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A systematic review of global occurrence of emerging mycotoxins in crops and animal feeds, and their toxicity in livestock

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ABSTRACT

Mycotoxins are the most frequently occurring natural contaminant in food and feed. Their occurrence in crops and animal feed represents an enormous challenge, particularly for livestock farmers in terms of increased production costs, reduced animal performance and profitability. This study investigates the scale of emerging mycotoxins contamination of crops and animal feeds globally, and evaluates their impacts on the health and performance of livestock, especially when they co-occur alongside regulated mycotoxins. Emerging mycotoxins including nivalenol, enniatins, beauvericin, diacetoxyscirpenol, fusaric acid, patulin, moniliformin and sterigmatocystin were found to be the most prevalent contaminants of cereals and other feed commodities worldwide. The pooled mean levels for beauvericin, nivalenol, enniatins, moniliformin, sterigmatocystin, diacetoxyscirpenol, fusaric acid, and patulin were 386, 421, 7,854, 204, 136, 126, 370 and 138 μg/kg, respectively. In terms of toxicity, co-occurrence of emerging mycotoxins with each other and also with regulated mycotoxins profoundly impacts livestock performance, even at low levels. Therefore, there is a need for cumulative risk assessments to evaluate the health risks associated with simultaneous exposure to emerging and regulated mycotoxins and also to develop effective mitigation strategies.

1. Introduction

Fumonisins (FUMs), deoxynivalenol (DON), aflatoxins (AFs), zearalenone (ZEN), T-2/HT-2 toxin and ochratoxins (OTs) are still considered the most important mycotoxins from food and feed safety standpoint due to their frequent occurrence in agricultural commodities, toxic effects on human and animal health and the fact they are heavily regulated in many parts of the world [1–3]. However, in recent years, substantial advances in food safety and mycotoxin analytical methods have led to the increasing number of studies investigating the occurrence and toxicity of emerging mycotoxins (EMs) in foods and feeds (Fig. 1). The most frequently detected EMs worldwide include fusaric acid (FUS), enniatins (ENNs), culmorin, apicidin, butenolide, fusaproliferin, alternaria toxins, aurofusarin, emodin, nivalenol (NIV), beauvericin (BEA), diacetoxyscirpenol (DAS), patulin (PAT), moniliformin (MON) and sterigmatocystin (STG) [1–3,4].

These EMs are generally described as mycotoxins that are not regulated and routinely determined in many mycotoxin monitoring programme [5]. They are also considered to be of less importance in terms of levels at which they naturally occur in food and feed as well as their toxic effects in human and animals [5]. Nevertheless, recent large-scale surveys showed that EMs are becoming frequent contaminants of crops and animal feed, with their occurrence and concentrations largely dependent on weather conditions,

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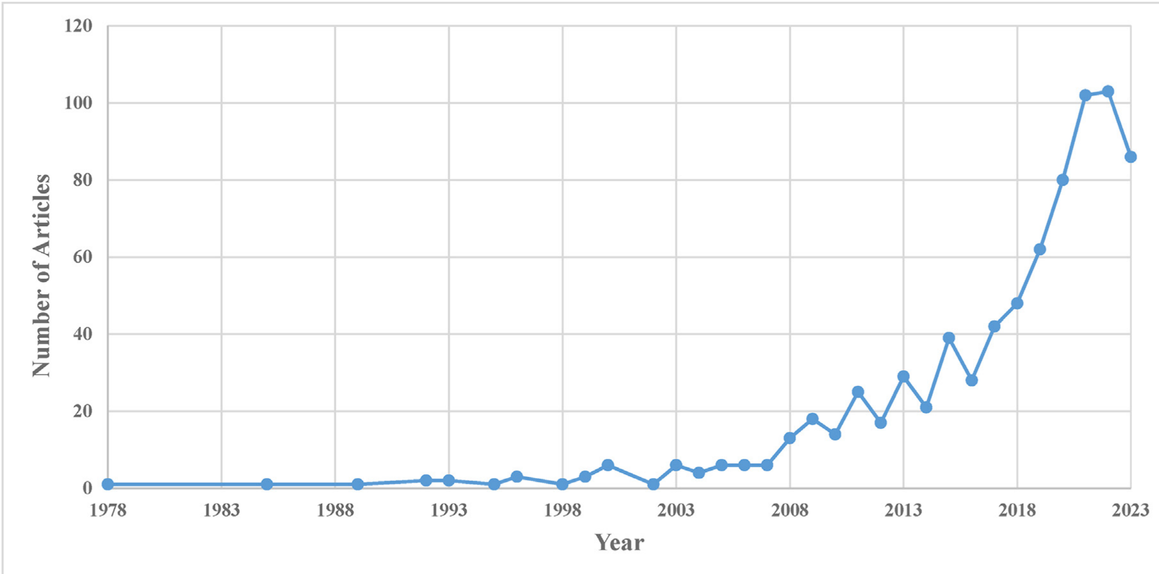

