Arch Toxicol (2014) 88:1915–1928
DOI 10.1007/s00204-014-1354-z

REVIEW

Deoxynivalenol: signaling pathways and human exposure risk assessment—an update

Zhonghong Wang · Qinghua Wu · Kamil Kuča · Vlastimil Dohnal · Zhihong Tian

Received: 16 August 2014 / Accepted: 27 August 2014 / Published online: 9 September 2014

Abstract Deoxynivalenol (DON) is a group B trichothecene and a common contaminant of crops worldwide. This toxin is known to cause a spectrum of diseases in animals and humans such as vomiting and gastroenteritis. Importantly, DON could inhibit the synthesis of protein and nucleonic acid and induce cell apoptosis in eukaryote cells. The transduction of signaling pathways is involved in the underlying mechanism of the cytotoxicity of DON. Mitogen-activated protein kinase and Janus kinase/signal transducer and activator of transcription seem to be two important signaling pathways and induce the inflammatory response by modulating the binding activates of specific transcription factors. This review mainly discussed the toxic mechanism of DON from the vantage point of signaling pathways and also assessed the profiles of DON and its metabolites in humans. Importantly, we conducted a human exposure risk assessment of DON from cereals, cereal-based foods, vegetables, water, and animal-derived foods in different countries. Some regular patterns of DON occurrence in these countries are suggested based on an analysis of global contamination with DON. This review should provide further insight for the toxic mechanism study of DON and human exposure risk assessment, thereby facilitating mycotoxin control strategies.

Keywords Deoxynivalenol · DON · Signaling pathways · MAPK · JAK/STAT · Exposure · Risk assessment

Abbreviations

DON	Deoxynivalenol
DOM-1	12,13-De-epoxy-DON
PKR	Double-stranded, RNA-activated protein kinase R
Hck	Hematopoietic cell kinase
MAPKs	Mitogen-activated protein kinases
JAK/STAT	Janus kinase/signal transducer and activator of transcription
DON-15-GlcA	DON-15-glucuronide
SAPK/JNK	Stress-activated protein kinase/c-Jun N-terminal kinase
CREB	CAMP response element-binding protein
ZON	Zearalenone
WWTP	Waste water treatment plant

Zhonghong Wang, Qinghua Wu and Kamil Kuča have contributed equally to this work.

Z. Wang
Department of Pediatrics, The First People's Hospital of Jingzhou, Jingzhou 434000, China

Q. Wu (✉) · Z. Tian (✉)
College of Life Science, Yangtze University, Jingzhou 434025, Hubei, China
e-mail: wqh212@hotmail.com

Z. Tian
e-mail: zhtian@yangtzeu.edu.cn

Q. Wu · K. Kuča
Faculty of Informatics and Management, Center for Basic and Applied Research, University of Hradec Kralove, Hradec Kralove, Czech Republic

K. Kuča
Biomedical Research Center, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic

V. Dohnal
Department of Chemistry, Faculty of Science, University of Hradec Kralove, Rokitanskeho 62, 500 03 Hradec Kralove, Czech Republic

Introduction

Deoxynivalenol (DON) is a type B trichothecene and one of the most common mycotoxins found in cereals. DON is produced mainly by fungi, such as *Fusarium graminearum*, *Fusarium culmorum*, and *Fusarium crookwellense*, which are common field pathogens of cereal crops, including wheat, barley, and maize (Wu et al. 2011). Cereals contaminated with DON are often contaminated with other *Fusarium* mycotoxins, such as 3-acetyl-deoxynivalenol (3-acetyl-DON), 15-acetyl-deoxynivalenol (15-acetyl-DON), DON-glucoside, and T-2 toxin. In animals, DON can be transformed into 12,13-de-epoxy-DON (DOM-1), a metabolite with much lower toxicity than DON (Wu et al. 2010) (Fig. 1). In animals, DON can cause emesis, diarrhea, hemorrhaging, and immunosuppression, as well as reducing the reproductive capacity of livestock (Wu et al. 2010). At the cellular and molecular level, DON can bind to ribosomes and inhibit protein, RNA, and DNA synthesis, as well as inducing cell apoptosis (Pestka 2008). Recent research has also shown that mitochondrial translation is a target of trichothecenes (Bin-Umer et al. 2011).

During the last decades, increasing studies are focusing on the toxic mechanism of trichothecenes, including DON, and some signaling pathways are found to involve in the toxic potential mechanism of trichothecenes. In mammalian cells, trichothecenes trigger a ribotoxic stress response and activate two kinases, double-stranded, RNA-activated protein kinase R (PKR) and hematopoietic cell kinase (Hck), and subsequently activated mitogen-activated protein kinases (MAPKs) signaling pathways. The three important subfamilies of MAPK, ERK, p38, and JNK, have different roles in the process of inflammatory response. p38 and ERK activation contribute to DON-induced transcriptional up-regulation of TNF-α, whereas JNK plays an important role in increasing mRNA stability (Chung et al. 2003). Moreover, through the signaling pathways, we have found that DON has a Janus face and could induce both the cell death and cell survival pathways (Zhou et al. 2005). Beside MAPK signaling pathway, Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway also plays important roles in the toxic mechanism of trichothecenes, especially in the process of cell apoptosis, and STAT1 and STAT3 are supposed to be the downstream targets for the regulation of proinflammatory response, cell proliferation, and apoptosis induced by trichothecenes (Wang et al. 2012). These earlier studies improved our understanding of the toxic mechanism of trichothecenes.

