Review

Aflatoxin, fumonisin, ochratoxin, zearalenone and deoxynivalenol biomarkers in human biological fluids: A systematic literature review, 2001–2018

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ABSTRACT

Human exposure to mycotoxins occurs mostly through dietary intake, although exposure through dermal and inhalation routes has also been shown. Depending on the type of mycotoxins, the applied dose and duration of exposure, a particular toxin can cause either chronic or acute illnesses such as kidney failure and cancer. Thus, understanding the biotransformation of mycotoxins and identification of reliable biomarkers in the human body is important for accurate risk assessment of mycotoxin exposure. This review provides a comprehensive overview of worldwide aflatoxins, fumonisins, ochratoxin, zearalenone and deoxynivalenol mycotoxin biomonitoring studies reported in the last 18 years. The studies performed in Africa, Europe, Asia and America are based on the measurement of a limited number of mycotoxin biomarkers and do not provide a comprehensive risk assessment of the mycotoxin exposure. Although the findings represent a small segment of a much larger health risk of mycotoxins exposure, it is acknowledged that a multianalyte approach covering bioconjugated and other metabolites of most often occurring mycotoxins would better reflect the extent of the global exposure problems with these highly toxic compounds.

1. Introduction

Mycotoxins, secondary metabolites of filamentous fungi, found in diverse agricultural crops worldwide, are posing a severe threat to human health. The most toxic fungal genera found in contaminated food are *Aspergillus*, *Fusarium*, *Penicillium* and *Alternaria* (Pitt and Hocking, 2009). The fungal contamination may happen during any stage of culturing, harvesting or storage (Marin et al., 2013; Williams et al., 2004). The main factors affecting mycotoxin contamination in human and animal food can be biological or ecological (Bhat and Reddy, 2017). Mycotoxin contamination of food is more common in developing countries where poor food quality control, warm climate, poor production technologies and bad crop storage conditions are suitable for fungal growth and toxin formation (Peraica et al., 1999). Food contamination by mycotoxins is considered inevitable and has raised global concerns as mycotoxins cannot be easily destroyed by temperature or by any chemical or physical treatment (Marin et al., 2013). Although, a great deal of effort has been devoted to avoid mycotoxin exposure, still human or animal consumption of food contaminated with mycotoxins is a major food safety problem worldwide.

Ingestion of contaminated food is the major route of mycotoxin exposure, while dermal and inhalation routes of mycotoxin exposure are not that common (Zain, 2011). Vomiting, nausea, diarrhea, fatigue, hemorrhage, abdominal pain, damage to hematopoietic tissues, skin inflammation and blistering are some of the symptoms of mycotoxicoses. The impact of mycotoxins on human health depends on the toxin type, its conjugation forms and concentration, period of exposure, pharmacokinetics and accumulation of the mycotoxins, age, gender as well as the immune system and health state of the exposed person (Bennett and Klich, 2003; Jonathan et al., 2004; Zain, 2011). Acute or chronic exposure to mycotoxins might have carcinogenic, nephrotoxic, tremorogenic, immunotoxic, hemorrhagic, teratogenic and dermatological consequences in humans (Bhat and Reddy, 2017). Thus, it is of utmost importance to identify the relevant mycotoxin exposure biomarkers in order to detect geographical areas and subpopulation with health impairing, high exposures. Parent mycotoxins, major phase I or phase II metabolites, protein adducts or DNA adducts are the usual biomarkers measured in biological fluids. The selection of biomarkers

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to be analyzed in a certain biological fluid is crucial. The absorption of some mycotoxins, such are aflatoxins and zearalenone, is rather quick after oral ingestion reaching peak concentration in blood within a few hours (Devreese, 2012). However, their clearance is also rapid unless they have formed adducts with macromolecules. Mycotoxin adducts with macromolecules have longer half-life in blood and can provide crucial information on the cumulative effects of mycotoxins. Another preferred biological fluid used to analyze mycotoxin biomarkers is urine, which might contain mycotoxin metabolites or the parent compound. The normalization with creatinine or specific gravity is recommended for urine samples (Sauvé, 2015) while normalization with albumin for the plasma/serum protein adducts. Also understanding the long-term and short-term biomarkers of exposure is crucial, as well as their sensitivity and dose-response relationship in the expression of biomarkers. The mycotoxin metabolism in relation to biomarkers of exposure has been recently reviewed by Vidal and colleagues in a comprehensive review (Vidal, 2018b).

Beside biomarker studies, the research should also focus to better assess health impacts of mycotoxins and their role in disease onset and development, to study the human, animal, animal and human microbiome and host plant mycotoxin metabolism and determine the efficacy of intervention strategies. The focus of this review is on the metabolism of mycotoxins, on the currently known biomarkers detected in biological fluids and so far reported exposure studies of major mycotoxins with human health concerns: aflatoxins, ochratoxin, fumonisins, zearalenone and deoxynivalenol (Sherif et al., 2009).

2. Metabolism and biomarkers of mycotoxin exposure in humans

2.1. Aflatoxin B1

Aflatoxins are produced by *Aspergillus* species and the main species responsible for aflatoxin production are *A. flavus*, *A. parasiticus* and *A. nomius* (Richard, 2007). There are four main types of aflatoxins: aflatoxin B1 (AFB1), B2 (AFB2), G1 (AFG1) and G2 (AFG2). AFB1 is considered the most toxic aflatoxin and the most potent carcinogenic substance, thus classified as Group 1 human carcinogen by the International Agency of Research on Cancer (IARC, 2002). AFG1, AFB2 and AFG2 are less carcinogenic and less mutagenic than AFB1 due to the lack of the presence of double bond in position 8,9 (Bbosa et al., 2013; Wild and Turner, 2002).

Aflatoxin metabolism differs between children and adults (Dohnal et al., 2014) and the aflatoxin pharmacokinetics is still not completely explored (Dohnal et al., 2014). Liver is the dominant site of aflatoxin metabolism, where aflatoxins are converted to 8,9-epoxide form during the phase I metabolism by primary cytochrome P450 (CYP) enzymes, such as CYP3A4, CYP3A5, CYP3A7 and CYP1A2 (Palacios et al., 2017; Wild and Turner, 2002). CYP3A4, CYP1A2 and CYP3A7 in the liver oxidize AFB1 to form AFB1-8,9-exoepoxide and AFB1-endo-epoxide. AFB1-8,9-exoepoxide can bind to DNA forming predominantly 8,9-dihydro-8(N7-guanyl)-9-hydroxy-AFB1 (AFB1–N7-Gua) adduct which is suggested to be responsible for the mutagenic properties of AFB1. However, a positive charge on the imidazole ring of AFB1-N7-Gua makes it unstable further promoting the release of AFB1-8,9-dihydrodiol, depurination and the opening of the imidazole ring and forming of stable AFB1-formamidopyrimidine adduct (Bedard and Massey, 2006; Groopman et al., 1981). The AFB1-formamidopyrimidine lesions are removed less efficiently than AFB1-N7-Gua in mammals, suggesting its role in AFB1-induced toxicity (Bedard and Massey, 2006).

AFB1-endo-epoxide is less toxic as it cannot bind to nucleic acids (Dohnal et al., 2014; Palacios et al., 2017; Wild and Turner, 2002). However, exo- and endo-epoxide through non-enzymatic hydrolysis can form AFB1-8,9-dihydrodiol which reacts with the ε-amino group of lysine in serum albumin and can be detected in blood (Dohnal et al., 2014; Wild and Turner, 2002). Oxidation of AFB1 by CYP3A4 and

CYP1A2 also yields other phase 1 metabolites such are hydroxylated AFM1, AFP1 and AFQ1 that can be detected in human urine (Dohnal et al., 2014; Bbosa et al., 2013), while the action of cytoplasmic reductase converts it to aflatoxicol. Furthermore, CYP2A13 was found to convert AFB1 to AFB1-8,9-epoxide and AFM1 to AFM1-8,9-epoxide in lungs and to catalyze AFB1-induced DNA damage (Dohnal et al., 2014).

The detoxification process of AFB1-8,9-epoxide mainly involves glutathione S-transferases (GST) that conjugates this metabolite with glutathione (GSH) forming AFB1-8,9-epoxide-GSH, followed by its further biotransformation to AFB1-mercapturic acid. If the GST function is impaired the AFB1-8,9-epoxide can by the action microsomal epoxide hydrolases be converted to AFB1-dihydrodiol (Kensler et al., 2003). AFB1-dihydrodiol in the basic conditions is transformed to ABF1-dialdehyde. Although aldo-keto reductases convert AFB1-dialdehyde to AFB1-dialcohol that is later conjugated to AFB1-glucuronide, protein lysine groups are susceptible to adduction with AFB1-dialdehyde that might affect protein structure and function (Guengerich et al., 2001).

In 2004, an outbreak of acute aflatoxicosis in Kenya was the largest mycotoxin poisoning incident which resulted in 317 intoxication cases with 125 deaths due to contaminated maize and maize products in the local food market. Mean values of the measured levels of aflatoxin in homegrown maize were significantly higher compared to kernels sampled from control households, 354.5 μg/kg and 44.1 μg/kg respectively. This was in agreement with the AFB1-lysine serum concentration, for which the mean was 1.2 ng/mg of albumin in the case patients compared to 0.15 ng/mg of albumin of controls. From this incident, serum aflatoxin B1-lysine adduct has been identified as a biomarker for aflatoxins and used to indicate aflatoxin exposure (Azziz-Baumgartner et al., 2005; Probst et al., 2007).

In the mycotoxin exposure study in rats, AFB1, AFP1 and AFM1 were detected in urine by LC-MS/MS (Everley et al., 2007). Urinary AFB1 such as AFM1, AFP1, AFQ1, Aflatoxin glucuronide, AFB1-N7-Gua and AFB1-mercapturic acid were used as biomarkers to assess the exposure of aflatoxins in other studies (Leong et al., 2012; Schleicher et al., 2013; Shirima et al., 2013; Wild and Turner, 2002). As AFM1 can be detected in human breast milk it can also serve as a biomarker of maternal and infant exposure to AFB1. Based on human and animal studies, AFB1-N7-Gua adduct in urine is considered the most reliable short term biomarker, with a half-life of 7.5 h, for evaluating hazards and exposure to carcinogenic AFB1 (Dohnal et al., 2014; Groopman et al., 1993; Jager et al., 2016; Wild and Turner, 2002). Moreover, AFB1-lysine and aflatoxin-albumin adducts are considered as one of the best biomarkers for long term exposure in blood, due to the albumin half-life of 20 days (Jager et al., 2016; Leong et al., 2012). In the study by Jager et al., (2016), amongst all tested markers urinary AFM1 was found to be a very sensitive biomarker for monitoring human exposure to food contaminated with AFB1 (Jager et al., 2016). However, urine AFM1 is a good biomarker only for recent exposure to aflatoxins, while for assessing the long term exposure, the AFB1-lysine in blood, with a long half-life, should be used as a biomarker (Groopman et al., 2014).

2.2. Ochratoxin A

Ochratoxins are common contaminants of food crops, dried nuts, dried fruits and some drinks based on grapes (Bayman and Baker, 2006). Ochratoxins (A, B and C, i.e. OTA, OTB and OTC) are produced by *Aspergillus* and *Penicillium* fungi species, mainly *A. ochraceus*, *A. carbonarius*, *A. niger* and *P. verrucosum* (Koszegi and Poor, 2016). Among the three ochratoxins, the ochratoxin A (OTA) is mainly responsible for severe adverse effects in both humans and animals (Koszegi and Poor, 2016) and is categorized by IARC as a possible carcinogen to humans (group 2B) (IARC, 1993).

