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Review

Deoxynivalenol: An Overview on Occurrence, Chemistry, Biosynthesis, Health Effects and Its Detection, Management, and Control Strategies in Food and Feed

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Abstract: Mycotoxins are fungi-produced secondary metabolites that can contaminate many foods eaten by humans and animals. Deoxynivalenol (DON), which is formed by *Fusarium*, is one of the most common occurring predominantly in cereal grains and thus poses a significant health risk. When DON is ingested, it can cause both acute and chronic toxicity. Acute signs include abdominal pain, anorexia, diarrhea, increased salivation, vomiting, and malaise. The most common effects of chronic DON exposure include changes in dietary efficacy, weight loss, and anorexia. This review provides a succinct overview of various sources, biosynthetic mechanisms, and genes governing DON production, along with its consequences on human and animal health. It also covers the effect of environmental factors on its production with potential detection, management, and control strategies.

Keywords: deoxynivalenol; food and feed contamination; human health; management strategies

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1. Introduction

Natural contaminants in food and feed are significant sources of human and animal health concerns [1–3]. Mycotoxins are deadly substances produced by fungi that flourish in food or feed, and they pose a major health risk to humans and animals [4–9]. When mycotoxins enter the bodily system, they are well-known for causing serious health problems in humans and animals, and they exhibit their effects in a variety of ways. Ingesting mycotoxin-contaminated food or animal feed has been shown to cause carcinogenic, mutagenic, teratogenic, and immunosuppressive consequences [10]. *Aspergillus*, *Fusarium*, and *Penicillium* are the most common mycotoxin-producing fungal genera. Contamination with mycotoxin is a global problem, but it is exacerbated in warm, humid areas that promote fungal growth and mycotoxin synthesis. Contamination with mycotoxins has a financial impact on agriculture and the food industry. Aside from the financial costs of mycotoxin contamination of crops and food

products, additional significant mycotoxin concerns include human and animal health difficulties, reduced agricultural production, and the recall and disposal of mycotoxin-infected commodities [11].

Deoxynivalenol (DON) is a prevalent mycotoxin identified in cereals around the world. It is a type-B trichothecene that *Fusarium graminearum* and *Fusarium culmorum* typically produce [12–14]. It is also known as vomitoxin because of its emetic effects in pigs and gastrointestinal complaints in people [15]. DON can also be found in pastures and silages, as well as cereals such as wheat, maize, barley, rye, oat, and safflower seed. Asia, Africa, America, Europe, and the Middle East are all affected by DON pollution [16]. DON is a naturally occurring foodborne mycotoxin that is easily caused by environmental changes and is typically present in grains during the preharvest, processing, drying, and storage processes (e.g., temperature, humidity). DON is also extremely thermostable, withstanding temperatures ranging from 170 to 350 °C (no reduction detected after 30 min at 170 °C treatment), rendering it a common dietary pollutant in mycotoxins pollution [15].

This article provides an overview of the main sources, chemistry and biosynthetic pathway, genes responsible for DON occurrence in food and feed, as well as the mechanism of toxicity and health effects on humans and animals, considering the numerous publications describing the toxicological consequences of mycotoxins. It also highlights the effect of environmental factors on DON production as well as discusses the management and control strategies with special emphasis on masked mycotoxins.

2. Major Source of Deoxynivalenol

DON is a naturally occurring metabolite produced by the fungi of the *Fusarium* genus, especially *Fusarium graminearum*, *Fusarium crookwellense*, and *Fusarium culmorum*, which contaminate the food and feed globally [17,18]. The fungi growth is enhanced by mild temperatures and high humidity during flowering and maturation periods [19]. Other environmental factors that affect growth and toxin accumulation are water activity (a_w), pH, and nutrient composition [20]. The most commonly infected food groups are cereals like wheat [21], maize [22], barley [23], rice [22], oats [24], and their products viz, breakfast cereals [25], infant cereals, meals, feed, and baby mix. Fusarium head blight (FHB) infection and DON contamination are dependent on agricultural practices such as crop rotation, tillage, fungicide application, FHB resistant varieties, and climatic factors such as spring rainfalls and warm temperatures that promote the infection and DON formation on cereal crops [26]. The most common disease caused by *Fusarium graminearum* in cereal crops like wheat and barley is FHB or scab, which causes not only economic loss but also safety concerns related to mycotoxin (DON) accumulation in products due to its stability [27]. The fungus grows as mycelia which develop into perithecia that release ascospores which are then carried by wind or rain to the crop plants [28]. DON suppresses protein synthesis by binding to the 60S ribosomal subunit's peptidyl transferase protein RPL3 and two *F. graminearum* strains can be distinguished by their production of 3-ADON or 15-ADON, which differ in the position of the acetyl group [29]. *Fusarium culmorum* is the major species that causes FHB in cereal crops, such as durum wheat, triticale, rye, and bread wheat in Europe, thus contaminating the grains with DON [30]. *Fusarium crookwellense* was responsible for causing infection and producing DON in oat kernels [31]. *Fusarium cerealis* has been known to cause FHB and DON accumulation in durum wheat [32]. Another strain causing the FHB and DON accumulation is *Fusarium equiseti*, which has also been studied to cause infection in wheat in South Africa [33]. Some of the species that have been recently reported to cause infection are *F. verticillioides*, *F. poae*, *F. proliferatum*, *F. subglutinans*, and *F. temperatum* [34].

