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Overview of the activities of the European Food Safety Authority on mycotoxins in food and feed

M. Eskola[1*#], A. Altieri[2] and J. Galobart[3]

[1]Center for Analytical Chemistry, BOKU-University of Natural Resources and Life Sciences Vienna, Department IFA-Tulln, Konrad Lorenz Str. 20, 3430 Tulln, Austria; [2]Evidence Management Unit, European Food Safety Authority EFSA, Via Carlo Magno 1A, 43126 Parma, Italy; [3]Feed Unit, European Food Safety Authority EFSA, Via Carlo Magno 1A, 43126 Parma, Italy; mari.eskola@boku.ac.at #paper authored as EFSA employee and submitted as BOKU employee

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REVIEW ARTICLE

Abstract

Mycotoxins are widely occurring in foods and feeds and dietary exposure to them can induce various types of adverse health effects in humans and animals. Since its establishment in 2002, the European Food Safety Authority (EFSA) has assessed risks of dietary exposure to mycotoxins for public health and for the health of farm and companion animals on the request of the European Commission and has assessed safety and efficacy of feed additives for the reduction of contamination of feed by mycotoxins within the European Union authorisation process for feed additives. Over 40 scientific opinions on risks of mycotoxins for human and animal health and other reports on mycotoxins have been issued by the authority for the use of the European risk managers. Mycotoxins belong to one of the important areas of the EFSA work. Occurrence data on mycotoxins submitted to EFSA by the European national food safety bodies and research institutions have been collected in the EFSA databases and have informed its scientific opinions and reports on mycotoxins. Similarly, many EFSA-funded projects conducted by the European research organisations, not only to generate data on occurrence, but also data on toxicity of mycotoxins, have provided valuable information for the risk assessments of EFSA. Aflatoxin and deoxynivalenol are the mycotoxins, for which EFSA has delivered most of its scientific mycotoxin opinions. Very recently also modified forms of mycotoxins have been included in the EFSA risk assessments. In this review paper an overview of many different EFSA activities on mycotoxins is given. It also includes a brief description how EFSA develops its scientific opinions and works.

Keywords: EFSA, opinion, risk assessment, public health, animal health

1. Introduction

Mycotoxins are widely occurring secondary metabolites of plant pathogenic fungi in foods and feeds. Since dietary exposure to mycotoxins can induce various types of adverse health effects such as carcinogenic, hepatotoxic, nephrotoxic, estrogenic, cytotoxic, immunotoxic and neurotoxic effects, and death in humans and animals, they are considered important agricultural contaminants in foods and animal feeds. Since the mankind started to cultivate crops and to store them from one harvest year to another, mycotoxins have possibly been present in the diets of humans and farm and companion animals (Pitt and Miller, 2016). Cereal grains have always been the main source of mycotoxins, although other crops are also affected and transfer from animal feed to foods of animal origin also takes place. Often aflatoxins (AFs), trichothecenes, zearalenone (ZEA), fumonisins, ochratoxin A (OTA), ergot alkaloids (EAs), patulin and citrinin are regarded agriculturally as the most consequential mycotoxins, although many other mycotoxins are known to contaminate crops (Asam *et al.*, 2017; Bennett and Klich, 2003; Pitt and Miller, 2016; Rychlik, 2017; Wu *et al.*, 2014). The mycotoxins typically co-occur in foods and feeds and their occurrence vary from year to year depending on the weather and other environmental conditions. Many modified forms of mycotoxins (also known as masked mycotoxins) have also been found (Asam *et al.*, 2017; Berthiller *et al.*, 2013; Dall'Asta and

Berthiller, 2016). It is expected that the evolving scientific research on mycotoxins, in particular related to analytical method development for determining the wide spectrum of metabolites of fungal and plant origin, will likely reveal new mycotoxins and modified forms (Berthiller *et al.*, 2017; Dall'Asta and Berthiller, 2016; Uhlig *et al.*, 2013). Whether the new discovered metabolites of mycotoxins are relevant, considering their occurrence and/or toxicity from the public health or farm and companion animal health view point, is to be elucidated in upcoming studies.

It has been well recognised for many years that large economical losses occur worldwide owing to the mycotoxin contamination in agricultural products as recently summarised by Pitt and Miller (2016). Climate change is expected in the coming decades to impact fungal growth and agricultural practices and, consequently, to the mycotoxin concentrations and incidence in the cultivated crops. Changes in climate will lead to shifts in the geographic distributions of mycotoxin-producing fungi and the patterns of mycotoxin occurrence. All this is further believed to influence economical losses linked to mycotoxin problem in crops and food security as discussed by Wu and Mitchell (2016). In order to reduce economical losses various pre- and post-harvest strategies to mitigate fungal growth and mycotoxin occurrence in crops have been developed and studied for many years, as recently comprehensively reviewed in the book of Leslie and Logrieco (2014).

