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Deoxynivalenol and its masked forms: Characteristics, incidence, control and fate during wheat and wheat based products processing - A review

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A R T I C L E I N F O

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A B S T R A C T

Background: Deoxynivalenol (DON) is a toxic secondary metabolite primarily produced by *Fusarium graminearum* and *Fusarium culmorum* that is common in grains, such as wheat and wheat-based products.

Scope and approach: This review points out on the main DON-producing fungi, the factors affecting DON production, its toxicological aspects and preventive measures to avoid contamination of foods by DON. Further, the article discusses the fate of DON throughout the processing of wheat, bread, and pasta and finally critically assesses data on the impact of specific steps of processing on DON contents in wheat-based products.

Key findings and conclusions: The proposed controls at pre- and post-harvest stages seem to comprise the most efficient strategies to manage the incidence of DON in wheat and wheat-based products. Prevention of plant infection by *Fusarium* species, managing crops and ensuring the rapid drying of wheat after harvest is the effective approaches for the elimination of DON contamination. There has been contradictory data in the literature on the fate of DON during wheat and wheat-based products processing Due to differences in processing, such as temperature, additives, processing time and loaf size in addition to the occurrence of modified (masked) forms of DON. Therefore, further research must be carried out aiming to reveal the formation and occurrence of modified forms of DON. These compounds can be formed throughout wheat processing, from pre-harvest to processing of wheat-based products, and for proper quantification, analytical methods able to quantify modified forms of DON are required.

1. Introduction

Wheat (*Triticum aestivum*) is amongst the most common farmed plants worldwide, and wheat-based products can be categorized as the primary sources of calories and protein originated from vegetable sources for the human diet (Jones, 2005). Wheat grains are typically processed into flours, which are employed in the manufacturing of bread, pasta, and cookies, for culinary purposes or in other industrial sectors. Moreover, wheat is highly relevant from both economic and nutritional points of view, but it is susceptible to fungal contamination. Fungal disease of wheat may culminate in the reduction of grain quality and the production of toxic metabolites, the so-called mycotoxins (i.e., secondary metabolites with toxic properties that are formed by fungi) (Filtenborg, Frisvad, & Thrane, 1996). In another word, humans and animals can be threatened by natural toxicants that occur in food and feed. Mycotoxins are "secondary metabolites produced by a few fungal species belonging mainly to the *Aspergillus*, *Penicillium* and *Fusarium* genera". They may be formed by these mycotoxigenic molds when growing in contaminated foods at different stages of, processing as well as during storage. Deoxynivalenol, trichothecenes, zearalenone, aflatoxins, patulin, fumonisin, ochratoxin, and ergotamine can be considered as the main types of mycotoxins which pose challenges to the safety of feed production and food processing due to consequence negatively effects on human health and the economy (Amirahmadi, Shoeibi, Rastegar, Elmi, & Mousavi Khaneghah, 2017; Campagnollo et al., 2016). Among them, the most common mycotoxin associated with wheat is deoxynivalenol (DON), which is also called vomitoxin (a type B trichothecene) (Sobrova et al., 2010). DON is produced mainly by *Fusarium* species such as *F. graminearum* (*Gibberella zeae* teleomorph) and *F. culmorum*. Both *F. graminearum* and *F. culmorum* are listed as pathogens for wheat that cause a disease named Fusarium head blight (FHB) which also identified as scab, leads to a reduced yield, lower grade and end-use quality of the wheat grains, as well as limiting crop rotation. The occurrence of FHB may result in accumulation of DON and other trichothecenes types in the plant, as affected by the chemotype of the fungus (Cirlini et al., 2014; Malbrán, Mourelos, Girotti,

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Balatti, & Lori, 2014). Furthermore, due to plant responses, matrix effects and reactions occurred during food processing, modified and other configurations of DON can be formed in wheat and wheat-based products (Berthiller et al., 2013; Rychlik et al., 2014). The presence of these modified forms of DON (i.e., masked mycotoxin) has been raising significant concerns regarding the safety of contaminated products. Also, the masked mycotoxins may represent analytical challenges, as the native mycotoxin may not be detected while the modified mycotoxin still retains the toxicological effects (Galaverna, Dall'Asta, Mangia, Dossena, & Marchelli, 2009).

Given the association of FHB and presence of DON, the consumption of contaminated wheat and wheat-based products, such as bread and pasta, appears to comprise a significant source of human exposure to DON. Also, DON is the primary compound responsible for economic losses due to the reduction of performance in animal husbandry (Morgavi & Riley, 2007). In implementing effective scientific-based control strategies to reduce consumers' and animal's exposure to DON, it is of foremost importance to know not only the real incidence of this mycotoxin in raw materials and final products but mainly the fate of this mycotoxin during wheat, bread, and pasta processing steps. Therefore, in this review, the characteristics of DON, toxicological-related aspects, primary producing fungi, masked forms and factors affecting DON production are examined. Besides, preventive measures to avoid DON production and the impact of wheat, bread and pasta processing on DON levels were also discussed.