3. Chemistry and Biosynthesis of Deoxynivalenol

DON (3,7,15-trihydroxy-12,13-epoxytrichothec-9-en-8-one) is a trichothecene mycotoxin present mainly in cereals and cereal-based products [35,36]. DON has a double bond with oxygen at carbon number 8 in its molecular structure, making it a type B tri-

chothecene [37]. In eukaryotic cells, DON is a potent inhibitor of protein synthesis [38]. It is hazardous to human and animal wellbeing, as well as playing a key role in plant infection. DON inhibits protein synthesis by binding to peptidyl transferase and mediates oxidative stress-induced DNA damage and apoptosis. DON toxicity in humans and livestock causes anorexia, malnutrition, gastroenteritis, endotoxemia, and even shock-like death [36].

DON is made by combining three mevalonate units derived from trans-farnesyl pyrophosphate (FPP), which are then cyclized to form tricodiene, a precursor to trichothecenes. DON biosynthesis is governed by fifteen genes distributed over three chromosomes that code for the enzymes and regulatory proteins involved [39]. The remaining loci include TRI1-TRI16 and TRI101, while one locus contains a set of 12 TRI genes. Trichothecene synthase, which is encoded by the TRI5 gene, catalyzes the reaction that produces trichothecene, which is followed by nine reactions catalyzed by enzymes encoded by the TRI4, TRI101, TRI11, and TRI3 genes, which produce various DON precursors. An acidic pH is a significant environmental element that encourages DON biosynthesis. The accumulation of ammonium is caused by the absorption of available nitrogen-containing compounds in food or the culture medium, which causes the pH to decrease. The TRI5 gene product, which is responsible for FPP cyclization and the production of tricodiene, a precursor to DON, is activated in this state. DON biosynthesis is also induced by plant defense mechanisms in response to fungi infection. DON is produced by *F. graminearum*, which causes fungi to develop hyphae and spread from an infected branch to a healthy branch. In addition, the toxin inhibits the thickening of plant cell walls, which will serve as a deterrent to fungal invasion [39].

4. Genes Responsible for Deoxynivalenol Production

All the TRI genes involved in trichothecene biosynthesis have been identified in *Fusarium graminearum* and *Fusarium sporotrichioides*. Except for TRI1, TRI16, and TRI101, the other TRI genes are included in the largest TRI gene cluster [40]. The biosynthesis of the mycotoxin DON in *Fusarium graminearum* is affected by several host and environmental factors and is controlled by two pathway-specific transcription factors, TRI6 and TRI10. The TRI6 binding site in the promoters of TRI genes has formerly been recognized and characterized. TRI10 deletion in *F. graminearum* suppresses the expression of the TRI gene, despite the fact that its exact function is unclear. However, how the transcription factors Tri6 and TRI10 are designed to regulate the expression of other TRI genes is unknown (Jiang et al., 2016). The cyclic adenosine monophosphate (cAMP) signaling pathway, as well as all three MAP kinase pathways, is required for DON biosynthesis in *F. graminearum* [41,42]. Extracellular signals are likely to activate TRI6 and TRI10, which regulate TRI gene expression, by any of these key signaling pathways. Extracellular signals are likely to activate TRI6 and TRI10, which regulate TRI gene expression, by any of these key signaling pathways [38]. In addition, the sequenced *F. graminearum* strain PH-1 lacks functional TRI13 and TRI7, preventing DON development and Nivalenol production (NIV). TRI5 is a key cluster gene that catalyzes the formation of trichodiene from farnesyl pyrophosphate, the first step in trichothecene biosynthesis [40].

5. Effects of Environmental Factors on Deoxynivalenol Production

The environmental factors that primarily affect mycotoxin production are temperature, moisture, water activity (a_w), substrate oxygen levels, physical damage, competition, and the presence of fungal spores [35,43]. The growth of the fungi, *Fusarium,* and its mycotoxin, DON, is dependent on weather conditions, such as high intensity warm and wet conditions and heavy precipitation, which makes the transfer of macroconidia to the upper parts of the plant easier through raindrops. The optimum temperature conditions are 10–25 °C during flowering and humidity greater than 85–90% [44]. High to extreme humidity during the growth and harvesting period enhances the growth of mold and hence the production of mycotoxin [35]. It has been shown by Pascari et al. [26] that warm temperatures and rainfall promote the growth and consequently mycotoxin formation in cereals. The other

factors that affect mycotoxin production are a_w and incubation time, and as reported by Han et al. [45], these factors affected the DON production through TRI5 gene expression under optimum conditions of 20–30 °C, 0.95–0.98 a_w, and 7–28 days of incubation. Rainfall positively affected the growth of mold and DON production as temperature and humidity are important factors for growth and flowering [46]. Ramirez et al. [47] studied the effect of temperature, a_w, and incubation time and observed that growth was optimum at 0.99 a_w and 25 °C, and the growth was negatively affected when the a_w of the medium was reduced. A temperature of 22 °C after 35 days of incubation time also favored the DON production, as shown by Martins and Martins [48].