While in general is believed, that mycotoxin occurrence in food and feed crops will increase with the changing climate, large variation in mycotoxin contamination is expected (Van der Fels-Klerx *et al.*, 2012a,b, 2016; Battilani *et al.*, 2013). Decreased occurrences of certain mycotoxins in crops have also been predicted to occur due to the climate change (Van der Fels-Klerx *et al.*, 2016). It has been estimated that amongst 500 million people living in sub-Saharan Africa, Latin America and Asia the exposure to mycotoxins is at a level that notably increases mortality and morbidity (IARC, 2015). The changing climate conditions leading to increased mycotoxin levels in food and feed crops, and consequently to higher human and animal dietary exposures, will worsen the health risks for both humans and animals if the mycotoxin concentrations are not kept at appropriately low levels (Wu and Mitchell, 2016).

Because of the common (co-)occurrence of mycotoxins in foods and feeds and the public health and farm animal health concern from their exposure, legal maximum levels (MLs) or indicative or guidance levels for the concentrations of many mycotoxins in foods and feeds have been set in the European Union (EU) and in over 100 nations worldwide (EC, 2006a,b and their amendments, 2013; EU, 1993, 2002; FAO, 2004; Wu *et al.*, 2014). In their risk management decisions (e.g. setting regulatory MLs), the EU risk managers (European Commission (EC) and EU Member States (EU MSs)) have to take into account the results of the respective risk assessments, opinions of the European Food Safety Authority (EFSA) and other relevant factors including societal, economic, traditional, ethical and environmental elements and the feasibility of controls. Food business operators, however, have the primary responsibility for ensuring compliance with the EU food law (Regulation (EC) No 178/2002; EC, 2002). In the European food safety system, risk assessment is done independently from risk management. Since its establishment in 2002, EFSA has supplied a large amount of scientific advice on food and feed safety at the European level, typically in the form of risk assessments, to the European risk managers. This advice forms the scientifically evidenced basis for the risk managers to adopt European policies to protect public health. While EFSA supports the EC and EU Member States in taking appropriate, effective and timely risk management decisions, it has no responsibility for risk management measures. Nor does the EFSA substitute the national food safety bodies, but cooperates with them. More information is available at www.efsa.europa.eu/.

This review gives an overview of the published scientific outputs of EFSA on mycotoxins and its currently on-going activities on them. Furthermore, the EFSA occurrence data collection and data quality requirements for mycotoxins, and data needs for risk assessment on feed additives reducing mycotoxin contamination are underlined. The purpose is not to provide details on the scientific opinions related to the risk assessments on mycotoxins and feed additives intended to reduce mycotoxin contamination, or the detailed explanation on risk assessment process.

2. EFSA and mycotoxins

EFSA's remit covers food and feed safety, nutrition, animal health and welfare, plant protection and plant health. In the process of developing its scientific advice (opinions), the ten EFSA Scientific Panels and Scientific Committee (SC) play a crucial role. While the Panels deal with the various scientific topics within their remit, the SC is responsible for horizontal scientific matters across EFSA's remit. To date, all requests for issuing scientific advice on mycotoxins have been received by EFSA from the EC. The request typically includes terms of reference to which the requestor expects EFSA to reply. The request can also be urgent when the scientific advice is needed by the requestor in a short period of time. The requests on mycotoxins fall within the remits of the EFSA Panels on Contaminants in the Food Chain (CONTAM Panel), EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) (Tables 1 and 2) or the EFSA Unit on Evidence Management (DATA). However, also the EFSA SC and the Emerging Risks Unit have worked on mycotoxins, and the EFSA Panel on Plant health assesses risks posed by

pests, including fungal diseases, and weeds to plant health. Most of the time a working group (WG) is set up under the Scientific Panel to answer to the request or the request is answered by an ongoing WG of the Panel. In the WG work, as in the Panel and Committee work, the external scientific experts of EFSA from all over Europe and worldwide are the important operators, as they draft the EFSA scientific opinions. The EFSA staff contributes to this work, and coordinates and supports it. The opinion finalised by the WG is discussed and eventually adopted by the Scientific Panel or Committee, after which it is published in the open access EFSA Journal and its scientific outcome is communicated by EFSA. The risk communication is done in cooperation with the EC. More information and Register of Questions for the requests are available at: www.efsa.europa.eu/.

Mycotoxins and the EFSA Panel on Contaminants in the Food Chain

The CONTAM Panel delivers risk assessments on mycotoxins in foods and feeds, but its remit covers also other chemical contaminants (process and environmental contaminants, natural toxicants and residues of unauthorised substances). To assess the risks for public health and farm and companion animal health from the exposure to mycotoxins, and hence to develop the related scientific opinions, the CONTAM Panel collects and scrutinises scientific information on the mycotoxins available in the public domain. Typically, this published evidence includes data on toxicokinetics and toxicity in experimental animals, humans, and farm and companion animals, but also information on analytical methods, occurrence data reported for foods and feeds (mostly) in Europe, and previous national risk assessments and evaluations on exposure of humans and farm and companion animals to mycotoxins mainly in the European countries.

