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Review

Mycotoxicoses in Veterinary Medicine: *Fusarium* Toxins, Grass Staggers, and Neothyphodium Toxins

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Abstract

Fungi are a large group of eukaryotic microorganisms that can readily adapt to diverse environments and occur in almost all climatic zones and continents. Although some fungi are inevitable in the environment for the decay and recycling of organic material, many species are known to produce secondary metabolites, and these mycotoxins, when ingested with food or feed materials, can adversely affect animal and human health. Among the toxigenic fungi, *Fusarium* species are recognized as so-called field fungi, invading crops and producing mycotoxins predominantly before harvest. *Fusarium* produces a wide array of mycotoxins, causing different plant diseases. Fusariosis causes significant economic losses in a wide range of crops. *Fusarium* secondary metabolites, particularly trichothecenes, are potent toxins in mammalian species and cause diverse adverse effects in humans and animals. Other prominent *Fusarium* toxins with entirely different chemical structures are zearalenone and its derivatives and fumonisins. With an entirely different life cycle, toxins of endophytes belonging to the genus Epichloë and *Neothyphodium coenophialum* and *Neothyphodium lolii* comprise an animal health risk, particularly for grazing animals. This review aimed to summarize the adverse effects of selected *Fusarium* and *Epichloë* toxins, with a special emphasis on their occurrence in roughages and their mechanisms of action, and describe their effect on animal health and welfare and the potentially related public health risks.

Keywords: mycotoxins; *Fusarium* toxins; Epicloë toxins; ergot alkaloids; endophytes

1. Introduction

Fungi are major pathogens for plants, causing significant economic losses. Fungal infestation of crops at the pre- and post-harvest stages is also a risk for animal health, as they produce secondary metabolites with a wide range of biological activities; some are severely toxic to humans and animals. These toxic metabolites are commonly denoted mycotoxins, and their adverse health effects are described as mycotoxicosis to differentiate their pathogenesis from fungal infections (mycosis), where fungi (mainly dermatophytes) invade the skin or other tissues of humans and animals, causing tissue damage and specific fungal diseases. Fungi are known to produce mycotoxins, particularly under stress conditions, and the current climate changes, with extreme weather conditions, have increased the risk of feed materials becoming contaminated by various mycotoxins, as documented in regular global overviews of the occurrence of mycotoxins in feed materials [1]. Animals are exposed to these mycotoxins predominantly via their feed; however, next to dietary exposure, respiratory (inhalation of toxin-containing fungal conidia) and dermal (feed dust) exposures must be considered in some cases. Mycotoxicosis is an example of poisoning by natural substances, and the clinical signs induced by individual mycotoxins are very diverse and depend on the chemical structure of the toxin, the associated mechanisms of action, the actual amount of the ingested toxin, and the duration of exposure, in addition to, the animal species and age category, the production stage, and the physiopathological condition of the exposed individual. As many fungal species produce more than one mycotoxin, interactions between these toxins and complex exposure scenarios in mixed rations or due to other contaminants or pollutants must be considered in the overall health risk assessments [2].

Toxinogenic fungi are ubiquitous, and their prevalence depends on their favorite growth conditions regarding moisture, pH, temperature, and nutrients. Several hundred fungal secondary metabolites have been identified, but only a few experimental or epidemiological data allow hazard identification and characterization for domestic animals [3]. As mycotoxins enter the food chain, the potential risk of residual amounts of mycotoxins in editable tissues, milk, and eggs has been investigated and is part of the overall risk characterization [4].

Contaminated feed remains the major source of mycotoxin intoxication in farm animals. While the majority of exposure assessments focus on the presence of mycotoxins in concentrates, generally composed of grains, maize, soya,

and other protein-rich plans and oil seeds, the contribution of roughages and modified mycotoxins to animal exposure is often neglected [5]. Two main classes of mycotoxins, which play a special role in the contamination of straw, hay, and pasture grass, are discussed here, with examples from common *Fusarium* toxins and toxins from endophytes occurring in pasture grasses.