Fig. 1. The number of studies investigating the occurrence, toxicity, and mitigation of emerging mycotoxins from 1978 to 2023.

agricultural practices, and geographical location [4,6–10]. Importantly, in many regional and global surveys, EMs have also been found to frequently co-occur with regulated mycotoxins (FUMs, DON, AFs, ZEN, T-2/HT-2, and OTs) in crops and animal feed [1–3,4]. This is not surprising as many of these EMs are also produced by fungal genera (*Aspergillus*, *Alternaria*, *Penicillium*, and *Fusarium*) responsible for the production of regulated mycotoxins [4,8].

There are still limited data on the toxicity of EMs; thus, it has been difficult to accurately determine the range of exposure levels that have detrimental impacts on human and animal health. Nevertheless, the available evidence from several *in vitro* and *in vivo* studies suggests that these emerging food and feed contaminants have significant negative effects on intestinal morphology, immune and reproductive systems, as well as on livestock performance (feed intake and body weight) [11–16]. In terms of regulation, only Israel and Canada have regulatory limits for DAS in feeds [17]. There are currently no established maximum permitted levels for EMs in crops and feeds in Europe and other parts of the world. As the changing climate and agricultural practices have been shown to continue to drive the increased occurrence of mycotoxins in crops, this paper provides a comprehensive review of the occurrence and concentrations of EMs in crops and finished feeds worldwide, as well as their toxic effects on livestock health and performance. The first section of this article focuses on the systematic review conducted to critically evaluate EMs occurrence and concentrations in crops and finished feeds intended for livestock consumption worldwide. The second section highlights the impact of EMs on livestock animals, particularly when they co-occur with each other, and with regulated mycotoxins. In addition, current strategies to mitigate the toxicity of EMs are highlighted.

2. Method

2.1. Database search strategy

The search protocol was in line with the guidelines of Preferred Reporting Items for Systematic Reviews (PRISMA). Three different databases: Scopus, Web of Science and PubMed, were searched to identify and retrieve studies on the occurrence of EMs in agricultural commodities and toxicity of EMs in livestock species. The systematic search strategy and keywords used for each of the database are illustrated in Table 1. Additionally, the references of retrieved articles found eligible were thoroughly searched to minimize the likelihood of excluding other relevant papers.

2.2. Eligibility criteria

In terms of inclusion and exclusion criteria, the following pre-defined conditions were used to select relevant studies for review and data extraction:

1. Original research articles on the occurrence of EMs in crops and feed ingredients (including cereals), and finished feeds (such as silage, poultry feed, aquaculture feed, pig feed and cattle feed).
2. Research articles with validated LC-MS/MS method.
3. Research articles that reported the mean, range, limit of quantification, and limit of detection.
4. Original research articles on the toxicity of EMs in cattle, poultry, pig and aquaculture.
5. Articles that are accessible with abstract and full text.

No restrictions were placed on the sample size, language, and publication date. The studies published in conference proceedings, qualitative research, commentaries, letters, reviews, and book chapters were excluded. The literature database search was first conducted in December 2022, with a subsequent search in January 2024 to ensure that no newly published studies were excluded.

2.3. Study selection and data extraction

All the retrieved papers were exported to Mendeley and then transferred to Covidence (https://www.covidence.org/) for deduplication, screening, and data extraction. Two authors independently conducted the search and evaluated the titles and abstracts of the retrieved articles in line with the pre-defined eligibility criteria. Then, the full texts of the eligible articles were then explored by the same authors to exclude irrelevant studies. Any disagreements were resolved by consensus.

For studies that met the inclusion criteria, the following specific information were extracted and inputted in a pre-designed Excel

Table 1
The systematic review search terms and strategy to retrieve relevant articles from different literature databases.

