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REVIEW

Hazard characterisation for significant mycotoxins in food

Frantisek Malir[1] · Darina Pickova[1] · Jakub Toman[1] · Yann Grosse[2] · Vladimir Ostry[3]

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Abstract

This review updates the current status of activities related to hazard characterisation for mycotoxins, with special reference to regulatory work accomplished within the European Union. Because the relevant information on these topics is widely scattered in the scientific literature, this review intends to provide a condensed overview on the most pertinent aspects. Human health risk assessment is a procedure to estimate the nature and potential for harmful effects of mycotoxins on human health due to exposure to them via contaminated food. This assessment involves hazard identification, hazard characterisation, exposure assessment, and risk characterisation. Mycotoxins covered in this review are aflatoxins, ochratoxin A, cyclopiazonic acid, citrinin, trichothecenes (deoxynivalenol, nivalenol, T-2, and HT-2 toxins), fumonisins, zearalenone, patulin, and ergot alkaloids. For mycotoxins with clear genotoxic/carcinogenic properties, the focus is on the margin of exposure approach. One of its goals is to document predictive characterisation of the human hazard, based on studies in animals using conditions of low exposure. For the other, non-genotoxic toxins, individual 'no adverse effect levels' have been established, but structural analogues or modified forms may still complicate assessment. During the process of hazard characterisation, each identified effect is assessed for human relevance. The estimation of a 'safe dose' is the hazard characterisation endpoint. The final aim of all of these activities is to establish a system, which is able to minimise and control the risk for the consumer from mycotoxins in food. Ongoing research on mycotoxins constantly comes up with new findings, which may have to be implemented into this system.

Keywords Food · Mycotoxins · Health risk assessment · Hazard characterisation · Total diet study

Abbreviations

15-AcDON	15-Acetyl-DON
3-AcDON	3-Acetyl-DON
ARfD	Acute reference dose (for acute exposure)
BMD	Benchmark Dose
BMDL	Benchmark dose lower confidence limit
$BMDL_{05}$	Benchmark dose lower confidence limit for an extra cancer/non-cancer risk of 5%
$BMDL_{10}$	Benchmark dose lower confidence limit for an extra cancer/non-cancer risk of 10%
DON-3-Glu	Deoxynivalenol-3-glucoside
ED	Exposure dose
HBGV	Health-based guidance value
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MOE	Margin of exposure
NOAEL	No observed adverse effect level
NOEL	No observed effect level
RIVM	Rijksinstituut voor Volksgezondheid en Milieu, National Institute for Public Health and the Environment
TDI	Tolerable daily intake (for chronic exposure)
UF	Uncertainty factor

✉ Frantisek Malir
frantisek.malir@uhk.cz

[1] Department of Biology, Faculty of Science, University of Hradec Kralove, Rokitanskeho 62, CZ-50003 Hradec Kralove, Czech Republic

[2] The IARC Monographs Programme, International Agency for Research On Cancer (retired), Lyon, France

[3] Center for Health, Nutrition and Food in Brno, National Institute of Public Health, Palackeho 3a, 61242 Brno, Czech Republic

Introduction

Mycotoxins are naturally occurring secondary metabolites of several toxigenic microfungi. They contaminate the entire food chain with variability from year to year, from the agricultural

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cultures to the consumer's dish (CAST 2003; Bryden 2007; Rossi et al. 2020).

Mycotoxins are mostly produced by fungal genera of *Alternaria*, *Aspergillus*, *Claviceps*, *Fusarium*, *Penicillium*, and *Stachybotrys* (Bennett and Klich 2003; Frisvad et al. 2007b; Karlovsky et al. 2016). Toxigenic microfungi can produce different mycotoxins simultaneously in food commodities. Moreover, food can be contaminated by multiple species of microfungi which cannot be fully eliminated even with good agricultural hygienic and manufacturing practices (Pitt 2000; Karlovsky et al. 2016; Pickova et al. 2021b).

The beginning of modern mycotoxicology started with the discovery of aflatoxins (AFs) in 1960 (Ramos et al. 2011; Pickova et al. 2021b). Since then, many other mycotoxins (e.g. ochratoxin A (OTA), cyclopiazonic acid (CPA), *Fusarium* and *Alternaria* mycotoxins) have appeared as significant food contaminants, many of which leading to intoxications (Bennett and Klich 2003; Malir et al. 2016; Fraeyman et al. 2017; Ostry et al. 2018b).