2. *Fusarium* Toxins

Fusarium species are known worldwide as the typical molds that invade grain and maize plants and are recognized as phytopathogens, reducing crop yield and quality. *Fusarium spp.*, after infecting the crops, including small grains such as wheat, will be able to produce mycotoxins before the plants are harvested. Additionally, *Fusarium* infection will result in low quality and safety of grains and a lowered crop growth rate, suggesting the beneficial impact of pre-harvest measures in controlling *Fusarium spp.* infections in plants [6]. From an economic perspective, many *Fusarium* species are not only pathogenic fungi for strategic crops globally, but they can also produce many mycotoxins that affect food and feed safety; more importantly, the mycotoxin-contaminated foods and feed cause several acute and chronic diseases in humans and animals [7]. At present, more than 100 *Fusarium* toxins have been identified, of which three chemically related groups, the trichothecenes, the fumonisins, and the lactone-derivative zearalenone have been detected as significant contaminants of animal feed [8–10]. It is worth noting that an increasing number of reports indicate that one of the influencing factors affecting mycotoxins' toxicity is their chemical structure. It was recently discovered that *Fusarium spp.*-related mycotoxins contain their metabolites (modified mycotoxins) and traditional parent mycotoxins. Previous studies have reported that most modified mycotoxins show higher toxicity due to the high number of functional groups in their chemical structure. For example, α-zearalenol, a hydroxylated metabolite, is a several times more potent estrogenic compound than its parent Zearalenone (ZEN) [11]. The chemical structures of some important *Fusarium* toxins are depicted in Fig. 1.

2.1 Trichothecenes

Trichothecenes, produced predominantly by *F. graminearum*, comprise a group of toxins that share a trichothecene structure with a characteristic 12,13-epoxide moiety, which seems to account for their immediate toxicity [12–14]. Trichothecenes in group A, such as T-2 toxin and deacetoxyscirpenol (DAS), are dermatotoxins and cause necrotic lesions after dermal or mucosal contact. Skin lesions due to feed dust containing the T-2 toxin have been described in pigs, and necrotic lesions in the upper gastrointestinal tract have been observed in poultry chicks following the consumption of T-2 toxin- or DAS-contaminated feed [15,16]. Subsequently, weight gain and feed conversion are reduced, which may reduce performance and fertility [17]. Gastrointestinal lesions, growth retardation, and increased susceptibility to infectious diseases are the major insults observed after trichothecene exposure [18].

Trichothecenes are rapidly absorbed from the gastrointestinal tract and are intensively metabolized in the liver, which results in partial de-epoxidation [19]. However, epoxides escaping liver metabolism, particularly at higher toxin concentrations, can affect other basic cellular functions, such as protein and DNA synthesis and, thus, cell replication. The general inflammatory response exerted, for example, by T-2 toxin, is accompanied by pancytopenia as cell maturation of progenitor cells is hampered. Clinical investigations confirm severe anemia with hemorrhages due to the simultaneously occurring thrombocytopenia, as well as leukopenia [20].

Tolerance to T-2 toxin in feeds varies considerably between animal species, as pigs are more sensitive than poultry, followed by ruminants. Meanwhile, the mean exposure concentration of T-2-toxin varied: 0.03–0.08 µg/kg bw per day in beef cattle and 1.13–1.47 µg/kg bw per day in milking goats [21]. Recent evidence suggested that domestic cats are even more susceptible to T-2 toxin, and severe intoxication and lethality can occur in cats due to their inability to exert T-2 toxin and its metabolites via glucuronide conjugation [22].

Deoxynivalenol (DON, vomitoxin) primarily represents group B trichothecene, including DON, nivalenol, and fusaric acid. It is less aggressive than T-2 toxin and does not provoke skin lesions but affects intestinal integrity by disrupting the tight junction network, followed by local and systemic inflammatory response [23]. In addition, after distribution by systemic circulation, DON reaches the area postrema, where it appears to trigger dopaminergic receptors, resulting in emesis; hence, the name vomitoxin has often been used in clinical literature for severe clinical intoxications. Vomiting and feeding refusal occur only at high concentrations, exceeding 2000 µg/kg in mixed diets [24,25]. Together with vomiting, transient feed refusal and weight loss have also been observed in pigs. DON reduces weight gain in all monogastric animal species investigated at in-feed concentrations $>$1000 µg/kg [26]. The initial feed refusal can partly explain this reduction in weight gain but seems to be mainly determined by impaired nutrient transport through the inflamed mucosa of the gut [27,28]. The definition of threshold toxicity levels for individual trichothecenes such as DON is hampered by the fact that more than one toxin is normally present in feed commodities. The first example of the outcome of the co-occurrence of *Fusarium* toxins was the description of the combination of fusaric acid and DON in corn grain (59.1%) and silage (82.7%) reported in the United States between 2013 and 2019 [29]. Meanwhile, co-exposure to individual toxins and their modified forms are well documented for DON,