The environmental factors affect not only the growth of mold but also other physiological processes that are important for survival and competition, such as the expression of hydrolytic enzymes playing a crucial role in a fungal establishment on a substrate [49]. DON production was maximum at 0.98 a_w, 30 °C, and 400–800 ppm of CO_2 [50]. It was also observed that the DON concentration was maximum at 0.97 a_w and 30 °C [51]. The favorable condition for DON production was 25 °C and 0.98–0.99 a_w, as observed by Rybecky et al. [52]. Further, the optimum growth of the fungus was observed at 0.99 a_w and the growth decreased as a_w was lowered from 0.97 to 0.94 [53]

6. Occurrence in Food and Feed, including Masked Mycotoxins

The most infected foodstuffs are cereals such as wheat, maize, barley, rice, oats, and their products viz; breakfast cereals, infant cereals, meals, feed, and baby mix. FHB infection and DON contamination are dependent on agricultural practices, such as crop rotation, tillage, fungicide application, FHB resistant varieties, and climatic factors, as spring rainfalls and warm temperatures promote the infection and DON formation on cereal crops [26]. In the real world, DON is always co-occurring with related metabolites, such as modified or masked versions and related molecules like Culmorin (CUL). CUL is classified as an "emerging mycotoxin" as it has yet to be controlled by food safety authorities, despite the fact that it has been found in a variety of foods, sometimes in significant amounts [54]. CUL contamination levels and natural occurrence have been linked to DON occurrence and levels, with CUL concentrations up to three times greater than DON in naturally contaminated samples [55,56]. Although CUL is mildly hazardous; there have been few studies on the possible health risks of CUL in food products; whether alone or in combination with DON [57,58]. As a result, the high frequencies and amounts of CUL and related compounds in cereal-based raise concerns regarding their co-occurrence with disguised DON mycotoxins. Contamination of DON in wheat and its by-products poses a significant danger to public health. The occurrence of DON in foods and feeds (Table 1) is a major concern for the food industry around the world.

Table 1. Occurrence of Deoxynivalenol in food and feed around the world.

Food/Feed Matrix	Country	Range (µg/kg)	Detection Technique	Reference
		Food		
Barley/Bakery products	Argentina	2360	HPLC-UV	[59]
	Brazil	310–15,500	LC-MS/MS	[60]
	Romania	0–4000	ELISA	[61]
	Tunisia	500–3600	HPLC	[62]
	Hungary	97–3065	HPLC	[63]
Corn	South Korea	3.3–232.56	HPLC	[64]
Corn/Corn germ meal	China	100–4320.9/100–4402.7	HPLC	[65]
Corn flour/Cornflakes	Serbia	931/878	HPLC	[66]

Table 1. *Cont.*

Food/Feed Matrix	Country	Range (µg/kg)	Detection Technique	Reference
		Food		
Maize	China	100–19,811	HPLC-UV	[67]
	Egypt	26–807	LC-MS/MS	[68]
	Hungary	225–2963	ELISA	[69]
	Poland	1–6688	HPLC	[70]
	Serbia	260.4–9050	ELISA	[71]
	South Africa	9176	LC-MS/MS	[72]
	Nepal	>1	HPLC	[73]
Oats	Canada	50–2340	HPLC-PDA	[74]
	Finland	21,608	GC-MS	[23]
	Portugal	17,900	HPLC	[75]
	Russia	50–1030	HPLC-MS	[76]
	Sweden	99–5544	HPLC/ESI-MS/MS	[77]
	UK	1866	LC-MS/MS	[78]
Noodles and Pasta	Italy	35–450	LC-MS/MS	[79]
Rice	Pakistan	6.99	LC-MS/MS	[80]
Wheat	Netherlands	100–11,000	LC-MS/MS	[81]
	Serbia	630–1840	HPLC	[82]
	Iran	23–1270	ELISA	[83]
	Romania	110–1787	LC-MS/MS	[84]
	Uruguay	1400–3400	HPLC/UV	[85]
	Norway	5–94	HPLC	[86]
	Sweden	1189	HPLC/ESI-MS/MS	[87]
	Hungary	1880	ELISA	[88]
	Argentina	9480	LC-MS/MS	[89]
	Switzerland	10,600	LC-MS/MS	[90]
	Israel	1.2–1746	LC-MS/MS	[90]
	Nigeria	119–2560	LC-MS	[91]
	Brazil	73–2794	HPLC	[92]
	Poland	10–1265	HPLC	[93]
	China	33–3030	HPLC	[94]
	Sweden	1189	HPLC/ESI-MS/MS	[87]
	India	70–4730	HPLC	[95]
	Canada	4700	HPLC-PDA	[74]
	Slovakia	788	ELISA	[96]
	Spain	6178	HPLC	[97]
	Italy	56–27,088	GC-MS	[98]
	Serbia	64–4808	HPLC/ELISA	[99]
	Iran	23–1270	ELISA	[83]
	Finland	5510	LC-MS/MS	[100]
	Serbia	154–16,528	ELISA	[101]
	Albania	1916	LCMS	[102]
Spring wheat	Lithuania	100–10,644	UPLC/MS	[103]
Wheat dust	Belgium	607–14,043	UPLC/MS	[104]
Winter wheat	Lithuania	100–1393	UPLC/MS	[103]
Winter wheat	Slovak Republic	20–2651.79	HPLC-DAD	[105]
Wheat flour	Spain	501	HPLC	[106]
Wheat flour and bread	Iran	0.78	ELISA	[107]
Infant Food	USA	10–224	HPLC-UV	[108]
Infant Food	India	5–228	ELISA	[109]
Barley/Pasta	Romania	21.52–721.88/28.23–173.55	ELISA and HPLC	[21]
Flour and breakfast cereals	Romania	31.56–172.37	ELISA and HPLC	[21]