Hazard identification and characterisation

Within the human and animal risk assessment process, the CONTAM Panel reviews the available published data on toxicokinetics and on *in vivo* and *in vitro* toxicity data on mycotoxins in experimental animals, humans, and farm and companion animals. The farm and companion animals covered in the risk assessments are ruminants (including small ruminants), pigs, poultry (broiler chicken, laying hens, turkeys and ducks), farmed fish, horses, farmed rabbits, farmed mink, dogs and cats. Based on the assessed toxicity data on mycotoxins in experimental animals and humans, the CONTAM Panel often establishes health-based guidance values (HBGVs) – such as the tolerable daily intake (TDI) to characterise chronic health risks or the acute reference dose (ARfD) to characterise acute health risks (Table 1). TDI is an amount per body weight that can be ingested daily over a lifetime without appreciable health risk and ARfD an amount per body weight that can be ingested in a period of 24 hours or less without appreciable health risk. The Panel can also use other approaches to identify reference points to characterise the risks for humans from mycotoxin exposure. Currently, modelling of the dose-response data of the identified adverse effect by using the benchmark dose (BMD) approach is often applied to inform on the reference point for human risk assessment. The modelling takes into account defined percent of an extra risk of the adverse effect and 95% lower confidence limit of the BMD (i.e. BMDL) is used as the reference point either to calculate a HBGV by applying uncertainty factors or a margin of exposure (MOE) between BMDL and estimated dietary exposure. However, particularly for the farm and companion animal risk assessments the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) are used as a reference point to characterise the chronic or acute risks from the exposure to mycotoxins (Table 1), but exceptions to this exist and the Panel has applied the BMD approach for animal risk assessment in its opinions too (EFSA, 2011a, 2017a). More detailed information on the BMD approach can be found in EFSA (2017b).

Dietary exposure assessment for humans, and farm and companion animals

For mycotoxins, either chronic dietary exposure or both acute and chronic dietary exposure estimates are calculated depending on the whether the mycotoxin induces chronic adverse health effects or both acute and chronic adverse effects. The mycotoxin exposures for mean and high (95th percentile) consumers are estimated for seven different age groups of the European population (infants, toddlers, other children, adolescents, adults, the elderly and very elderly). From the special consumer groups, vegetarians are often considered as a separate population group when calculating the exposures to mycotoxins (see e.g. EFSA, 2017a). Acute dietary exposure is calculated by using probabilistic approach. It is assessed for each reported day on consumed food by multiplying the total amount of food consumption for each food category by a mycotoxin concentration randomly drawn among individual results available in the EFSA occurrence database for that food category. Respective intakes of the foods consumed on that day are summed and finally divided by the body weight of the individual consumer. This process is iterated 100 times for each day of consumption reported by each participant in the dietary surveys of the EU Member States. From the resulted distributions, the acute exposures for mean and high consumers are calculated for different dietary surveys. For the estimates of the chronic dietary exposure, deterministic approach is applied. The chronic exposures are calculated by combining mean mycotoxin concentrations available in the EFSA occurrence database for each food

Table 1. Mycotoxin opinions of the EFSA CONTAM Panel including the health-based guidance values (HBGVs) and reference points used in the human and animal risk assessments, where reported.[1]

Mycotoxin(s) covered in the opinion	Opinion on		Reference points for risk assessments		Year of EFSA reference
	Food	Feed	HBGV for human risk assessment	Reference points for animal risk assessment[2]	
Aflatoxin B_1		x		not identified	2004a
Deoxynivalenol		x		NOAELs, LOAELs	2004b
Zearalenone		x		not identified	2004c
Ochratoxin A		x		LOAELs	2004d
Ergot alkaloids		x		not identified	2005a
Fumonisins		x		NOAELs, LOAELs	2005b
Ochratoxin A	x		TWI 120 ng/kg bw		2006
Aflatoxins[3]	x		BMDL 170 ng/kg bw per day		2007a
Aflatoxins[4]	x				2009
Ochratoxin[5]	x				2010a
Zearalenone	x		TDI 0.25 µg/kg bw		2011b
Alternaria toxins	x	x	TTC approach applied	NOAELs, LOAELs	2011c
T-2 and HT-2 toxins	x	x	group TDI 100 ng/kg bw	NOAELs, LOAELs, BMDL	2011a
Ergot alkaloids	x	x	group ARfD 1 µg/kg bw group TDI 0.6 µg/kg bw	NOAELs	2012b
Phomopsins	x	x	not established	not identified	2012c
Citrinin	x	x	other approach, see opinion	NOAELs, LOAELs	2012d
Sterigmatocystin	x	x	other approach, see opinion	not identified	2013a
Nivalenol	x	x	TDI 1.2 µg/kg bw	LOAELs	2013b
Deoxynivalenol[6]	x		PMTDI 1 µg/kg bw[7]		2013c
Beauvericin and enniatins	x	x	other approach, see opinion	NOAELs, other approach, see opinion	2014a
Fumonisins, zearalenone, T-2 and HT-2 toxins and nivalenol + modified forms	x	x	group PMTDI 2 µg/kg bw for fumonisins + modified forms[7] HBGVs established by EFSA (2011b,a, 2013b) used for other toxins	NOAELs, LOAELs, BMDL	2014b
Zearalenone + modified forms	x		group TDI 0.25 µg/kg bw		2016a
T-2 and HT-2 toxins + modified forms	x		group ARfD 0.3 µg/kg bw group TDI 0.02 µg/kg bw		2017c
Nivalenol + modified forms	x		group ARfD 14 µg/kg bw group TDI 1.2 µg/kg bw		2017d
Zearalenone + modified forms		x		NOAELs, LOAELs	2017e
Deoxynivalenol and acetylated + modified forms	x	x	group ARfD 8 µg/kg bw per eating occasion group TDI 1 µg/kg bw	NOAELs, BMDLs	2017a