2. Characteristics and toxicological aspects

2.1. DON

DON [(3α,7α)-3,7,15-trihydroxy-12,13-epoxytrichothec-9-en-8-one] ($C_{15}H_{20}O_6$) has a molar mass of 296.3 g/mol and exists as colorless thin crystals that are solvable in polar organic solvents, such as aqueous solutions of chloroform, ethanol, acetonitrile, methanol and ethyl acetate. Some previous investigations have reported that DON is a stable compound at temperatures ranging from 170 to 350 °C (Generotti et al., 2015; Gärtner, Munich, Kleijer, & Mascher, 2008; Lancova et al., 2008; National Toxicology Program, 2009; Numanoglu, Uygun, Koksel, & Solfrizzo, 2010). However, a report from the World Health Organization states that "*DON is stable at 120 °C, moderately stable at 180 °C and partially stable at 210°C*" (WHO, 2001). It can be categorized in the group of trichothecenes, which are sesquiterpenoids containing a central nucleus of hexane cyclic rings and tetrahydropyran (Fig. 1, Table 1). *Fusarium* species could synthesize different sorts of mycotoxins such as mycoestrogens and trichothecenes. The four types of trichothecenes, which are types A, B, C, and D, with T-2 toxin and HT-2 (HT-2) synthesized by *F. poae, F. langsethiae* and *F. sporotrichioides* toxin being classified as a type A trichothecene. Type C and D trichothecenes are not related to wheat diseases (Foroud & Eudes, 2009). The most common forms of trichothecenes are deoxynivalenol (DON, type B along with nivalenol (NIV) and NIV by-products) by *F. graminearum* and *F. culmorum* (Liang et al., 2014; Pasquali & Migheli, 2014).

DON was classified in group 3 by the International Agency for Research on Cancer (IARC), which means that this mycotoxin is not carcinogenic to humans (IARC, 1993; Ostry, Malir, Toman, & Grosse, 2017). The provisional maximum tolerable daily ingestion of DON is one μg/kg body weight (including DON acetylated derivatives, i.e., 3-Ac-DON and 15-Ac-DON). In humans, the level improbable to cause acute intoxication was established as 50 μg/kg body weight (JECFA, 2011). In order to represent the susceptibility of animals to DON, Pestka (2007) proposed a rank: "pigs > mice > rats > poultry ≈ ruminants."

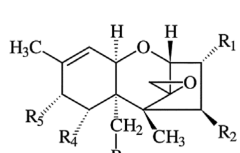

Fig. 1. Trichothecenes structure. (Schothorst & Jekel, 2001; with permission).

The ingestion of DON can result in both acute and chronic toxic effects. The acute symptoms include abdominal discomfort, malaise, diarrhea, increased salivation, vomiting, and anorexia. The most frequently observed effects of chronic exposure to DON can be classified as altered nutritional efficiency, weight loss, and anorexia (Pestka, 2007). Nonetheless, sensitivity to DON can vary according to the metabolism, absorption, circulation, and elimination of DON by the organism (Sobrova et al., 2010).

The toxicity of trichothecenes is related to the inhibition of protein synthesis in eukaryotes. When trichothecenes bind to the 60S of the ribosomes, as result of interaction with peptidyl transferase enzyme, inhibition of translation occurs (Sudakin, 2003). Moreover, activation of kinase proteins by trichothecenes can lead to the induction of apoptosis via the response to ribotoxic stress (Iordanov et al., 1997). The kinase proteins PKR (kinase protein activated by RNA) and HCK (hematopoietic cell kinase) are involved in the activation of (mitogens) MAPKs, consequently of transcription factor expression induced, gene expression and apoptosis increased. Leucocytes are the primary targets of trichothecenes and depending on the dose, frequency and exposure time; trichothecenes can cause immunosuppression or immune stimulation (Pestka, 2007).

DON and its acetyl derivatives [3-acetyl-DON (3-Ac-DON) and 15-acetyl-DON (15-Ac-DON)] were defined as Acute Reference Dose (ARfD) with eight μg/kg b × w, by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2010 (European Food Safety Authority, 2013). Furthermore, the established limits by EC for DON in different categories of food products can be summarized as foodstuffs derived from barley, maize and wheat, (1000 μg/kg), bread, cereal snacks pastries, breakfast cereals and biscuits (500 μg/kg), pasta (dry) (750 μg/kg), processed cereal-based foods for toddlers and young children (200 μg/kg) (European Food Safety Authority, 2013).

2.2. DON – modified forms

Even though properties and toxicological effects of the native (free) form of DON have been well known, data on modified or matrix-associated forms of mycotoxins (masked mycotoxins) comprise a topic of increased interest (Berthiller et al., 2013; Rychlik et al., 2014). Because of their growing importance, a categorization consisting of four hierarchic levels has been suggested (Rychlik et al., 2014). The modified mycotoxins can be first divided into free, matrix-associated and modified forms. Matrix-associated mycotoxins can be found as complexes (dissolved or trapped) or covalently bound, while modification can be biologically or chemically driven. The third level in biological modification includes functionalization and conjugation, with the latter being powered by plants, animals, and fungi (fourth level). The third level of chemically modified mycotoxins includes thermally and non-thermally modified forms (Rychlik et al., 2014).

The great concern over the natural occurrence of matrix-associated or modified mycotoxins in raw materials and food products are supported by the fact that their chemical behavior can pose challenges for analytical quantification while the structures can still retain toxic effects (Galaverna et al., 2009). These forms of mycotoxins could be potentially reactivated at specific conditions such as in gastrointestinal tract (Berthiller et al., 2013). For example, the ingestion of foods containing DON-3-Glc is of concern due to resistance properties of DON against the acidic conditions in the stomach and the action of digestive enzymes. The conversion of DON-3-Glc to DON due to the action of bacteria belonging to the *Lactobacillus, Enterococcus, Enterobacter* and *Bifidobacterium* genera (as normal microflora of gut) was demonstrated *in vitro* (Berthiller et al., 2011). Thus, the toxic effects associated with DON consumption can be worse than those estimated based on the