Table 1. *Cont.*

Food/Feed Matrix	Country	Range (µg/kg)	Detection Technique	Reference
		Food		
		Feed		
Broiler feeds	Thailand	33.58–60.81	LC-MS	[110]
Cattle compound feed	Spain	289.9	UPLC–MS/MS and UPLC–QTOF–MS	[111]
Cattle/Chicken/Pig feed	South Korea	91.65–950.25/ 3.3–603.10/32.38–932.48	HPLC	[64]
Concentrated feed/Formula feed/Premixed feed	China	11.6–277.6/47.1–864.5/ 97.4–776.3	UPHLC-MS	[112]
Dairy concentrate feed	Kenya	18.53–179.89	ELISA	[113]
Duck complete feed	China	100–2613.7	HPLC-UV	[67]
Finished feed	South Africa	9805	LC-MS	[72]
Forage maize	Northern Germany	2237–3038	LC-HRMS	[114]
Compound feeds	South Africa	3.22–56.52	UHPLC-MS/MS	[115]
Feed	Egypt	1516	LC-MS/MS	[68]
Pig complete feed (powder)/(pellet)	China	100–2767.6/100–3346.0	HPLC	[65]
Silage	Brazil	300	HPLC	[116]
	Spain	43.1–6685.6	LC-MS	[117]
	England	10–7111	UPLC	[118]
	Poland	1–7, 860	HPLC	[70]
Poultry/Sheep/Swine compound feed	Spain	250/250/254.9	UPLC–MS/MS and UPLC–QTOF–MS	[111]
Swine feed	Hungary	137–997	ELISA	[69]

7. Mechanism of Toxicity

Consumption of DON contaminated food and feed is a potential risk to the health of both humans and animals. DON is the most reported mycotoxin in cereals and is linked with gastroenteritis and immune disorders [119,120]. Exposure to the toxin can result in numerous problems such as digestive problems, feed refusal, diarrhea, reproductive problems, nutrient malabsorption, increased incidence of diseases, and endocrine disruption [121–123]. DON also causes oxidative stress due to the production of free radicals, which then damage DNA and the cell membrane. It also causes degradation of the ribosome, inducing ribotoxic stress, inhibiting protein synthesis, and ultimately apoptosis [121,124,125]. Studies have proven that DON is associated with the rise of reactive oxygen species, triggering lipid peroxidation and hepatoxicity as the liver is the main organ to get affected by oxidative stress [122,126–128]. Exposure to a high dose of DON, even for a short period, causes gastrointestinal problems in both humans and animals.

At doses as low as 25 ng/mL, DON-induced cytokine and chemokine production can be generated in human blood monocytes [129]. Induction of these mediators, like endotoxin, may play a role in DON-induced anorexia. DON inhibits intestinal cell development and is absorbed via the intestinal epithelium via simple diffusion [130]. DON activated p38 ERK and JNK as well as disrupted intestinal permeability at levels equivalent to those reported in nature. DON suppresses the activity of numerous intestinal transporters [131].

8. Effects on Human Health

DON causes hematopoietic progenitor cells less harm in vitro than T-2 toxin [132]. Human platelet progenitors (CFU-MK) are cytotoxic to DON; however, human red blood cell progenitors (CFU-GM) are not (BFU-E). In CD34+ cells, DON does not cause DNA fragmentation or annexin-V binding, both of which are apoptotic markers [133]. In addition, Bensassi et al. [134] studied DON toxicity in human colon cancer cells (HT 29), finding

that the toxin caused DNA breakage as well as p53 and caspase-3 activation. DON causes direct DNA damage, according to scientists, and might be categorized as a genotoxic agent capable of causing apoptotic cell death.

DON has been linked to gastroenteritis in humans, but its long-term effects are unknown [135]. DON directly suppresses protein synthesis, but it also has an indirect effect on DNA and RNA synthesis, inflammatory responses (ribotic stress response), and neurological functioning [136]. Two species typically used to evaluate DON toxicity include the pig, a highly sensitive food-producing animal with economic ramifications, and the mouse, a model widely used in human disease and safety investigations [136].

9. Effects on Animal Health

The sensitivity of the DON varies in different species, age groups, and sex of the animals. Hogs are the most sensitive to DON contamination, along with the ruminants, poultry, cats, dogs, and rodents [137,138]. The qualitative and quantitative production rates of the egg, meat, and milk get reduced by the DON contamination. The DON concentration in the range of 0.1–2 μg/mL can inhibit the protein synthesis related to the lymphocytes and fibroblasts due to cytotoxicity [139]. In addition, DON contamination results in weak offspring, dead birth, stiff hog, female pig's abortion, reduced quality and quantity of the produced eggs in poultry, as well as decreased production performance in cattle [140]. Further, the increased rate of embryo deformity in chicken and chromosomal aberration due to DON contamination has been reported [141]. In cows, a slight reduction in the consumption of the feed was reported when the DON quantity increased from 1.5 to 6.4 mg/kg [142]. In hogs, the absolute feed refusal was found at 12 mg/kg of DON, and at 20 mg/kg of DON, they started vomiting. Compared to hogs, chickens are less sensitive to DON and the reduced weight gain and feed refusal were observed when the feed concentration of DON increased up to 16–20 mg/kg [143].