[1] ARfD = acute reference dose; BMDL = 95% lower confidence limit for the benchmark dose response (note that BMDL is not a health based guidance value but a reference point from which it could be calculated by applying uncertainty factors); bw = body weight; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PMTDI = provisional maximum tolerable daily intake; TDI = tolerable daily intake; TWI = tolerable weekly intake; TTC = threshold of toxicological concern.

[2] Due to the lack of data on adverse effects, reference points are often identified for some farm and companion animal species only.

[3] Scientific opinion related to the potential increase of consumer health risk by a possible increase of the existing maximum levels for aflatoxins in almonds, hazelnuts and pistachios and derived products.

[4] Scientific statement of the CONTAM Panel on increase of the level for total aflatoxin from 4 to 10 µg/kg for tree nuts other than almonds, hazelnuts and pistachios.

[5] Scientific statement of the CONTAM Panel on recent scientific information on the toxicity of ochratoxin A.

[6] Scientific statement of the CONTAM Panel on the risks for public health related to a possible increase of the maximum level of deoxynivalenol for certain semi-processed cereal products.

[7] Established previously by Joint FAO/WHO Expert Committee on Food Additives (JECFA).

category with a daily average consumption for each food at the individual consumer level reported in the dietary surveys. The exposures from different foods are summed and divided by the body weight of the individual consumer. Consequently, individual average exposures per body weight and per day are obtained for the consumers. Based on the resulted distributions, the exposures for mean and high consumers are calculated for the different dietary surveys. Since the food consumption data have been collected using different methods, the exposure estimates for mycotoxins are presented as a range comprising the different dietary surveys of the different EU Member States. While the human dietary exposure assessments for mycotoxins for different population groups in Europe are done by the EFSA DATA Unit (see below), the farm and companion animal dietary exposure estimates for mycotoxins are typically calculated by the WG experts using the mycotoxin occurrence data from the EFSA occurrence database and identified information on body weights, diets, diet compositions and feed intakes. This information is based on published guidelines on animal nutrition and feeding (e.g. AFRC, 1993; EFSA, 2012a; OECD, 2009) and also on information provided by the European feed manufacturers. Because the range of different livestock rearing and feeding systems across the Europe varies widely, the animal diets used by the CONTAM Panel to calculate exposure estimates do not represent average diets or feeding systems which are typical all over Europe. These are Panel's estimates concurring with common practice of farm and companion animal nutrition and feeding in Europe.

Risk characterisation and uncertainties

When characterising the risk from exposure to mycotoxins for humans and for farm and companion animals, the CONTAM Panel compares the dietary exposure estimates to the established HBGVs or calculated BMDL for humans or in the case of farm and companion animal species to the identified NOAELs/LOAELs or calculated BMDL for different animal species. In the last part of the opinion, the Panel concludes on the possible health risks for humans and animals and describes the uncertainties identified for the risk assessments. Owing to these uncertainties, the Panel often makes recommendations for generating new scientific data, which would allow refinement of the risk assessments and reducing their uncertainties in the future. More detailed information on the risk assessment of chemical contaminants can be found at http://www.efsa.europa.eu and in Alexander *et al.* (2012), and for example in Benford (2017), Dorne and Fink-Gremmels (2013) and Yoe (2012).

CONTAM Panel scientific opinions on mycotoxins in food and feed

Since 2002, the CONTAM Panel has issued 26 opinions on mycotoxins (Table 1), of which three have been short scientific statements of the Panel. The scientific opinions on natural toxins, including mycotoxins, comprise the largest topic area amongst all the chemical contaminants assessed by the CONTAM Panel; approximately 50% of the scientific opinions are on natural toxins either in food, feed, or in both.