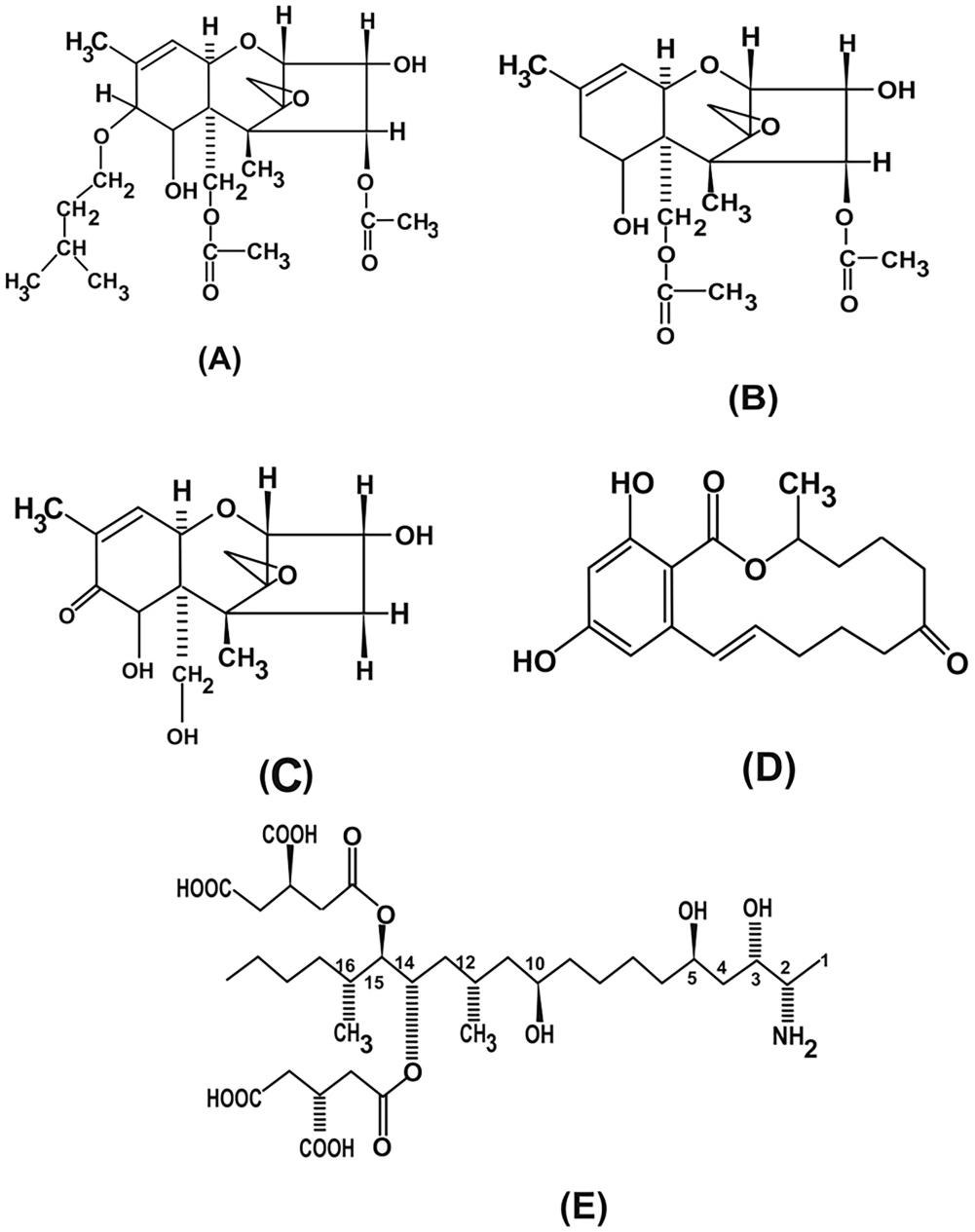

Fig. 1. Chemical structures of important *Fusarium* toxins. (A): T-2 toxin, **(B)**: Diacetoxyscripenol, **(C)**: Deoxynivalenol, **(D)**: Zearalenone and **(E)**: Fumonisin B1.