The estimated mean dietary concentration of the DON and its derivatives range between 64.2–996 μg/kg for lactating cows and beef sheep. Ruminants are less sensitive to DON as compared to poultry. In cows, poultry, and hogs, the transmission of the DON from their feed to foodstuffs was reported. The concentration of DON at 9 mg/kg of feed can negatively affect the chickens [142]. Even exposure to a lower dose for a long time poses a potential risk. A study by Huang et al. [144] administered different doses of the toxin via oral gavage (0, 0.03, 0.1, 0.3, 1, and 3 mg/kg/day) to female rats (F0 generation) during gestation and then to offspring (F1 generation) up to 27 days postnatal. The results showed that a dose of up to 3 mg/kg/day has no effect on the body weight or survival of the F0 generation, but a decrease in body weight was observed in offspring (F1 generation) at a dose of 3 mg/kg/day. As there was no significant data on maternal toxicity either during gestation or lactation, the decrease in the bodyweight of F1 rats could be considered a direct effect of DON.

Further, DON is known to cause neurotoxicity. In a study by Wang et al. [145], piglets were fed on a DON-based diet of different concentrations (1.3 and 2.2 mg/kg) for 60 days and observed for its effect on their hippocampus, cerebral cortex, and cerebellum. The increasing concentration of the toxin was found to be linked with oxidative damage in brain parts, where the damage in the cell structure of the hippocampus was revealed using scanning electron microscopy. Moreover, an increase in the concentration of calcium and Ca^{2+} calmodulin-dependent kinase II (CaMKII) was observed. Other studies have suggested that the calcium ions are linked with neurotransmitter release and cell proliferation, and the disruption in Ca^{2+} homeostasis can negatively affect the neuronal circuits of the hippocampus [146,147]. Wang et al. [145] further suggested that DON toxicity involves Ca^{2+}/CaM/CaMKII signaling pathways in neurotransmission and lipid peroxidation. The cytotoxic effect of DON has also been studied in mammary epithelial cells. Research indicated a lower yield of milk when cows were fed contaminated feed [148,149]. Lee et al. [150] investigated the effect of DON on mammary epithelial cells (MAC-T) in bovine animals. Different concentrations of the toxin (1–10 μM) were used for their impact

on MAC-T cells. Results showed a significant reduction in proliferation activity of the cells with the increase in toxin level with the highest effect at 10 µM. The phosphorylation of phosphoinositide-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) signaling molecules increased in MAC-T cells, demonstrating that DON regulates these signaling pathways.

10. Detection Techniques including Masked Mycotoxins

The conventional analytical methods for detecting DON includes gas chromatography-mass spectrometry (GCMS), high-performance liquid chromatography (HPLC) [151,152] and liquid chromatography-tandem mass spectrometry (LCMS/MS) [153,154]. Although these methods benefit from high sensitivity and specificity, the downsides are that they are time-consuming for sample preparation, require expensive instrumentation, and highly qualified personnel to operate [151]. Other methods for convenient, cheap and high sensitivity detection include enzyme-linked immunosorbent assay (ELISA) [155], lateral-flow immunochromatographic assay [156], lateral flow immunoassay [84], fluorescence [157], surface-enhanced Raman scattering (SERS) [158,159], and electrochemical detection [160].

To meet the need for real-time monitoring of mycotoxin, methods like lateral flow immunoassays (LFA) [161,162] and biosensing assays [163–165] were developed. LFA is supposed to be the cheapest, fastest and simplest way of detecting mycotoxins [166]. Jin et al. [167] developed a new dual near-infrared fluorescence-based LFA for detecting DON in maize. 5 g chopped maize sample was combined with 25 mL 70% methanol and vortexed for 2 min for sample preparation. The extracted solution was centrifuged at 5000× *g* for 5 min, and the supernatant was diluted 10 times with phosphate buffer saline, PBS (0.01 M, pH 7.4), followed by Tween 20 added to get a final 0.5% (*v*/*v*), and 200 µL of the diluted sample was evaluated by the NIR-based LFA. Further, Zhao et al. [168] developed a fast lateral flow fluorescence microsphere immunoassay test strip (FM-ICTS) for detecting DON residues in a variety of agricultural goods. 5 g of material was shaken for 8 min with 25 mL of extraction solution, then centrifuged (8000× *g* for 12 min). The supernatant was diluted 10-fold in 10 mM PBS + 3% Rhodasurf® On-870 before being detected with FM-ICTS. For identifying DON residues in agricultural goods, this approach is easy, reliable, and sensitive.

In addition, electrochemical and bio-sensors are powerful tools with high transmission and easy and low-cost operation [169,170]. Ong et al. [171] developed a selective biosensing device based on iron nanoflorets graphene nickel (INFGN) for selective detection of DON. Furthermore, Li et al. [172] developed a sensitive and selective antibody-like sensor based on molecularly imprinted poly(L-arginine) on carboxylic acid-functionalized carbon nanotubes for detecting DON in agri-food products. The sample was made by mixing wheat flour with acetonitrile/deionized water (84:16, *v*/*v*), ultrasonic extraction for 30 min, centrifugation at 15,000 rpm for 10 min, and collecting the supernatant. Finally, the supernatants were filtered and incubated at 4 °C through a 0.22 µm sterile membrane. This method provides a realistic biomimetic sensing platform for identifying mycotoxins in food and agriculture.