During the first years of EFSA in 2003-2005, the CONTAM Panel developed scientific opinions on mycotoxins in feed. The opinions on aflatoxin B_1 (AFB_1), deoxynivalenol (DON), ZEA, OTA, EAs (ergot) and fumonisins as undesirable substances in animal feed addressed the adverse health effects and possible health risks for farm and companion animals from the feed containing these mycotoxins (EFSA, 2004a,b,c,d, 2005a,b). Although the reference points were identified for the adverse effects in some animal species, the occurrence data on mycotoxins in feed were not available precluding the estimation of dietary exposures. Therefore, the Panel was not able to perform complete risk assessments for the animals.

The first opinion on mycotoxins in food is from 2006 when OTA was addressed. The CONTAM Panel reviewed the previous OTA opinion on food of the Scientific Committee on Food (SCF) from 1998, taking into account the results from toxicity studies published after the SCF opinion and the latest occurrence data from the EC-project report on 'Scientific cooperation on questions relating to food' (EFSA, 2006). At the time EFSA did not yet collect the occurrence data and the EFSA food consumption database was in its draft state. Nevertheless, the dietary exposure to OTA for adults was assessed and tolerable weekly intake was established. OTA was considered again in a short statement in 2010 in which recent scientific information on the toxicity of OTA was evaluated by the Panel (EFSA, 2010a). The Panel has adopted two risk assessments on AFs in food (EFSA, 2007a; 2009). A potential increase of consumer health risk, if the existing MLs for AFs in almonds, hazelnuts and pistachios and derived products were increased, was evaluated in 2007, and a similar evaluation was made on the increase of the MLs for total AFs from 4 µg/kg to 10 µg/kg for tree nuts other than almonds, hazelnuts and pistachios in the Panel statement in 2009. In the 2007 opinion, the BMD approach was used for the first time in the mycotoxin opinions and the MOE was calculated by comparing the calculated BMDL value to the dietary exposure estimates.

In 2010, the CONTAM Panel received nine requests from the EC for risk assessments (mainly on *Fusarium* toxins) to address both the risks for public health and for the health of farm and companion animals, and one request in which possible risks for humans from the exposure to

ZEA in presence of increased levels of it in wheat bran were requested to be assessed. A year later, an opinion on the risks for public health on the presence of ZEA in all foods, not only in wheat bran, was delivered (EFSA, 2011b). This was the first mycotoxin opinion for which EFSA collected occurrence data through a call for data from the European countries and in which the food consumption data, collected by EFSA from the European countries for its food consumption database, were used. From the nine EC requests, the opinion on *Alternaria* toxins in food and feed was finalised first (EFSA, 2011c). For its preparation, the relevant information from an EFSA funded project was used (Battilani *et al.*, 2009). Due to the weak database on toxicity and occurrence data, only risks for humans from the exposure to alternariol (AOH), alternariol monomethyl ether (AME), tenuazonic acid (TeA) and tentoxin in foods and risks for some poultry species from the exposure to AOH and TeA in feeds were assessed. This was the first mycotoxin opinion in which the Panel applied the threshold of toxicological concern (TTC) approach to assess the relative level of concern of *Alternaria* toxins. TTC is an approach to screen and prioritise chemicals when toxicity data are incomplete but dietary exposure can be estimated (EFSA/WHO, 2016). The Panel decided that the use of TTC approach was appropriate because there were only few or no relevant toxicity data on *Alternaria* toxins available, the chemical structures of the four toxins were known and dietary exposures were estimated. Since the TTC approach was used, the Panel also assessed the potential for genotoxicity of the toxins. The outcome of the TTC approach showed that additional compound specific toxicity data for AOH and AME were needed, which was also recommended by the Panel, and thus EFSA funded a project to generate these data (Schuchardt *et al.*, 2014). The new toxicity data, however, did not change the outcome of the *Alternaria* toxins opinion. Later, the TTC approach was also considered for beauvericin (BEA) and enniatins (ENNs) (EFSA, 2014a).

To facilitate the preparation of the risk assessment on T-2 toxin (T-2) and HT-2 toxin (HT-2) in food and feed (EFSA, 2011a), EFSA had earlier funded two projects, one on compilation of published occurrence data and one on toxicity data (Schuhmacher-Wolz *et al.*, 2010; Van der Fels-Klerx, 2010). The relevant information was used in the assessment. On request by the EC, in this opinion the CONTAM Panel considered the results from the toxicity studies published since the human risk assessment of the SCF in 2001 on T-2 and HT-2 and assessed whether the group TDI for T-2 and HT-2 established by the SCF was still appropriate. In addition, updated human dietary exposure assessment and risk assessment for farm and companion animals were carried out. In this assessment the Panel also updated its approach to assess the risks for the health of farm and companion animals, particularly the exposure assessment. Since then, this approach has been applied. In the assessment of T-2 and HT-2, the BMD approach was used to derive a HBGV for human risk assessment and for the first time the BMDL value was used as a reference point to characterise the health risks for farm and companion animals. Unlike many other risk assessments on mycotoxins for farm and companion animals, in this assessment the toxicity and occurrence databases were complete enough to allow the Panel to assess the risks of adverse health effects for many different animal species (ruminants including small ruminants, pigs, poultry, horses, farmed rabbits, farmed fish and dogs) from the feed contaminated with T-2 and HT-2.

