

Review

Occupational Exposure to Mycotoxins: Current Knowledge and Prospects

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Abstract

Occupational exposure to mycotoxins is supposedly very frequent, but it is rarely reported in the scientific literature. Several recent studies described occupational exposure to the aflatoxin B₁ (AFB₁) mycotoxin in different occupational settings. Previously, exposure to other mycotoxins was shown in the animal husbandry and food processing sectors, confirming that occupational exposure cannot be negligible. However, no guidelines or standard methodologies are available for helping occupational hygienists to consider mycotoxin exposure in their interventions. This article reviews the literature on this problem and recommends some actions for the better management of this risk factor in occupational settings, especially where environmental conditions are favorable to fungal presence.

Keywords: exposure assessment; fungi metabolites; occupational risk factor; organic dust

Introduction

Workers in numerous sectors are exposed to organic dust originating from such diverse organic matter as soil, plants, animals, food, and fecal matter. This dust contains lots of different bacteria and fungi and their components such as endotoxins and glucans. Furthermore, some fungi can actively produce secondary metabolites called mycotoxins.

Some mycotoxins can have serious human health effects when ingested, but their health effects following inhalation or dermal contact are insufficiently

documented. Occupational assessments of biological risks in workplaces usually include the monitoring of bioaerosols in the air. This measurement of airborne biological agents usually only includes an estimation of the concentration of cultivable bacteria and fungi and sometimes a measurement of endotoxin concentrations. Indeed, guidances and recommendations for occupational exposure limits exist mainly for these three contaminants. Although some researchers have started to measure biological substances with potential impact in human health, such as mycotoxins, in the workplace, the measurement has never been done routinely.

The goals of this review are to take stock of the current knowledge about occupational exposure to mycotoxins and to discuss the important things to consider when performing an occupational risk assessment of activities that may result in exposure to mycotoxins.

What is a mycotoxin? What are the most common? What are the fungi responsible for their production?

Mycotoxins are fungi metabolites produced by specific fungal genera, primarily *Aspergillus*, *Penicillium*, *Alternaria*, *Fusarium*, and *Claviceps* (Bennett and Klich, 2003; Marin *et al.*, 2013). Mycotoxin molecules are small and stable, with a low molecular mass. To date, more than 300 mycotoxins have been identified; more will surely be discovered in the near future. Only 30 of these mycotoxins have been subjected to research aimed at highlighting their toxic properties (Surai *et al.*, 2008). A specific fungal species may produce several different mycotoxins due to the influence of various types of environmental stress (Halstensen, 2008).

As reviewed in Halstensen (2008), mycotoxins can be present in the environment even in the absence of any visible fungi since they can resist adverse environmental factors such as high or low temperatures and can persist long after the death and disintegration of the fungal species responsible for their production. They are also difficult to eliminate or inactivate from the source even after being exposed to temperatures such as boiling or roasting processes (Peraica *et al.*, 1999).

Aflatoxin B1 (AFB₁) is perhaps the most hazardous mycotoxin found in agricultural products since it is an hepatocarcinogen, inducing DNA adducts leading to genetic changes in target liver cells (Chen *et al.*, 1997; Vineis and Xun, 2009). It has been found on grains, peanuts, and other human and animal foodstuffs (Rocha *et al.*, 2014).

Aspergillus flavus and *Aspergillus parasiticus* are the most common species associated with aflatoxin contamination. However, recently, additional species of section *Flavi* (closely related species that cannot be clearly distinguished morphologically) have been reported to be responsible for aflatoxin production (Varga *et al.*, 2015; Lamoth, 2016). Contamination can occur naturally on crops or after incorrect storage and/or process conditions. The dust generated during the handling of these products can also contain AFB1 (Brera *et al.*, 2002).

Besides aflatoxin, the other relevant groups of mycotoxins found in food are the following: ochratoxin A produced by both *Aspergillus* and *Penicillium*; sterigmatocystin produced by *Aspergillus*; trichothecenes (type A: HT-2 and T-2 toxin; type B: deoxynivalenol),

zearalenone, fumonisins B1 and B2, and the emerging mycotoxins (fusaproliferin, moniliformin, beauvericin, and enniatins) produced mainly by *Fusarium* species; ergot alkaloids produced by *Claviceps*; and altenuene, alternariol, alternariol methyl ether, altertoxin, and tenuazonic acid produced by *Alternaria* species (Bottalico and Logrieco, 1998; Barkai-Golan and Paster, 2008; Marin *et al.*, 2013). Some of these toxigenic genera (*Aspergillus* and *Penicillium*) are commonly found on assessments done to moisture-damaged buildings (Viegas *et al.*, 2015).

Particular attention should be given to these mycotoxins since, currently, they are unregulated and were shown to occur frequently in agricultural products. The evidence of their incidence is rapidly increasing and gaps in toxicological knowledge have been identified for several compounds not allowing a proper risk assessment (Gruber-Dorninger *et al.*, 2017).

Routes of exposure

Occupational routes of exposure to mycotoxins are inhalation and dermal contact.