Database	Search keywords	Number of articles
Scopus	DOCTYPE (ar) TITLE (emerging mycotoxin* OR mycotoxin* OR beauvericin OR enniatin* OR diacetoxyscirpenol OR moniliformin OR fusaric acid OR tentoxin OR nivalenol OR sterigmatocystin OR patulin) ABS (animal feed* OR "compound feed" OR fish feed* OR " poultry feed " OR commodities* "cattle feed" OR wheat OR rice OR sorghum OR soybean OR silage OR alfaalfa* OR pig feed*) ABS (livestock* OR poultry OR pig OR aquaculture OR ruminant) ABS (toxicity*)	351
Web of Science	(((TI = emerging mycotoxin* OR mycotoxin* OR beauvericin OR enniatin* OR diacetoxyscirpenol OR moniliformin OR fusaric acid OR tentoxin OR nivalenol OR sterigmatocystin OR patulin) AND AB=(animal feed* OR "compound feed" OR fish feed* OR " poultry feed " OR commodities* "cattle feed" OR wheat OR rice OR sorghum OR soybean OR silage OR alfaalfa* OR pig feed*) AND AB=(livestock* OR poultry OR pig OR aquaculture OR ruminant) AND AB=(livestock* OR poultry OR pig OR aquaculture OR ruminant) AB = ABS (toxicity*))	355
PubMed	((((emerging mycotoxin *[Title] OR mycotoxin *[Title/Abstract] OR beauvericin *[Title/Abstract])) OR enniatin [Title/Abstract]* OR diacetoxyscirpenol [Title/Abstract] OR moniliformin [Title/Abstract] OR fusaric acid [Title/Abstract] OR tentoxin [Title/Abstract] OR nivalenol [Title/Abstract] OR sterigmatocystin [Title/Abstract] OR patulin [Title/Abstract] AND (animal feed [Title/Abstract]* OR "compound feed" [Title/Abstract] OR fish feed* OR " poultry feed " OR commodities* [Title/Abstract] "cattle feed" [Title/Abstract] OR wheat [Title/Abstract] OR rice [Title/Abstract] OR sorghum [Title/Abstract] OR soybean [Title/Abstract] OR silage [Title/Abstract] OR alfaalfa* [Title/Abstract]OR pig feed* [Title/Abstract] AND ABS (livestock* [Title/Abstract] OR poultry [Title/Abstract] OR pig [Title/Abstract] OR aquaculture [Title/Abstract] OR ruminant [Title/Abstract]) ABS (toxicity*[Title/Abstract]	332

spreadsheet: authors' name, country and year of study, type of commodity, type of EM, sample size, prevalence (%), mean and range of mycotoxin levels (μg/kg), limit of detection (LOD) and limit of quantification (LOQ). The extracted data were cross verified for typographic errors and accuracy.

3. Results and discussion

3.1. Literature search results

The literature search yielded 1.038 articles and, after applying the predefined eligibility criteria, a total of eligible 82 studies were selected for further analysis. The selection process for the inclusion and exclusion of studies retrieved from the various literature databases is illustrated in Fig. 2. In terms of results, crops and finished feed samples were collected and analysed in many countries, mostly in Europe (43 %), followed by Asia (24 %), Africa (18 %), North America (6 %), South America (5 %) and Oceania (4 %) (Fig. 3). The number of samples collected and analysed for EMs ranged from 10 to 1,117. Regarding the sample type, cereals (including rice, wheat, rye, sorghum, maize, and oats) were the most abundant, followed by compound/finished feed, and silages. The compound feeds consisted of poultry, ovine, fish and ruminant feeds, while the silages were chiefly corn, alfalfa, and legumes. The full details of studies selected for analysis, including country of origin, number of samples analysed, occurrence, mean levels of EMs are provided in Supplementary Tables 1–8.

3.2. Occurrence of emerging mycotoxins in crops and animal feed

The major crops – cereals and soybean – provide essential nutrients and are mostly utilized as energy and protein source in human and livestock diets. These agricultural commodities are, however, susceptible to fungal contamination both before and after harvest, leading to the accumulation of fungal toxic metabolites [6,7,9,15]. Based on the results obtained from the metadata of eligible studies investigating the occurrence of EMs, NIV, ENNs (A, A1, B and B1), BEA, DAS, FUS, PAT, MON, and STG are the major contaminants of crops and finished feed worldwide. In terms of frequency of occurrence and level of contamination, however, NIV, BEA and ENNs were found to be the most prevalent sometimes at exceedingly high concentrations (Supplementary Tables 1, 3 and 5) (Fig. 4). The concentrations of NIV, BEA and ENNs in all the agricultural commodities ranged from, respectively, 0.1 to 15,600, 0.01 to 8854 and 0.25 to 10,000 μg/kg. In addition, samples from Europe, Africa, and Asia were mostly found to contain high occurrence of BEA, NIV, ENNs (Supplementary Fig. 1). Overall, the pooled mean levels for BEA, NIV, ENNs, MON, STG, DAS, FUS, and PAT were 386, 421, 7,854, 204, 136, 126, 370 and 138 μg/kg, respectively.