The risks to public and animal health from the dietary exposure to the main EAs (ergometrine, ergotamine, ergosine, ergocristine, ergocryptine, ergocornine and their -inine epimers) in food and feed were assessed by the CONTAM Panel in 2012 (EFSA, 2012b). This assessment also updated the EFSA (2005b) on EAs as undesirable substances in animal feed. Also for the preparation of this opinion, EFSA had earlier financed two projects to collect literature data and to generate occurrence data (Battilani *et al.*, 2009; Diana Di Mavungu *et al.*, 2011). While this assessment was the first human risk assessment on EAs of the Panel, the main outcome for the farm and companion animals did not change from the EFSA (2005). Both opinions on phomopsins in food and feed and on citrinin in food and feed, highlighted that the limitations and uncertainties in the database were high and the Panel recommended that more data were needed on the toxicity and occurrence of these toxins to do full human and animal risk assessments (EFSA, 2012c,d). It was also recommended that analytical methods should be developed. For citrinin no HBGV for humans was established owing to the lack of toxicity data, but other approach (see the opinion for the details) was taken to give an indication on possible risk from the dietary exposure. The animal risk assessment for citrinin in feed remained incomplete. For the preparation of the phomopsins opinion, the relevant information gathered in the EFSA project of Battilani *et al.* (2009) was used, and the recommendation to generate more data on citrinin occurrence was addressed by the EFSA funded project of López Sánchez *et al.* (2017). The project revealed new information on the occurrence of citrinin in food and the Panel is currently in process to evaluate the results and will decide whether it updates its previous opinion.

Sterigmatocystin (STC) was the next mycotoxin of the nine EC requests for which the risks for public and animal health from the exposure to STC were assessed (EFSA, 2013a). Again, the relevant information gathered by Battilani *et al.* (2009) was used for the development of the opinion. The absence of food occurrence data prevented the application of the MOE approach for STC, which was concluded to be genotoxic and carcinogenic, and therefore its risks for human health could not be characterised. Similarly, the absence of occurrence data on STC in feed precluded the animal risk assessment. Therefore, EFSA funded a project to

generate occurrence data on STC in food (Mol *et al.*, 2015). Based on the new STC occurrence data from the project, the Panel decided in 2015 to update the STC opinion in the future. In 2013, the CONTAM Panel also finalised its assessment of risks from nivalenol (NIV) in food and feed for public and animal health (EFSA, 2013b). The risks to farm and companion animals from NIV in feed had not been previously assessed and for this reason in the EFSA project of Battilani *et al.* (2009) literature data on NIV in feed were collected. In this opinion, the Panel noted that more information also on the occurrence of modified forms of NIV should be collected and it further recommended that more toxicity data were required. Later, new *in vivo* toxicity data on NIV and DON were reported in 2014, as the outcome of the EFSA funded project of Le Hégarat *et al.* (2014). These new data informed the 2017 DON assessment (EFSA, 2017a), and confirmed the previous findings of the opinion on NIV (2013b). In the same year, the opinion on BEA and ENNs (ENNs A, A1, B and B1) in food and feed was adopted by the Panel but a full risk assessment for humans and farm and companion animals was not possible due to the overall lack and limitations in the available toxicity data (EFSA, 2014a). The TTC approach was applied and it was concluded that compound-specific toxicity data were needed for BEA and ENNs. Based on the recommendation by the Panel, EFSA funded a project in 2016 to generate these data. Several other recommendations for new data were also proposed by the Panel to carry out reliable risk assessment for these toxins in the future.

The 2013 request from the EC for the risk assessment on human and animal health related to modified forms of fumonisins, ZEA, T-2 and HT-2, and NIV in food and feed led to Panel's first opinion on the modified forms of mycotoxins (EFSA, 2014b). The outcome of the risk assessment for human and animals was incomplete because no occurrence data on the modified forms were submitted to EFSA and because it was assumed that, due to the absence of toxicity data on modified forms, their toxicities were equal to those of their parent mycotoxins. Amongst the many recommendations, one notably asked for the standardisation of nomenclature for mycotoxins and their modified forms. As a follow-up of the first opinion on the modified mycotoxins, a year later the EC requested four separate opinions for the same four mycotoxins and asked to evaluate appropriateness and feasibility to establish group HBGVs for the parent mycotoxins and their modified forms. The dietary exposure assessments were not required and therefore the risk for human health was not assessed. The opinions on ZEA and its modified forms and on T-2 and HT-2 and the modified forms were published in 2016 and 2017 (EFSA, 2016a, 2017c). For the first time in the mycotoxin opinions, relative potency factors were set for the parent mycotoxin and the modified forms and used factoring in the differences in their toxicological potencies. The group TDI for ZEA and its modified forms was established (EFSA, 2016a). In 2017, the previous animal risk assessment on ZEA of EFSA (2004c) was updated, considering also the modified forms of ZEA, and the risks for sheep, pigs, farmed fish and dogs were assessed (EFSA, 2017e). Owing to the new findings in the toxicity of NIV and T-2 and HT-2 since the earlier opinions in 2011 and 2013, the Panel updated the HBGVs for these toxins covering also their modified forms and established group ARfDs and group TDIs (EFSA, 2017c,d). Many recommendations to generate new information for modified mycotoxins were made by the Panel. Currently, two opinions on fumonisins and their modified forms in food and feed are under preparation. The latter updates the previous opinion of EFSA (2005b) on fumonisins as undesirable substances in animal feed.