Numerous studies describe detailed OTA metabolism for animals and some of the findings can be translated or can shed light on the metabolic processes of OTA in humans. OTA is metabolized in kidneys,

intestines and liver but it also binds to serum proteins such is albumin. OTA half-life in human serum is 35 days and may accumulate in human body tissues or fluids (e.g. plasma and serum) (Koszegi and Poor, 2016; Reddy and Bhoola, 2010; Studer-Rohr et al., 2000; Wu et al., 2011). OTA biotransformation is triggered by the action of cytochrome P450 enzymes, such as CYP3A4, CYP3A5 and CYP2B6. The main metabolic pathway of OTA includes hydrolysis, which occurs by carbox-ipeptidases enzyme and results in ochratoxin-α (OTα) during cleavage of the peptide bond (Ringot et al., 2006; Wu et al., 2011). OTα, a metabolite with lower toxicity then OTA, was found in animals and humans (Wu et al., 2011). OTA may be hydroxylated by CYPs or per-oxidases to form 4-(R)-hydroxyochratoxin A (4-OH-OTA) in humans and rats, 4-(S)-hydroxyochratoxin A in pigs and 10-hydroxyochratoxin A in rabbits (Wu et al., 2011). OTC has analogous toxicity as OTA since it can be converted to OTA in the body (Wu et al., 2011). In addition, lactone opened OTA (OP-OTA) is produced through lactone hydrolysis of OTA in rats and is highly toxic. The loss of chlorine at C5 position of OTA yields OTB that is further transformed to 4-OH-OTB and ochra-toxin-β (OTβ). OTα and OTβ are less toxic metabolites than the parent compound or OP-OTA metabolite. Nonetheless, OTA can be deactivated through sulphate and glutathione conjugation, which will lead to their secretion (Ringot et al., 2006; Wu et al., 2011). Recent studies de-monstrated that ß-glucuronidase/arylsulfatase enzymatic hydrolysis of phase II metabolites returned significantly higher values for OTα in urine samples indicating that glucuronidation, and possibly sulfation, is involved in the detoxification process of OTα (Duarte et al., 2011; Klapec et al., 2012; Munoz et al., 2017).

Thus currently used biomarkers of human Ochratoxin A exposure are OTA, OTα, OTβ and 4-OH-OTA. OTA can be detected in human plasma, serum and urine (Assaf et al., 2004; Karima et al., 2010). Re-cent study assessed the infant exposure to OTA by determining the concentration of OTA in maternal plasma, breast milk and infants' urine samples. All maternal plasma samples analyzed in the period of 2 weeks–4 months of breastfeeding period were positive for OTA with concentrations that ranged between 0.072 and 0.573 ng/ml. The average concentration that was found in breast milk and infants' urine was several times lower than OTA concentration in plasma samples with average values at 4 months of breastfeeding period 0.030 ng/mL and 0.036 ng/mL, respectively (Munoz et al., 2014). Another pilot study, conducted in Belgium, analyzed OTA and 4-OH OTA in 40 human urine samples and identified the presence of both compounds in only one sample, where the concentration of 4-OH OTA was lower than the LOQ concentration (< 0.24 ng/ml) and OTA concentration was 0.6 ng/mL. Furthermore, three samples contained OTα concentrations 5.1 ng/mL, 7.0 ng/mL and 15 ng/mL (Ediage et al., 2012).

A review by Duarte et al. summarizes the data on the OTA exposure biomarkers (Duarte et al., 2011). In depth discussion on the usefulness or limitations of each in different biological fluids is provided. How-ever, due to the limited information on OTA toxicokinetics further studies are needed to identify reliable and accurate biomarkers of OTA exposure.

2.3. Fumonisins

Fumonisins are produced by diverse fungi species such as *Fusarium verticillioides* and *F. proliferatum* (EFSA, 2005) as well as *A. niger* (Frisvad et al., 2011). Today, 28 fumonisins have been isolated, which are di-vided into four groups, A, B, C and P (Alberts et al., 2016; Rheeder et al., 2002).

The most widespread naturally occurring fumonisins are fumonisin B analogues, which includes FB1, FB2 and FB3. Among these, the most poisonous is FB1 and has been classified as a member of group 2B human carcinogen by IARC (IARC, 2002). FB2 is a deoxy analogue of FB1, is less abundant than FB1 but has important toxicological effect. FB3 and FB4 are present in lower concentrations and have lower tox-icological significance.

Fumonisins are similar to sphingoid bases structure and thus in-terfere with the sphingolipid metabolism (Stockmann-Juvala and Savolainen, 2008; Yazar and Omurtag, 2008). The metabolic route starts with sphinganine formation, followed by acylation to dihy-droceramide and ceramide by the enzyme sphinganine N-acyl-transferase (ceramide synthase) (Stockmann-Juvala and Savolainen, 2008). The FB1 can inhibit ceramide synthase leading to an increase in highly toxic compounds like intracellular sphinganine and other sphingoid bases (Stockmann-Juvala and Savolainen, 2008). This results in increased oxidative stress, impairment of the regulation of the cell cycle, cellular differentiation, apoptosis or necrosis (Stockmann-Juvala and Savolainen, 2008). These impairments can be responsible for fu-monisin-induced toxicity and carcinogenicity. Indeed, studies have proved that FB1 ingestion causes and imbalanced increase in urinary sphinganine (Sa*)* and sphingosine (So) levels in mice and Sa levels in kidneys, liver, and small intestine with consequent increase in the Sa*/* So ratio. Furthermore, the same study demonstrated that FB1 sup-presses ceramide synthase activity in rats (Stockmann-Juvala and Savolainen, 2008). Based on this mechanism of action, the Sa/So ratio is the unique indicator of fumonisin exposure and can serve as a sen-sitive biomarker for both blood and urine (EFSA, 2005). Level of ex-posure to FB1 was also correlated with the changes in Sa 1-phosphate (1-P) and the Sa 1-P/So 1-P ratio (Riley et al., 2015). Fumonisin half-life in human serum is approximately 128 min and can be detected in urine and feces, possibly as a result of secretion or due to partial adsorption (Persson et al., 2012).

Biomarkers of fumonisin in humans were detected in hair, nails, blood serum, urine and stool (Shephard et al., 2007). Urinary bio-markers of fumonisins are FB1, FB2 and FB3. Many studies have sug-gested that the increase of Sa/So ratio in biological fluids and tissue can be used as sensitive biomarkers of fumonisin exposure (EFSA, 2005; Riley et al., 2015; Voss and Riley, 2013). However, one needs also to consider that sphingoid bases naturally occur in blood making this biomarker unreliable for exposure to low levels of FBs (Shephard et al., 2007). Studies in pigs demonstrated high FB stability, low FB absorp-tion and low FB metabolism. The major excretion route for FB is feces where most of the FB is detected in the free form (Souto et al., 2017). Thus feces should be the matrix of choice for the short term exposure. However, as FB1 also accumulates in human hair (Bordin et al., 2015), the selection of hair for the long term exposure studies should be pre-ferred.

2.4. Zearalenone

Zearalenone (ZEN), 6-(10-Hydroxy-6-oxo-trans-1-undecenyl)-beta-resorcylic acid lactone, is produced by different species of *Fusarium*, mainly *F. graminearum* and *F. culmorum* (Bhatnagar et al., 2002) and mostly found in corn and grain crops (García-Cela et al., 2012). ZEN is a non-steroidal estrogenic mycotoxin resembling the structure of 17-β-estradiol, whose biotransformation differs between the fungal species (Binder et al., 2017). The major and the main biologically active and reductive metabolites of ZEN in animals and humans are α-zearalenol (α-ZEL) and β-zearalenol (β-ZEL) (Pfeiffer et al., 2010). The α-ZEL is known as estrogen agonists in mammals. The α-ZEL and β-ZEL meta-bolites are hydroxylated by 3α- or 3 β-hydroxysteroid dehydrogenase (HSD), and conjugated with glucuronic acid by uridine diphosphate glucuronosyltransferase (UDPGT) yielding α and β-zearalenol-14-glu-curonide (α and β-ZEL14GlcA) (Binder et al., 2017; Pfeiffer et al., 2010). ZEN is transformed to zearalenone-14-glucuronide (ZEN14GlcA) by UDPGT enzyme, while zearalenone-14-sulfate (ZEN-14-S) is a bio-conjugated form of ZEN, which was detected in swine urine samples (Binder et al., 2017).

Free ZEN and ZEN metabolites detected in humans are ZEN, α-ZEL, β-ZEL, α-ZAL β-ZAL, ZEN14GlcA. To date, zearalanone (ZAN), a deri-vative of zearalenone that is produced by several species of Fusarium, has not been detected in the human body (Binder et al., 2017; Mally

et al., 2016; Pfeiffer et al., 2010).

The administration studies in studies in pigs showed that ZEN metabolites can mainly be detected 24 and 48 h post administration in urine and feces (Binder et al., 2017). Interestingly some biomonitoring studies in humans that investigated the presence of ZEN and its metabolites did not show the difference in the incidence of target analytes (Shephard et al., 2013; Solfrizzo et al., 2014; Ezekiel et al., 2014) while some showed higher incidence of ZEN compared to its metabolites (Wallin et al., 2015; Sarkanj et al., 2018). Thus the type of sample and the time of collection after exposure is crucial.

2.5. Deoxynivalenol

Deoxynivalenol (DON), that belongs to trichothecene (TC) group of mycotoxins, is widely found in grains such as wheat, corn and barley while it is less present in rice, oats, sorghum and rye (Creppy, 2002). *Fusarium* species, *F. graminearum* and *F. culmorum* are essential in the flora pathogens and are the main source of TC mycotoxins. Among TC mycotoxins, DON, also denoted as vomitoxin, is the most common and has been classified as a group 3 human carcinogen by IARC (Ostry et al., 2017).

The main sites of DON metabolism are liver and intestine. The major metabolic pathway involves conjugation of DON to glucuronic acid and elimination of the bioconjugated form via the urine. The two major metabolites of DON in mammals are DON Glucuronide (DON-GlcA) and de-epoxy deoxynivalenol (DOM-1) (Qing-Hua et al., 2014; Warth et al., 2016; Wu et al., 2014). However, DOM-1 is mostly generated by the intestinal microbiota of mammals, particularly in cattle and is not a major human metabolite (Wu et al., 2014). Free DON and DON-GlcA are the main biomarkers for the assessment of human exposure to DON (Wu et al., 2014). The metabolism of DON in human liver microsomes yields DON-3-Glucuronide (DON-3-GlcA), DON-15-Glucuronide (DON-15-GlcA), DON-7-Glucuronide (DON-7-GlcA) and DON-8-Glucuronide (DON-8-GlcA) (Qing-Hua et al., 2014; Warth et al., 2016; Wu et al., 2014).

Human exposure to DON is monitored by analyzing the free or bioconjugated forms of DON such as DON-GlcA, DON-15-GlcA, DON-3-O-glucoside (DON3GlcA), DON-7-GlcA, DOM-1 (Qing-Hua et al., 2014) and DON-3-GlcA (Qing-Hua et al., 2014; Warth et al., 2016; Wu et al., 2014; Heyndrickx et al., 2015; Sarkanj et al., 2013). Biomonitoring studies in human reported higher incidence of glucuronidated forms of DON in urine, especially DON-15-GlcA, compared to free DON (Abia et a. 2013; Gerding et al., 2014; Heyndrickx et al., 2015; Sarkanj et al., 2013). This was recently validated (Vidal et al., 2018a) and thus DON-3-GlcA and DON-15-GlcA are reliable urine biomarkers of DON exposure.