With regard to EMs contamination of commodities, cereals (wheat, oats, barley, maize, and sorghum) were generally found to contain high occurrence and levels of all the EMs, excluding PAT. Whereas, finished feeds for poultry, ovine, pig, cattle and fish were contaminated with mainly STG, BEA, PAT, MON, NIV and ENN, with very little to no occurrence of DAS and FUS. The silage samples had high occurrence and levels of only FUS, ENNs, NIV and BEA. The statistical distribution of EMs concentrations in different agricultural commodities (cereals, feed and silage) is illustrated in Fig. 5.

The metadata obtained from eligible studies also clearly showed high occurrence of EMs co-occurrence in crops and animal feeds. This can be attributed to the fact that many mycotoxigenic fungal species have the capacity to produce different mycotoxins and, under favourable environmental conditions, more than one toxigenic fungal species can infect crops simultaneously, resulting in multiple EMs contamination [18,19]. The combinations of 1) BEA and ENNs, 2) BEA, ENNs and MON, and 3) BEA, ENNs and NIV, were the most frequently detected in the studies analysed. In total, 24 different EMs combinations were recorded. Further, more than 90 % of the studies assessed detected two or more EMs in the samples analysed. The list of different combinations of EMs in crops and animal feed is shown in Supplementary Table 9.

NIV, ENNs (A, A1, B and B1), BEA, DAS, FUS, MON are mostly produced by *Fusarium* species, including *F. acuminatum, F. avenaceum, F. bulbicola, F. denticulatum, F. lactis, F. oxysporum, F. phyllophillum, F. poae, F. pseudocircinatum, F. sporotrichioides, F. sambucinum, F. subglutinans, F. succisae and F. tricinctum, F. langsethiae, F. moniliforme, F. proliferatum* [5,8,9]. STG and PAT are produced by *Aspergillus* species such as *A. versicolor, A. amstelodami, A. aureolatus, A. chevalieri, A. nidulans, A. quadrilineatus, A. ruber and A. sydowii B. nivea, B. fulva, P. dipodomyicola, P. expansum, P. griseofulvum, P. antarcticum, P. carneum, P. clavigerum, P. concentricum, P. camemberti, P. paneum, P. vulpinum, P. verrucosum, P. roqueforti, A. terreus, A. flavus, A. clavatus, A. giganteus, A. longivesica, A. ochraceus, and A. oryzae* [4,10]. The chemical structures of these EMs are illustrated in Fig. 6.

A substantial annual variation in the occurrence and concentrations of EMs were also observed in few of the studies we evaluated. For instance, around 711 corn and 1117 silage samples collected between 2013 and 2014 from different parts of the United States were found to contain higher levels of EMs when compared to samples collected in 2015–2019. The authors linked these variations to fluctuating weather patterns [10]. Similarly, 190 Serbian