Most mycotoxins are not volatile. However, mycotoxins can be present in airborne dust (Flannigan, 1987; Brera *et al.*, 2002) and in the fungal spores and fragments (Brasel *et al.* 2005; Huttunen and Korkalainen, 2017). Therefore, airborne dust, spores, and hyphae fragments can act as carriers of mycotoxins to the lungs (Brasel *et al.* 2005; Huttunen and Korkalainen, 2017) and potentially, exposure in occupational settings occurs essentially via inhalation, particularly in the form of airborne dust (Brera *et al.*, 2002; Lavicoli *et al.*, 2002; Mayer *et al.*, 2007; Mayer, 2015; Viegas *et al.*, 2016).

Moreover, dermal contact could also be a frequent route of workplace exposure, especially where workers without protection have to handle contaminated materials such as food. This is particularly relevant in occupational settings where the use of short-sleeved clothes is possible or when hands are in contact with solutions containing mycotoxins (Degen, 2008; Boonen *et al.*, 2012; Viegas *et al.*, 2016). Moreover, dust particles containing mycotoxins can be deposited in the skin promoting dermal absorption. Additionally, work surfaces contaminated with dust particles can also be touched creating opportunities for further skin contact (Boonen *et al.*, 2012).

Health effects

Several factors influence the severity of the disease caused by mycotoxins exposure, namely the toxicity of the mycotoxin, the exposure route, the extent of exposure (duration and intensity), the age and nutritional

status of the individual, and the potential synergistic effects with other chemicals, including other mycotoxins, to which the individual has been exposed (Peraica *et al.*, 1999).

Although effects on human health are well known via the ingestion of contaminated food, very few studies have investigated the health effects of mycotoxins via inhalation or dermal contact.

The symptoms and effects attributed to the inhalation of mycotoxins are mucous membrane irritation, skin rash, nausea, immune system suppression, acute or chronic liver damage, acute or chronic central nervous system damage, endocrine effects, and cancer (Olsen *et al.*, 1988; Huttunen and Korkalainen, 2017).

Regarding local effects, the nasal passage is a primary target for several inhaled toxicants (Harkema *et al.*, 2006; Huttunen and Korkalainen, 2017); its epithelial lining is often the first tissue to be directly injured, for example, by the spores or mycotoxins of *Stachybotrys chartarum* (Huttunen and Korkalainen, 2017). Pestka *et al.* (2008) also suggested that the toxicity of trichothecenes might be a reason for many of the adverse effects of *S. chartarum*.

Concerning systemic effects, several mycotoxins have caused human health effects following exposure via inhalation. For instance, there is some evidence that inhalation of AFB₁ can cause lung cancer (Dvoráková, 1976; Dvoráková and Píchová, 1986; Hayes *et al.*, 1984; Olsen *et al.*, 1988). The mechanism behind its carcinogenicity in the lung is suggested to be oxidative DNA damage (Guindon-Kezis *et al.*, 2014; Huttunen and Korkalainen, 2017). Inhalation of ochratoxin (OTA) has been linked to acute renal failure and respiratory distress in workers exposed to *Aspergillus* producers of OTA in a granary (Di Paolo *et al.*, 1994). OTA has been found in the sinonasal tissue and mucus of 22% of chronic rhinosinusitis patients, and in the urine of 83% of patients suffering from chronic fatigue syndrome (Brewer *et al.*, 2013).

Moreover, it is important to note that some studies have demonstrated that the inhalation of some mycotoxins can be more harmful than oral exposure due to the health effects that can be caused in the respiratory system (Creasia *et al.*, 1990; Amuzie *et al.*, 2008; Degen, 2011).

Although there is no detailed information about cellular local concentration of the different mycotoxins in the skin, local skin effects can be expected. Apoptosis of epidermal cells and development of skin tumors were already observed after dermal mycotoxin exposure (Rastogi *et al.*, 2006; Boonen *et al.*, 2012). Another aspect to consider is the fact that mycotoxins can

accumulate and persist in the skin cells (Baert and De Spiegeleer, 2011) and in this way not only the workers exposed continuously but also the ones exposed sporadically have an increased risk for epidermal apoptosis, skin cancers, and immune related diseases (Boonen *et al.*, 2012).

Occupational exposure to mycotoxins

Evidence from air or surface metrology studies

Dust containing mycotoxins is released during tasks involving high exposure to organic dust, such as storage work, loading, handling, or milling contaminated materials (grain, waste, and feed), and others such as caring for animals in animal husbandry settings. Animal feed processing plants are particularly risky for mycotoxin exposure since the authorized level of concentration in this type of food is 10 times higher than it is for human food. As example, the maximum levels authorized for deoxynivalenol in unprocessed maize is 1750 µg kg⁻¹ while it is 750 µg kg⁻¹ in cereals intended for direct human consumption (Pinotti *et al.*, 2016).

Specific environmental and ecological conditions—temperature, relative humidity, availability of nutrients, and use of fungicides—can enhance or limit fungal growth and dissemination. In 2015, Mayer made an extensive review aiming to identify previously reported incidents of occupational mycotoxin exposure (Mayer, 2015, 2016).

Table 1 summarizes the results of measurements performed in specific workplaces. To the best of our knowledge, 15 studies reported occupational exposure to mycotoxins between 1981 and 2017. The articles were dedicated to settings related to animal husbandry, farming, or food and feed processing. After 2000, the number of articles increased and the focus changed from studying one mycotoxin at a time to studying several mycotoxins across the same sample. This was probably due to the development of analytical resources allowing the characterization of occupational exposure to several mycotoxins simultaneously. All the studies demonstrated the presence of mycotoxins in working environments and therefore the possibility for workers to be exposed to mycotoxins via inhalation or dermal contact.

