Urine | GC-MS/MS | [131–133] |
| DON, DOM-1, 3-ADON, 15-ADON, ZON, α-ZOL, β-ZOL, ZAN, α-ZAL, β-ZAL | Urine | GC-MS/MS | [134] |
| OTA | Breast milk | HPLC-FLD | [135] |
| AFM1, OTA | Breast milk | HPLC-FD, ELISA | [136] |
| ZON | Breast milk | ELISA, HPLC-FD | [137] |
| DON, 3-ADON, NIV, FUSX, NEO, DAS, HT-2, T-2, ZON, α-ZOL, β-ZOL, FB1, FB2, FB3, EN A, EN A1, EN B, EN B1, BEA, AFB1, AFB2, AFG1, AFG2, AFM1, STG, OTA, OTα | Breast milk | UHPLC-HRMS | [138] |
| AFB1, AFB2, AFG1, AFG2, AFM1, OTA | Breast milk | HPLC-FLD | [139] |
| OTA, OTα | Serum urine | HPLC-FLD | [140,141] |
| CIT | Serum urine | HPLC-FLD | [141,142] |
| ENs, BEA | Serum urine | LC-MS/MS | [143] |
| OTA, OTB | Feaces | HPLC-FLD | [144] |
| TCT, AFs, OTA | Urine and nasal secretions | ELISA, Fluorometry | [145] |
| AFB1, AFB2, AFG1, AFG2, AFM1, OTA, NIV, T-2, HT-2, 3-ADON, 15-ADON, NEO, FUS-X, DAS, MAS, ZON, ZAN, α-ZOL, β-ZOL, α-ZAL, β-ZAL, T-2 triol, T-2 tertraol, DOM-1, FB1, FB2 | Urine, blood, feces, saliva, nasal secretions, breast milk, amniotic fluid of pregnant women | HPLC-MS/MS | [146] |
Aflatoxins are one of the most well-studied mycotoxins with a metabolism that is familiar to scholars. Four different aflatoxins aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), and aflatoxin G2 (AFG2) are often detected and quantified as foodstuff contaminants. However, AFB1 is the most important not only because it is abundant but because of its toxicity. Biochemical reactions (hydroxylation and epoxidation) occurring in metabolism determine the form it will end up in. Hydroxylation at C-7 leads to the formation of aflatoxin M1 (AFM1) and epoxidation at C-8, C-9 ends up either in endo- or in exo-configuration. This makes AFM1 the first described metabolite and validated biomarker of aflatoxin exposure with an average conversion rate of about 1.5% [147] and can be determined in different biological fluids such as urine and breast milk [148]. Epoxidized form of AFB1 reacts with DNA (exo-epoxide only), glutathione, or is hydrolyzed to AFB-diol. Further complex metabolism of AFB-DNA-adducts is described in [21], but in short, aflatoxin B1-N7-guanine (AFB1-N7-guanine) and aflatoxin B1-glutathione conjugates are excreted via urine as aflatoxin B1-mercapturic acid conjugates (Aflatoxin B1-N-acetyl-cysteine, AFB1-NAC) and can serve as biomarkers [149,150]. For blood samples, the aflatoxin biomarker is an aflatoxin-albumin adduct and is the most common matrix for aflatoxins detection in urine, breast milk, and blood. It is usually determined via high-performance liquid chromatography coupled with fluorescence detection (HPLC-FLD) [64,65,151–153]. A faster and cheaper method, enzyme-linked immunosorbent assays (ELISA) can also be applied in aflatoxin and aflatoxin-metabolite analysis in blood and urine. Xue et al. [154] reported an almost completely non-invasive and utterly simple AFB1-albumin adduct detection from dried blood spots.