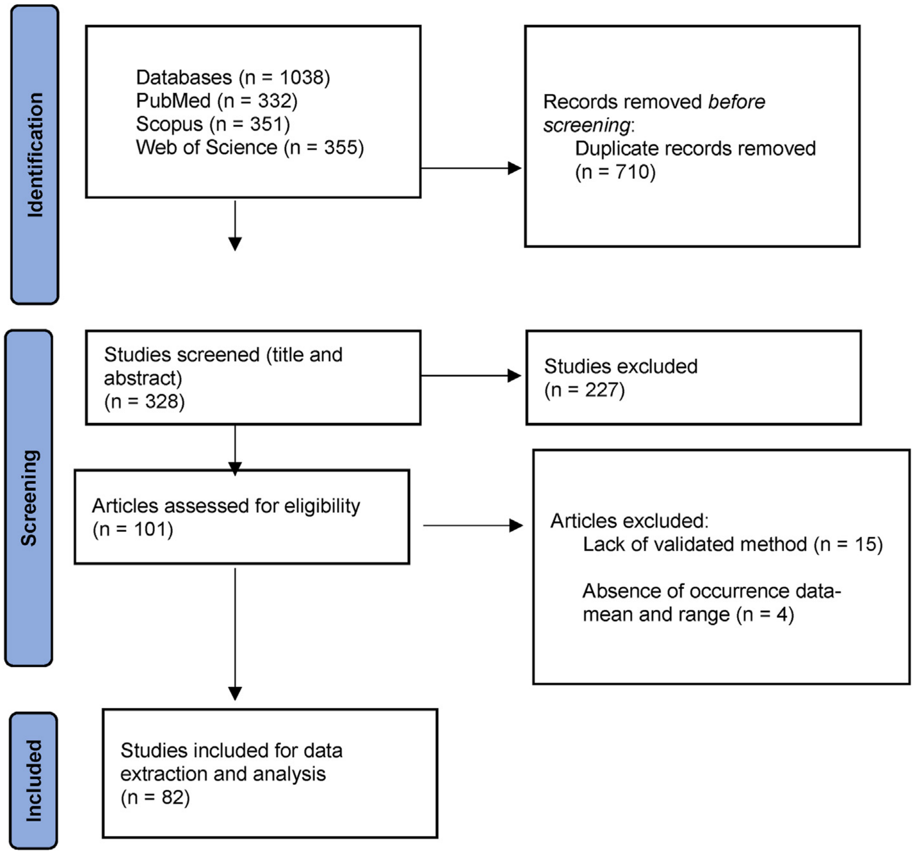

Fig. 2. The systematic process of retrieving studies from various literature databases, with the inclusion and exclusion of studies based on the pre-defined eligibility criteria.

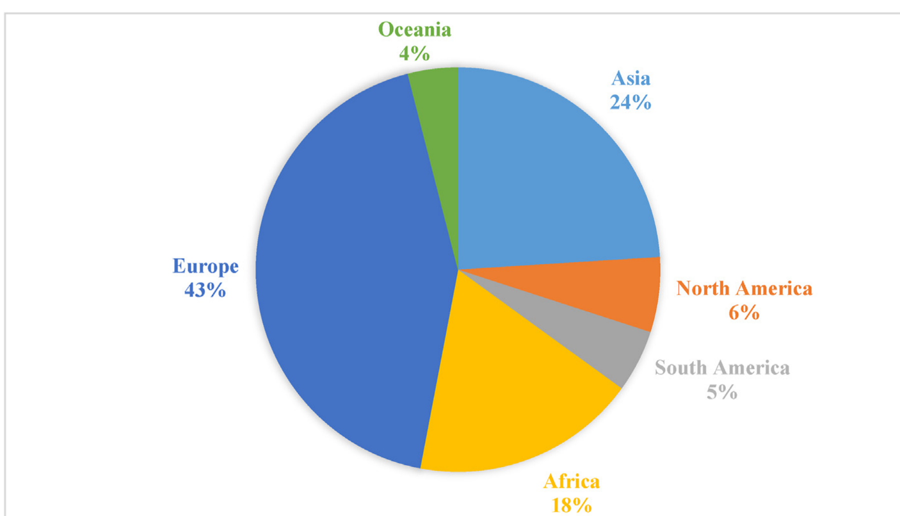

Fig. 3. Geographical distribution of samples collected for emerging mycotoxins analysis.

maize samples analysed for the presence of ENNs, BEA, MON and FUS were found to contain high levels of BEA and MON in up to 80 % of the samples collected in 2016; higher levels of MON, FUS, and BEA were detected in samples collected in 2017 and 2018. This elevated increase was correlated with high precipitation and warm weather during the silking phase of maize when the crops were very susceptible to *Fusarium* infections [9]. A 2-year survey of mycotoxins in farm silages carried out by McElhinney et al. [6] also showed that the level of ENNB detected in silage samples in 2013 was significantly higher than samples analysed in 2014.

The climate change will continue to drive significant increase in the occurrence and levels of different types and combination of mycotoxins. Thus, there is a need for continuous and long term (multi-year) monitoring of agricultural commodities for the presence of both emerging and regulated mycotoxins to ensure that food and feed in the supply chains do not pose food safety risks to

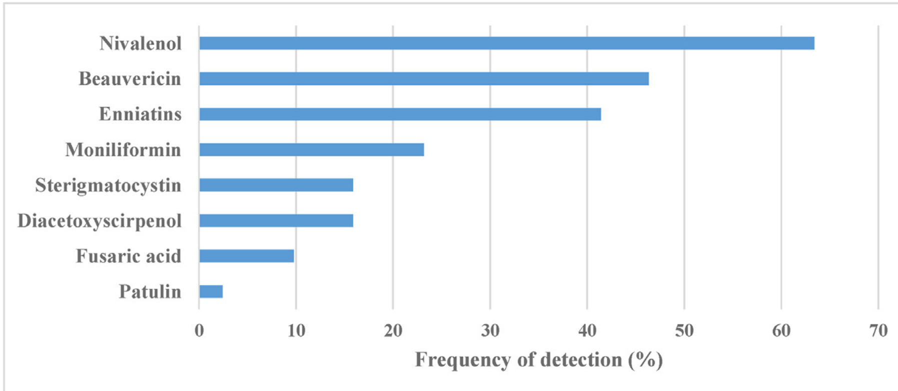

Fig. 4. Percentage detection frequency of eight emerging mycotoxins (enniatins, beauvericin, sterigmatocystin, fusaric acid, nivalenol, moniliformin, patulin and diacetoxyscirpenol) in different agricultural commodities.