Evidence from biomonitoring studies

One study, carried out in India, showed that aflatoxins were significantly more frequently detected in the serum of food-grain workers than in the urine of a control group suggesting an occupational exposure (Malik *et al.*, 2014). In Egypt, concentrations of serum aflatoxin were significantly higher in workers exposed to wheat (millers

Table 1. Results of measurements performed in these specific workplaces.

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD–LOQ	Matrix	Main findings
<i>Astrup et al.</i> (1991) ^a	Denmark	Animal feed production	Aflatoxin B1 (AFB ₁)	No data available	Dust samples collected at selected sites in factories	ELISA	Dust samples (0.9 mg)	Dust samples presented high levels at one site (8 µg kg ⁻¹ dust); companies' efforts to reduce levels of AFB ₁ in raw materials and to encapsulate the work process will reduce exposure significantly
<i>Selim et al.</i> (1998)	United States	Farms handling grain	AFB ₁	No data available	24 samples of airborne dust collected during animal feeding; 14 samples from 11 farms during bin cleaning; 14 samples of settled dust, and 18 samples of bulk corn	HPLC LOD = 1 ng	Airborne dust, settled dust, and samples of bulk corn	Detection of AFB ₁ in airborne dust during harvesting, grain loading and unloading, bin cleaning, and animal feeding operations provided evidence that farmers could be exposed to potentially hazardous levels of AFB ₁
<i>Krysinski-Traczyk et al.</i> (2001)	Poland	Farms	Moniliformin, deoxynivalenol (DON), nivalenol, and ochratoxin	No data available	10 farms where 10 samples of stored wheat grain and 10 samples of settled grain dust were collected	TLC and HPTLC Different LOD–LOQ for each mycotoxin	Stored wheat and settled dust	The majority (70%) of wheat grain and settled dust samples presented notable quantities of fusarium toxins; ochratoxin was found in 60% of both kinds of samples
<i>Skaug et al.</i> (2001)	Norway	Dairy farms	Ochratoxin A (OTA)		Air samples collected with stationary samplers	HPLC LOD = 1.5 pg	Air samples and settled dust	Exposure to OTA from inhalation of dust and conidia is possible and peak exposures can be considerable

Table 1. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Brera <i>et al.</i> (2002) ^a	Italy	Warehouses for green coffee, black pepper, and cocoa beans	Aflatoxins and OTA		44 airborne dust samples collected using stationary samplers: 18 by area (4 for green coffee, 4 for black pepper, 7 for nutmeg, and 3 for cocoa) and 26 by personal sampling	HPLC LODs (ng) AFB ₁ and AFB ₂ 0.0025 AFG ₁ and AFG ₂ 0.0200 OTA 0.0020	Airborne dust samples	A wide range of toxin amounts was found in personal and stationary samples, depending on the job and the distance from the raw materials Dust and mycotoxin amounts collected in the handling and processing areas were lower than those found for personal samples in the same areas OTA represents a source of occupational risk, in addition to other mycotoxins potentially present in the workplace
Iavicoli <i>et al.</i> (2002) ^a	Italy	Factories processing coffee, cocoa beans, and spices	OTA		44 airborne dust samples	HPLC LOD = 0.002 ng	Dust samples	Results found were higher than previously reported; mainly DON, HT-2, and T-2 toxins were found; these were associated with local fungal forecast, cereal species, visible mold damage, and storage
Nordby <i>et al.</i> (2004)	Norway	Grain farms	Trichothecenes: 3-A—DON, DON, nivalenol, T-2 toxin, HT-2 toxin, 4,5-diacetoxyscirpenol, 1,5-monoacetoxyscirpenol, Fusarenon-X	No data available	109 grain dust samples. Sampling done on different surfaces.	LOD from 10 to 50 µg kg ⁻¹ , depending of the mycotoxin	Settled dust	

Table 1. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Haltsen et al. (2006)	Norway	Grain farms	Trichothecenes Mycotoxins	No data available	109 samples of newly settled grain dust released during threshing or storage work for 1999 and 2000 crops of spring wheat, oats, and barley	GC-MS LOD = detection limits (DL) were 50–100 µg kg ⁻¹ for T-2; 50 µg kg ⁻¹ for nivalenol (NIV); 40 µg kg ⁻¹ for fusarenon-X; 30 µg kg ⁻¹ for HT-2; 20 µg/kg for DON, 3-acetyl-DON, and 4,15 diacetoxyscirpenol (DAS); and 10 µg kg ⁻¹ for monoacetoxyscirpenol (MAS)	Settled dust	The dominant trichothecenes in settled grain dust were HT-2, DON, and T-2; no 3-acetyl-DON or fusarenon-X were found; median amount of detected trichothecenes was 69 µg kg ⁻¹ (range 0–6000 µg kg ⁻¹); trichothecenes found in settled dust suggested that similar contamination could be expected in airborne dust
Tangni and Pussemier (2007)	Belgium	Private farmers and cereal storage companies	Ergosterol, citreoviridin, citrinin, cyclopiazonic acid, gliotoxin, helvolic acid, mycophenolic acid, nivalenol, ochratoxin, patulin (PT), penicillic acid, secalonic acid D, sterigmatocystin, zearalenone and zearalenone (ZEA)	No data available	184 settled grain dust samples from storage facilities	HPLC-UV Different LOD-LOQ for each mycotoxin	Settled dust was mixed before analysis to ensure homogeneity	An assessment of worker exposure, using median values, indicated that mycotoxin uptake through dust inhalation may simultaneously contribute to 0.5%, 0.5%, 0.7%, and 0.1% of the respective tolerable daily intake of OTA, PT, DON, and ZEA; multi-contamination of grain dusts associates exposure to several mycotoxins simultaneously