3. Biomonitoring of human mycotoxin exposure

The aim of the risk assessment is to provide an overview of the potential dangerous exposure to mycotoxin. As previously mentioned, the main cause of contamination with mycotoxin, for humans and animals, is through consumption of contaminated food. In light of that, the strategy of estimation of exposure can be separated in two: (i) *risk assessment of dietary exposure to mycotoxins* – uses statistical data on the food consumption of the population, average body weight of the population and concentration estimation of the contaminant in food products (ii) *risk assessment using biomarker quantification* – uses the excreted levels of the contaminant in urine or the level of the contaminant in blood and aims to estimate the intake level. Several possible sources of uncertainty can affect the estimation of the actual intake of mycotoxin and consequently can lead to erroneous risk assessment. For the first strategy, dietary exposure risk assessment, the uncertainties can occur due to inaccurate consumption recall, and often, snack foods – a potential source of contamination – are not declared. In the case of the former strategy, if only a low fraction of the mycotoxin is excreted through urine then the estimation will be erroneous (IARC, 2012). Furthermore, a selection of matrix is crucial, as consumption of contaminated food may have strong correlation with the biomarkers in one matrix compared to the other (Gilbert et al., 2001). The second approach of risk assessment can lead to bias when biomarker in biofluid does not correlate well with exposure. This correlation depends on multiple factors such as the type of the sampled biofluid, the applied sensitivity of the analytical method to quantify mycotoxin, the pharmacokinetic of the mycotoxin, time elapsed between exposure and body fluid sampling, which parameters are often not available in biomarker based exposure studies.

Molecular biomarkers of mycotoxins such as mycotoxin metabolites or mycotoxin bioconjugated forms are used to measure human exposure and were used to assess the relationship between mycotoxin exposure and development of disease (Sangare-Tigori et al., 2006; Grosso et al., 2003; Hassen et al., 2004; Zaied et al., 2011; Domijan et al., 2009; Ozcelik et al., 2001; Brewer et al., 2013).

3.1. Risk assessment of dietary exposure to mycotoxins

Human exposure to mycotoxin should be monitored with accurate analytical approaches that enable quantification of a wide range of mycotoxins. Several international organizations such as JECFA (Joint Expert Committee on Food Additives), FAO/WHO and European Commission have outlined hazardous limits for the level of mycotoxins in human food and animal feed expressed as tolerable daily intake (TDI) and tolerable weekly intake (TWI). On the other hand, there are some countries that have no monitoring limits of mycotoxin in foodstuff such as South Korea, Mexico and Pakistan. Mycotoxin exposure levels in dietary intake can be calculated via Estimated Daily/Weekly Intake (EDI, EWI) exposure levels (Adhikari et al., 2017). The national regulations in some cases may be different from the toxicity levels determined by WHO. More specifically, India has a limit of mycotoxin based on Food Safety and Standards Authority of India (FSSAI).

$$EDI\,(g/kgbw/day) = \sum_{i=1}^{n} \frac{Amount \times \overline{Rt}}{Body\,Weight} \tag{1}$$

Here, EDI is estimated as a daily intake in g/kg body weight/day for all food type consumed, *Amount* signifies the quantity of one particular type of food, index *i* takes values between 1 and *n*, where *n* defines the number of consumed food type, $\overline{Rt}$ is the concentration of a specific mycotoxin ingested from one particular type of food.

Table 1
Tolerable daily/weekly intake of mycotoxin in human body determined by the different food safety/control authorities.

Mycotoxin	Tolerable Daily intake (TDI)	Reference
Aflatoxin	< 1 ng/kg of body weight	Leblanc et al. (2005)
Fumonisins B1, B2 and B3	Maximum TDI is 2 μg/kg	WHO (2002)
Ochratoxin A	TDI is 14 ng/kg bw	(WHO, 2002)
	Tolerable weekly intake (TWI) is 100 ng/kg of body weight	
Zearalenone	TDI is 0.25 μg/kg body weight per day	EFSA (2014)
Deoxynivalenol	Maximum TDI is 1 μg/kg of body weight. This value was extended to its acetyl derivatives and 15-acetyl-DON by JECFA.	(WHO,SCF, 2002) (JECFA 2010)

FAO/WHO and EFSA have determined hazardous quotient for the daily and weekly consumption of several mycotoxins. Table 1 includes TDI and TWI for the major mycotoxins described previously in section 2. Due to the lack of data on DON and DON metabolites absorption and toxicity the regulatory limits have not been set yet, although they are considered by EFSA (EFSA, 2013).

For aflatoxins, a small amount detected, such as 1 ng/kg or even less, is considered to exceed the TDI, as this compound is categorized as class 1 carcinogen (Bennett and Klich, 2003; Leblanc et al., 2005; Oyedele et al., 2017; Raad et al., 2014; Van de Perre et al., 2015). Moreover, aflatoxin amounts that are tolerable for adults can be fatal for children (Williams et al., 2004).

The risk assessment in case of AB1 is typically based on the margin of exposure (i.e. MoE). MoE is the ratio between the no-observed-effect-level (NOEL) and EDI previously described. Alternatively, MoE can be calculated using benchmark dose lower confidence limit, i.e. BMDL1,BMDL05 or BMDL10, obtained from animal studies, divided by EDI. Here, subscript 1, 5 and 10 represent the percentage of the confidence level of the dose response curve. In other words, MoE indicates how large is a "safe level" (i.e. a level at which cancer did not occur) of a carcinogenic compound, with respect to the estimated intake of the carcinogen (EFSA, 2007). The larger is the MoE, the lower is the risk. Benford et al., (2010) used the dose response curve from the study of Wogan et al., (1974) to assess the risk of dietary exposure to Aflatoxin (Benford et al., 2010; Wogan et al., 1974). The levels of MoE beyond which the risk is insignificant, are still a matter of debate. However, a widely accepted value is 10.000 (Nugraha et al., 2018).

It has been suggested by Codex Committee that the maximum concentration for AFM1 are 0.05 and 0.5 μg/kg for additives and contaminants of food respectively, since at this concentration, the risk of carcinogenic potential would be very low (WHO, 2002). The assessment of the risk exposure consists of calculation of EDI or EWI (eq. (1)) and comparison with TDI or TWI respectively. In analytical studies of mycotoxin exposure, EDI is calculated for recruited population and compared to TDI/TWI to determine, which mycotoxin exceeds the established limit of TDI and TWI (Gerding et al., 2014).

Alternatively, Tresou and colleagues (Tressou et al., 2004) expressed the probability ($r(d)$) of exceeding a specific hazardous quotient (i.e. TDI or TWI) as follows:

$$r(d) = \frac{n(K_i \geq d)}{N} \tag{2}$$

In equation (2), d represents TDI or TWI, depending on the study; $n(K_i \geq d)$ is the number of food sources (e.g. food types) that has exceeded the toxicity limit, N is the total number of food intake sources for a person. To exemplify, if from 3 different types of food that a person consumes, 2 exceeded TDI for Ochratoxin, then the probability to have a high exposure risk to Ochratoxin is $r\left(EDI > 2000 \, ^{ng}/_{kg \, bw}\right) = \frac{2}{3}$.

3.2. Risk assessment using biomarker quantification

The study made by Solfrizo and co-workers estimates the so-called Probable Daily Intake (PDI) using the following expression:

$$PDI = C \cdot \frac{V}{W} \cdot \frac{100}{E} \tag{3}$$

where C, in the above equation, is the concentration of the mycotoxin biomarker in urine, V is the mean of the urine volume excreted in 24 h, W is mean human body weight and E is the mean urinary excretion of mycotoxin in 24 h post intake.

The main difference between EDI and PDI is that the latter is based on the measurements of the concentration of the biomarkers linked to mycotoxins and represents the value which is used to provide an approximate estimation of the level of consumption. Further, PDI is often compared with TDI to estimate the potential risk of exposure of the

subject to the mycotoxins. More specifically, if PDI exceeded TDI, further enquiries must be made in order to establish the source of contamination.

The daily intake of OTA can be estimated from plasma analysis using Klassen equation as demonstrated in two recent studies (Miraglia et al., 1996; Woo and El-Nezami, 2016):

$$k_0 = Cl_{renal} \cdot \frac{C_p}{A} \tag{4}$$

Here, k_0 is the estimated daily intake of OTA (ng/kg bw/day), C_p is the concentration of OTA in plasma (ng/mL), while A represents the bioavailability of the toxin, Cl_{renal} is the renal daily clearance (mL/kg bw/day). Commonly used values for renal clearance are 0.67 (Hagelberg et al., 1989), which is derived from the clearance of insulin or 0.99, which is a value determined based on a single human experiment using OTA kinetics (Miraglia et al., 1996; Schlatter et al., 1996).

Numerous studies worldwide have evaluated human exposure to mycotoxins. In this review, we discuss chronic exposure to mycotoxins based on previous studies that targeted small cohorts of a healthy population of different age groups.

3.3. Mycotoxin biomonitoring studies in Africa

In the last 18 years, twenty studies assessed the occurrence of aflatoxin, fumonisin, ochratoxin, zearalenone and deoxynivalenol biomarkers in human biological fluids in African countries (Table 2). Most of the biomonitoring studies originate from Tunisia and Nigeria in that period. Although studies covered the research of the presence of mycotoxin biomarkers in urine, blood, blood components and maternal breast milk were the most commonly investigated matrix. Even though the cohort of the majority of the studies were healthy adults, a significant number of studies focused on the incidence of mycotoxin biomarkers in children and patients.

Studies performed in Ghana, Guinea, Tanzania and Nigeria have shown that more than 60% of children are exposed to aflatoxin (Jolly et al., 2006; Polychronaki et al., 2008; Chen et al., 2018; McMillan et al., 2018; Shirima et al., 2013; Sarkanj et al., 2018). The children in Tanzania were found to be mainly exposed to fumonisin with more than 80% of positive samples (Chen et al., 2018; Shirima et al., 2013) compared samples collected and measured in Cameron (Njumbe Ediage et al., 2013) and Nigeria (Ezekiel et al., 2014), where less than 15% samples were positive for either FB1 or FB2. The presence of aflatoxins or fumonisins in children samples raised particular health concerns as many studies detected high concentration of aflatoxin in urine, blood, stool, liver, lungs and brain of kwashiorkor in children. This disease causes uncontrolled behavior, pneumonia and may lead to death (Cherkani-Hassani et al., 2016; Peraica et al., 1999). Furthermore, one third of children urine samples were positive for OTA while the presence of DON and ZEN biomarkers of exposure was found in less than 18% and 10% of the analyzed samples, respectively (Ezekiel et al., 2014; Njumbe Ediage et al., 2013).

Based on the studies covered with this survey, more than half of the mothers in Africa with young children are exposed to aflatoxins, which is class I carcinogens. Namely, a high incidence of aflatoxin biomarker AFM1 was found in 54% and 82% of the maternal breast milk in mothers originating from Sudan and Nigeria, respectively (Adejumo et al., 2013; Elzupir et al., 2012). Furthermore, all analyzed samples from Kenya women showed the presence of AFB1-lysine conjugate (Leroy et al., 2015). The high level of aflatoxins in maternal breast milk present a serious threat to infants. Indeed, the mean concentration of AFM1in urine was higher in partially weaned infants than fully weaned infants in Cameron, which may indicate the transfer of AFM1 from the mother's milk to the child (Njumbe Ediage et al., 2013).

In Tunisia, the OTA levels have been assessed in different geographical areas in healthy volunteers and patients with diseased of Nephropathy (Grosso et al., 2003; Hassen et al., 2004; Karima et al.,

Table 2
Summary of studies measuring mycotoxin levels in human samples from Africa.