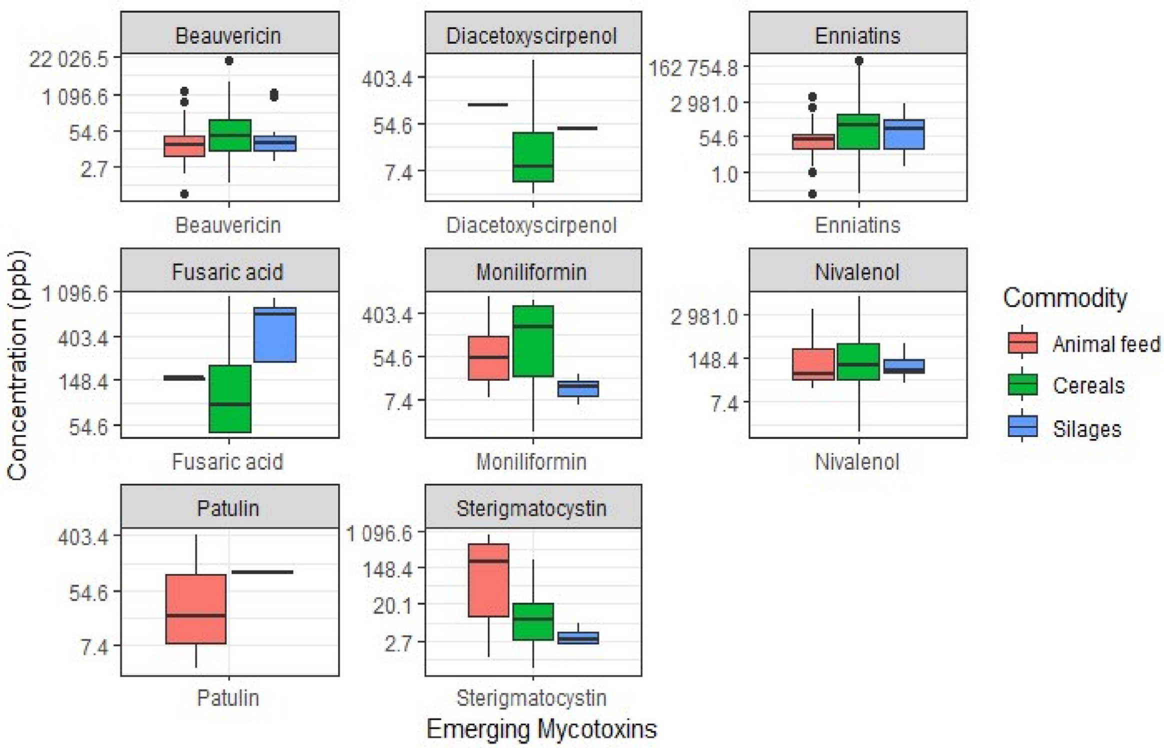

Fig. 5. The levels of eight emerging mycotoxins (enniatins, beauvericin, sterigmatocystin, fusaric acid, nivalenol, moniliformin, patulin and diacetoxyscirpenol) in global agricultural commodities. The box plots centre lines indicate the median level of each emerging toxin, while the box limits indicate the 25th and 75th percentiles. The box whiskers represent the range, and the sample outliers are represented by dots. Agricultural commodities intended as feed ingredients or for direct livestock consumption were categorised under "animal feed". Grains mostly meant for human consumption were classified under "cereals". Other commodities undergoing fermentation or termed as silages for animal consumption by authors were classified as "silages". There are very reports on soybean.

human and animals.

Systematic reviews enable the evaluation of large number of studies for evidence synthesis and to identify gaps and provide valuable information for researchers and policymakers. Like many systematic reviews, this study is also associated with few limitations. Firstly, most of the studies we reviewed originated mostly from Europe and Asia. This imply that the reported results reflect the scenarios in these regions and not applicable to other regions due to different climate and agricultural practices. Additionally, most of the available studies analysed a wide range of crops and feed samples collected randomly from different areas or agroecological zones, which led to high heterogenous results. In addition, the samples were collected at a single time point and there are no detailed methods on how the samples were collected. Thus, there are potential sampling errors in most of the reviewed studies, which may ultimately impact the accuracy of results.