Besides these, multiplex immunochromatographic assays (mICAs) are employed for screening mycotoxins with rapid and excellent selectivity [173]. Recently gold nanoparticles (AuNPs) and quantum dots (QDs) [174,175] have been used as signal tags for detecting multiple mycotoxins in foodstuffs. Semiconductor QDs with a unique luminescent property are utilized for developing highly sensitive biosensors based on Forster resonance energy transfer (FRET). Goryacheva et al. [176] developed a FRET-based fluorescent immunoassay for detecting DON. 25 g of wheat samples were mixed with 100 mL of methanol/water (70/30, *v*/*v*) for 15 min on a horizontal shaker at room temperature. The wheat particles were precipitated via centrifugation (4000× *g*, 20 °C, 15 min). The supernatant was used for analysis after dilution of 1:5 with PBS.

As conventional immunochromatographic assays (ICAs) based on AuNPs have low sensitivity, Li et al. [177] developed a highly sensitive ICA based on polydopamine coated

zirconium metal-organic frameworks labeled antibodies for visual determination of DON. Still, AuNPs-based mICAs show low sensitivity while QDs-based mICAs have interference between multiple analytes and recognition molecules [178,179]. Thereby, a multiplex immunochromatographic assay (mICA) was developed by Zhao et al. [168] based on novel α-Fe2O3 nanocubes (FNCs) for the simultaneous detection of DON. For 15 min, 5 g of samples were mixed with 10 mL methanol–water (70:30, v/v) and then sonicated for 10 min, followed by centrifugation (5439× g, 10 min) and dilution to 10-fold with 10 mM PBS (pH 7.4) solution to get the supernatant. The FNCs-mICA method provided sensitive, quick, and repeatable detection of multiple mycotoxins on-site.

Similarly, Huang et al. [180] developed an immunochromatographic test strip for rapid and simultaneous detection of fumonisin B1 and DON in grains. 1 g sieved sample was combined with 5 mL ultrapure water in a vortex mixer for 5 min, allowed to stand for 10 min, and the supernatant was filtered through 0.45 and 0.22 µm filter membranes to get clear solutions for the analysis. The developed technique was suitable for the on-site screening of large-scale samples. Furthermore, Subak et al. [181] developed a voltametric aptasensor for detecting DON in food and feed samples. A high-speed blender was used to mix 25 g of maize flour with 50 mL of 50% ethanol/water (v/v) for 5 min. The supernatant was collected and evaporated to dryness under a nitrogen flow after centrifugation at 5000 rpm for 5 min. The dried sample obtained was suspended in affinity buffer and differential pulse voltammetry measurements were used to record the response.

DON can bind with proteins or carbohydrates to form a varied structure known as "modified mycotoxins", which include both "biologically and chemically modified" forms [182–184]. The term "masked mycotoxins" especially refers to "biologically modified" forms conjugated by plants [184]. Masked form of DON forms Deoxynivalenol-3-β-D-glucoside (D3G) by enzymatic interaction with glucose [39,185,186] while 3-Acetyl-deoxynivalenol (3Ac-DON) and 15-Acetyl-deoxynivalenol (15Ac-DON) [187,188] are formed during deacetylation of DON. DON and its masked forms, namely D3G, 3Ac-DON, and 15Ac-DON, have been reported in cereal and cereal-based products [189]. There is limited study on the toxicodynamics of these forms; however, their absorption, bioavailability, and toxicity have been studied [186,190].

These modified or masked forms of mycotoxins remain undetected by conventional analytical techniques leading to underreporting [184,185]. Hence, there are serious health concerns associated with masked/modified DON. They can even re-convert to their native form [187], which raises further toxicity concerns in mammals [3–6,191]. Therefore, Fan et al. [112] developed and validated an Ultra-High-Performance Liquid Chromatography-tandem Mass Spectrometry Method (UHPLC-MS) for simultaneous detection of masked DON in various feed samples. Further, Olopade et al. [192] used LC-MS/MS procedure to quantify DON and its masked forms, 3Ac-DON and 15Ac- DON. Despite this, their combined effects are unknown [193], necessitating additional toxicokinetic studies of masked versions [194]. To address these concerns, modified DON could be transformed using a hydrolytic process involving alkaline, acidic, or enzymatic methods [195,196] as well as an integrated strategy for qualitative and quantitative analysis of modified mycotoxins, as suggested by Lu et al. [194].

11. Legislation

Due to its widespread occurrence and severe impacts on human and animal health, DON has attracted international attention. As a result, measures for preventing, excluding, or inactivating DON in meals and feeds must be developed. DON contamination might be difficult to avoid from preharvest to manufacture. DON management strategies have been developed to (a) minimize DON formation or contamination prior to harvest, (b) degrade or eliminate DON from polluted foods and feeds, and (c) reduce DON bioavailability by reducing gastric absorption [16]. Table 2 summarizes the permissible limits of DON in various foods and feeds set by various regulatory organizations. The permissible limits of DON in various foods and feeds are higher in Europe than that set by US-FDA and

FAO. Further, among the cereal category, the limits for maize and maize-based products are higher. In a real-world situation of an eco-environmental system, DON contamination occurs in combination with other mycotoxins, as well as its masked forms in food and feeds. This could be the reason behind the variation in permissible limits depending on the type of food and feed and their geographical location, which poses new challenges for government organizations with setting scientific legislation, regulations, and standards [15].