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/ LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
Cameroon	Children (1–5yrs) Urine	220	14	AFM1 (0.01/n.s.)	0.33 (0.06–4.7)*	LC-MS/MS (SPE)	Njumbe Ediage et al., (2013) (ᶜ)
			32	OTA (0.03/n.s.)	0.20 (0.04–2.4)*		
			17	DON (0.04/n.s.)	2.22 (0.1–77)*		
			11	FB1 (0.01/n.s.)	2.96 (0.06–48)*		
			4	ZEN (0.1/n.s.)	0.97 (0.64–5.0)*		
			8	β-ZOL (0.01/n.s.)	1.52 (0.02–12.5)*		
			4	α-ZOL (0.31/n.s.)	0.98 (0.26–1.3)*		
Cameroon	Adults (18–58 yrs) HIV sero-positive Urine	145	10	AFM1 (0.05/0.17)	0.05 (< LOQ -1.38)	LC-MS/MS	Abia et al. (2013)
			3	FB1 (0.5/1.7)	0.63 (< LOQ-14.8)		
			1	FB2 (0.5/1.7)	< LOQ (n.a.)		
			17	OTA (0.05/0.17)	0.08 (< LOQ-1.87)		
			6	DON (4/13)	< LOQ (n.a.)		
			43	DON-15-GlcA (3/11)	5.49 (< LOQ-96.2)		
			11	DON-3-GlcA (6/20)	3.93 (< LOQ-22.5)		
			3	ZEN (0.4/1.3)	0.22 (< LOQ-1.42)		
			3	ZEN-14-GlcA (1/3.3)	0.81 (3.38–31)		
			1	α-ZEL (0.5/1.7)	< LOQ (n.a.)		
Egypt	Children (1–2.5yrs) Urine	50	2	AFB1 (0.025/n.s.)	0.189 (n.a.)	HPLC-FLUO (IAC)	Polychronaki et al., (2008)
			10	AFB2 (0.00035/n.s.)	0.0014 (n.d.-2.2)		
			4	AFG1 (0.05/n.s.)	0.0766 (n.d.-0.0811)		
			24	AFG2 (0.0008/n.s.)	0.0022 (n.d.-0.008)		
			8	AFM1 (0.005/n.s.)	0.0055 (n.d.-0.0062)		
Egypt	Pregnant women Serum	98	82	OTA (0.2/0.2)	0.26 (0.20–1.53)	HPLC-FLUO (SPE)	Woo et al. (2016)
Ghana	Adults (19- > 70yrs)						Jolly et al. (2006).
	Plasma	140	100	AFB1 (0.01 pmol/mg ALB/n.s.)	0.89 (0.12–3 pmol/mg ALB)	RIA	
	Urine	91	91.2	AFM1 (0.01/n.s.)	1800.14 (n.d.-11562.36 pg/ mg CRN)	HPLC-FLUO (IAC)	
Guinea	Children (2–4yrs) Urine	50	16	AFB1 (0.025/n.s.)	2.682 (n.d.-18)	HPLC-FLUO (IAC)	Polychronaki et al., 2008
			58	AFB2 (0.00035/n.s.)	0.0057 (n.d.-0.043)		
			2	AFG1 (0.05/n.s.)	0.709 (n.a.)		
			36	AFG2 (0.0008/n.s.)	0.019 (n.d.-0.199)		
			64	AFM1 (0.005/n.s.)	0.097 (n.d.-0.801)		
Ivory Coast	Healthy people			OTA (n.s./n.s.)		HPLC-FLUO (IAC)	Sangare-Tigori et al. (2006)
	Blood	63	43.9		0.83 (0.01–5.81)		
	NEPH patients						
	Blood	39	20.5		1.05 (0.167–2.42)		
Kenya	Women Serum	844	100	AFB1-lysine (0.2 pg/ mg ALB/n.s.)	7.82 (6.04–8.90)* pg/mg ALB	HPLC-FLUO (SPE)	Leroy et al. (2015)
Morocco	Adults plasma	309	60	OTA (n.s./0.4)	0.29 (0.08–6.59)	HPLC-FLUO	Filali et al. (2002)
Nigeria	Maternal breast milk	50	82	AFM1 (0.01/0.05)	n.s. (0.00349–0.035)	HPLC-FLUO (IAC)	Adejumo et al., (2013) (ᶜ)
Nigeria (North)	Children, adolescents and adults Urine	120	14.2	AFM1 (0.05/0.15)	0.3 (n.d.-1.5)	LC-MS/MS	Ezekiel et al. (2014)
			0.8	DON (4/4)	< LOQ		
			5	DON-15-O-GlcA (4/6)	3.5 (n.d.-8)		
			13.3	FB1 (2/2)	4.6 (n.d.-12.8)		
			1.7	FB2 (2/0.7)	< LOQ		
			28.3	OTA (0.05/0.15)	0.2 (n.d.-06)		
			0.8	ZEN (0.4/0.6)	< LOQ		
			6.7	ZEN-14-GLcA (1/1)	9.5 (n.d.-44.5)		
Nigeria	Children (6–48 mos) Plasma	58	100	AFB1-lysine (0.022/ 0.022)	2.6 (0.2–59.2 pg/mg ALB)	LC-MS/MS	McMillan et al. (2018)
Nigeria (North)	Children, adolescents and adults Urine	120	72.5	AFM1 (0.0003/0.001)	0.04 (0.001–0.62)	LC-MS/MS (SPE)	Sarkanj et al., (2018) (ᶜ)
			19.2	DON (0.05/0.15)	2.37 (0.08–6.22)		
			70.8	FB1 (0.001/0.01)	1.09 (0.08–14.88)		
			78.3	OTA (0.0003/0.001)	0.05 (0.003–0.31)		
			81.7	ZEN (0.001/0.003)	0.75 (0.03–19.99)		
			4.2	α-ZEL (0.003/0.01)	1.27 (0.52–2.52)		
			5.8	β-ZEL (0.001/0.003)	0.88 (0.06–2.74)		

Table 2 (*continued*)

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/ LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
South Africa	Females (19–97 yrs)	54	87	FB1 (0.01/0.02)	0.342 (0.007–2.27 ng/mg CRN)	Single biomarker LC-MS/MS (SPE & IMA)	Shephard et al., (2013) [c]
	Urine		100	DON (0.25/0.5)	20.4 (0.445–353 ng/mg CRN)		
			96	FB1 (0.04/0.12)	1.52 (0.026–9.99 ng/mg CRN)	Multiple biomarker LC-MS/MS (IMA & SPE)	
			87	DON (0.45/1.51)	11.3 (0.312–190 ng/mg CRN)		
			92	α-ZEL (0.009/0.029)	0.614 (0.006–13.2 ng/mg CRN)		
			75	β-ZEL (0.016/0.054)	0.702 (0.010–21.1 ng/mg CRN)		
			100	ZEN (0.002/0.007)	0.529 (0.012–11.2 ng/mg CRN)		
			98	OTA (0.002/0.007)	0.041 (0.001–0.629 ng/mg CRN)		
			0	AFM1 (0.01/0.02)	n.a.		
			59	FB1 (0.1/0.3)	n.s. (n.d.-2.59 ng/mg CRN)	LC-MS/MS	
			13	DON (4/13)	n.s. (n.d.-21.3 ng/mg CRN)		
			26	DON-3-GlcA (6/20)	< LOQ		
			55	DON-3-GlcA (3/11)	n.s. (n.d.-109 ng/mg CRN)		
Sudan	Maternal breast milk	94	54.25	AFM1 (0.013/n.s.)	0.401 (0.007–2.561) ng/g	HPLC-FLUO	Elzupir et al., (2012) [c]
Tanzania	Children (12–22 mos)						Shirima et al. (2013)
	Plasma	146	84	AF-alb (3 pg/mg ALB/ n.s.)	12.9 (9.9–16.7)* pg/mg	ELISA	
	Urine	147	96	FB1 (0.02/n.s.)	167.3 (135.4–206.7)* pg/ mg	HPLC/MS (SPE)	
Tanzania	Children (24 mos)						Chen et al. (2018)
	Plasma	60	72	AFB1-lysine (0.4 pg/ mg ALB)	5.1 (0.28–25.1) pg/mg ALB	LC-MS/MS (SPE)	
	Children (24 & 36 mos)						
	Urine	94	80	FB1 (0.01/n.s.)	1.3 (<LOD-16.6)	LC/MS (SPE)	
Tunisia (SouthEast)	Non-NEPH patients		100	OTA (n.s./0.1)		HPLC-FLUO (IAC)	Grosso et al., (2003) [c]
	serum	62			0.53 (0.12–8.06)		
	NEPH patients (wo BT)						
	serum	26			1.116 (< LOQ-5.80)		
	NEPH patients (with BT)						
	serum	21			0.339 (< LOQ-0.74)		
Tunisia	1st study CIN patients[a]			OTA (n.s./n.s.)		HPLC-FLUO (SPE)	Hassen et al. (2004)
	Blood	20	93		44.4 (17.4–140.5)		
	1st study CIN patients[b]						
	Blood	40	83		8.11 (n.d.-73.19)		
	1st study Healthy people						
	Blood	20	71		2.6 (n.d.-7.5)		
	2nd study CIN patients[a]						
	Blood	20	100		50.4 (18.4–171.25)		
	2nd study CIN patients[b]						
	Blood	20	78		12.36 (1.68–29)		
	2nd study Healthy people						
	Blood	20	62		1.22 (n.d.-3.2)		
Tunisia	Adults (20–84 yrs) Serum	107	28	OTA (0.5/2)	0.49 (n.d.-3.43)	HPLC-FLUO (SPE)	Karima et al., (2010) [c]
Tunisia	Adults (17–75 yrs)			OTA (0.05/0.15)		HPLC-FLUO	Zaied et al., 2011 [c]
	Serum	138	49		3.3 (1.7–8.5)		
	NEPH patients (18–88 yrs)						
	Serum	270	76		18 (1.8–65)		

ALB - albumin; BT - bladder tumor; CRN - creatinine; IMA - multiantibody cleanup; NEPH - Nephropathy; RIA - radioimmunoassay; mos – months; yrs – years; n.a. – not applicable; n.s. – not specified.

[a] Chronic interstitial nephropathy patients of unknown etiology.

[b] Chronic interstitial nephropathy patients of known etiology.

[c] Validated method.

2010; Zaied et al., 2011). Majority of the samples analyzed in Tunisia were positive for OTA, however the OTA levels were significantly higher in the nephropathy patients without bladder tumor (Grosso et al., 2003) and chronic interstitial nephropathy patients of known etiology (Hassen et al., 2004). Indeed, the high levels of OTA in Tunisia have already been associated with chronic nephritic disease in this area at the end of the last century (Maaroufi et al., 1995). High levels of OTA (7.8 and 11.76 ng/ml) were also reported in two samples of healthy adults, compared to the mean OTA concentration of the rest of the samples (0.49 ± 0.04 ng/mL). Interestingly, higher incidence of OTA was observed in the healthy population (44%, range 0.01–5.81 ng/mL) compared to the nephropathy patients (20%, range 0.17–2.42 ng/mL) living in Ivory Coast (Sangare-Tigori et al., 2006). A similar amount of OTA was also reported for the healthy population of Morocco (Filali et al., 2002) where 60% of analyzed samples were positive for OTA.