Table 1. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Mayer <i>et al.</i> (2007)	Germany	Grain elevators	Ochratoxin A (OTA) DON Zearalenone (ZEA)	2005 harvest period, and continued until spring 2006	35 settled grain dust samples collected from several locations in 13 grain elevators	HPLC (OTA, LOD 0.01 ng g ⁻¹), (DON, LOD 15 ng g ⁻¹), (ZEA, detection limit 6 ng g ⁻¹)	Dust samples	Nearly all settled dust samples contained OTA (96%), DON (100%), and ZEA (100%), with median concentrations of 0.4 ng g ⁻¹ , 416 ng g ⁻¹ , and 126 ng g ⁻¹ , respectively Dust samples with 6–11 µg kg ⁻¹ dust (7.93 ± 1.49 µg kg ⁻¹); AFB ₁ not detected in any air sample
Mo <i>et al.</i> (2014)^a	China	Sugar production factory	AFB ₁	No data available	15 airborne dust samples collected from the bagasse house and presser workshop Air samples also collected with an air sampler at 1.5 m height, with a 20 l min ⁻¹ flow rate	ELISA 5–100 mg kg ⁻¹	Dust sample	
Lai <i>et al.</i> (2014)^a	China	Sugar and paper-making factory	AFB ₁	Between October and March	15 dust samples (0.9 mg) collected from the sugarcane bagasse warehouse and presser and paper production workshops	ELISA	Dust samples	The concentration of AFB ₁ in dust samples collected from the sugarcane bagasse warehouse and the presser and paper production workshops, were 7.2 ± 1.30, 8.0 ± 1.23, and 8.6 ± 1.82 µg kg ⁻¹ , respectively; the concentration of AFB ₁ in dust samples was not statistically significant in these sites (<i>P</i> = 0.35); AFB ₁ was not detected in any of the rice samples

Table 1. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Straumfors <i>et al.</i> (2014)	Norway	Grain elevators and compound feed mills	70 fungal metabolites were detected: trichothecenes, depsipeptides, ergot alkaloids, and other metabolites from <i>Fusarium</i> , <i>Claviceps</i> , <i>Alternaria</i> , <i>Penicillium</i> , <i>Aspergillus</i> , and other fungi	Winter 2008 (<i>n</i> = 9 samples), Autumn 2008 (<i>n</i> = 15 samples) and winter 2009 (<i>n</i> = 9 samples)	33 settled grain dust samples (1.5–15 g) collected from 20 grain elevators and compound feed mills	LC-MS	Settled dust	The main mycotoxins found were from the <i>Fusarium</i> genus; particularly large quantities of DON, depsipeptides, aurofusarin, avenacin Y, and culmorin were found; all samples contained multiple mycotoxins, indicating a highly complex pattern of possible inhalational exposure
Mayer <i>et al.</i> (2016)	Different European countries and New Zealand	Onion sorting	Aflatoxin G2, aflatoxin G1, aflatoxin B2, AFB ₁ , agroclavine, beauvericin d, DON, DON-3-glucoside, deepoxy-deoxynivalenol, 3-acetyl-deoxynivalenol, diacetoxyscirpenol dihydroergosin, enniatin A, enniatin A1, enniatin B, enniatin B1, ergocornin, ergotamin, ergovalin, fumonisin B1, hydrolyzed fumonisin B1, fumonisin B2 fusarenon X, HT-2 toxin, moniliformin, monoacetoxyscirpenol, neosolaniol, nivalenol, ochratoxin α, OTA, ochratoxin B, patulin, T-2 toxin, verrucarol, A, verrucarol, α-zearalenol, β-zearalenol, zearalenone, zearalenone-4-glucoside, zearalenone-4-sulfate	Not available	12 representative samples of dry outer onion skins	Liquid chromatography with electrospray ionization and triple quadrupole mass spectrometry	Onions	In 6 of the 12 samples, tests were positive for DON, fumonisin B1, and fumonisin B2 mycotoxins in quantitatively detectable amounts of 3940 ng g ⁻¹ for fumonisin B1 and in the ranges of 126–587 ng g ⁻¹ for deoxynivalenol and 55–554 ng g ⁻¹ for fumonisin B2