Ochratoxin A is characterized as nephrotoxic and carcinogenic mycotoxin, often found in food and feed [30,155,156]. It can be found in human serum even after 30 days [157] and serves as a biomarker for ochratoxin A exposure [158]. Detection of ochratoxin A in urine is not as precise and accurate since only quantities of ingested OTA end up in urine (<3% per day) [157,159], but a less invasive method, many research data originate from values obtained from urine samples [81,140,160]. Continuous and current studies are investigating the metabolic pathways involving OTA [116,161,162] and its forms (hydroxylated ochratoxin A (4R-OH-OTA) and ochratoxin a (OTA)) [140,160,163]. OTA can be detected in blood plasma [163–166] and method improvement is ongoing [5,140]. OTA can also be detected in dried blood spots and quantified using HPLC-MS/MS technique [167,168]. ELISA can also be applied for the analysis of ochratoxin A in plasma and has been widely used for the screening of samples [169–171]. Orti et al. [172] reported the first method for the analysis of OTA in human urine, but with simultaneous detection of ochratoxin A and aflatoxin B1. Some scholars [13] worked toward the improvement of these methods. In 2010 Munoz et al. published the protocol for HPLC-MS/MS analysis of OTA and OTA in urine [140]. Several authors [173,174] reported working on a molecular imprinted polymers method which can be employed for OTA purification from urine. In 2020 a group of scholars [175] conducted research on mycotoxin exposure assessments in a multi-center European validation study by 24-h dietary recall and biological fluid sampling where they established a positive correlation between the ochratoxin A (and several other mycotoxins) levels, 24 h exposure time and serum. This could help scholars and professionals to identify chronic exposure biomarkers and to easier assess a single-time point exposure.

Zearalenone (ZEN) is a Fusarium toxin that exhibits estrogenic properties after ingestion. In the gastrointestinal tract, it undergoes both, phase I and phases II metabolism described in detail by Metzler et al. [176]. In short, it can be reduced to α- or β-zearalenol (α-/β-ZAN) with α-ZAN being predominantly found in humans and pigs while β-ZAN can be found in cows. Following biochemical reactions lead to forming α-/β-zearalanol (α-/β-ZAN). This form can be found in sheep [177]. Oxidative metabolism can result in the formation of 8-hydroxy ZEN which was confirmed in vivo in the liver and urine of rats dosed with ZEN but not yet in humans [178,179]. Glucuronic acid conjugates of ZEN, ZAN, α-/β-ZAN, and α-/β-ZAN are known but only ZEN-14-O-β-glucuronide (ZEN-14-GlcA) is detected in human urine [122,129,180]. Analysis of ZEN and its metabolites in blood and
urine samples using the HPLC-MS technique is currently the most used method and many scholars are working on improvements [122,181–183].

Deoxynivalenol and its acetylated forms, 3-acetyl-deoxynivalenol (3-AcDON), and 15-acetyldeoxynivalenol (15-AcDON) are designated as the most prevalent mycotoxins [184]. However, plant metabolites relating to deoxynivalenol are also gaining popularity and significance among scientists. DON causes gastrointestinal problems and oxidative damage, inhibits DNA, RNA, and protein biosynthesis by interaction with ribosomes [185–187]. The metabolism of DON is studied in animals and a small amount of data exist considering human metabolism. DON needs a short time to be excreted from the body [188]. They reported that cca 30% of DON uptake is excreted via urine in 24 h, but 40% of DON in urine can be recovered as the unmodified mycotoxin [188]. DON metabolism results with its masked forms (deoxynivalenol-3-O-β-glucuronide (DON-3-GlcA), deoxynivalenol-15-O-β-glucuronide (DON-15-GlcA) and deoxynivalenol-O-glucuronide (DON-7-GlcA), deepoxy DON (DOM-1), and its glucuronide, DON-3-sulfate are some successfully detected in humans [126,189–194]. Due to the polarity of DON, blood screening is of no importance for biomonitoring [188], but detection and quantification of DON in urine and its metabolites via the HPLC-MS/MS technique is a common and reliable method [129,182,188]. Reportedly, DON levels, after oral administration, in human samples of urine span from 0.003 to 0.008 µg/mL [109]. Urinary daily excretion of 35.2 µg DON was determined in humans after 49.2 µg of DON daily intake, representing 68.3% of the established DON provisional maximum tolerable daily intake (PMTDI) [131].