OTA has also been analyzed in 98 serum samples from Egyptian pregnant women. EDI for pregnant women was calculated based on the serum OTA level by using the Klaassen equation and the EDI for fetal exposure was evaluated based on maternal data (Woo and El-Nezami, 2016). However, the highest exposure of OTA in pregnant women was 3.26 ng/kg BW/day, which is lower than the estimated daily intake for Negligible Cancer Risk Intake (NCRI, 3.38 ng/kg BW/day) while the highest exposure group of OTA for fetal exposure was nearly double the NCRI number and the margin of exposure (MOE) is $2.5 \cdot 10^3$. The OTA concentration in pregnant women was in the range of 0.20–1.53 ng/ml and the estimated OTA range in fetus was 0.40–3.06 ng/ml. For this reason, essential solutions to reduce the risk of mycotoxin contamination are recommended e.g. by monitoring food mycotoxin contamination and removing food with high mycotoxin concentration from the food market in Egypt (Woo and El-Nezami, 2016). A South African study examined the exposures of farmers to mycotoxins with the occurrence of esophageal cancer (Shephard et al., 2013). In this area, 90% of the population consumes maize daily. Therefore, the study involved collection of raw and cooked maize samples to measure contamination level of mycotoxin in food samples and in urine samples of 54 female individuals. Urine samples have been analyzed by single and multi-biomarker detection as shown in Table 4. The mycotoxins ZEN, DON, FB1 and FB2 were positively identified in 90% of the samples, which may have originated from maize. OTA however, although not detected in maize samples, it was detected in urine samples with the mean urinary level for OTA of 0.024 ng/ml. Furthermore, the concentration of FB1 was high in urine, indicating considerable exposure of the population to FB1.

In northern Nigeria, Ezekiel and coworkers have assessed mycotoxin exposure in rural areas from different age groups (19 children, 20 adolescents, and 81 adults). Population of Nigeria rely significantly on crops such as groundnuts, maize, sorghum and millet. For this reason, besides urine samples, samples from consumed meals have been collected and analyzed to assess mycotoxins exposure and to identify the source of human intoxication (Ezekiel et al., 2014). Mycotoxins were detected in all measured human samples grouped by age yielding 50.8% positive detection rate. However, OTA had the highest incidence, affecting 28.3% of the subjects with a mean concentration of 0.2 ng/ml followed by AFM1 and FB1 with a mean concentration of 0.3 ng/ml and 0.6 ng/ml respectively. Aflatoxins and FB1 (both potent carcinogens) were detected in most of the samples which may consequently lead to considerable health risk (Ezekiel et al., 2014), and must be communicated in order to raise awareness among consumers and health authorities. Reanalysis of the same samples by the improved mycotoxin detection method showed the presence of mycotoxin biomarkers in all samples, and the co-occurrence of AFM1 and FB1 in 57% of samples analyzed (Sarkanj et al., 2018).

A study in Cameroon explored the presence of mycotoxin biomarkers in HIV-sera positive samples (Abia et al., 2013). Among all the biomarkers analyzed, aflatoxins, fumonisin, ochratoxin, ZEN and DON metabolites, majority of the samples (> 60%) showed the presence of DON biomarkers of exposure, followed by the presence of OTA (25%) and AFM1 (15%), while ZEN and fumonisin biomarkers were found in less than 6% of the samples.

3.4. Mycotoxin biomonitoring studies in Europe

A total of 42 studies on biomonitoring of mycotoxin exposure in Europe, conducted since 2001, have been included in this survey (Table 3). Among all countries, the highest number of studies originate from Portugal, followed by Germany, Turkey and Italy. The most commonly investigated human sample type in European studies was urine, while similar number of studies was performed on maternal breast milk and blood and blood components. The cohort of majority studies were healthy adults, while less than 10% of the studies focused on the incidence of mycotoxin biomarkers in children and patients with disease endemic NEPH and urinary disorders.

A recent study from Belgium reported the presence of DON biomarkers in all children urine samples, while OTA was present in half of the samples (Heyndrickx et al., 2015). The BIOMYCO study aimed to detect 33 potential biomarkers and metabolites of multiple mycotoxins including aflatoxins, OTA, fumonisins, TCs, zearalenone and DON (Heyndrickx et al., 2015). In this study, urine samples of 155 children and 239 adults were analyzed. Only 9 out of 33 biomarkers were detected in the analyzed samples as shown in Table 3. OTA was detected in most of the samples from the Belgian population. Furthermore, 100% of samples contained DON15GlcA with the highest mean concentration of 58.4 ng/ml and 53.8 ng/ml for children and adults respectively. It is worth mentioning that OTA levels were almost 3 times higher in children compared to the adults (Heyndrickx et al., 2015). High incidence of OTA was also observed in 93% and 100% of children samples from Poland (Postupolski et al., 2006) and from the south of Italy (Solfrizzo et al., 2014) respectively. Interestingly, the study from Poland showed that although OTA was detected in all serum samples from nursing mothers less than a quarter of maternal breast milk samples were positive (Postupolski et al., 2006). A significant incidence (above 60%) of OTA and its biomarkers in biological fluids such as milk, plasma, serum and urine was reported in most of the studies originating from Bulgaria (Petkova-Bocharova et al., 2003), Czech Republic (Dohnal et al., 2013; Ostry et al., 2005), Italy (Biasucci et al., 2011; Galvano et al., 2008), Germany (Ali et al., 2017b; Munoz et al., 2010; Follmann et al., 2016), Hungary (Fazekas et al., 2005), Portugal (Duarte et al. 2009, 2010, 2012; Lino et al., 2008; Pena et al., 2006), Spain (Coronel et al., 2011; Manique et al., 2008),Turkey (Akdemir et al., 2010; Erkekoglu et al., 2010) and UK (Gilbert et al., 2001). Contrary, lower incidence of the same mycotoxin was reported for Croatia (Domijan et al., 2009; Sarkanj et al., 2013), Germany (Gerding et al., 2015), Norway (Skaug et al., 2001), Slovakia (Dostal et al., 2008) and Sweden (Wallin et al., 2015).

The study of Lino et al., (2008) examined OTA level in serum from an urban and rural population in three regions of Portugal and correlated the results of OTA levels in serum with those in whole blood samples. The ratio of serum/blood was 2.0 ± 0.7 which is in agreement with a previous study (Lino et al., 2008). However, OTA was detected in all serum samples within the range of 0.14–2.49 ng/ml. The EDI levels in this study were 0.19–3.35 ng/kg bw, which do not exceed the estimated TDI of 5 ng/kg bw set by the Scientific Committee on Foods (SFC) of the European Union in 2002. Interestingly, the OTA level in rural adult male serum samples was significantly higher than in adult females. A study from southern Italy, found mycotoxin biomarkers in the samples from all the participants (Solfrizzo et al., 2014). OTA, ZEA and α-ZEL were present in all urine samples, while the incidence rates for β-ZEL, DON, FB1 and AFM1 were present in 98%, 96%, 56% and 6% of samples respectively (Solfrizzo, 2014). The mean concentration of DON was the highest compared to other mycotoxins (11.89 ng/ml) and detected in 96% of the samples with 40% of the samples exceeding TDI for DON. PDI levels exceeded TDI level for DON. OTA was considerably greater than TDI in 94% of the urine samples,

Table 3

Summary of studies measuring mycotoxin levels in human samples from Europe.

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/ LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
Austria	Adults (20–60yrs) Urine	27	22	DON (4/13.4)	n.a. (n.d.- < LOQ)	LC-MS/MS	Warth et al. (2012)
			56	DON-3-GlcA (6/20)	n.a. (n.d.-13)		
			96	DON-15-GlcA (3.2/ 10.6)	n.s. (n.d.-43)		
Belgium	Children (3–12 yrs) Urine	155	70	DON (0.2/n.s.)	5.2 (0.5–32.5)	LC-MS/MS	Heyndrickx et al., (2015) ([b])
			91	DON-3-GlcA (0.2/n.s.)	10.6 (0.7–43)		
			100	DON-15-GlcA (0.2/ n.s.)	58.4 (4.3–343)		
			17	DOM-GlcA (0.2/n.s.)	91.7 (1.1–526.1)		
			51	OTA (0.001/n.s.)	0.0795 (0.0038–3.683)		
			n.d.	α-ZEL (0.061/n.s.)	n.d (n.a.)		
			n.d.	β-ZEL14GlcA (0.117/ n.s.)	n.d (n.a.)		
	Adults (19–65 yrs) Urine	239	37	DON (0.2/n.s.)	3.9 (0.5–129.8)		
			77	DON-3-GlcA (0.2/n.s.)	7.5 (0.5–126.2)		
			100	DON-15-GlcA (0.2/ n.s.)	53.8 (1.1–460.8)		
			22	DOM-GlcA (0.2/n.s.)	16.9 (0.6–172)		
			35	OTA (0.001/n.s.)	0.0278 (0.0027–0.3681)		
			0.4	α-ZEL (0.061/n.s.)	5 (5–5)		
			0.8	β-ZEL14GlcA (0.117/ n.s.)	0.8 (0.6–1)		
Bulgaria	Adults (20–30yrs) Serum Urine	16		OTA serum (n.s./0.1)		HPLC (IAC)	Petkova-Bocharova et al., (2003) ([b])
			100	OTA urine (n.s./4)	0.00159 (0.0001–0.0109)		
			95		0.0508 to 0.16864 (0.01–1.91)		
Croatia	Area of residence			OTA (0.005/n.s.)		HPLC-FLUO (IAC)	Domijan et al., (2009) ([b])
	Endemic NEPH	45 (2000[a])	43		0.007 (0.005–0.086)		
	Urine	45 (2005[a])	18		0.001 (0.005–0.015)		
	Control	18 (2000[a])	28		0.003 (0.005–0.02)		
	Urine	18 (2005[a])	6		0.005 (0.01)		
Croatia	Pregnant women (26–33 yrs)	40	76	DON (4/13)	18.3 (4–275)	LC–MS/MS	Sarkanj et al. (2013)
	Urine		98	DON-15-GlcA (3/11)	120.4 (3–1237.7)		
			83	DON-3-GlcA (6/20)	28.8 (6–298.1)		
			10	OTA (0.05/0.17)	< LOQ		
Czech Republic	Healthy volunteers						Ostry et al., (2005) ([b])
	Urine	100 (1997[a])	72	AFM1 (n.s./0.000125)	367 (19–6064) pg/g CRN	ELISA (IAC)	
		105 (1998[a])	46		414 (21–19219) pg/g CRN		
	Serum	2206	94.2	OTA (n.s./0.1)	0.28 (0.1–13.7)	HPLC-FLUO	
Czech Republic	Females (19–40yrs)	115	100	OTA (n.s./0.05)		ELISA	Dohnal et al., (2013) ([b])
	Serum				0.135 (n.d.-1.073)	HPLC-FLUO (IAC)	
					0.140 (0.050–1.130)		
Italy	Maternal breast milk	82	5	AFM1 (0.003/0.007)	0.05535 (< 0.007–0.14)	HPLC (IAC)	Galvano et al., (2008) ([b])
			74	OTA (0.002/0.005)	0.03043 (< 0.005–0.405)		
Italy	Nursing mothers	130		OTA milk (0.0005/ 0.001)			Biasucci et al., 2011 ([b])
	Maternal breast milk		78.8		0.01 (0.0011- > 0.0751)	HPLC-FLUO (IAC)	
	Serum		99.2	OTA serum (0.025/ 0.05)	0.4998 (0.084–4.835)		
Italy (South)	Children and Adults (3–85 yrs)	52	6	AFM1 (n.s./0.02)	0.068 (Max 0.146)	UPLC-MS/MS	Solfrizzo et al., (2014) ([b])
	Urine		100	OTA (n.s./0.006)	0.144 (Max 2.129)		
			96	DON (n.s./1.5)	11.89 (Max 67.36)		
			56	FB1 (n.s./0.01)	0.055 (Max 0.352)		
			98	β-ZEL (n.s./0.054)	0.09 (Max 0.135)		
			100	α-ZEL (n.s./0.03)	0.077 (Max 0.176)		
			100	ZEN (n.s./0.007)	0.057 (Max 0.120)		
Germany	Adults (20–57yrs)	13	100			HPLC-FLUO (IAC)	Munoz et al., (2010) ([b])
	Urine			OTA (0.02/0.05)	0.07 (0.02–0-14)		
				OT α (0.02/0.05)	2.88 (0.49–7.12)		
	Plasma			OTA (0.07/0.1)	0.25 (0.19–0.29)		
				OT α (0.07/0.1)	0.95 (0.07–1.64)		
Germany	Adults (19–65 yrs)		29.41	DON (0.5/2)	3.38 (2.48–17.34)	LC-MS/MS	Gerding et al., (2014) ([b])
	Urine	101	82.35	DON-3-GlcA (2/4)	12.21 (4.37–92.95)		
			3.96	ZEN-14-GlcA (0.75/ 1.5)	< LOQ		
Germany	Adults	50	8	DON (1/4)	2.0 (< LOQ)	LC-MS/MS	Gerding et al., (2015) ([b])
	Urine		27	DON-GlcA (1/4)	11.2 (< LOQ-60.9)		
			15	OTA (0.01/0.075)	0.040 (< LOQ-0.082)		
			0	AFM1 (0.025/0.1)	n.d.		
			0	FB1 (0.0125/0.1)	n.d.		
			0	α-ZAL (0.125/0.25)	n.d.		