Table 1. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Niculita-Hirzel <i>et al.</i> (2016)	Grain industry	Swiss	DON, 3-ADON, 15-ADON, nivalenol (NIV), and Zearalenone (ZEA)	15 July and 9 August 2010	Aerosols collected during threshing of 78 winter wheat fields and unloading of 59 grain lots in six grain terminals	HPLC MS/MS	Aerosols and grain dust	Wheat harvesting generated on average 28, 20, and 1 ng m ⁻³ of DON, NIV, and ZEA, respectively, and grain unloading generated 53, 46, and 4 ng m ⁻³ ; personal sampling revealed that working in a cab was an efficient protective measure; however, it was insufficient to avoid chronic exposure to multiple mycotoxins; the most exposed activity was cleaning, exposing workers to DON, NIV, and ZEN at concentrations as high as 65, 59, and 3 ng m ⁻³ , respectively
Ferri <i>et al.</i> (2017) ^a	Italy	Feed mill workers	AFs (M1, G2, G1, B1, B2) and aflatoxinol (AFOH)	March to April 2014	Dust samples collected to assess possible individual exposure by inhalation	Liquid chromatography-mass spectrometry (LC-MS/MS) LOD was 0.5 µg kg ⁻¹ for each aflatoxin. LOQ different for each mycotoxin	Inhalable dust samples (environmental and individual exposure)	Airborne filters showed levels of aflatoxins in several areas of both plants, whereas personal air-filter devices only showed aflatoxins in one plant; the area at the greatest risk of worker exposure was the unloading area in plant A (0.027 ng m ⁻³)

TLC, thin-layer chromatography method; HPLC, high-performance liquid chromatography method; HPTLC, high-performance thin-layer chromatography method.

^aStudies with biomonitoring data.

and bakers) than in controls (Saad-Hussein *et al.*, 2014). In Portugal, AFB₁ was detected in the serum of 50% of poultry workers, whereas it was absent from all the serum from controls (Viegas *et al.*, 2016). On the other hand, a study in Germany using biomonitoring to assess exposure to certain mycotoxins in mill workers failed to reveal such exposure in urine spot samples (Föllmann *et al.*, 2016). Indeed, no significant difference in biomarker levels was observed between mill workers and control group.

A recent study using intact and damaged human skin in an *in vitro* Franz diffusion cell set-up showed that beauvericin and enniatins can penetrate the skin (Tavernier *et al.*, 2016).

Table 2 summarizes the results obtained in 15 studies which used biomonitoring to assess occupational exposure to mycotoxins; some of these studies also used environmental samples and are therefore already mentioned in Table 1. Similarly to the studies reported in Table 1, until 2015, studies focused on one mycotoxin alone (aflatoxins and ochratoxins were the most studied); but some studies were subsequently able to report on several mycotoxins in the same biological sample, as analytical resources expanded. These articles (Föllmann *et al.*, 2016; Ferri *et al.*, 2017; Viegas *et al.*, 2017) again demonstrated that the most common exposure scenario is co-exposure to several mycotoxins. However—and this is one of the limitations of using biomonitoring—it is impossible to conclude whether exposure results solely from the working environment or whether food intake is also a contributing factor. Most of these studies (12/16), however, had included a control group, usually including workers from administrative companies in the same locality, which enabled to take into account the exposure by food intake and a better understanding of the role of working environments in the total burden of mycotoxin exposure (Viegas *et al.*, 2013b).

Exposure assessment—What to consider?

Levels of exposure can vary greatly between different tasks within the same industry, and characterizing exposure implies performing measurements on each task separately to identify those most at risk. For example, in swine husbandry, Viegas *et al.* (2013b) suggested that feed was one of the contamination sources since AFB₁ exposure was higher in workers performing animal feeding than in workers doing other type of tasks. In a waste management setting, where high exposure to AFB₁ was also measured, waste was supposed to be the source of contamination (Viegas *et al.*, 2015) and exposure remains stable over a working day since workplace

conditions and tasks are the same during the entire work shift.

Moreover, within the same task, levels of exposure could also vary over time depending on the quality of the materials and products handled. For example, in food processing plants, certain batches of products (foodstuffs) could be highly contaminated, whereas other batches were contaminant free. Therefore, the contamination of the material should be checked before handling and actions taken to avoid or prevent exposure. As an example, contaminated material should be rejected or collective preventive measures reinforced or, as a last resort, personal protective equipment (respiratory protections, gloves, and goggles) worn. Even if the mycotoxin concentration in a product or material is low, handling high amounts of it can cause an elevated airborne mycotoxin concentration in the workplace at a specific moment that then endures depending on how tasks develop (Mayer, 2015). For example, in France, measurements in food industries (cereals, vegetables, and spices) showed no contamination of the products handled above regulatory limits. However, workers' exposure via inhalation was high for all settings since the air measurements revealed significant levels of mycotoxins bound to dust particles (Jargot and Melin, 2013). Dry products or materials with high specific surface areas, like hay or plant fibers, tend to release large amounts of dust that act as the carrier for fungi and mycotoxins and increase the probability of inhalation. Similarly, the manual sorting or transport of contaminated products will contribute to an elevated release of contaminated dust and consequently to potentially high exposure to mycotoxins. Some tasks common to all food and agriculture processing plants, such as cleaning activities involving sweeping or dust removal using compressed air, are well known to be associated with high exposure to dust (Mayer, 2015).

Another very significant point to consider is that co-exposure to different mycotoxins is very likely to occur since the contamination of foodstuffs by several mycotoxins has frequently been demonstrated (Grenier and Oswald, 2011; Gerding *et al.*, 2014; Assunção *et al.*, 2015; De Ruyck *et al.*, 2015; Alassane-Kpembi *et al.*, 2017). Synergistic or additive effects should therefore also be taken into account when performing a risk assessment, and measurements should look for several mycotoxins. It is also well known that the proximity of a worker's head to the material handled increases exposure risk (Mayer, 2015; Viegas *et al.*, 2016). Therefore, besides identifying the tasks generating high exposure, it is important to identify workers' behaviors (such as not wearing protection equipment such as gloves or

Table 2. Results from biomonitoring studies.