T-2 toxin, and ZEN, and mixtures of *Fusarium* toxins are included in the clinical interpretation of analytical data from mixed animal rations. These analytical controls are often limited to the analysis of concentrates (grains, mixed feeds). However, recent studies have shown that in plants, such as small grains, including wheat, not only do the kernels (grains) contain DON, but the entire plant is also contaminated. Subsequently, straw and other by-products must be included in the exposure assessment. Within the plant, DON is glycosylated, and these glucose conjugates of the toxin (previously denoted as masked mycotoxins) also contribute to overall exposure [30]. This alternative route of exposure is indeed often neglected but remains a common risk factor for animals, predominantly pigs and poultry, as well as (small) ruminants, cattle, and even horses, as they certainly contribute to the detrimental effects on gut health.

2.2 Fumonisins

Fumonisins (polyhydroxy alkylamines) represent a group of at least six distinct *Fusarium* toxins produced by *F. verticillioides* (previously denoted *F. moniliforme*). The chemical structure of fumonisins resembles the sphin-

golipids of mammalian cell membranes [31,32]. The basic mechanism of action of fumonisins, of which fumonisin B1 (FB1) is the most toxic, is their ability to inhibit the enzyme ceramide synthetase, an N-acetyl-transferase catalyzing the synthesis of complex sphingolipids. Subsequently, the intracellular concentration of free sphinganine and sphingosine increases to toxic levels [33]. In turn, the ratio of urinary sphinganine sphingosine is increased, which serves as a diagnostic marker of fumonisin exposure [34,35]. Despite recognizing the principal biochemical effects exerted by fumonisins, the diversity in clinical intoxications induced in different animal species remains to be elucidated.

In horses, an acute fumonisin intoxication is described as equine leukoencephalomalacia (ELEM) and is characterized by progressive necrosis of the neurons in the central nervous system [36]. Such specific neurotoxic effects have not been observed in other animal species. In pigs, fumonisin intoxication is characterized by pulmonary edema (PPE—porcine pulmonary edema), which seems to be related to cardiac dysfunction rather than to a specific impairment of pulmonary endothelial function and a pulmonary inflammatory response [37]. In addition, following chronic exposure, pigs develop hepatic hyperplasia with increased liver enzyme concentration in serum and pancreatic acinar cell degeneration [38,39]. In large ruminants, experimental doses of fumonisins induced only mild hepatic symptoms [40], and in cattle and small ruminants, the kidney was identified as the target organ [41].

Fumonisins are polar compounds, and the gastrointestinal tract absorption rate is very low (about 1%–2%), even in monogastric species. The ruminal flora does not degrade fumonisins and seems to be absorbed in the same ratio in ruminants as in monogastric species, namely in the small intestines [42]. After absorption, the toxins are rapidly metabolized and excreted, which makes it virtually impossible to measure plasma levels under field conditions. Toxic threshold levels still need to be defined for individual species and range at present from 6 mg/kg in horse feed to 8–10 mg/kg in pig feed and up to 400 mg/kg in cattle rations, reflecting again the very low bioavailability of fumonisins in comparison to other *Fusarium* toxins [43].

In contrast to other *Fusarium* toxins, fumonisins had been found predominantly in corn cops and cob mixes. Given the increasing use of corn cob mixed silages in cattle and the nutrition of horses and pigs, exposure levels may be higher than expected. However, according to the previously published report, in Europe, the risk of adverse effects of FB1-, FB2-, and FB3-containing feeds was considered very low for ruminants, low for poultry, horses, and fish, but as a potential health concern for pigs [44].