Table 2. Permissible limits of DON in various foods and feeds established by different governing bodies.

Governing Body	Food/Feed Type	Permissible Limit (mg/kg)	Reference
European Commission	Cereals and cereal-based products (except for maize by-products)	8	[197]
	Maize by-products	12	
	Complete feedingstuffs and complementary with the exception of:	5	
	Complete feedingstuffs and complementary for pigs	0.9	
	Complete feedingstuffs and complementary for calves (<4 months), lambs, and kids	2	
United States Food Drug & Administration (US-FDA)	Wheat products (e.g., bran, flour, and germ) for human consumption	1	[137]
Food and Agricultural Organization (FAO) of the United States/Codex Alimentarius	Maize, barley, and raw wheat	2	[137]
	Maize or barley derived flour, semolina, meal, and flakes, wheat	1	
	Cereal-based infant foods	0.5	

12. Management and Control Strategies, including Pre-Harvest Preventive Strategies and Post-Harvest Treatments and Detoxification Strategies

The development and implementation of efficient management and control strategies are necessary to reduce the DON contamination in food and feed when pre- and post-harvesting strategies cannot control them [198]. This detoxification technique is classified into physical, chemical, and biological methods [139]. Physical methods include washing, cleaning, dehulling, segregation, sieving, heat treatments, gamma, UV, and visible light radiations [199]. This method is most suitable for food compared to feed. Thermal treatment in food processing techniques has been divided into dry methods (baking, roasting, and frying) and wet methods (steaming and cooking) [200] and is considered to be an important tool for DON mitigation in foods, but the degradation products formed can have different toxic behavior than the parent mycotoxin [201].

Stadler et al. [202] concluded that baking of food could cause a partial degradation of DON because a considerable reduction in DON was observed with increased baking time and temperature, and the degradation of by-products was less toxic. The reduction during baking is either due to binding to matrix compounds or due to the transformation into other toxins but not the actual destruction of toxins [203]. During roasting, an effective reduction in DON was observed between 180 °C to 220 °C for 30 min and the reduction increased with increasing temperature [35]. However, frying had no significant effect on DON levels due to the high thermal stability and release of bound forms [200]. Further, Kalagatur et al. [204] observed that high pressure (1000–5500 bar) between 30–60 °C for 10–30 min during cooking significantly reduced DON levels in foods. More than a 40% reduction in DON was observed in the boiled product due to the leaching of DON into the broth [205]. In addition, gamma radiations have successfully reduced DON levels in wheat [198]. Several works

have also reported degradation of DON using UV [206,207], where significant was observed without any changes in color and protein content of the treated food samples [208].

Chemical and biological methods are suitable for both food and feed samples. The chemical method uses chemicals such as calcium hydroxide monomethylamine and sodium bisulfite [209–211], moist and dry ozone [210,211], ascorbic acid and ammonium hydroxide [139], acid and alkaline electrolyzed water [212], and ammonia [213]. However, the physical and chemical methods have several disadvantages, such as limited efficacy, high cost, harmful chemical residues, loss of nutritional value, sophisticated equipment requirements coupled with safety issues; hence, environmentally-friendly techniques using microorganisms and enzymes have been developed [214].

Biological detoxification involves the use of bacteria, fungi, and actinomycetes to reduce or eliminate DON from products either through adsorption or enzymatic degradation [215,216]. Li et al. [217] observed that *Bacillus subtilis* had the highest detoxification rate out of 16 strains of bacteria and showed a synergistic effect with *Lactobacillus plantarum, B. velezensis* RC 218, and *Streptomyces albidoflavus* RC 87B showing up to 51% DON reduction in durum wheat, hence a potential biocontrol agent [218]. *B. subtilis* ASAG 216 degraded 81.1% DON under optimum temperature (35–50 °C), time period (8 hr), and pH (6.5–9.0) conditions because of degradation ability inherent in extracellular enzymes or proteins [219]. *Bacillus licheniformis* strain YB9 also reduced 82.6% DON [220]. Further, the bacterial consortium C20 was able to degrade DON at 30 °C and pH 8 [221]. *Devosia insulae* A16 was also able to degrade 88% DON within 48 hrs at 35 °C at pH 7 [222]. *Slackia* sp. D-G6 reduced DON by deep oxidation between 37–47 °C and pH 6–10 with non-toxic DOM-1 as a degradation by-product [223]. In addition, *Pseudomonas* sp. Y1 and *Lysobacter* sp. S1, soil-derived bacteria, had a significant DON degrading ability by an enzymatic transformation of DON into less toxic, 3-epi-DON [224]. *Pelagibacterium halotolerans* ANSP101 degraded DON by transforming it into less toxic 3-keto-deoxynivalenol at 40 °C and pH 8 [225]. *Devosia* strain D6-9 completely removed DON in wheat by catabolizing it into 3-keto-DON and 3-epi-DON [226]. Several works listed by Gao et al. [223] have shown the biodegradation of DON by fungi. DON detoxification can also be achieved by enzymatic reactions such as deep oxidation, oxidation, epimerization, and glycosylation and the formation of by-products like DOM-1, 3-keto DON, 3-epi DON, and DON-3-glucoside (D3G) [188].