(*continued on next page*)

Table 3 (*continued*)

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
Germany	Controls adult males Urine	13	100	DON (0.15/0.300)	6.850 (1.013–14.634)	LC-MS/MS (IAC) HPLC-FLUO (for OTs)	Follmann et al., (2016) ([b])
			38	DOM-1 (0.100/0.200)	0.085 (n.d.-0.184)		
			100	ZEN (0.002/0.005)	0.031 (0.007–0.090)		
			46	α-ZEL (0.01/0.025)	0.016 (n.d.-0.075)		
			23	β-ZEL (0.01/0.025)	0.008 (n.d.-0.021)		
			77	OTA (0.01/0.02)	0.066 (n.d.-0.185)		
			62	OTα (0.01/0.02)	0.085 (n.d.-0.194)		
	Mill workers males Urine	12	100	DON (0.15/0.300)	6.500 (3.275–13.820)		
			54	DOM-1 (0.100/0.200)	0.105 (n.d.-0.216)		
			100	ZEN (0.002/0.005)	0.042 (0.004–0.100)		
			33	α-ZEL (0.01/0.025)	0.015 (n.d.-0.040)		
			17	β-ZEL (0.01/0.025)	0.009 (n.d.-0.037)		
			100	OTA (0.01/0.02)	0.110 (0.016–0.228)		
			33	OTα (0.01/0.02)	0.032 (n.d.-0.144)		
Germany	Adults, urine	50	100	DON (0.16/0.3)	9.02 (1.06–38.44)	LC-MS/MS	Ali et al., (2016b) ([b])
			40	DOM-1 (0.1/0.2)	0.21 (n.d.-0.73)		
Germany	Male 30 yrs, plasma	7		OTA (0.05/0.1)	0.42 (0.34–0.58)	HPLC-FLUO	Ali et al., (2017b) ([b])
				OT α (0.05/0.1)	0.45 (0.39–0.52)		
	Male 30 yrs, urine			OTA (0.01/0.02)	0.06 (0.04–0.16)		
				OT α (0.01/0.02)	0.06 (0.02–0.11)		
	Male 60 yrs, plasma	7		OTA (0.05/0.1)	1.64 (1.14–1.97)		
				OT α (0.05/0.1)	0.20 (0.08–0.31)		
	Male 60 yrs, urine			OTA (0.01/0.02)	0.24 (0.06–0.62)		
				OT α (0.01/0.02)	2.22 (0.21–3.78)		
	Adults, urine	50	100	OTA (0.01/0.02)	0.21 (0.02–1.82)		
			78	OT α (0.01/0.02)	1.33 (n.d.-14.25)		
Hungary	Healthy volunteers (8–80 yrs) Urine	88	61	OTA (0.004/0.006)	0.013 (0.006–0.065)	HPLC-FLUO (IAC)	Fazekas et al., (2005) ([b])
Norway	Maternal breast milk	80	21	OTA (0.01/0.01)	0.03 (0.01–0.182)	HPLC-FLUO	Skaug et al. (2001)
Poland	Lactating women Serum	30		OTA serum (0.02/0.06)		HPLC-FLUO (IAC)	Postupolski et al. (2006)
			100	OTA milk (0.005/	1.14 (0.14–3.41)		
	Maternal breast milk Foetal serum		16.6	0.015)	0.0056 (n.d.-0.017)		
			93		1.83 (n.d.-5.42)		
Portugal	Adults (19–82 yrs) Urine	60	70	OTA (n.s./0.02)	0.038 (0.021–0.105)	HPLC-FLUO (IAC)	Pena et al., (2006) ([b])
Portugal	NEPH patients Serum	95	n.s.	OTA (n.s./0.05)	0.49 to 0.50 (0.12–1.52)	HPLC-FLUO (IAC)	Dinis et al., (2007) ([b])
Portugal	Healthy volunteers (15–67 yrs) Urine	30	43.3	OTA (n.s./0.007)	0.019 (0.011–0.208)	HPLC-FLUO (IAC)	Manique et al., (2008) ([b])
Portugal	Adults (19–92 yrs) Serum	104	100	OTA (n.s./0.1)	n.s. (0.14–2.49)	HPLC-FLUO (IAC)	Lino et al., (2008) ([b])
Portugal	Adults (18–75 yrs) Urine	43	72.1	OTA (n.s./0.008)	0.026 (n.d–0.071)	HPLC-FLUO (IAC)	Duarte et al., (2009) ([b])
Portugal	Adults (18–96 yrs) Urine	155	92.2	OTA (n.s./0.008)	0.018 (n.d. − 0.069)	HPLC-FLUO (IAC)	Duarte et al., (2010) ([b])
Portugal	Adults (20–83 yrs) Urine	95	81.1 (summer) 87.4 (winter)	OTA (0.0024/0.008)	0.016 (n.d.-0.040) 0.022 (n.d.-0.071)	HPLC-FLUO (IAC)	Duarte et al., (2012) ([b])
Portugal	Maternal breast milk	67	32.8	AFM1 (0.005/n.s.)	0.0074 (0.0051–0.0106)	ELISA	Bogalho et al. (2018)
Serbia	Maternal breast milk	10	60	AFM1 (0.0015/ 0.005 ng/g)	0.01 (0.006–0.022) ng/g	ELISA	Kos et al., (2014) ([b])
Slovakia	Maternal breast milk	76	30.2	OTA (0.0048/0.0144)	n.s. (n.d.-0.0603)	HPLC-FLUO	Dostal et al., (2008) ([b])
Spain	Adults (18–53 yrs) Urine	31	80.6	OTA (n.s./0.007)	0.032 (0.007–0.124)	HPLC-FLUO (IAC)	Manique et al., (2008) ([b])
Spain	Adults (18–45 yrs) Urine	72				HPLC-FLUO	Coronel et al., (2011) ([b])
			12.5	OTA (0.034/0.112)	0.237 (0.057–0.562)		
			61.1	OTα (0.023/0.076)	0.441 (0.056–2.894)		
Sweden	Adults Urine	252	63	DON (n.s./0.2)	3.37 (n.s.)	LC-MS/MS (IAC)	Wallin et al. (2015)
			8	DOM-1 (n.s./0.89)	0.18 (n.s.)		
			37	ZEA (n.s./0.01)	0.03 (n.s.)		
			21	α-ZEL (n.s./0.04)	0.03 (n.s.)		
			18	β-ZEL (n.s./0.04)	0.02 (n.s.)		
			6	FB1 (n.s./0.01)	0.004 (n.s.)		
			23	FB2 (n.s./n.s.)	0.01 (n.s.)		
			51	OTA (n.s./0.006)	0.46 (n.s.)		
Turkey	Healthy volunteers Serum		n.s.	OTA (0.2/n.s.)		Fluorescence	Ozcelik et al. (2001)
		40			0.4 (0.19–1.43)		
	Urinary disorders patients Serum	93			n.s. (0.3–5.5)		
Turkey	Adults (18–65 yrs) Urine	233	83	OTA (0.006/0.018)	14.34 (n.d.-75.60 ng/g CRN)	HPLC-FLUO (IAC)	Akdemir et al., (2010) ([b])

Table 3 (*continued*)

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
Turkey	Adults (6–80yrs) Serum	239	98 (summer) 81 (winter)	OTA (0.025/0.025)	0.312 (0.028–1.496) 0.137 (0.0306–0.887)	ELISA	Erkekoglu et al. (2010)
Turkey	Maternal breast milk	75	100 100	AFB1 (0.005/0.005) AFM1 (0.005/0.005)	n.s. (0.0945–4.1238) n.s. (0.0609–0.29999)	HPLC-FLUO	Gurbay et al. (2010)
Turkey	Maternal breast milk	73	24.6	AFM1 (0.01/n.s.)	3.01 (1.3–6.0) ng/l	ELISA	Atasever et al., (2014) ([b])
UK	Plasma Urine	50	100 92	OTA plasma (0.1/n.s.) OTA urine (n.s./0.01)	n.s. (0.15–2.17) n.s. (n.d.-0.058)	HPLC-FLUO (IAC)	Gilbert et al. (2001)
UK	Adults (21–59 yrs) Urine	210	94.2	DON (0.5/n.s.)	11.6 (n.d.-78.2)	LC–MS (IAC)	Turner et al. (2010)
UK	Adults (21–59 yrs) Urine	34	68 3	DON (n.s./0.5) DOM-1 (n.s./0.06)	2.4 (0.5–9.3) n.s.	LC–MS	Turner et al. 2011a,b
UK	Healthy volunteers, urine	54	100	DON (n.s./0.1)	n.s. (0.3–43.1)	LC-MS/MS	Gratz et al. (2014)

ALB - albumin; CRN - creatinine; NEPH - Nephropathy; mos – months; yrs – years; n.a. – not applicable; n.s. – not specified.
[a] Year of sample collection.
[b] validated method.

while FB1 and ZEA levels were much less than TDI in all the samples. The exposure to aflatoxin in this region was limited to measurement of AFM1, which was detected in only 3 urine samples (Solfrizzo et al., 2014). Similarly, AFM1 was present in 5% of maternal breast milk samples of Italian residents (Galvano et al., 2008). Controversial findings were reported for the nursing mothers in Turkey, where one study reported the presence of AFB1 and AFM1 in all breast milk samples (Gurbay et al., 2010) while a more recent one identified AFM1 in 25% breast milk samples (Atasever et al., 2014). This discrepancy could be most likely attributed to the different mycotoxin detection method used, i.e. the first study used HPLC with fluorescence detection and the later one used ELISA assay. The 60% and above incidence of AFM1 in human biological fluids was also reported for the populations of Czech Republic (Ostry et al., 2005) and Serbia (Kos et al., 2014) while in Portugal the AFM1 was detected in 32.8% of maternal breast samples (Bogalho et al., 2018).

Another study in southern Italy assessed OTA level in 327 plasma samples from the adult population and OTA was detected in 99.1% of the samples. The level of OTA in 17 plasma samples exceeded 0.5 ng/ml which indicate an increased risk for cancer and kidney toxicity (di Giuseppe et al., 2012). The results of this study confirmed the report of the "European Scientific Committee on Food (SCF)" (SCF, 2002) which mentioned that Italian food products such as coffee, cereals, pork meat and olive oil are contaminated with OTA. This study concluded that wine in Italy is seemingly the most mycotoxin contaminated food product (di Giuseppe et al., 2012).