3.3. The toxic effects of mixtures of emerging and regulated mycotoxins

In terms of toxicity of EMs in human and animals, many researchers have shown that these toxins can induce a wide range of detrimental effects including genotoxicity, suppression of immune system, reproductive and intestinal disorders [11–16]. However, as

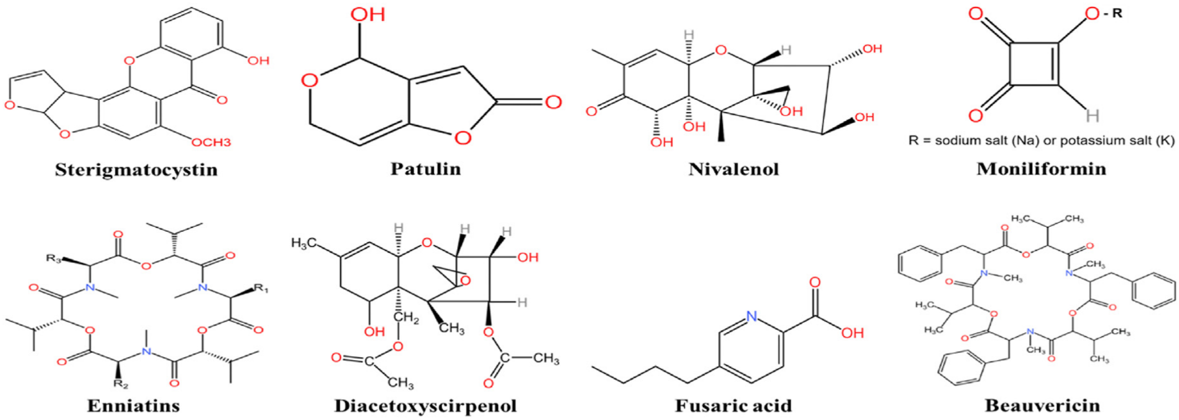

Fig. 6. Chemical structures of the eight emerging mycotoxins found to be frequent contaminant of crops and finished feed worldwide.

regulated and emerging mycotoxins have been shown to often contaminate feed commodities simultaneously, we reviewed and evaluated the severity of EMs toxicity in livestock animals (aquaculture, poultry and pigs) when they occur alone and co-occur with regulated mycotoxins (DON, AFs, ZEN, OTs, FBs and T-2/HT-2). There are no reports on the toxicity of EMs on ruminant species.

A number of feeding experiments demonstrated that exposure of monogastric animals (poultry and pig) to BEA and ENNs at concentrations of >10,000 mg/kg do not have any significant effects on feed consumption and body weight [5]. However, due to their rapid absorption and lipophilic properties, they can be carried over from feed and bio-accumulate in animal derived products such as meat, muscles, liver, skin, and egg [5,20]. This may lead to indirect human exposure to EMs, but it is currently unclear the range of BEA and ENNs levels that is capable of inducing observable toxic effects in human.

The European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) considered DAS level of >2 mg/kg to cause intestinal toxicity, reduced feed intake and body weight in pigs fed a DAS-contaminated diet; while DAS levels ranging from 0.3 to 20 mg/kg can induce oral lesions and negatively affect broilers feed conversion efficiency, as well as fertility and egg production in laying hens [21–25]. Similarly, MON levels ranging from 25 to 100 mg/kg of feed can reduce monogastric body weight, feed intake and egg production, as well as alter key haematological parameters [26–33]. For NIV, STG and PAT, there are very limited studies in terms of their effect on livestock animals [34,35].

In addition to the impact of individual EM on livestock, several researchers have also investigated the combined toxic effects of emerging and regulated mycotoxins on livestock health and performance. Piglets exposed to a diet co-contaminated with BEA (up to 3578 μg/kg), ENNs (up to 1830 μg/kg) and DON (2524 μg/kg) had significantly decreased weight gain, with organ lesions and altered microbial community composition when compared to animals fed diets contaminated with only BEA and ENNs [13]. Similarly, diets contaminated with DON (2 mg/kg), NIV (1.3 mg/kg) and ZEN (1.5 mg/kg) induced a more significant negative effects on the weight and feed consumption of pigs in comparison to animals fed NIV alone. Chronic ingestion of co-contaminated diets by pigs also led to a significant increase in histological changes in the intestine, liver, and lymphoid organs [11]. Increased vomiting and reproductive disorder were also reported in pigs fed diets co-contaminated with ZEN (3.0 mg/kg) and NIV (11.5 mg/kg) compared to pigs fed NIV alone [36].

For poultry, a long-term feeding trial used to evaluate the effect of low doses of mycotoxin mixtures on the performance of broiler chickens fed with naturally contaminated diets showed that prolonged exposure of broilers to mixtures of DON, ZEN, FBs, BEV, ENNs and DAS had a detrimental impact on birds' ability to efficiently convert feed [19]. Correspondingly, diets co-contaminated with combinations of DAS, T-2 toxin and AFs induced diarrhoea, reduced growth and feed efficiency in broiler chickens compared to broilers given feed contaminated with individual mycotoxins [37]. Outbreak of liver disease in equine was also recently linked to the ingestion of forages contaminated with mixtures of emerging and regulated mycotoxins, including FBs, 15-acetyl-DON, DON, NIV, ZEN, AFs, methylergonovine, verruculogen, and wortmannin [38].