To date, more than 500 mycotoxins have been identified (Haque et al. 2020), but the total number is still not final. Aflatoxins B_1, B_2, G_1, and G_2 (AFB_1, AFB_2, AFG_1, and AFG_2); OTA; trichothecenes such as deoxynivalenol (DON), nivalenol (NIV), T-2 toxin (T2), and HT-2 toxin (HT2); fumonisins (FUMs) B_1, B_2, and B_3 (FB_1, FB_2, FB_3); zearalenone (ZEN); citrinin (CIT); patulin (PAT) (Selvaraj et al. 2015; Karlovsky et al. 2016; Smith et al. 2016; Ojuri et al. 2018); CPA (Ostry et al. 2018b); *Alternaria* mycotoxins such as tenuazonic acid (Ostry 2008); and ergot alkaloids (EAs) (Karlovsky et al. 2016) are considered among the most significant known mycotoxins in terms of their high abundance in agri-food commodities and known toxic effects. Mycotoxins have been implicated in a range of human diseases and occur in foodstuffs of plant and animal origin (Shephard 2008; Wild and Gong 2010; da Rocha et al. 2014). Humans may be exposed to their combined toxic effects (Speijers and Speijers 2004; Grenier and Oswald 2011; Smith et al. 2016). Dietary exposure to mycotoxins is a worldwide problem for the human population, which is mainly exposed to mycotoxins through the consumption of contaminated food commodities (Sirot et al. 2013; Carballo et al. 2019; Pustjens et al. 2022).

Human health risk assessment is the process to estimate the probability and nature of adverse health effects in human beings exposed to mycotoxins through contaminated food (EFSA 2016a). Human health risk assessment includes four steps: hazard identification, hazard characterisation, exposure assessment, and risk characterisation (see Fig. 1).

The objective of hazard characterisation, the extrapolation stage of risk assessment, is to establish a predictive characterisation of hazard to humans under conditions of low exposure, based on extrapolation from animal studies (extrapolation from high to low dose). In the hazard characterisation stage, each effect identified will be evaluated in terms of its relevance to the human situation. The 'safe dose' estimation is the endpoint of hazard characterisation. Hazard characterisation, a dose–response assessment, includes defining the nature of the adverse health effects associated with mycotoxins in food. If possible, the process should involve an understanding of the doses and related responses as are toxicological reference points, e.g. LOAEL (lowest observed adverse effect level), LOEL (lowest observed effect level), NOAEL (no observed adverse effect level), NOEL (no observed effect level), mathematical modelling BMD (benchmark dose) — BMDL (benchmark dose lower confidence limit), used for calculation of (i) health-based guidance value (HBGV) — toxicological reference values, e.g. tolerable daily intake (TDI), provisional maximum tolerable daily intake (PMTDI), acute reference dose (ARfD), uncertainty factor (UF); (ii) margin of exposure (MOE), exposure dose (ED) (Kuiper-Goodman 1999; EFSA 2005, 2012a, 2017a, 2022b; SCHER/SCCP/SCENIHR 2009; WHO/IPCS 2009).

$$\text{HBGV} = \text{NOAEL or LOAEL or } \text{BMDL}_{10(05)}/\text{UF}.$$
$$\text{MOE} = \text{BMDL}_{10(05)} \text{ or NOAEL/ED}.$$

Information sources

In this review, 145 literature sources (see References) published from 1944 to 2022 were included. Search terms included the combination of mycotoxins, AFs, OTA, DON and their forms, NIV, T2 and HT2, ZEN, FUMs, CIT,

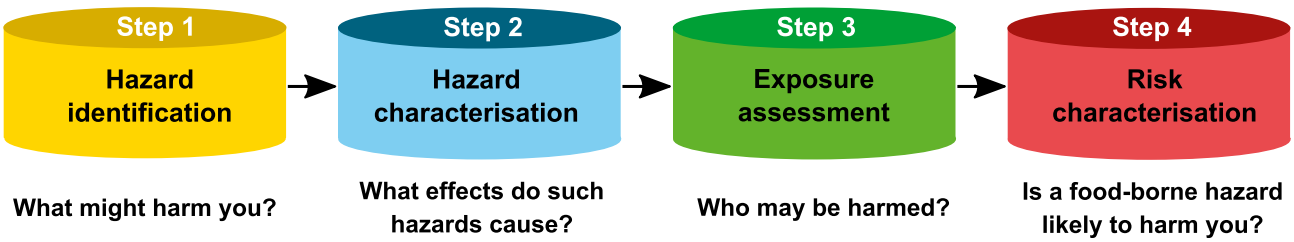

Fig. 1 The four steps of human health risk assessment (based on EFSA 2022a)

PAT, CPA, EAs, and information about mycotoxins from PubChem, mycotoxins producers, mycotoxins contamination of foodstuffs and food, carcinogenic hazard evaluation by the International Agency for Research on Cancer (IARC), and mycotoxins hazard characterisation. Information from books and book chapters was excluded.

Aflatoxins

AFs are among the most harmful mycotoxins. There are more than 20 AFs, and the most widespread are AFB_1 (PubChem CID: 186907), AFB_2 (PubChem CID: 2724360), AFG_1 (PubChem CID: 14421), and AFG_2 (PubChem CID: 2724362), with AFB_1 being the major representative in food crops. Aflatoxin M_1 (AFM_1) (PubChem CID: 15558498) and M_2 (AFM_2) (PubChem CID: 10903619) are the hydroxylated metabolites of AFB_1 and AFB_2, respectively (EFSA 2020a; Nazhand et al. 2020; Pickova et al. 2021b); AFM_1 can be excreted in mammals' milk (EFSA 2020a).