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Astrup <i>et al.</i> (1991)	Denmark	Animal feed production	AFB ₁ (measured AFB ₁ albumin adducts)	No data available	45 workers	ELISA LOD = 5 pg AFB ₁ mg albumin ⁻¹	Serum	Findings suggest occupational exposure to AFB ₁ ; all the workers exposed to AFB ₁ were employed by company B, but with different job descriptions and different types of prescribed personal protection
Brera <i>et al.</i> (2002)	Italy	Warehouses for green coffee, black pepper, and cocoa beans	OTA	No data available	26 workers	HPLC LOD = 0.02 ng ml ⁻¹ LOQ = 0.05 ng ml ⁻¹	Serum	The range of OA levels in the serum of occupationally exposed workers examined was 0.94–3.28 ng ml ⁻¹ ; results indicate that occupational exposure to OTA led to serum levels higher than those in unexposed subjects
Iavicoli <i>et al.</i> (2002)	Italy	Three factories for coffee, cocoa beans, and spices	OTA	Not data available	26 workers and 23 controls	HPLC	Serum	Results showed that, in cases where there was a lack of preventive measures applied in workplaces, occupational exposure could result in increased OA levels in serum; this suggests that both environmental and biological monitoring should be undertaken in workplaces where OA contaminated-products are handled or processed
Degen <i>et al.</i> (2007)	Germany	Grain handling companies	OTA	July 2005 and March 2006	61 samples from a cohort of male workers	HPLC LOD = 0.05 ng ml ⁻¹ plasma	Blood	Data did not provide evidence for a significant inhalatory burden of OTA in grain workers; since deoxynivalenol and zearalenone were also detected in the dust samples in concentrations much higher than that of OTA, additional research should try to assess the potential relevance of inhalation exposure to these mycotoxins

Table 2. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Oluwafemi et al. (2012)	Nigeria	Feed mill	Aflatoxins: B ₁ , B ₂ , G ₁ , and G ₂	Located in the tropical rain forest zone with high humidity and temperature	28 workers and 30 controls	HPLC	Blood	The mean concentrations of AFB ₁ , AFB ₂ , AFG ₁ , and AFG ₂ in the blood of feed mill workers varied from 73.4 to 189.2, 0.1 to 0.5, 0.3 to 1.9, and <0.1 to 3.4 ng ml ⁻¹ , respectively; poorly ventilated mills resulted in higher blood AFB ₁ levels; AFB ₁ was not detected in control group
Viegas et al. (2012)	Portugal	Poultry production	AFB ₁ (free AFB ₁ and AFB ₁ bound to albumin)	Spring	31 workers	ELISA LOD=5 pg AFB ₁ mg ⁻¹ albumin	Serum	Results suggest that exposure to AFB ₁ by inhalation occurs and represents an additional risk in this occupational setting
Viegas et al. (2013a)	Portugal	Swine husbandry	AFB ₁ (free AFB ₁ and AFB ₁ bound to albumin)	Autumn	28 workers and 30 controls	ELISA LOD = 1 ng ml ⁻¹	Serum	21 workers (75%) showed detectable levels of AFB ₁ with values ranging from <1 to 8.94 ng ml ⁻¹ and with a mean value of 1.91 ± 1.68 ng ml ⁻¹ ; in the control group, AFB ₁ values were all below 1 ng ml ⁻¹ ; data indicated that exposure to AFB ₁ occurs in swine barns and may be related to different causes and contamination sources
Mo et al. (2014)	China	Sugar production factory	AFB ₁ (measured AFB ₁ albumin adducts)	No data available	120 workers and 80 controls	ELISA	Serum	AFB ₁ albumin adducts positive in 67 workers (57.4%). Values ranging between 6.4 and 212 pg mg ⁻¹ albumin adducts (mean value: 51 ± 4.62 pg mg ⁻¹ albumin).
Lai et al. (2014)	China	Sugar and paper-making factory	AFB ₁	Between October and March	181 workers and 203 controls	ELISA	Serum	The difference in the serum AFB ₁ albumin adduct levels of workers and controls was statistically significant; serum AFB ₁ albumin adducts were detected in 102 (56.35%) workshop employees, with values ranging from 8 to 212 pg mg ⁻¹ albumin (mean value 38.51 ± 44.80 pg mg ⁻¹