Since 2002, three scientific opinions on DON have been developed by the CONTAM Panel (EFSA, 2004b, 2013c, 2017a). While the first opinion covered the assessment of health risks to farm and companion animals from the exposure to DON as an undesirable substance in animal feed, in the next one (scientific statement of the CONTAM Panel) the risks for public health related to a possible increase of the ML of DON for certain semi-processed cereal products were assessed, and the last opinion was a comprehensive human and animal risk assessment on DON, its acetylated (3-acetyldeoxynivalenol (3-ADON); 15-ADON) and modified (deoxynivalenol-3-glucoside (DON-3G)) forms (EFSA, 2017a). While the previous animal risk assessment of EFSA (2004) was updated, this was the first full human risk assessment on DON by the Panel. For the first time in its mycotoxin opinions, the Panel used human biomonitoring data. These data on DON, collected from the published literature and from the EFSA funded project (Brera *et al.*, 2015), supported the human risk assessment. The results of the EFSA project on *in vivo* toxicity data on NIV and DON (Le Hégarat, *et al.*, 2014) were also used. The Panel established the group HBGVs to characterise the risks for acute and chronic effects from the exposure to DON, 3-ADON, 15-ADON and DON-3G in food. The available toxicity data allowed identification or calculation of reference points for acute and chronic adverse effects in many farm and companion animal species, and health risks for ruminants (including small ruminants), pigs, poultry species, horses, farmed rabbits, farmed fish, farmed mink, cats and dogs were characterised. For the first time in the recommendations for the new research on mycotoxins, climate change was listed as one of the influencing factors, and therefore monitoring for the changing trends of the co-occurrence of DON, its acetylated and modified forms was suggested. Similarly, for the first time in the history of the mycotoxin opinions, the Panel recommend new research in the area of human biomarkers. From the nine EC requests, the Panel is currently developing the last two opinions on moniliformin and diacetoxyscirpenol in food and feed, for which the relevant information collected by Battilani *et al.* (2009) in the EFSA project will be used.

Mycotoxins and the EFSA DATA unit

The Regulation (EC) No 178/2002 requires that the EU Member States submit consumption and occurrence data to EFSA (EC, 2002). The EFSA DATA unit collects these data which are used to calculate the estimates of dietary exposure. The first food consumption database in the EU – EFSA Concise European Food Consumption Database – was operational in 2008 and it contained information from individual dietary surveys from 19 EU Member States. As it only had consumption data for a limited number of broad food categories, the EFSA Comprehensive European Food Consumption Database replaced it in 2010 (EFSA, 2011d; Huybrechts *et al.*, 2011; Merten *et al.*, 2011). At present the database, updated in 2015, has results from 51 dietary surveys from 23 EU Member States, and it contains the most complete and detailed data currently available in Europe. The ongoing EU Menu project of EFSA aims at providing standardised and more accurate food consumption data in all EU countries and regions. The first EFSA food classification system was created in 2006. It was replaced in 2009 by the FoodEx1 classification system, which was updated in 2011 to FoodEx2. FoodEx is an hierarchical system based on 20 main food categories which are broken down into subgroups of up to maximum four levels (EFSA, 2011d,e,f). The FoodEx2 complemented the FoodEx1 with more detailed food group levels and allowed reporting of additional information through the use of facets and facet descriptors (EFSA, 2015).

EFSA invites all European national authorities and similar bodies, research institutions, academia, food business operators and other stakeholders to submit occurrence data on chemical contaminants, including mycotoxins, in food and feed. The occurrence data were collected within *ad hoc* requests until 2011 when continuous annual occurrence data collection started at the former DATA unit. Currently, the submission deadline is in October each year and the occurrence data should be submitted in a standardised manner as agreed by EFSA and the EU Member States. The EFSA guidance on Standard sample description for food and feed (EFSA, 2010b, 2013d) details the requirements the submitted data need to comply with. The data can be submitted either in structured electronic format (XML) or in the Microsoft Excel format using the EFSA web interface. More information and instructions on the occurrence data submission and on on-line transmission are available at http://www.efsa.europa.eu/en/data/call/datex101217 and http://www.efsa.europa.eu/en/data/toolbox, and in the EFSA guidance on data exchange (EFSA, 2014d).