AFs are produced by 22 species of *Aspergillus* section *Flavi* (*Aspergillus flavus*, *A. parasiticus*, and *A. nomius* being the most important), 4 species of *A.* section *Nidulantes*, and 2 species of *A.* section *Ochraceorosei* (Pickova et al. 2021a).

AFs contaminate a wide range of crops such as almonds, groundnuts, nuts like pistachio nuts, hazelnuts, and Brazil nuts, followed by maize, rice, spices, dried figs, and melon seeds. Animal tissues and milk contribute to a lesser extent to human exposure to AFs (EFSA 2007; Mahato et al. 2019; Pickova et al. 2021a).

The IARC classified all AFs in group 1 'carcinogenic to humans' (IARC 2012; Ostry et al. 2017).

Hazard characterisation of aflatoxins

The European Union has been working for many years to harmonise certain standards for AFs in food based on their toxicological evaluation. The ALARA principle ('as low as reasonably achievable') was previously applied to AFs as genotoxic carcinogens (EFSA 2005, 2012a; SCHER/SCCP/SCENIHR 2009; Herrera et al. 2019).

The European Food Safety Authority (EFSA), Panel on Contaminants in the Food Chain (EFSA CONTAM Panel), considers that the hepatocarcinogenicity of AFs is the principal effect for risk assessment. Considering that AFs are genotoxic, the EFSA CONTAM Panel concluded that it was inappropriate to establish a TDI. Based on rodent studies (Wogan et al. 1974), the EFSA CONTAM Panel selected a BMDL for an extra cancer risk of 10% ($BMDL_{10}$) on 0.4 µg/kg body weight (bw) per day for the hepatocellular carcinoma incidence in male rats exposed to AFB_1 to be applied using a margin of exposure (MOE) approach (EFSA 2012a, 2020a).

The BMDL calculation from human data has been considered inappropriate; instead, in 2016, the potencies of cancer estimated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) were used (JECFA FAO/WHO 2018).

The MOE is calculated by dividing the reference point $BMDL_{10}$, by the estimated human exposure dose (ED) (Benford et al. 2010a, b; EFSA 2012a). Regarding the carcinogenic effect, a MOE of 10,000 is considered of low concern for public health. The calculated MOE was lower than 10,000, which is of high public health concern (EFSA 2020a).

Ochratoxin A

OTA (PubChem CID: 442530) is one of the most important mycotoxins from the public health perspective.

OTA is produced by microfungi of the genera *Aspergillus*, e.g. *A. carbonarius*, *A. foetidus*, *A. lacticoffeatus*, *A. niger*, *A. sclerotioniger*, *A. steynii*, *A. tubingensis*, and *A. westerdijkiae*, and *Penicillium*, e.g. *P. nordicum* and *P. verrucosum* (Frisvad et al. 2007b; Ostry et al. 2013).

OTA often contaminates a wide range of foodstuff of both plant origin, e.g. beer, cereal products, chocolate, cocoa, coffee, grape juice, liquorice, dried grape, spices, and wine and animal origin, e.g. cheese, crude meat, liver, pork, pork blood products, poultry kidney, and salted and smoked fish (Ostry et al. 2013; Skarkova et al. 2013; EFSA 2020b; Kumar et al. 2020).

OTA is known for its nephrotoxic, hepatotoxic, immunotoxic, genotoxic, teratogenic, and neurotoxic effects (Bui-Klimke and Wu 2015; Heussner and Bingle 2015; Malir et al. 2021) characterised by sex and species sensitivity differences. In addition, OTA has been classified by the IARC in group 2B 'possibly carcinogenic to humans' (Ostry et al. 2017).

Hazard characterisation of ochratoxin A

Carcinogenesis is supported by both direct and indirect genotoxic modes as well as non-genotoxic modes of action. Due to the uncertainty on the mode of action for kidney carcinogenicity raised by the latest studies on OTA, it was considered inappropriate to establish an HBGV, so the MOE approach was applied.

For non-neoplastic effects characterisation, a $BMDL_{10}$ of 4.73 µg/kg bw per day was calculated from pig kidney lesions. A calculated MOE of above 200 is considered of low concern for public health regarding non-carcinogenic effects (EFSA 2020b). For neoplastic effects characterisation, a $BMDL_{10}$ of 14.5 µg/kg bw per day was calculated from rat kidney tumours incidence (Rached et al. 2007; Dai et al. 2014; Qi et al. 2014a, b). An MOE of 10,000 is considered of low concern for public health with respect to the carcinogenic

effect. The calculated MOE was lower than 10,000, which is of high public health concern (EFSA 2020b).

Deoxynivalenol and their forms

DON (PubChem CID: 40024) and its derivatives 3-acetyl-DON (3-AcDON) (PubChem CID: 104759), 15-acetyl-DON (15-AcDON) (PubChem CID: 10382483), and deoxynivalenol-3-glucoside (DON-3-Glu) (PubChem CID: 14806531) are trichothecenes type B displaying a sesquiterpenoid structure.