Table 2. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Malik <i>et al.</i> (2014)	India	Food grain workers	Aflatoxins	Not data available	46 workers and 44 controls	ELISA	Serum	albumin); in contrast, only 12 (5.9%) controls had detectable levels of AFB ₁ albumin adducts, with values ranging from 8 to 26 pg mg ⁻¹ albumin (mean value 15.58 ± 6.42 pg mg ⁻¹ albumin) Aflatoxins were detected in 32.6% of food grain workers and 9.1% of nonfood grain workers; a significant difference was also found between the two groups in BAL culture for <i>Aspergillus</i> ; about 47.8% of food grain workers and 11.4% of nonfood grain workers had chronic respiratory symptoms
Saad-Hussein <i>et al.</i> (2014)	Egypt	Wheat handlers, including millers and bakers	AFB ₁ (AFB ₁ bound to albumin—AFB ₁ /Alb)	Not data available	190 wheat handlers; 100 flour-mill workers and 90 bakers; plus 64 controls	ELISA	Serum	AFB ₁ /Alb was significantly higher among workers employed as bakers than in mill workers and controls; mill workers had higher levels of AFB ₁ /Alb than controls; AFB ₁ /Alb was significantly higher among hepatocellular carcinoma cases than in the other groups; AFB ₁ /Alb was significantly correlated with the duration of exposure in bakers
Viegas <i>et al.</i> (2015)	Portugal	Waste management	AFB ₁ (free AFB ₁ and AFB ₁ bound to albumin)	Spring and summer	41 workers and 30 controls	ELISA LOD = 1 ng ml ⁻¹	Serum	All the workers showed detectable levels of AFB ₁ with values ranging from 2.5 to 25.9 ng ml ⁻¹ and with a median value of 9.9 ± 5.4 ng ml ⁻¹ ; in the control group, AFB ₁ values were all below 1 ng ml ⁻¹ ; results from this work suggest that exposure to AFB ₁ occurs in waste management settings and may be related with the high contamination of waste being handled
Viegas <i>et al.</i> (2016)	Portugal	Poultry slaughterhouse	AFB ₁ (free AFB ₁ and AFB ₁ bound to albumin)	Winter	30 workers and 30 controls	ELISA LOD = 1 ng ml ⁻¹	Serum	14 workers (47.0%) showed detectable levels of AFB ₁ with values from 1.06 to 4.03 ng ml ⁻¹ and a mean value of 1.73 ng ml ⁻¹ ; in the control group, AFB ₁ values

Table 2. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Föllmann <i>et al.</i> (2016)	Germany	Three grain mill workers	DON, ZEN, OTA, and citrinine (CIT; (DON-1), α - and β -zearelenol (α - and β -ZEL), ochratoxin alpha (OTA α), and dihydrocitrinone (DH-CIT)	No data available	Samples provided by 12 male and 5 female workers. Control group comprised 12 workers	HPLC-LC (OTA and OTA α) LC-MS/MS (CIT and its metabolite HO-CIT) LC-MS (DON and its metabolite DOM-1) LOD and LOQ different for each mycotoxin	Spot urine samples	were all below 1 ng ml ⁻¹ ; exposure to AFB ₁ occurs in slaughterhouse settings and skin also seems to be an important exposure route in some workplaces Citrinin, DON, OTA, and ZEN were detected in nearly all urine samples from mill workers and controls; mycotoxin biomarker levels in urine from mill workers and controls were not significantly different
Saad-Hussein <i>et al.</i> (2014)	Egypt	Wheat handlers, including millers and bakers	AFB ₁	No data available	90 bakers, 100 flour milling workers, and 100 controls with no exposure to flour	ELISA	Serum	Serum AFB ₁ -Alb adduct was significantly higher in bakers than in milling workers; AST and ALT liver enzymes were significantly higher in milling workers and bakers than in controls ($P < 0.05$, $P < 0.0001$), respectively; exposure duration was significantly correlated with serum AFB ₁ in bakers; moreover, there was significant correlation between serum AFB ₁ and both ALT and AST levels in bakers
Ferri <i>et al.</i> (2017)	Italy	Feed mill workers	AFs (M1, G2, G1, B1, B2) and aflatoxinol (AFOH)	March to April 2014	29 exposed workers and 30 controls	HPLC-FLD LOD = 0.025 ng ml ⁻¹ for AFB ₁ , AFG ₁ , AFM ₁ and AFOH and 0.006 ng ml ⁻¹ for AFB ₂ and AFG ₂)	Serum and urine	No quantifiable presence of free aflatoxins was found in serum samples; quantifiable levels of AFB ₁ , AFB ₂ , AFG ₁ , AFG ₂ , and AFM ₁ were found in urine; none of the samples was positive for AFOH; findings revealed the presence of higher AFs concentrations in exposed workers than

Table 2. Continued

Reference	Country	Occupational setting	Investigated mycotoxin(s)	Season	Sampling details	Method LOD-LOQ	Matrix	Main findings
Viegas et al. (2018)	Portugal	Waste management	Beauvericin, citrinin, enniatin A/A1/B1, fumonisin B1, zearalanone, α/β -zearalenol, dihydrocitrinone deoxynivalenol, 10 hydroxyochratoxin A, ochratoxin A, ochratoxin α , T 2 toxin, HT 2 toxin, zearalenone, alternene, alternariol, alternariol-alternariol-monomethyl ether, 2'R ochratoxin A, deoxynivalenol-3-glucuronic acid and HT-2-4-glucuronic acid	Spring and summer	41 workers	HPLC-MS/MS	Serum	in non-exposed controls, although these differences are to be considered consistent with random fluctuations In addition to the AFB ₁ reported in Viegas et al. (2015) , enniatin B (EnB) and ochratoxin A (OTA) were quantified, as was 2'R ochratoxin A (2'R OTA); besides confirming co-exposure to several mycotoxins, results probably indicated different exposure routes for the mycotoxins reported

respiratory protection devices) or workplace specificities which might influence exposure. Personal sampling in the worker's inhalation zone should always be preferred to stationary sampling since it is a better assessment of the true occupational exposure.