Type A trichothecenes—T-2 and HT-2 toxin, nivalenol (NIV), and fusarenon X (FUS-X) are also considered toxicologically relevant food contaminants. T-2 toxin is a type A trichothecene. It is a result of the metabolism of different Fusarium spp., and can be found in cereals and cereal-based products [195]. T-2 toxin is an inhibitor of protein synthesis and mitochondrial function and displays immunosuppressive and cytotoxic effects. Toxicity of HT-2 toxin (HT-2) has been less investigated because T-2 toxin is rapidly metabolized to HT-2 in vivo and for that reason, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reported that the toxic effects of T-2 and HT-2 cannot be differentiated. T-2 toxin is rapidly absorbed, as the other trichothecenes, and excreted in feces and urine [196]. On that note, HT-2, as the dominant compound in vitro and in vivo studies, should be considered as the main T-2 biomarker in urine and plasma samples [197]. Hydroxylated products and glucuronide forms could also be used as biomarkers for T-2 exposure. Hence, several studies detected T-2 and HT-2 in human urine [130,133]. The lack of commercial reference standards only HT-2-4-glucuronide has been detected in human urine [130]. The implementation of novel methods should allow the detection of additional T-2 metabolites, especially the dominant metabolite, 3′-OH-HT-2. NIV is classified as a type B trichothecene. It is common in wheat [198] and displays immunotoxic, hematoxic, myelotoxic, developmental, and reproductive toxicity properties. Exposure to dietary NIV has been associated with an increased incidence of oesophageal and gastric carcinomas in certain regions of China [199]. Since NIV is water-soluble it can be easily absorbed, distributed, and eliminated without accumulation in all investigated animals (rodents, pigs, and poultry) [200,201]. Scholars investigating NIV in human urine determined moderate-to-high NIV concentrations in the urine samples due to the limit of detection (LOD) used in their study (>4.0 ng/mL) [182]. NIV can presumably be excreted in the glucuronidated form, similar to DON (>90% DON-3-glucuronide and DON-15-glucuronide) [126]. In short, NIV was scarcely studied regarding its metabolic and toxicokinetic properties but its high similarity with DON molecules can indicate that NIV-glucuronides are yet to be identified. However, deepoxy-NIV can be found in feces. FUS-X is also a type B trichothecene that can be found in cereals. It usually co-occurs with DON and NIV, but in lower levels [202]. As reported by [203], its toxicity is more potent than other type B-trichothecenes. It affects hematopoietic tissues, the spleen, and the thymus, and exerts intestinal inflammation, inhibits protein synthesis, induces apoptosis, and alters genetic material causing cell cycle delays, chromosomal aberrations, and sister chromatid exchanges [204]. According to
several studies, FUS-X is absorbed from the gastrointestinal tract of different animals and oral bioavailability is dependent on the particular species in question [205–207]. FUS-X is converted to NIV (>90%) in the liver and kidney. FUS-X biomarker analysis should focus on quantification of NIV both in urine and in plasma [208].

Fumonisins (FUM) also originate from *Fusarium* fungi. Even though more than 30 compounds are designated as fumonisins, the most familiar are fumonisin B1 (FB1) and fumonisin B2 (FB2). Fumonisins are classified as carcinogens and can cause different anomalies in children [86,209]. FB1 in urine is the basis for HBM [87,210], based on data retrieved from research on humans that showed a 0.12–2% excretion via urine which is enough since high amounts of FB1 can be found in food [87,211,212]. Analytical methods for the detection of FB1 are usually based on urine and are done via the HPLC-MS system. The oral bioavailability is generally below 5% for FB1 [171].

Multi-mycotoxin detection unites several fungal species (*Fusarium* sp., *Aspergillus*, *Penicillium*) and monitors the co-exposure to several mycotoxins. Saving money and adding a new dimension to BMH, this method is getting more attention. In 2010 Ahn et al. [117] developed a method for urine samples in which they detected AF, OTA, and FUM via HPLC-MS/MS. Rubert et al. [118] determined T2/HT-2, DON, FB1, FB2, AFB1, AFB2, AFG1, AFG2, ZEN, and OTA. Emerging mycotoxins and mycotoxin metabolites should be included in multi-mycotoxin HBM [213,214] and legislative frames. However, they demand an unspecific sample treatment [129,215] which makes the analysis that much difficult and complex.

Based on data collected from the consumption of contaminated foodstuffs and the average occurrence of the toxin, the exposure to certain contaminants can be derived by calculation [31]. However, the classical analytical approaches provide valuable data. The estimation of exposure via biomarkers correlates the direct exposure assessment with the dietary mycotoxins ingestions [22]. HBM is by definition the analysis of mycotoxin biomarkers in body fluids and tissues and serves to estimate the internal exposure of humans to food contaminants [216,217]. Assessing exposure through mycotoxin levels in biological matrices has a certain advantage when compared to solely analyzing the occurrence of toxins in food and combining the obtained data with information on food consumption. Namely, HBM can neglect the contamination source (orally or by inhalation) since this information is not important for this method. HBM also requires a single determination per person and food sampling methods and consumption data collection are not necessary. For that reason, HBM should be conducted continuously and worldwide [218].