2.3 Zearalenone

Many *Fusarium* species, such as *F. graminearum* and *F. culmorum*, which can produce trichothecenes, also produce zearalenone (ZEN, previously also denoted ZEA or F-2 toxin) [45]. ZEN is found worldwide, particularly in corn (maize) and its by-products. ZEN is a resorcyclic acid lactone and a ligand for estrogen receptors in various target tissues [46]. The binding affinity to these receptors is considerably lower than that for 17-β-estradiol but differs between the parent mycotoxin and its metabolism-derived derivatives [47]. Alpha-zearalenol, as a hydroxylated metabolite, is up to 60 times more active than the parent compound [48]. Pigs, particularly prepubertal gilts, seem to be the most sensitive animal species, and clinical presentations following ingestion of ZEN-contaminated feeds include vulva swelling and discoloration, enlargement of the uterus and the mammary glands, as well as a prolapsed rectum, uterus, and vagina in severe cases [49,50]. The onset of puberty may also be delayed, and cycling gilts exposed to ZEN at a prepubertal age may exhibit extended interestrus intervals and reduced fertility with persistent *corpora lutea* [51]. Sows may farrow an unusually small or large litter, with high perinatal death rates, inconsistent piglet development, and weight gain [52]. Prepubertal boars show preputial enlargement and young boars have a reduced libido and lower plasma testosterone concentrations together with reduced spermatogenesis following ZEN exposure [53].

Thus, clinical signs vary with age, sex, and exposure period. In piglets and prepubertal pigs, levels exceeding 100 µ/kg in feed have been associated with clinically visible signs of hyperestrogenism, while in cyclic sows and fattening pigs, the tolerance is higher, with levels between only 250 and 500 µg/kg ZEN seemingly tolerated before major clinical signs such as a prolonged cycle and anestrus occur [48,54]. Poultry and ruminants are more resilient to ZEN (in feed, concentrations ranging up to 500 µ/kg are generally well-tolerated). These differences between species seem to be associated with the species-specific fate of ZEN in the body, where, for example, it is metabolized into the more estrogenic α-ZEL in pigs [49] and the less potent β-ZEL in the more tolerant species. The rate of metabolism varies even between related species; poultry chicks are less sensitive than turkeys, but it also depends on hormone status (sexual cycle), breed, and feeding regimen [55].

3. Grass Staggers and Neothyphodium Toxins

Neotyphodium species comprise a family of endophytic fungi with a unique symbiotic co-existence with various forage grasses. Recently, the entire group of endophytes has been taxonomically reallocated as members of the genus *Epichloë*. However, as the available clinical and toxicological literature refers mainly to the old taxonomy, both names are given here for easier readability. *Neotyphodium* species typically invade grasses, and their toxins can contaminate grass leaves. However, the endophyte is transmitted by grass seeds, which also contain high concentrations of fungal metabolites as a natural insecticidal and nematocidal defense mechanism. Promi-

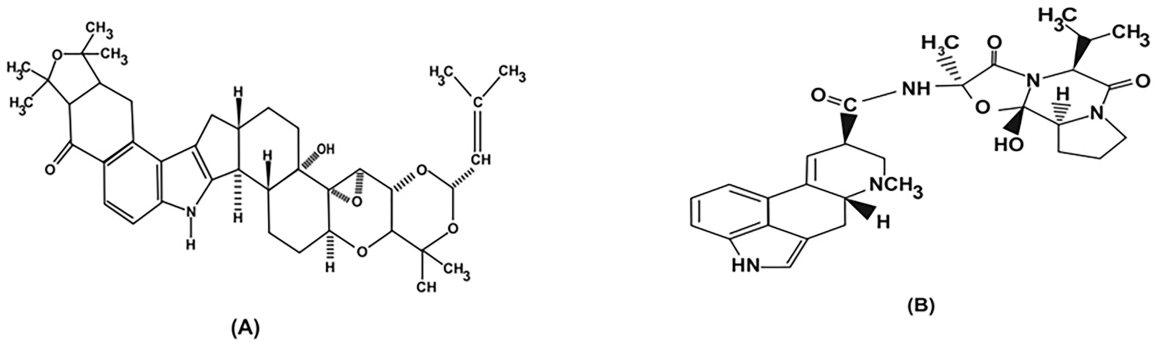

Fig. 2. Chemical structures of (A) Lolitrem B and (B) Ergovaline, as typical examples of mycotoxins produced by endophytes in pasture grass.