In terms of aquaculture, several studies have investigated the potential adverse effects of regulated mycotoxins, particularly on Atlantic salmon [39,40]. While this specie can tolerate OTA and ZEA, they are very sensitive to DON [39,40]. Due to the significant increases in the level and occurrence of EMs in aquaculture feeds. A number of researchers have investigated the impact of EMs, particularly BEA and Enniatin B (ENNB), on the performance of Atlantic salmon. Exposure of salmon to feed contaminated with ENNB (0.3, 5.2, 83 mg/kg) and BEA (0.3, 4.8, 46 mg/kg) led to a dose-dependent decrease in body weight, feed conversion efficacy and protein digestion, with a marked effect of ENNB when compared with BEA [41]. Both EMs have also been shown to cause increased energy expenditure of hepatocytes in salmon, and elevated oxidative stress. Moreover, they can induce the onset of pathways linked to acute intestinal inflammation, particularly at low to moderate levels [42,43].

As outlined in Supplementary Table 2, many studies have investigated the combined toxic effects of emerging and regulated mycotoxins on farm animals. However, most animal trials were carried out using either mycotoxin standard solutions or fungal cultures, resulting in extremely high contamination levels that are not applicable or relative to the levels of these toxins in field conditions. Moreover, most of these studies exposed farm animals to a single mycotoxin concentration, thus lacking dose–response data. Therefore, it is challenging to decipher the doses at which toxic and no toxic effects were observed. Nevertheless, pig and poultry generally exhibited more marked detrimental effects (synergistic and additive effects) after exposure to feed crops and compound feed co-contaminated with emerging and regulated mycotoxins, compared to diets contaminated with only EMs (see Supplementary Table 10). Therefore, a cumulative risk assessment, especially at low exposure levels, is needed for this compound group to mitigate against their economic, welfare and health impacts.

There are currently few studies on effective strategies to mitigate the toxicity of EMs in farm animals. A recent study that compared the capacity of a wide range of commercial mycotoxin binders to reduce the levels of EMs in a simulated *in vitro* gastrointestinal model found that only one of the ten products evaluated can simultaneously bind ENNs, STG, NIV, DAS and BEA [44]. Other *in vitro* studies available also indicate the potential of certain products, such as isothiocyanates − allyl isothiocyanate, benzyl isothiocyanate and phenyl isothiocyanate [45−47], as well as fibres (including galactomannan, glucomannan, citrus, bamboo, carrot, b-glucan, xilan, cellulose, whey, β-lactoglobulin and calcium caseinate), and probiotics (lactic acid bacteria), have the potential to reduce the levels of BEA and ENNs [48,49].

4. Conclusion

The occurrence of emerging mycotoxins in food and feed is a growing issue in developing and developed countries. Following a thorough systematic review, eight EMs (ENNs, MON, NIV, BEA, STG, PAT, FUS and BEA) were found to be the most frequently occurring EMs in feed and crops worldwide. Other EMs such as alternariol, tentoxin, and mycophenolic acid were either not detected or monitored in many of the studies evaluated. In terms of EMs toxicity in livestock animals, many studies showed that EMs have the potential to cause a wide range of adverse health effects in farm animals only at concentrations that are oftentimes well above the levels commonly found in field conditions. Nevertheless, exposure of livestock to feeds with co-occurring EMs and regulated mycotoxins at moderate to low levels can yield synergistic or additive effects, resulting in notable adverse effects on the health and performance of livestock.

The effects of climate change and agronomic practices will continue to drive the increased occurrence and levels of EMs in commodities. Therefore, there is a need for continuous surveillance and monitoring of both EMs and regulated toxins in food and feed using sensitive state-of-the-art analytical techniques to provide occurrence data for exposure assessments. Furthermore, due to unavoidable co-occurrence of emerging and regulated compounds, cumulative risk assessments for both group of mycotoxins at low exposure levels are needed to accurately understand the potential adverse effects following human and livestock exposure, and to develop an effective risk mitigation plan.

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CRediT authorship contribution statement

Oluwatobi Kolawole: Conceptualization, Data curation, Methodology, Visualization, Writing − original draft. **Wipada Siri-Anusornsak:** Project administration, Writing − review & editing. **Awanwee Petchkongkaew:** Funding acquisition, Project administration, Writing − review & editing. **Christopher Elliott:** Conceptualization, Funding acquisition, Project administration, Writing − review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.emcon.2024.100305.

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