However, due to certain limitations of physical, chemical, and biological methods such as low efficacy, the requirement of expensive chemicals, sophisticated equipment, and the formation of harmful chemical residues [227], a novel technology such as photocatalytic degradation has been developed that is easy to use, inexpensive, environmentally friendly, reusable, and has high stability [228]. This technique degrades the target toxin using a suitable photocatalyst such as the TiON@PdO nanoparticle [229], carbon-supported TiO_2 [230], ZnO@graphene hybrids [231], upconversion nanoparticles@ TiO_2 composite [215], and dendritic-like-Fe_2O_3 [232]. Another technique is electrochemical oxidation (ECO), which has emerged as a new oxidation technology that destroys DON by several mechanisms; in an experiment using graphite as an electrode, DON was significantly reduced due to the high potential and acidic conditions of the technique [233]. Atmospheric cold plasma technology (ACP) is another novel non-thermal approach for detoxification of DON, which utilizes plasma under low atmospheric pressure conditions with the main advantage of high chemical reactivity and efficacy compared to ozone or UV treatments and resulting in decontamination of DON within seconds [227,234].

With food safety becoming a global concern, significant focus on the control and prevention of accumulation of DON and its entry into the food supply chain is achievable through scientific agricultural interventions at pre-and post-harvest conditions [235]. These interventions involve good agricultural practices (GAPs), good storage practices (GSPs), and good management practices (GMPs) [236].

The mycotoxin contamination occurs during the growing period of crops, so it becomes necessary to identify appropriate pre- and post-agronomic practices to avoid grain contamination [237]. Pre-harvest strategies include the use of resistant varieties, removal

of weed and damaged kernels, soil analysis, use of herbicide, fungicide and insecticide, seedbed treatment, crop rotation, tillage and plowing, the use of fertilizers, and genetically modified plants for suppression of mycotoxins [238–240]. The most effective practice to control the disease is the use of genetic resistant varieties, pedigree selection, and identification of primary infection pathways, such as silk channels, during the flowering time [46]. An attractive technology is to employ gene editing to resist fungus growth or to prevent mycotoxin formation in plants through kernel-specific RNA interference (RNAi) gene cassette targeting the aflC gene involved in the mycotoxin biosynthetic pathway [241]. Crop rotation or tillage is also suggested as a control measure of the disease as it decreases and manages the crop residue where most of the fungi survive [242]. The use of fertilizers, particularly nitrogen, boosts *Fusarium* development together with a favorable effect on plant growth, and, therefore, mycotoxin contamination rises [243].

During harvesting, it is important to consider the time of harvesting as a greater number of over mature or immature seeds can increase the mycotoxin levels in final products [244]. Crop stress during harvesting should also be minimized by avoiding early harvesting, damaged kernel collection, mechanical damage, and kernel contact with soil [245]. While transporting the harvested grain, the containers and vehicles should be clean, dry, and free of insect and fungal growth [246]. After harvesting and before storage, it is important to dry the grains to reduce the moisture level, which is responsible for fungal growth, and it can be done by the use of solar dryers instead of sun drying as slow drying increases the mycotoxin concentration [247]. During storage, it is necessary to control moisture, temperature, and relative humidity of the grain to prevent deterioration through fungal growth and mycotoxin production, with the ideal temperature being 1–4 °C in winter and 10–15 °C in summer, the water activity of less than or equal to 0.70 and relative humidity less than 70% [248]. Along with these storage conditions, the storage rooms should be clean, well ventilated, and protected from rain, drainage, insects, rodents, and birds and aeration of place with the circulation of air to maintain a uniform temperature [246]. For best management practices of stored grains, the most important principle is SLAM (sanitation, loading, aeration, and monitoring) [249].

To lower mycotoxin levels, post-harvest management strategies include adequate drying, shipping, and packaging, sorting and cleaning, drying, smoking, insect control, and pesticide use in storage rooms. These interventions can also involve best-practices teaching and awareness initiatives. It is critical to maintaining appropriate hygiene and the application of natural and chemical agents after harvesting the crop during storage [250]. From farm to table, a successful application of the Hazard Analysis Critical Control Point (HACCP)-based postharvest strategy should include measures for prevention, control, and quality [248].

13. Conclusions

DON mycotoxin is found in agricultural products worldwide, presenting a health risk to humans and animals. The extensive prevalence of DON in small grain cereals worldwide necessitates the application of fast and effective techniques. This is particularly important in developing countries, where DON and its transformed forms are underappreciated. Relevant food safety initiatives should be prioritized, with an emphasis on the unknown health effects of these mycotoxins co-occurring in vulnerable populations. The most effective way to monitor the occurrence of total mycotoxins in cereals and cereal-based products is to take preventive steps before and after harvest. Future studies should concentrate on elucidating previously unknown pathways of both individual and cumulative toxic impacts, as well as being more objective in determining the risk level of chronic DON toxicity in both humans and animals, which is essential for designing more precise policies and regulations to ensure of food and feed safety and security.

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