Biomarkers, however, have to be validated to assure that they accurately represent the level of intake of the considered food, that the sample type and time of sampling are appropriate for the intended use, and that the analytical method is valid according to current standards. Validation of biomarkers is an important factor for analytical validity measured according to the prescribed standards as well as a matter of biological (nutritional) validity. Different variables affect the content of biomarker precursors in foods and subsequently their metabolism and kinetics in individuals. Therefore, validation criteria must refer to biological aspects of the biomarkers as well [219–221].

### 4. Exposure Assessment

Exposure assessment is a difficult and synergistic approach including all available data is crucial for a sound conclusion. According to several authors, HBM, in correlation with different dietary surveys can be more useful for confirmation of exposure to mycotoxins, because it connects exposure to certain foods but it can expose the influence of other factors (differences in exposure due to socioeconomic or regional factors) to the results [116,222,223]. In short, HBM can be more of use in human health and dietary studies, than its use in exact exposure assessment of daily intake [224]. Exposure assessment of daily intake from blood or urine concentration remains difficult unless the human toxicokinetics and inter-individual differences are better understood [116,224].
4.1. Relevant Strategies for Data Collection

To assess the shifts in mycotoxins exposure, food consumption surveys are regularly updated. However, increased consumption of nutty cereals or beer may increase the exposure to mycotoxins present in nuts and cereals (malt), such as deoxynivalenol, aflatoxins, or ochratoxin A. Monitoring studies and data collections are important for analyzing trends in mycotoxin occurrence in raw materials and foods. The timely and continuous follow-up results with an updated exposure assessment, which is very important for HBM studies, and most importantly can lead to appropriate reactions and reduction recommendations. There are several methods, described below, that ensure data collection for further processing.

Food consumption surveys are conceived as questionnaires filled by volunteers who individually and in detail reminiscence at least two days of their diet. Such data sets are useful in aiming the assessment of dietary exposure to certain mycotoxin in the general population [225,226]. The major EU institution for such assessments is the European Food Safety Authority (EFSA), which formed the Comprehensive European Food Consumption Database, also called EFSA Comprehensive Database [227]. Global assessments are done by the Food and Agriculture Organisation (FAO) of the United Nations. EFSA also implemented the food classification system named FoodEx1 which serves to codify all foods and beverages present in the database. FoodEx2 is an upgraded version and enables more precise reporting of consumption patterns. These databases are holding information about food consumption patterns of infants, toddlers, children, adolescents, adults, and the elderly for the different Member States. Complex statistical methods are applied and the amount of data resulting from these surveys is vast. However, these summary statistics is a useful and quick screening tool in assessing chronic and acute exposure to hazardous substances. EFSA uses the detailed underlying consumption data at the individual level to perform more refined exposure assessments, both acute and chronic. System for Food Contamination Monitoring and Assessment Program, commonly known as GEMS (Global Environment Monitoring)/Food operated by WHO implements the program in cooperation with a network of Collaborating Centers and acknowledged worldwide national institutions. WHO and FAO have actively worked toward obtaining as much new data and have recently developed a new database for Individual Food Consumption Data which provides summary statistics at three levels of food categorization and can be used for an indication of the dietary exposure at a national level.

Data Collection

Data collection for exposure assessment can be related to several methods described in the following sections.

Food monitoring studies aim to investigate the prevalence and concentration of various contaminants, in an ingredient or food [1]. The procedure of sampling includes a random collection of samples from various points in the supply chain. An important point, is that this allows for the tracking of food products and relates this tracking back to the producer. Sampling can be done over a designated time. Samples can also be provided by surveys which are frequently published in the literature and available to the public [228–231]. For such studies, classification and description of foodstuffs play an important role in exposure estimations for the general population based on the geographical origin. This also contributes to the diversification of consumers to sensitive groups in the population (infants or people with specific diets) [232]. Important parameters such as sample size, sampling strategy, and sample preparation have to be noted as they could influence the results [233]. Immunoassays can be utilized as a screening method and can be a useful tool in assessing exposure. If not to determine the presence of a compound then to exclude its presence above a certain limit.