DON, 3-AcDON, and 15-AcDON are mainly produced by *Fusarium culmorum* and *F. graminearum* (Frisvad et al. 2007b; Desjardins and Proctor 2007). DON-3-Glu is formed after detoxification (by glucosylation) of DON in plants (Poppenberger et al. 2003).

DON, 3-AcDON, and 15-AcDON are widely detected worldwide in cereals, such as barley, maize, oats, rye, and wheat (Sugita-Konishi et al. 2006; EFSA 2017b). They are resistant to the principal industrial processes, e.g. heating, milling, and manufacturing and, consequently, easily enter the food chain (Larsen et al. 2004; Sugita-Konishi et al. 2006). After decades of investigations, knowledges, about DON and the most adequate way to manage it, are constantly made available. However, an important work still needs to be achieved because DON remains a complex challenge, exacerbated by evolving fungal populations, climate change, and the constant necessity for global food safety (Sumarah 2022).

Trichothecenes type B were reported as being immunosuppressive and immunomodulatory (Pestka and Smolinski 2005; Pinton and Oswald 2014; Escrivá et al. 2015; Bertero et al. 2018). DON has been classified in group 3 'not classifiable as to its carcinogenicity to humans' by the IARC (Ostry et al. 2017).

Hazard characterisation of deoxynivalenol and their forms

The JEFCA has established a PMTDI for DON and its acetylated derivatives (3-AcDON and 15-AcDON) of 1 µg/kg bw/day using a NOEL of 0.1 mg/kg bw per day (Iverson et al. 1995) based on decreased body weight gain observed in a 2-year feeding study in mice and application of a safety factor of 100 (Bondy 2009; JECFA FAO/WHO 2011; Bondy et al. 2016).

A current group TDI of 1 µg/kg bw/day was established for the sum of DON, 3-AcDON, 15-AcDON, and DON-3-Glu based on reduced body weight gain observed in both male and female mice (Schiefer et al. 1985; Tomar et al. 1987; Girardet et al. 2011a, b; Flannery et al. 2011; Wu et al. 2014a, b), considered the critical chronic effect for human risk assessment. Based on this endpoint, a $BMDL_{05}$ of 0.11 mg/kg bw/day was calculated for reduced body weight gain using the default UF of 100 for inter-species and intra-species variability. A group acute reference dose (ARfD) of 8 µg/kg bw per eating occasion for the sum of DON, 3-AcDON, 15-AcDON, and DON-3-glucoside, based on a NOAEL of 26 µg DON/kg bw per eating occasion for emesis, was calculated. In establishing the ARfD, a UF of 3.16 for toxicokinetic differences in the human population was applied (EFSA 2017b).

Nivalenol

NIV (PubChem CID: 5284433) is also a trichothecene type B with a sesquiterpenoid structure.

NIV is produced primarily by *Fusarium culmorum*, *F. graminearum*, and *F. tricinctum* (Frisvad et al. 2007b; Desjardins and Proctor 2007).

Worldwide, NIV is widely occurring in cereals, such as barley, maize, oats, rye, and wheat (Gareis et al. 2003; Schollenberger et al. 2007; Edwards 2009a, b, c; Gottschalk et al. 2009).

Toxic effects of NIV include haematological disturbances, leukopenia, immunosuppression, and immunomodulatory effects (Ohtsubo et al. 1989; Takahashi et al. 2008; Sugita-Konishi et al. 2008). The IARC has classified NIV in group 3 'not classifiable as to its carcinogenicity to humans' (Ostry et al. 2017).

Hazard characterisation of nivalenol

NIV is probably not genotoxic; therefore, the CONTAM Panel considered it useful to establish a TDI. For the TDI determination, a UF of 3 for gaps in the database and the standard UF of 100 to account for inter-species and intra-species differences were used, and based on a $BMDL_{05}$ of 0.35 mg/kg bw/day, a TDI of 1.2 µg/kg bw/day was calculated (EFSA 2013).

T-2 and HT-2 toxins

T2 (PubChem CID: 442400) and HT2 (PubChem CID: 10093830) are type A trichothecenes, and both are related epoxy-sesquiterpenoids.

T2 and HT2 are produced primarily by *F. langsethiae* and *F. sporotrichioides* (Frisvad et al. 2007b; Desjardins and Proctor 2007).

Grain-based foods and grains, especially bread, breakfast cereals, fine bakery wares, and grain milling products contribute the most to the sum of T2 and HT2 exposures. T2 and HT2 are relatively stable substances during baking and cooking (van der Fels-Klerx and Stratakou 2010; EFSA 2017c).

T2 inhibits protein, DNA and RNA synthesis, and there are indications that it induces apoptosis and tissue necrosis, and also lipid peroxidation, which influences the integrity

of cell membranes (Ostry et al. 2020). T2 causes haematotoxicity and myelotoxicity linked to haematopoietic impairment in the bone marrow (Escrivá et al. 2015; Adhikari et al. 2017; Steinkellner et al. 2019). The IARC classified T2 in group 3 'not classifiable as to its carcinogenicity to humans' (Ostry et al. 2017).