In Central Europe, DON-GlcA and DON were detected in 82% and 29% of the analyzed samples, respectively, from a sample set that is composed of 101 urine samples from a German population (Gerding et al., 2014). A total of 12% of the samples exceeded TDI for DON (1 μg/kg bw according to SCF, 2002) with the highest provisional daily intake of 5.67 μg/kg bw. Furthermore, the same study correlated the results with BMEL, the annual German harvest report of 2013 which mentioned that 99% of raw grains in Germany are contaminated with DON. The study analyzed 23 mycotoxin biomarkers and found either single or multiple mycotoxin biomarkers in 87% of the analyzed urine samples. Interestingly, the same study did not detect any aflatoxin metabolite (AFB1, AFB2, AFG2 and AFM1) in any sample. Gerding and coworkers later reported that the German population has in general low exposure to mycotoxins except for DON. This is in agreement with the more recent study from Germany (Ali et al., 2016b) that detected DON in 100% of samples and DOM-1 in 40% of samples. High incidence of DON and its metabolites was also reported in samples for Austria (Warth et al., 2012), Croatia (Sarkanj et al., 2013), Sweden (Wallin et al., 2015) and

UK (Turner et al. 2010, 2011a).

3.5. Mycotoxin biomonitoring studies in Asia

Biomonitoring studies in Asia covered by this survey include 19 studies, with the majority originating from Iran and Malaysia (Table 4). The cohort of all studies included healthy adults while only one study from South Asia also included children. More than 70% of studies from Asia focused on the exposure to the class I carcinogen aflatoxin by measuring the AFB1, AFM1 and AFB1-lysine biomarkers of exposure. In majority of the countries the incidence of aflatoxin biomarkers was above 93% regardless of the analyzed sample type (Azarikia et al., 2018; Groopman et al., 2014; Leong et al., 2012; Maleki et al., 2015; Mohd Redzwan et al., 2014; Omar 2012; Sabran et al., 2012). Incidence of AFM1 in nephrophaty patients from Sri Lanka was reported to be 61% (Desalegn et al., 2011). Leong and colleagues (Leong et al., 2012) have evaluated the presence of AFB1-lysine in blood for the Penang population in Malaysia where people consume large quantities of nuts products. Only 2 samples exceeded the concentration of 20 AFB1-lysine pg/mg albumin. Furthermore, based on the amount of adducts found (0.20–23.16 pg/mg albumin) the study calculated the dietary intake EDI to be in the range of 0.01–0.60 μg AFB1 per day. According to this study, 97% of serum samples contained AFB1-lysine adducts which, despite the low amounts detected, indicates that the population of Penang is exposed to AFB1(Leong et al., 2012). Lower exposure to aflatoxins has been reported for the population of Bangladesh, where the positive samples ranged between 26% in winter to 40% in summer with the maximum mean value of 27.7 pg/mL AFM1 (Ali et al., 2017a). Low incidence of aflatoxins was also reported for another study from Bangladesh (Gerding et al., 2015) as well as in the study conducted in Thailand (Warth et al., 2014).

Several studies also investigated human exposure to OTA and DON (Afshar et al., 2013; Ali et al. 2015, 2016a, 2016b; Assaf et al., 2004; Dehghan et al., 2014; Meky et al., 2003; Turner et al., 2011b). A study conducted in Lebanon (Assaf et al., 2004) evaluated OTA in the most popular foodstuffs by analyzing plasma samples from 250 volunteers from different regions of the country such as north, south, capital city and village. The analysis of foodstuff showed that 82% of beer samples, 61% of burghul samples, 12% of wheat samples and 7.6% of maize samples were contaminated with OTA. In addition, 33% of the total plasma samples showed traces of OTA. The consumption of large amounts of cereals and burghul has been correlated with higher incidence of OTA in plasma samples. However, the mean concentration of plasma samples did not vary considerably (0.16–0.18 ng/ml) between

Table 4
Summary of studies measuring mycotoxin levels in human samples from Asia.

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
Bangladesh	Adults Urine	95	0	DON (1/4)	n.d.	LC-MS/MS	Gerding et al., (2015) ([a])
			0	DON-GlcA (1/4)	n.d.		
			72	OTA (0.01/0.075)	0.203 (< LOQ-2.010)		
			8	AFM1 (0.025/0.1)	0.06 (< LOQ-0.12)		
			1	FB1 (0.0125/0.1)	n.s.		
			0	α-ZAL (0.125/0.25)	n.d.		
Bangladesh	Healthy volunteers Urine	62 (summer)	72	OTA (0.01/0.02)	0.06 (n.d.-0.55)	HPLC-FLUO	Ali et al., (2016a) ([a])
			53	OT α (0.01/0.02)	0.21 (n.d.-6.1)		
		62 (winter)	98	OTA (0.01/0.02)	0.19 (n.d.-1.75)		
			62	OT α (0.01/0.02)	0.09 (n.d.-0.79)		
Bangladesh	Pregnant women (18–36yrs)	54	52	DON (0.16/0.30)	0.86 (n.d.-7.16)	LC-MS/MS (IAC)	Ali et al., (2015) ([a])
Bangladesh	Adults Urine					LC-MS/MS (IAC)	Ali et al., (2016b) ([a])
		62 (summer)	27	DON (0.16/0.3)	0.17 (n.d-1.78)		
		95 (winter)	31	DON (0.16/0.3)	0.16 (n.d.–1.21)		
				DOM-1 (0.1/n.s.)	n.d.		
Bangladesh	Adults			AFM1 (0.0017/0.005)			Ali et al., 2017a ([a])
	Urine	62 (summer)	40		13.5 (1.7–104) pg/mL	HPLC-FD (IAC)	
		62 (winter)	42		27.7 (1.8–190) pg/mL	ELISA	
	Pregnant women Urine	54	31		13.9 (1.7–141.5) pg/mL		
China	Females (19–75yrs), urine	15	100	DON (4/n.s.)	37 (14–94)	HPLC-MS (IAC)	Meky et al., (2003) et al. 2003
China	Adults (40–70 yrs) Urine	60	96.7	DON (0.5/n.s.)	5.9 (n.d. - 30.5) ng/mg CRN	HPLC (IAC)	Turner et al., (2011b) ([a])
Iran	Maternal breast milk	136	3.7	OTA (n.s./n.s.)	n.s. (< 0.005–0.01642)	ELISA	Afshar et al. (2013)
			0.7	AFM1 (n.s./n.s.)	n.s. (0–0.01358)		
			2.72	OTA (n.s./0.5)	0.09 and 0.14	HPLC-FLUO	
			0.7	AFM1 (n.s./0.1)	0.01358 (1 positive)		
Iran	Maternal breast milk	87	96.6	OTA (n.s./n.s.)	0.02457 (0.0016–0.06)	ELISA	Dehghan et al. (2014)
Iran	Maternal breast milk	85	100	AFM1 (n.s./n.s.)	0.00591 (0.002–0.01)	ELISA	Maleki et al. (2015)
Iran	Maternal breast milk	88	93.2	AFB1 (0.01/0.0157)	0.02418 (0.01–0.08)	ELISA	Azarikia et al., (2018) ([a])
			100	AFM1 (0.00004/0.00625)	0.00316 (0.0001–0.0136)		
Jordan	Maternal breast milk	80	100	AFM1 (n.s./0.01)	67.78 (9.71–137.18) ng/kg	ELISA	Omar et al. (2012)
Lebanon	Adults (16- ≥ 60 yrs) Plasma	250	33	OTA (n.s./0.6)	0.17 (n.d.-0.87)	HPLC-FLUO	Assaf et al. (2004)
Malaysia	Adults (18–85 yrs) Serum	170	97	AFB1-lysine (0.4/n.s. pg/mg ALB)	7.67 (0.20–23.16) pg/mg ALB	HPLC-FLUO	Leong et al. (2012)
Malaysia	Adults (25–55 yrs) Urine	22	100	AFM1 (0.0247/n.s.)	0.0421 (0.0289–0.1547)	ELISA	Sabran et al., (2012) ([a])
Malaysia	Adults (23–75 yrs) Serum	71	100	AFB1-lysine (0.05/0.17)	6.85 (1.13–18.85) pg/mg ALB	HPLC-FLUO	Mohd Redzwan et al., 2014 ([a])
Nepal	Women, early pregnancy serum or plasma	141	94	AFB1-lysine (n.s./0.2 pg/mg ALB)	25.28 (0.45–2939.30) pg/mg ALB	UPLC-MS	Groopman et al. (2014)
Sri Lanka	NEPH patients	31	61	AFs (0.005/n.s.)	0.012 (n.d.-0.800)	ELISA	Desalegn et al. (2011)
			84	OTs (0.005/n.s.)	0.020 (0.006–0.360)		
			19	FBs (0.035/n.s.)	n.s. (n.d.-0.130)		
	Relatives Controls	6	100	AFs (0.005/n.s.)	0.298 (0.020–0.800)		
			100	OTs (0.005/n.s.)	0.104 (0.032–0.223)		
			17	FBs (0.035/n.s.)	n.a. (0.093)		
Thailand	Adults (20–76yrs) and adolescents (10–19yrs)	60	5	DON-3-GlcA (4/6)	4.3 (< LOQ-7.0)	LC-MS/MS	Warth et al. (2014)
			11.6	DON-15-GlcA (2/3)	8.1 (< LOQ-16.8)		
	Urine		5	AFM1 (0.05/0.15)	0.33 (0.16–0.55)		
			1.7	OTA (0.05/0.15)	< LOQ		

ALB - albumin; NEPH – nephropathy; yrs – years; n.a. – not applicable; n.s. – not specified.

*year of sample collection.

[a] validated method.

the analyzed regions. EDI have been calculated in plasma samples based on the eq. (4). (i.e. EDI of OTA (ng/kg bw per day) = concentration of OTA in plasma (ng/mL) · 1.34). The value of EDI for the mean concentration of OTA in all plasma samples was 0.23 ng/kg bw/day, which is considerably lower than the maximum allowed level set by JECFA (see Table 3 for TDI levels). Even the highest value detected in plasma (0.87 ng/ml) was lower than EDI limit (1.16 ng/kg bw per day). A study by Assaf and co-workers (Assaf et al., 2004) showed that the most commonly consumed food in Lebanon (i.e. wheat, burghul, beans, lentil

and beer) contained considerable amounts of OTA. In this case, OTA concentration found in the beer samples (0.42 and 1.12 ng/ml) was higher than the level advised by the European Union (i.e. 0.2 ng/ml).

The DON Biomonitoring studies reported the incidence of positives in more than 96% of the analyzed sample from China (Turner et al., 2011b) and 27% or 31% of samples collected in summer or winter, respectively from Bangladesh (Ali et al., 2016a,b). Mean DON values were significantly higher in China compared to the reported value for urine samples from Bangladesh population. In a study by Turner and

Table 5

Summary of studies measuring mycotoxin levels in human samples from South and North America.