Most of the occurrence data on mycotoxins in food and feed are submitted to EFSA by the national food safety bodies in the EU, European research organisations and the EC. The remaining data are submitted by the food and feed industry. In the data cleaning and validation step different parameters, such as sampling strategy, sampling method, sampling year, sampling country, analytical methods, reporting unit, limit of detection, limit of quantification, and the sample codification according to the FoodEx classification are checked by the DATA Unit following its standard operating procedures. From the submitted occurrence data, which pass this step, the statistical descriptors are calculated, which are then combined with the dietary consumption data to estimate the human and animal dietary exposures (see above). Over the years, the DATA Unit has developed scientific reports on occurrence and exposure on AFs, DON, T-2 and HT-2, *Alternaria* toxins and EAs (EFSA, 2012e; 2013e,f; 2016b; 2017f,g) to further advice the EU risk managers.

Mycotoxins in the EFSA Panel on Additives and Products or Substances used in Animal Feed

EU Regulation (EC) No 386/2009 (EU, 2009) defines a specific functional group of technological feed additives 'substances for reduction of the contamination of feed by mycotoxins', which are intended to 'suppress or reduce the absorption, promote the excretion of mycotoxins or modify their mode of action'. This regulation stipulates that the aim of the use of these additives is not to increase maximum or guidance levels of mycotoxins in feed, but to improve the quality of the feed for animal nutrition, and further to guarantee the protection of animal and public health. The EU-authorisation process of feed additives (Regulation (EC) No 1831/2003) stipulates that EFSA conducts risk assessment to ensure the additive is safe and efficacious based on the information provided by the applicant seeking authorisation for its product. The EFSA FEEDAP Panel is responsible for these assessments following the submission of the application via the EC. The Panel delivers its scientific opinion on the additive by taking into account the principles for the assessment of the additives intended to reduce the contamination of feed by mycotoxins detailed in the FEEDAP Panel's guidance (EFSA, 2012a).

FEEDAP Panel scientific opinions and authorisation of the feed additives for the reduction of mycotoxins in feed

In the event of a positive opinion of the FEEDAP Panel, the EC authorises the use of the additive in the EU for 10 years. Since 2009, 14 applications have been submitted for authorisation as feed additives for the reduction of contamination of feed by mycotoxins. Most of them were related to authorisation of clays (mainly montmorillonite) as a binder for AFB_1. Two applications were related to a microorganism which degrades trichothecenes, and two others on fumonisin esterase. Of the 14 applications, eight opinions have been finalised and five authorisations have been given (Table 2). The list of the authorised feed additives in EU is available at https://ec.europa.eu/food/safety/animal-feed/feed-additives/eu-register_en.

Table 2. Opinions of the EFSA FEEDAP Panel on feed additives authorised in the EU for reduction of mycotoxins in feed.

Feed additive	Function	Target animals	Year of EFSA reference
Bentonite	binder for AFB_1	ruminants, pigs and poultry[2]	2011g,h
Fumonisin esterase EC 3.1.1.87 produced by *Komagataella pastoris* DSM 26643	degrades fumonisins	pigs[3]	2014e
Fumonisin esterase EC 3.1.1.87 produced by *Komagataella pastoris* DSM 26643	degrades fumonisins	avian species[4]	2016c
Micro-organism strain DSM 11798 of the *Coriobacteriaceae* family	de-epoxidation of DON to de-epoxynivalenol (DOM(-1))[1]	pigs[2]	2013g
Micro-organism strain DSM 11798 of the *Coriobacteriaceae* family	de-epoxidation of DON to DOM(-1)	poultry[4]	2017h

[1] Use extended to all trichothecenes.
[2] Use authorised for these animals in the EU in 2013.
[3] Use authorised for these animals in the EU in 2014.
[4] Use authorised for these animals in the EU in 2017.

Other EFSA activities on mycotoxins

Over the years, EFSA funding for mycotoxin projects has been awarded to many European research organisations for the preparatory work of the CONTAM Panel opinions and for generating new scientific information (Battilani *et al.*, 2009; Brera *et al.*, 2015; Diana Di Mavungu *et al.*, 2011; López Sánchez *et al.*, 2017; Mol *et al.*, 2015; Schuchardt *et al.*, 2014; Schuhmacher-Wolz *et al.,* 2010; Van der Fels-Klerx, 2010). Consideration of the EFSA Emerging Risks Unit on the changing patterns in mycotoxin occurrence being a potential concern, led to the EFSA funded project on modelling, predicting and mapping the emergence of AFs in cereals in the EU due to climate change (Battilani *et al.*, 2012). An EFSA funded project on developing a holistic, innovative and flexible risk assessment modelling approach for mycotoxin mixtures in food and feed started in 2017. An urgent scientific advice (i.e. Statement of EFSA) on mycotoxins was delivered by EFSA in six weeks, following a request received by the EC from an EU MS for a temporary derogation to the MLs for DON, ZEA and fumonisins in maize and maize based foods for the 2013 harvest (EFSA, 2014c).

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