Hazard characterisation of T-2 toxin and HT-2 toxin

Based on a LOEL of 0.029 mg/kg bw per day from a 3-week dietary pig study, a PMTDI (UF, 500) of 60 ng/kg bw per day was determined for T2 and HT2 alone or their combination. Based on the reduction of the antibody response to a specific antigen in a subchronic study with pigs, a group TDI of 100 ng/kg bw/day was established for the sum of T2 and HT2 (Rafai et al. 1995a, b; JECFA FAO/WHO 2001).

In a subchronic study in rats, a reduction in total leukocyte count was reported as being the toxicity endpoint for the TDI determination. From this endpoint, a $BMDL_{10}$ of 3.33 µg T2/kg bw/day was calculated by applying a UF of 200 for interspecies and intra-species variability, and a new group TDI for T2 and HT2 was set at 20 ng/kg bw/day (EFSA 2017c).

Emetic effects, reported in an acute toxicity study in minks exposed to both T2 and HT2, were identified as being the toxicity endpoint for establishing a group ARfD for T2 and HT2, and benchmark dose calculations led to a $BMDL_{10}$ of 2.97 µg T2 or HT2/kg bw/day. Using a UF of 10, a group ARfD of 0.3 µg T2 and HT2/kg bw was set. An interspecies factor was not applied since it was assumed that human beings are not more sensitive than minks to this effect (EFSA 2017c).

Zearalenone

ZEN (PubChem CID: 5281576) is part of *Fusarium* (*F.*) mycotoxins other than trichothecenes. ZEN is a phenolic resorcylic acid lactone.

ZEN is produced mainly by *F. culmorum* and *F. graminearum* (Frisvad et al. 2007b; Desjardins and Proctor 2007; Bertero et al. 2018).

ZEN exposure is linked to its presence in grains and grain-based foods, mainly bread, breakfast cereals, fine bakery wares, and grain milling products (Zinedine et al. 2007; De Boevre et al. 2013).

ZEN causes reproductive toxicity in some animal species and probably in humans, because ZEN is a non-steroidal estrogenic agent (Gao et al. 2018). In foetuses and infants, exposure to ZEN can cause breast enlargement, premature thelarche, and pubarche. ZEN also causes delayed implantation, foetal growth retardation, and loss of conceptuses (Zinedine et al. 2007; Kunishige et al. 2017; Gao et al. 2018). The IARC has classified ZEN in group 3 'not classifiable as to its carcinogenicity to humans' (Ostry et al. 2017).

Hazard characterisation of zearalenone

In a 15-day pig study (Edwards et al. 1987), based on a NOEL of 40 µg/kg bw per day, a PMTDI for ZEN was set at 0.5 µg/kg bw per day (JECFA FAO/WHO 2000).

Based on pig estrogenicity, the EFSA has set a current TDI of 250 ng/kg bw per day for ZEN based on a NOEL of 10 µg/kg bw per day by applying a UF of 40 (4 for interspecies toxicokinetic differences, as humans were not considered more sensitive than female pigs, and 10 for intra-human variability (EFSA 2011, 2016b; Lorenz et al. 2019).

Fumonisins

FUMs are one of the most important and harmful mycotoxins. They contain two tricarballylic acid moieties. More than 28 FUMs are known, essentially categorised into the A-series, B-series, C-series, and P-series; FB_1 (PubChem CID: 2733487), FB_2 (PubChem CID: 2733489), and FB_3 (PubChem CID: 3034751) are the most frequent.

FUMs are produced by *Fusarium* species, e.g. *F. anthophilum*, *F. dlamini*, *F. napiforme*, *F. nygamai*, *F. oxysporum*, *F. proliferatum*, *F. verticillioides*, and *A. niger* (FB_2). *F. verticillioides* and *F. proliferatum* are the most significant species that produce FUMs (Frisvad et al. 2007a, b; Desjardins and Proctor 2007).

The most frequently contaminated crop is maize, and FUMs are the most prevalent mycotoxins in maize, although these mycotoxins may also be present in some other crops. FUMs have also been found in asparagus, figs, garlic, millet, onion, pea, raisins, sorghum, and soybean. FB_2 was detected in coffee beans, pine nuts, and red wine (Braun and Wink 2018).

FUMs cause pulmonary oedema in pigs, rat liver cancer, and leukoencephalomalacia in horses (Marasas 2001). Among other species, FUMs toxic effects (e.g. in the liver, kidney, or other organs) have been studied in cattle, lambs, poultry, and fish (EFSA 2018). FUMs show teratogenic and immunotoxic effects (Stockmann-Juvala and Savolainen 2008) and have also been associated with human neural tube defects and oesophagal cancer (Franceschi et al. 1990; Dragan et al. 2001; Missmer et al. 2006). FB_1 and FB_2 have been classified in group 2B 'possibly carcinogenic to humans' by the IARC (Ostry et al. 2017).