nent examples of endophyte-infected grasses with a risk to animal health are *Neotyphodium coenophialum* (now denoted *Epichloë coenophiala*), the main producer of Ergovaline (an ergopeptine alkaloid) occurring in *Festuca* grass species and associated with Fescue foot, a common intoxication in cattle in North America, as well as *Neothyphodium lolii*, now denoted *Epichloë festucae var. lolii,* which produce various neurotoxin mycotoxins, including the Lolitrems [56]. Another issue that must be considered is facial eczema (pithomycotoxicosis) due to ryegrass staggers and tall fescue, which affect grazing animals, including cattle and sheep [57]. It is worth noting that previous reports indicate that the reaction and metabolite production of endophytic fungi could be affected by season, host plant life cycle, and grass endophytic species. For example, a great difference was found between infected and uninfected grass-*Epichloë* endophyte associations in the profile of volatile organic compounds [58]. The chemical structures of Lolitrem B, the major toxin in the Lolitrem group and Ergovaline, are shown in Fig. 2.

Ergovaline has been identified as the major toxic agent in tall fescue toxicosis, a disease related to the ingestion of fescue grass. In horses, the primary toxic effect of ergovaline is associated with its dopamine-like effects. As an antagonist of prolactin, it causes agalactia and delayed delivery in mares with dystonia of the foal [59]. In cattle, ergovaline induces vasoconstriction (fescue food), hyperthermia, temperature intolerance, and general malaise in cattle, accompanied by weight loss and poor carcass quality [60]. More than two million cattle are estimated to suffer annually from this mycotoxicosis in the USA, and numbers are still increasing. Although life-threatening conditions are rare, the economic losses caused by ergovaline mycotoxicosis are considerable [61]. Ergovaline has been identified as the most prominent toxin involved in typical clinical conditions. However, infected forage grasses may also be contaminated with other clavines and smaller amounts of lysergic acid, pyrrolizidine alkaloids, and pyrrolopyrazine [62].

Lolitrem B is the main representative of a group of fungal indole terpenoids found in the perennial ryegrass *Lolium perenne* in Europe, New Zealand, Australia, and South America (Argentina) [63,64]. As perennial ryegrass is widespread in Europe, historical cases of ryegrass staggers have been documented. The increasing use of ryegrass ornamental grass lawns and sports fields has resulted in the selection (and import) of endophyte-contaminated grass seeds due to the peramine content of the seeds, which conveys insect and nematode resistance. Subsequently, ryegrass staggers have been observed in horses, cattle, and sheep in Europe [65]. Typical clinical presentations include disorientation, with ataxic movements progressing into convulsions if the animal is forced to move [66]. In addition, slight parasympathomimetic symptoms occur infrequently [67]. The condition often remains undiagnosed or misdiagnosed, as only the analysis of grass or hay for the presence of lolitrems would support the clinical interpretation of the syndrome.

The mechanism of action of lolitrems and related toxins is controversially discussed. Different results have been reported in experimental trials with individual toxins and natural cases of intoxication when animals are exposed to multiple related indole derivatives produced by the endophyte. Originally, clinical symptoms were associated with toxin interactions and GABAergic pathways, with an increase in excitatory amino acids in synaptosomes of the central nervous system being proposed as the main mechanism [68]. However, particularly in small ruminants such as sheep, smooth muscle activity and motility in the intestines were also regularly observed, and the interaction of these indole diterpenes with BK channels was also discussed and demonstrated through both *in vitro* and *in vivo* experiments [69]. Despite the neurotoxic symptoms, typical neurological lesions are absent, and animals may recover completely when withdrawn from the infected grass. Particularly in horses, the clinical diagnosis should thus be supported by toxin analysis in the incremented grass or hay. In sheep and cattle, the maximal tolerable toxin concentration is close

to 2 mg/kg dry matter. In contrast, horses already exhibited clinical symptoms in some cases following ingestion of lolitrem at a concentration of 0.8 mg/kg dry matter, and more severe symptoms were observed when the lolitrem concentration exceeded 1.2 mg/kg [68]. It is worthwhile to mention that lolitrem B is degraded by the natural microflora present in hay, and thus, the risk for intoxication decreases during storage in the winter season [70].