Total diet studies evaluate food samples which collectively make up a sample of the whole diet. Samples are collected, prepared, and pooled into composite samples per food category, as described in Ref. [234]. In such studies it is important to include seasonality
because some foods may contain various mycotoxins levels due to climatic conditions). Geographical variation [235] is also important to incorporate since it covers the potential geographical differences. According to food safety authorities, EFSA, WHO, and FAO, the food list should cover about 90% of the food intake, should be as close as possible to the actual whole diet, and should include beverages and drinking water [234]. Representative food items and food processing habits should be as close as possible to the habits of the investigated population. In a total diet-like study, the food items for which contamination levels of the relevant (group of) substances are expected are sampled separately [235].

EFSA employs two types of total diet studies [235]:

a) total diet study for screening (limited number of composite food samples for common food categories). In the case of high exposures, further examinations are performed to identify the source.

b) total diet study for refined exposure assessment (a large number of samples for smaller, more refined, food categories).

Duplicate diet studies aim to provide a copy of all food items and beverages as consumed by one person at a certain time, e.g., during a 24 h period. Such studies measure the actual exposure of consumers to compounds of interest, but the effects of food processing and preparation are also considered [236]. Duplicate diet studies have various different version. For example, where only a portion of the diet is collected, or where foods are collected based on standardized or average diets [1]:

a) cyclic sub-portion duplicate diet,
b) subpopulation duplicate diet,
c) targeted food duplicate diet and,
d) the total population diet.

Some of the methods for exposure assessment are described in the Dietary Assessment: A resource guide to method selection and application in low resource settings, a detailed handbook issued by the FAO in 2018 [237].

4.2. Exposure Assessment

Exposure assessment is defined as the qualitative and/or quantitative evaluation of the likely intake of chemical agents via food as well as exposure from other sources if relevant [1]. According to several authors, to estimate the dietary exposure of humans to mycotoxins, it is important to manage as much information on prevalence and levels in foods as possible and to combine them with consumption data [3,237]. Strategies employed to assess exposure can detect acute or chronic exposure.

Point estimate—a single mycotoxin concentration is combined with a single input parameter for consumption. The result is a single exposure estimation with a high degree of uncertainty. Data on concentration commonly originates from a food monitoring study or a total diet study which makes the conduct of such studies considerably facile [1].

Observed individual mean—is defined as the mean mycotoxin concentration per food product, combined with the food consumption per day per consumer, averaged over the days available in the survey and, divided by the individual’s body weight [238] (average exposure/kg of bw/person/day).

A probabilistic approach is designated to assess acute and chronic exposure.

a) acute exposure—can be assessed by combining daily individual consumption patterns from a food consumption survey with randomly selected levels per food product from a databank with mycotoxin levels in individual samples [1].

b) chronic exposure—statistical models that use the same input as the observed individual mean approach (see the previous section) help in gaining exposure to the certain mycotoxin.

The positives and negatives for both methods are in detail described in [1].

Dietary exposure using duplicate diet studies conducts the analyses of the compounds, resulting in an actual exposure level per day for that individual. The collected food
consumption data can be used to evaluate the possible sources of exposure. Acute exposure can be evaluated if duplicate portions are collected on one day per individual.

The heterogeneous distribution in the matrix, differences between geographical regions, climate, and processing methods can make the assessment of mycotoxins to be difficult and complicated. Low concentrations, co-occurrence, and biotransformation to modified forms also make this kind of research complicated.

5. Prospects and Conclusions

Human biomonitoring studies are relevant tools for monitoring the global health situation. As mentioned in the review, climatic changes will only enhance the relevance of biomonitoring since mycotoxins levels in cereals important for human consumption are expected to rise. Improvements of analytical methods and techniques will surely strive toward higher levels of precision and accuracy and novel, emerging mycotoxins will be defined and detected in lower and lower doses. Intensive research of metabolic pathways will lead to the discovery of new biomarkers whose detection and quantification could simplify and evade the invasive methods such as drawing blood. Finally, a combination of different strategies and methods, combining research fields and overlapping scopes, should result in much more efficient and wider data collection for future research and, most importantly, application in human health protection.

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