Hazard characterisation of fumonisins

For FB_1, FB_2, and FB_3, alone or in combination, a PMTDI was set at 2 µg/kg bw per day based on a NOAEL of 0.2 mg/

kg bw per day for kidney toxicity and a UF of 100 (JECFA FAO/WHO 2012).

For FB_1, based on a $BMDL_{10}$ of 0.1 mg/kg bw per day derived for megalocytic hepatocytes induction in mice and a UF of 100 for intra-species and inter-species variability, a TDI was set at 1.0 µg FB_1/kg bw per day (EFSA 2018). The CONTAM Panel also concluded that FB_2, FB_3, and FB_4 (excluding the modified FUMs) should be placed in the same group TDI with FB_1 with respect to their similar structure and assuming similar mode of action and toxic potencies, despite of the lack of relevant data.

Citrinin

CIT (PubChem CID: 54680783) is a polyketide mycotoxin produced worldwide in foodstuffs by microfungi of the genera *Aspergillus*, e.g. *A. niger*, *Monascus*, e.g. *M. purpureus*, and *Penicillium*, e.g. *P. expansum* (Frisvad et al. 2007b; Ostry et al. 2013; Nejati et al. 2014).

Data on the occurrence of CIT in foodstuffs are still insufficient to accurately estimate CIT exposure in humans (EFSA 2012b; Ostry et al. 2013). Nonetheless, CIT has been reported in grapes before storage (Aziz and Moussa 2002) and in grape must (Ostry et al. 2018a). CIT has also been detected in beans, fruits, fruit and vegetable juices, herbs, and spices (EFSA 2012b; Ostry et al. 2013).

CIT is nephrotoxic to animals: in repeat-dose toxicity studies, kidney has been identified as the main target organ of CIT, and significant species differences in the susceptibility to CIT have been demonstrated (EFSA 2012b). In humans, CIT also affects the renal system (Schulz et al.2018). CIT has been classified in group 3 'not classifiable as to its carcinogenicity to humans' by the IARC (Ostry et al. 2017).

Hazard characterisation of citrinin

EFSA has assessed the toxicity of CIT and concluded that CIT is nephrotoxic, with a NOAEL of 20 µg/kg/ bw per day (highest dose tested) derived from a 90-day study in male rats (Lee et al. 2010; EFSA 2012b). Because of database limitations, a derivation of the HBGV was considered inappropriate, but a 'level of no concern for nephrotoxicity' of 0.2 µg/kg bw per day was set (EFSA 2012b).

The Netherlands National Institute for Public Health and the Environment (RIVM) has assessed CIT toxicity using a benchmark dose analysis for another endpoint (RIVM 2017); the lowest BMDL of 48 µg/kg bw per day derived from the endpoint 'decreased crown-rump length' proposed by Singh et al. (2014), which was assumed to be an appropriate departure point for risk assessment. This BMDL is 2.4 times higher than the NOAEL established by the EFSA in 2012 (EFSA 2012b).

Patulin

PAT (PubChem CID: 4696) is a water-soluble lactone produced by numerous species of *Aspergillus*, *Byssochlamys*, and *Penicillium* genera (Frisvad et al. 2007b). *P. expansum* is one of the principal PAT producers and is frequently found in apple products. *P. expansum* causes a postharvest rot in many different fruits such as apples, apricots, blackcurrants, cherries, citrus fruits, grapes, melons, peaches, pears, plums, and strawberries (Snowdon 1990; Larsen et al. 1998; Ostry et al. 2018a).

PAT mainly causes gastrointestinal disorders including bleeding, distension, and ulcers. PAT provokes congestion and oedema of the gastrointestinal, hepatic, and pulmonary blood vessels and tissues (Wouters and Speijers 1996; Puel et al. 2010). PAT has been classified in group 3 'not classifiable as to its carcinogenicity to humans' by the IARC (Ostry et al. 2017).

Hazard characterisation of patulin

In a long-term carcinogenicity and toxicity study in rats, a dose level of 0.1 mg/kg bw per day of PAT produced no effect in terms of decreased body weight gain in males (Becci et al. 1981). However, as PAT was administered only three times per week for 24 months, the NOEL derived from this study was 43 µg/kg bw per day, and the PMTDI for PAT was set at 0.4 µg/kg bw per day (using a safety factor of 100) (JECFA FAO/WHO 1995).

Similarly, the Scientific Committee on Food (SCF) of the European Commission also set a PMTDI of 0.4 µg/kg bw/day for PAT (SCF 2000).

Cyclopiazonic acid

CPA (PubChem CID: 54695722) is produced by a number of *Penicillium*, e.g. *P. camemberti*, *P. commune*, *P. dipodomyicola*, and *P. griseofulvum*, and *Aspergillus* species, e.g. *A. flavus*, *A. oryzae*, and *A. tamarii* (Frisvad and Samson 2004; Frisvad et al. 2007b; Ostry et al. 2018b).

CPA is widely found in naturally contaminated agricultural raw commodities. CPA occurs in food commodities such as cereals, cheese, dried figs, meat products, milk, nuts, and oilseed. CPA can be also detected in maize and peanuts; the presence of CPA and AFs in peanuts and maize contaminated with *A. flavus* indicates that synergy of effects may occur (Ostry et al. 2018b).