Country	Sample type	No. of samples	Positive samples (%)	Mycotoxin type (LOD/LOQ) ng/mL	Mean (Range) ng/mL	Method of detection	Reference
Argentina	Adults			OTA (0.012/0.019)		HPLC-FLUO (IAC)	Pacin et al. (2008)
	Mar del Plata, plasma	199	63.8		0.15 (0.019–50)		
	General Rodrigues, plasma	236	62.3		0.43 (0.019–80)		
Brazil	Maternal breast milk	50	2	AFM1 (n.s./0.01)	n.a. (0.024)	HPLC-FLUO (IAC)	Navas et al., (2005) [a]
			4	OTA (n.s./0.01)	n.a. (0.011 and 0.024)		
Brazil	Maternal breast milk	100	2	AFM1 (0.0003/0.0008)	n.a. (0.0003 and 0.0008)	LC-FLUO (IAC)	Iha et al., (2014) [a]
			66	OTA (0.0003/0.0008)	n.s. (< 0.0003–0.021)		
Brazil	Maternal breast milk	94	5.3	AFM1 (0.004/0.021)	0.018 (0.013–0.025) ng/g	HPLC-FLUO (IAC)	Ishikawa et al., (2016) [a]
Brazil	Adults (18–60 yrs)					UPLC-FLUO (IAC)	Jager et al., (2016) [a]
	Serum	113	0	AFB1-lysine (6/20 pg/mg ALB)	n.d.		
	Urine	113	65	AFM1 (0.075/0.25 pg/mg CRN)	0.37-1.7 (0.25–12.68) pg/mg CRN		
			0	AFB1-N7-guanine (0.003/0.01)	n.d.		
Chile	Adults (18–83 yrs)	88		OTA (0.1/0.4)		HPLC-FLUO (IAC)	Munoz et al., (2006) [a]
	Colbu'n zone, plasma		54		0.44 (0.07–2.75)		
	San Vicente de zpn, plasma		91		0.77 (0.22–2.12)		
Chile	Lactating women			OTA milk (0.01/0.03)		HPLC-FLUO (IAC)	Munoz et al., (2014) [a]
	Maternal breast milk	50	79	OTA plasma (0.07/0.1)	0.052 (0.01–0.639)		
	Maternal plasma	45	95.5	OTA urine (0.03/0.05)	0.200 (0.072–0.639)		
	Infant urine	39	n.s.		0.0652 (0.03–0.433)		
Columbia	Maternal breast milk	50	90	AFM1 (0.0006/0.0018)	0.052 (0.0009–0.0185)	HPLC-FLUO (IAC)	Diaz et al., (2015) [a]
Ecuador	Maternal breast milk	78	13	AFM1 (0.33/0.66)	0.045 (0.017–0.458)	HPLC-FLUO (IAC)	Ortiz et al., (2018) [a]
			9	AFB1 (0.023/0.046)	0.024 (0.012–0.291)		
Haiti	Adults	142	24	DON (1/4)	3.2 (< LOQ-16.9)	LC-MS/MS	Gerding et al., (2015) [a]
	Urine		30	DON-GlcA (1/4)	17.0 (< LOQ-104.3)		
			47	OTA (0.01/0.075)	0.109 (< LOQ-0.225)		
			11	AFM1 (0.025/0.1)	0.06 (< LOQ-0.14)		
			4	FB1 (0.0125/0.1)	0.44 (0.23–0.70)		
			4	α-ZAL (0.125/0.25)	1.46 (0.52–2.49)		
Mexico	Maternal breast milk	112	89	AFM1 (0.00092/0.00279)	0.01278 (0.00301–0.03424)	ELISA	Cantu-Cornelio et al. (2016)
USA	Adults (18–83 yrs)	184				HPLC-FLUO (SPE)	Johnson et al. (2010)
	Serum		20.6	AFB1-lysine (0.01/n.s.)	3.84 (1.01–16.57) pg/mg ALB		
	Urine		11.7	AFM1 (0.005/n.s.)	223.85 (1.89–935.49) pg/mg CRN		
USA	CFS patients	112				ELISA	Brewer et al., (2013) [a]
	Urine		12	Aflatoxins (1/n.s.)	4.67 (1.1–9.4)		
			44	TCs (0.2/n.s.)	0.85 (0.21–5.72)		
			83	OTA (2/n.s.)	6.2 (2–14.6)		

[a] validated method.

colleagues (Turner et al., 2011b) the free and conjugated forms of DON were determined in 70 urine samples obtained from female individuals originating from Shanghai. In the Shanghai region, the population consumes large quantities of rice and wheat daily. However, DON biomarkers have been detected in 96.7% of the samples with a mean concentration of 4.8 ng/ml. In contrast, DON-1 was not detected in any of the samples. The results of this study were compared to the results of a study conducted on the female cohort from the UK. DON mean concentration in urine samples from UK females was twice higher than the concentration measured in the samples from Chinese females. Although based on the survey studies, the amount of daily intake of wheat in UK is 4 times higher than the amount of wheat consumed by the Chinese population. This probably means that wheat in China is more contaminated with DON than in UK but due to dietary habits, it represents lower risk than for population in UK (Turner et al. 2008a, 2008b, 2009, 2010).

3.6. Mycotoxin biomonitoring studies in America

This survey covers 13 studies reported for both South and North America (Table 5). Majority of the studies monitored the exposure to aflatoxin and ochratoxin A in breast milk, blood and urine. Most of the biomonitoring studies targeted healthy adults and lactating woman, except (Brewer et al., 2013) study, which targeted patients with chronic fatigue syndrome.

As presented on Table 5, nursing mothers are exposed to aflatoxin at various level. AFM1 was detected in 90% and 89% of maternal breast milk samples collected in Columbia and Mexico, respectively (Cantú-Cornelio et al., 2016; Diaz and Sanchez, 2015), while the incidence of AFM1 was found in less than 15% of maternal breast milk samples from Brazil (Iha et al., 2014; Ishikawa et al., 2016; Navas et al., 2005) and Ecuador (Ortiz et al., 2018). Another study of aflatoxin exposure in Brazil found AFM1 in 65% of Brazilian samples within lower mean (range) concentration 0.37 (0.25–12.68) pg/mg CRN (Jager, 2016) while a study in USA found AFM1 positive in 11% of the analyzed samples with high mean (range) concentration of 223.85 (1.89–935.49) pg/mg CRN (Johnson, 2010). Furthermore, AFB1-lysine was detected in American healthy adults within mean (range) concentration of 3.84 (1.01–16.57) pg/mg ALB, but not detected in Brazilian healthy adults. Furthermore, Aflatoxins biomarkers have been detected in CFS american patients with elevated mean (range) concentration of 4.67 (1.1–9.4) ng/ml (Brewer et al., 2013).

Exposure to ochratoxin A was reported in seven studies covered by this survey. Based on the collected data it is evident that more than half of the both North and South American healthy population are exposed to OTA. It seems that population in Chile is the most exposed to OTA (Munoz et al. 2006, 2014), followed by population in Argentina, Haiti and Brazil (Pacin et al., 2008; Gerding et al., 2015; Iha et al., 2014; Navas et al., 2005). Interestingly, the highest concentration of OTA was reported for CFS American patients with the incidence of 83%, where the mean (range) concentration was 6.2 (2–14.6) ng/ml (Brewer et al., 2013).

ALB - albumin; CFS - Patients with Chronic Fatigue Syndrome; CRN - creatinine; FLUO - fluorescence; yrs – years; n.a. – not applicable; n.d. - not detected; n.s. – not specified.

4. Conclusion

The current review summarizes studies of the population exposure in four continents i.e. Asia, Africa, Europe and America, to major mycotoxins which include AFB1, OTA, FB1, ZEN and DON. The search of the current literature did not identify any biomonitoring study in the last 18 years for Australia. This review also outlines the metabolism of mycotoxins in the human organism and the use of these metabolites as biomarkers to assess mycotoxin exposure. The vast majority of the human mycotoxin exposure studies have assessed the main mycotoxins which have been classified by IARC either as carcinogenic group 1, 2 and 3. Human exposure to mycotoxins is one of the major food borne health concerns, especially in developing countries. Since the major source of contamination is food, the most efficient risk assessment approach to assess population exposure is to evaluate the mycotoxin intake from food. JECFA, FAO/WHO and European Commission established hazardous limits for the tolerated daily and weekly intakes as well as regulations specifying analytical approaches to measure the level of mycotoxins in animal feed and human food in order to prevent the consumption of contaminated feed/food. Yet, several countries still lack monitoring efforts and regulatory enforcement of mycotoxin in foodstuff such as Pakistan (FAO, 2004).

Information on mycotoxin biomarkers and biotransformation of mycotoxin at the molecular level is important to assess the actual exposure to mycotoxins and to evaluate the current biomonitoring approach to measure all forms of mycotoxins in food and in the human body. This has particular importance since exposure analysis should include measurement of all metabolites and bioconjugated forms of mycotoxin to accurately assess the toxicity and risk for disease upon exposure. Biomonitoring of all metabolites and bioconjugated forms of mycotoxins could lead to a better causality determination between the elevated level of certain mycotoxin forms and various chronic diseases. Evaluating all possible forms of mycotoxins in easily accessible body fluids such as blood and urine allow to select the best set of compounds and the best sample type to assess mycotoxin exposure. However, this requires to setup a complex study where all mycotoxin forms are measured in body fluids over a period of time following exposure to allow identification of long, medium and short term exposure biomarkers. Since intentional human exposure cannot be performed, planning of such study is challenging as the exposed individual can be identified either when an accidental, non-intentional exposure becomes known or selected from a population study where the exposed individual is detected. The maximal permissible levels in food taking into account all mycotoxin forms should be revised to minimize human exposure. Strict control and enforced legislation should be followed by the development of more sensitive analytical methods and constant biomonitoring worldwide to control mycotoxins exposure of the human population. The first method for biomarker detection was developed for AFB1 almost 30 years ago. However, only from 2010 researchers started to develop and adopt multianalyte protocols to detect a large number of mycotoxins and their metabolites as well as the bioconjugated forms (Turner et al., 2012). Despite these analytical efforts the

biological activity of each compound remains to be elucidated.

As evident from this review, most of the cited papers analyzed mycotoxins by liquid chromatography coupled to mass spectrometry and the most commonly investigated human sample was urine. However, the selection of body fluids and biomarkers of exposure is crucial due to the difference in the metabolism of each. Furthermore, as shown in this review the LOD and LOQ values vary among different laboratories which led to the variance in the estimation of the mycotoxin exposure due to the different sensitivity of the methods. Namely, methods with greater sensitivity returned higher number of positive samples. Moreover, the method validation and its use with the adequate matrix is necessary, to ensure accuracy and reproducibility of the results as well as the data normalization for matrices such is urine. In Asia, the exposure to AFB1 and DON was proven to be common, while the most significant exposure results were found in African children who have been exposed to the most toxic mycotoxins such as AFB1 and FB1. In other parts of Africa such as South Africa, exposure to DON and ZEN are prevalent. Even in Europe, DON, ZEN and OTA have been detected in a majority of the population involved in mycotoxin exposure studies. There is a lack of knowledge on the DON and ZEN exposure in both North and South America in the last 18 years. Recent studies proved that there is a significant underestimation of the amount of mycotoxin actually ingested through food and accumulation effects in different body parts should be addressed in future human population exposure studies. Moreover, mycotoxin biotransformation and deposition in organs has not been fully studied by the scientific community, which information is required to fully understand the impact of mycotoxin on human health. To improve the risk assessment, future studies should monitor different forms of mycotoxins such as glucuronide conjugates as well as mycotoxins that have been rarely addressed such as T-2/HT-2 toxin, nivalenol, citrinin (Warth et al., 2013). In addition, some of the mycotoxin biomarkers are difficult to analyze due to the lack of analytical standards and reference materials. Therefore, synthetic laboratories should put more efforts in synthesizing mycotoxin bioconjugates and metabolite standards (Pierron, 2016) and in developing novel analytical techniques that will overcome the obstacles such as the extraction and analysis of chemically diverse mycotoxins and their derivatives with large differences in their physico-chemical properties such as polarity and solubility properties (Murugesan et al., 2015). We are persuaded that multi-analyte biomonitoring approaches will contribute to improve the risk assessment of mycotoxins exposure and will contribute to identify population subgroup, which is at higher risk towards mycotoxin exposure such as patients with renal dysfunction.

5. Conflict of interest

The authors declare that they have no conflict of interest.

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