Difficulties in interpreting exposure measurements

The absence of exposure limits makes it difficult to interpret exposure measurements. Currently it is not possible to determine acceptable workplace exposure concentrations of mycotoxins to ensure workers' good health. Keeping exposure as low as possible should undoubtedly be an objective. Because these compounds are so infrequently monitored in occupational environments it is impossible to compare exposure levels between different workplaces and to have an idea of what constitutes a normal background concentration. This highlights the great importance of documenting exposures using standard methods of sampling and analysis. Currently, because it is possible to quantify airborne fungi more easily, this is often used as an indirect indicator of the presence of mycotoxins (Halstensen *et al.*, 2006). However, this approach lacks reliability since mycotoxins can be present in the environment long after fungi have been eliminated. Also, not all the fungi produce mycotoxins (Halstensen, 2008; Alborch *et al.*, 2011). Finally, exposure to mycotoxins is frequently characterized by simultaneous exposure to several mycotoxins (see details in Tables 1 and 2). This co-occurring exposure to several mycotoxins is also the most common scenario in the food and feed sector (Grenier and Oswald, 2011; Assunção *et al.*, 2015; De Ruyck *et al.*, 2015; Viegas *et al.*, 2016; Alassane-Kpembi *et al.*, 2017). This aspect brings new challenges to occupational risk assessment.

Measurement, methodology, and biomonitoring

The French National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) has developed a validated method for measuring seven of the most frequently occurring mycotoxins in the workplace; it comes with a detailed sampling and analytical protocol (fiche MetroPol) and meets the criteria required for reproducibility and reliability. Air samples are collected on foam pads, using the CIP 10 personal aerosol sampler (<http://www.bio-rad.com/en-ch/product/cip10-m-air-sampler>) which has an inhalable health-related aerosol fraction selector. Samples are solvent extracted, cleaned using immunoaffinity columns, and analyzed using liquid chromatography with fluorescent detection (Jargot and Melin, 2013). This method allows

the measurement of ochratoxin A, fumonisins and aflatoxins and zearalenone, in the dust extract to which they are normally bound. The method ensures that mycotoxin measurements using conventional analytical equipment is applicable to occupational assessment (Jargot and Melin, 2013).

As an alternative or as a complement to air monitoring, biomonitoring is another way of assessing exposure to mycotoxins. Biomonitoring can include the detection, in easily accessible body fluids such as blood and urine, of the parent compound (mycotoxin) and its metabolites (De Nijs *et al.*, 2016). However, the use of biomonitoring implies the availability of information related with each mycotoxin toxicokinetics, metabolism, and bio-availability to be able to interpret correctly the results (Escrivá *et al.*, 2017).

Recent research using biomarkers (Warth *et al.*, 2013a,b; Gerding *et al.*, 2014, 2015; Heyndrickx *et al.*, 2014) revealed a level of exposure to mycotoxins from food consumption which was above the widely accepted tolerable daily intake values (Assunção *et al.*, 2015). It is important to note that data on background dietary exposure to mycotoxins is needed to determine the additional burden of respiratory and dermal exposure in the workplace (Degen, 2008). If this background data are unavailable, a control group of individuals from the general population should be included to exclude the possibility of exposure by diet (Degen, 2008).

However, as mentioned above, the most common exposure scenario is simultaneous co-exposure to several mycotoxins. This exposure is due to several factors, including the ability of some fungi to produce several mycotoxins simultaneously (Wallin *et al.*, 2015). It is, therefore, extremely relevant, from an occupational health point of view, to be able to measure several mycotoxins in one sample, and the most recent research has indeed developed approaches using multi-mycotoxin biomonitoring (Warth *et al.*, 2013a; Gerding *et al.*, 2014; Solfrizzo *et al.*, 2014; Wallin *et al.*, 2015; Osteresch *et al.*, 2017). Additionally, approaches measuring several mycotoxins in the same sample from different environmental matrices allow to understand and recognize the true exposure scenario (Schenzel *et al.*, 2012; Jargot and Melin, 2013; Van de Perre *et al.*, 2014; Mayer *et al.*, 2016; Viegas *et al.*, 2017) and to perform a more accurate exposure and risk assessment.

Conclusions

Despite increasing numbers of recent published works on the subject, there remains much to be done to have mycotoxins recognized as real and common

occupational risk factors in certain specific settings. It is therefore extremely important to properly characterize mycotoxin exposure (which mycotoxins, at which concentrations, for which duration) in the occupational settings where exposure is probable and to understand which factors can influence that exposure. Standardized methodologies (sampling and analysis) are needed to allow comparisons between different studies. Moreover, to date, there have been insufficient epidemiological studies to assess the acute and chronic health effects of occupational exposure and provide a clear picture of the health risks. This is particularly challenging since one mycotoxin can elicit more than one type of effect and these can occur at different exposure levels.

These studies are also crucial to the future development and implementation of occupational exposure limits for each mycotoxin separately and for mixtures of different mycotoxins that produce the same health effect or share the same mode of action.

Only once this has been accomplished will it be possible to ensure appropriate occupational health interventions: implementation of exposure monitoring programs, application of suitable preventive and protective measures, and implementation of an adequate health surveillance programs for workers who are potentially exposed.

In the meantime, researchers should work together to select/develop an optimal sampling and analysis methodology and participate in large-scale, multi-center, epidemiological studies to obtain relevant data. Occupational hygienists must be aware of these risks and able to recognize critical situations; they should anticipate exposure by implementing preventive measures.

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