CPA is toxic to various animal species, such as pigs, guinea pigs, rats, dogs, and poultry. Following the ingestion of CPA-contaminated feed, the animals developed severe gastrointestinal disturbances and neurological disorders. The principal target organs were the digestive tract, kidney, liver, and heart, in which degenerative changes and necrosis were reported (Voss 1990; Burdock and Flamm 2000; Chang et al. 2009).

Hazard characterisation of cyclopiazonic acid

In the available studies on CPA, no BMD, LOAEL, or NOAEL could be identified for any pertinent endpoint. Indeed, toxicity data for risk assessment are rather limited. Consequently, no risk assessment was performed by the EFSA or the JECFA. While the acceptable daily intake (ADI) should only be applied to food additives, veterinary drugs, or pesticide residues in food, Burdock and Flamm (2000) proposed an ADI of 10 µg CPA/kg bw based on a NOEL of 1.0 mg/kg bw/day derived from a 2-week study in pigs (Lomax et al. 1984).

On the approach of Burdock and Flamm (2000) responded De Waal (2002) who suggested a TDI of 0.1 µg/kg bw per day CPA, based on a NOEL of 0.1 mg/kg bw per day observed in the 90-day dog study by Nuehring et al. (1985). A composite UF of 1000, based on intra-species variability and the uncertainties in the extrapolation from test animals to humans, was used (De Waal 2002). The TDI of De Waal (2002) could be reached by a 70 kg adult consuming 50 g of maize containing CPA at a dose of 0.14 µg/g per day. There is probably no basis for establishing a TDI due to the lack of adequate data, in particular, those data reported in the relevant subchronic studies (Ostry et al. 2018b).

Ergot alkaloids

EAs are produced by some members of the fungal orders of Eurotiales and Hypocreales. In Europe, *Claviceps purpurea* is the most prevalent of *Claviceps* (*C.*) species within the Hypocreales (Pazoutova 2001). The principal EAs identified in sclerotia of *C. purpurea* are ergotamine (PubChem CID: 8223), ergosine (PubChem CID: 105137), ergometrine (PubChem CID: 443883), ergocristine (PubChem CID: 31116), ergocryptine (PubChem CID: 99049) (which is a mixture of α- and β-isomers), ergocornine (PubChem CID: 73453), and the corresponding–inine epimers (Orlando et al. 2017; Grusie et al. 2018).

All *Claviceps* species may infest plant species from *Poaceae* (cereal crops, and cultivated and wild grasses). *C. purpurea* commonly affects cereals such as barley, millets, oats, rye, triticale, and whea, and EAs occur mainly in barley, rye, triticale, and wheat (Orlando et al. 2017; Grusie et al. 2018).

C. purpurea produces a number of toxic EAs effects such as agalactia, convulsions, hallucinations, hyperthermia, and gangrene when ingested (Haarmann et al. 2009; Burrows and Tyrl 2012; Klotz 2015; Reddy et al. 2020).

In a 2-year carcinogenicity study in rats, the incidence of ear neurofibroma was increased after administration of ergotoxine. In a companion study, crude ergot containing approximately the same amount of ergotoxine caused up to a sixfold increase in ear neurofibroma incidence (Fitzhugh et al. 1944). The evidences from the above study point at a non-genotoxic mode of action according to the CONTAM Panel (EFSA 2012c). IARC has not evaluated the carcinogenicity to humans of EAs.

Hazard characterisation of ergot alkaloids

For EAs, a group TDI was established at 0.6 µg/kg bw per day based on a $BMDL_{10}$ of 0.33 mg/kg bw per day that was derived from the incidence of tail muscular atrophy in a 13-week ergotamine feeding study in rats (Speijers 1993). An additional UF of 2 was used for extrapolation from subchronic to chronic studies, and an overall UF of 600 was applied (EFSA 2012c, 2017d).

A group ARfD of 1 µg/kg bw per eating occasion based on a $BMDL_{10}$ of 0.33 mg/kg bw per day was derived from the incidence of tail muscular atrophy in the same above study (Speijers 1993). In setting the ARfD, a UF of 3 was used to consider database deficiencies such as incomplete information on reproductive toxicity, together with the default UF of 100 for intra-species and inter-species differences. Overall, a UF of 300 was used (EFSA 2012c, 2017d).

This article provides an overview of the hazard characterisation for significant mycotoxins in food. For greater clarity, a summary of the toxicological reference points for mycotoxins in food is also provided in Table 1.

Discussion

The topic of this article is important because of the global impact of mycotoxins on human health. The article brings current information on the hazard and human health risk assessment of the most toxic mycotoxins and describes the recent approaches to hazard characterisation of mycotoxins. The global impact of mycotoxins on human health is often underestimated, although mycotoxins are a hot topic and determining the risk associated with their uptake is an ongoing and evolving process.