4. Methods of Prevention

Since both *Fusarium* toxins and ergot alkaloids are formed at the pre-harvest stage, only a change in agricultural practice could avoid the risk of animal exposure. However, since this is not feasible in most farm operations and under the current agricultural practice, only risk reduction methods can be recommended. In pasture grasses, these include the control of endophyte infestation, while in small grains and maize, natural *Fusarium* control by crop rotation, soil, good agriculture practices, harvest management, and eventually, the use of fungicidal agents is common practice [6]. Creating awareness by farmers alongside regular analytical controls of harvested crops and roughages used in animal diets and proper ensiling are recommended and currently very well supported by advanced multi-mycotoxin analytical methods [71]. In addition, under the pressure of increasing mycotoxin levels in animal diets, an array of feed additives have been developed to mitigate the adverse effect of mycotoxins in farm animals [72]. These so-called mycotoxin mitigation substances may include mineral clays, which indeed successfully bind aflatoxins and, to some extent, other polar mycotoxins, as well as prebiotics (yeast and algae cell walls) and probiotics (living yeast cells, *Lactobacilli*, and others) [73]. More recently, degrading enzymes, such as lactonases (ZEN), epoxidase (DON, T-2 toxin), and hydroxylases (fumonisins), have become commercially available as feed additives. Finally, phytogenics (herbs or herbal blends) with antioxidant, hepatoprotective, and anti-inflammatory properties are often recommended to reduce the adverse effects of mycotoxins in animals [74]. While it is beyond the scope of this review to discuss individual commercial products in more detail, many of them are well supported by preclinical and clinical studies. To prevent food contamination (animal-derived products), silica clays are generally recommended to reduce the risk of contamination of daily milk by aflatoxin M1.

5. Public Health Aspects

Mycotoxins occur in agriculture products worldwide and pose a risk to human and animal health. Considering the current global warming and the increasing prevalence of extreme weather conditions, the risk of mycotoxin contamination is increasing. Human exposure is predominantly associated with ingesting contaminated grains, fruits, nuts, and spices. The contribution of animal products, such as milk, meat, and eggs, is generally low and estimated to remain below 10% of the overall human exposure. An exception is aflatoxin M1, excreted in milk by dairy animals after ingesting aflatoxin-contaminated feeds. As infants consume relatively high amounts of milk and dairy products related to their body weight, exposure to Aflatoxin M1 (AFM1) should be monitored regularly, and preventive measures such as adding mineral clay products to the ration of dairy cows should be considered and recommended for dairy farmers, as mentioned above [75]. Therefore, there should be different mycotoxin management measures to ensure safe food and feed, including good agriculture practices, establishing global mycotoxin regulations, developing advanced and multi-mycotoxin analytical methods, and using effective decontamination and mitigation methods.

6. Conclusion

In the last decade, increasing concerns about mycotoxins as natural and apparently unavoidable contaminants of animal feeds have stimulated intensive research activities about their mechanism of action and risk for human and animal health. Most of these findings and reviews refer to mycotoxins commonly found in grains, maize, soya beans, oil seeds, and other commercial feed commodities. In contrast, mycotoxins in grassland, hay, and other roughages, including straw, are less well documented and often underestimated in exposure assessments of farm animals and straw, and the associated clinical symptoms are often underreported. With the current availability of sensitive multi-mycotoxin analytical methods, more data are expected to become available soon, and farmers and nutritionists should be encouraged to have the full diets of their animals analyzed, as mycotoxins have become one of the most prominent differential diagnoses on animal farms.

Author Contributions

HM collected data, drafted the first version of the manuscript and edited, AA helped in the preparation of figures, data collection and analyses and JFG substantially discussed the items single by single, edited and revised the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors read and approved the final manuscript and contributed to editorial changes in the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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