This article on current approaches to risk characterisation for mycotoxins could be beneficial for toxicologists, risk assessors, risk managers, and the mycotoxin professional community. It can be also useful as a foundation or starting point for newcomers to the mycotoxicology field to be

Table 1 Compilation of key toxicological data for mycotoxins covered in this review

Mycotoxins	Toxicological reference point	Toxicological reference value	References
Aflatoxin B_1	$BMDL_{10}$: 0.4 µg/kg bw/day	MOE ≥ 10,000	EFSA 2020a
Ochratoxin A	$BMDL_{10}$: 4.73 µg/kg bw/day for non-neoplastic effects	MOE ≥ 200	EFSA 2020b
	$BMDL_{10}$: 14.5 µg/kg bw/day for neoplastic effects	MOE ≥ 10,000	EFSA 2020b
Deoxynivalenol and their forms	NOEL: 0.1 mg/kg bw/day	PMTDI: 1000 ng/kg bw/day	JECFA FAO/WHO 2011
	$BMDL_{10}$: 0.21 mg/kg bw/day	Group ARfD: 8 µg/kg bw	JECFA FAO/WHO 2011
	$BMDL_{05}$: 0.11 mg/kg bw/day	TDI: 1000 ng/kg bw/day	EFSA 2017b
	NOAEL: 26 µg DON/kg bw/day	Group ARfD: 8 µg/kg bw per eating occasion	EFSA 2017b
Nivalenol	$BMDL_{05}$: 0.36 mg/kg bw/day	TDI: 1.2 µg/kg bw/day	EFSA 2013
T-2 and HT-2 toxins	LOEL: 0.029 mg/kg bw/day	PMTDI alone or in combination: 60 ng/kg bw/day	JECFA FAO/WHO 2001
	$BMDL_{10}$: 3.33 µg/kg bw/day	Group TDI for T2 and HT2: 20 ng/kg bw/day	EFSA 2017c
	$BMDL_{10}$: 2.97 µg/kg bw/day	Group ARfD for T2 and HT2: 0.3 µg/kg bw	EFSA 2017c
Zearalenone	NOEL: 40 µg/kg bw/day	PMTDI: 0.5 µg/kg bw/day	JECFA FAO/WHO 2000
	NOEL: 10.4 µg/kg bw/day LOEL: 17–200 µg/kg bw/day	TDI: 250 ng/kg bw/day	EFSA 2016b
Fumonisins	NOAEL: 0.2 mg/kg bw/day	PMTDI for FB_1, FB_2, FB_3, alone or in combination: 2 µg/kg bw/day	JECFA FAO/WHO 2012
	$BMDL_{10}$: 0.1 mg/kg bw/day	TDI for FB_1: 1.0 µg/kg bw/day	EFSA 2018
Citrinin	NOAEL: 20 µg/kg bw/day	Level of no concern for nephrotoxicity: 0.2 µg/kg bw/day	EFSA 2012b
	BMDL: 48 µg/kg bw/day	Not specified	RIVM 2017
Patulin	NOEL: 0.043 mg/kg bw/day	PMTDI: 0.4 µg/kg bw/day	JECFA FAO/WHO 1995
	NOEL: 0.043 mg/kg bw/day	PMTDI: 0.4 µg/kg bw/day	SCF 2000
Cyclopiazonic acid	NOEL: 0.1 mg/kg bw/day	TDI: 0.1 µg/kg bw/day	De Waal 2002
Ergot alkaloids	$BMDL_{10}$: 0.33 mg/kg bw/day	Group TDI: 0.6 µg/kg bw/day	EFSA 2012c, 2017d
	$BMDL_{10}$: 0.33 mg/kg bw/day	Group ARfD: 1 µg/kg bw per eating occasion	EFSA 2012c, 2017d

ARfD acute reference dose, *$BMDL_{05}$* benchmark dose lower confidence limit for an extra cancer/non-cancer risk of 5%, *$BMDL_{10}$* benchmark dose lower confidence limit for an extra cancer/non-cancer risk of 10%, *bw* body weight, *EFSA* European Food Safety Authority, *FAO/WHO* Food and Agriculture Organisation/World Health Organisation, *JECFA* The Joint FAO/WHO Expert Committee on Food Additives, *LOAEL* lowest observed adverse effect level, *LOEL* lowest observed effect level, *MOE* margin of exposure, *NOAEL* no observed adverse effect level, *NOEL* no observed effect level, *PMTDI* provisional maximum tolerable daily intake, *RIVM* Rijksinstituut voor Volksgezondheid en Milieu, National Institute for Public Health and the Environment, *SCF* Scientific Committee on Food, *TDI* tolerable daily intake

directed to deeper sources of information. Additionally, the realisation of Total Diet Study at the national level can be assessed using this information on risk characterisation.

Moreover, it would be appropriate to conduct new studies because of the paucity of adequate chronic or subchronic studies for some mycotoxins, e.g. CPA, and also as the emerging mycotoxins such as enniatins, beauvericin, or *Alternaria* mycotoxins.

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Declarations

Conflict of interest The authors declare no competing interests.

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