Human could easily expose to DON through food and water. Urine is usually used for analysis of the DON level to assess the human exposure. The metabolic fate of DON in humans shows some regional differences. For example, the de-epoxy metabolite DOM-1 was detected in most urine samples from French farmers, but was never detectable in UK adults and the women in Shanghai, China (Turner et al. 2010). In addition, the investigation reveals that DON-15-glucuronide (DON-15-GlcA) is the major conjugated metabolite followed by DON-3-glucuronide (DON-3-GlcA) and other conjugates, which are not identified (Warth et al. 2012).

The risk assessment of human exposure of mycotoxins, including DON, is always an important issue for the human health in the whole world. In most countries, DON is detectable in cereals, including maize, wheat, oats, and barley. DON is the most frequently detected mycotoxin in Spain, and it is usually present at the highest concentration (Montes et al. 2012). In the Czech Republic, 3.5 % of the cereal samples analyzed, including 1.6 % of barley samples, exceeded the maximum DON limit

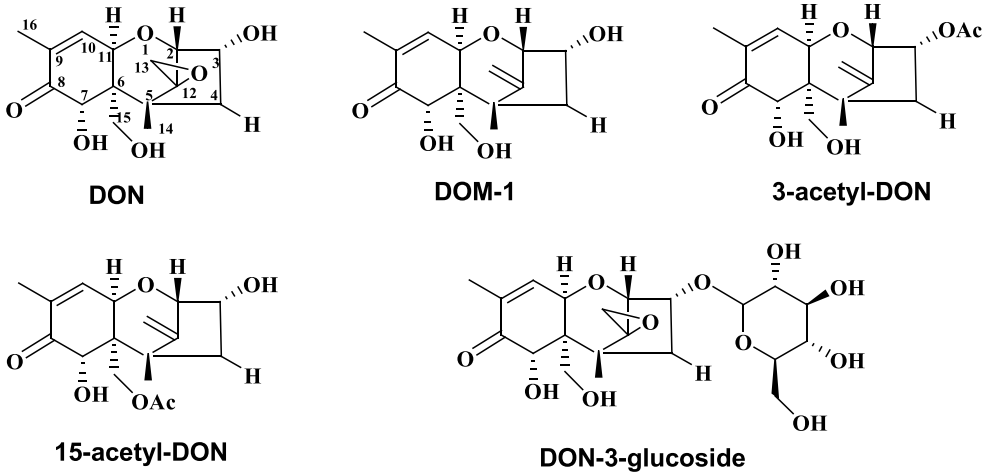

Fig. 1 The chemical structure of DON and its related products

(1,250 μg/kg) (Polišenská and Tvarůžek 2007). In Croatia, DON was detected at a high rate of 57.14 % in the malt barley harvest during 2004. In Serbia, sunflower has the highest frequency of DON contamination, followed by maize and wheat (Jajić et al. 2008a). In Canada (Tran et al. 2012), conjugated DON was detected in 83.7 % of the corn samples analyzed. In Jiangsu and Anhui provinces in China (Cui et al. 2013), 89.3 % of the wheat samples were contaminated by DON (259–4,975 μg/kg). Thus, the widespread occurrence of DON contamination in cereals means that this problem has become a global issue. The European Commission (2006a) has established maximum levels for DON contamination (1,250 μg/kg in cereals and 200 μg/kg in processed cereal-based food and baby food).

In general, DON is quite stable during extrusion processing at high temperatures and high pressure; thus, DON persists in cereal-based food and feeds (Eriksen and Alexander 1998; Wu et al. 2011). In Spain, over 60 % of the milled grain-based products obtained from supermarkets and smaller shops contained DON contamination, followed by HT-2 toxin. A high frequency (94 %) of DON contamination was found in bakery products in the Czech Republic (Malachova et al. 2011). DON contamination was also detected in maize meal (100 μg/kg) in South Africa, where it is the major foodstuff (Shephard et al. 2010). The issue of DON contamination also affects animal feeds as well as human food. DON contamination of feeds has important effects on livestock production in both economic terms and for the maintenance of the health and productivity of animals (Chaytor et al. 2011).

Importantly, DON can persist in meat, milk, and eggs after livestock and poultry animals have been fed with DON-contaminated feed. In addition, DON contamination of water systems is a potential problem at present. Mycotoxins can contaminate rivers if fields are cultivated with fungi-infected cereals, in addition to waste from farm animals and human excretion via sewerage systems (Schenzel et al. 2012b).

In this review, we aim at discussing the toxic mechanism of DON from the vantage point of related important signaling pathways and also try to assess the profiles of DON and its metabolites in humans. Importantly, we want to conduct a human exposure risk assessment of DON from cereals, cereal-based foods, vegetables, water, and animal-derived foods in different countries. Moreover, we have identified some regular patterns of DON occurrence in these countries based on an analysis of global contamination with DON. We consider that this review provides a comprehensive overview of toxic mechanism and the risk assessment of human exposure of DON. Moreover, it will cast some light on the toxicology and the mycotoxin control strategies.

Signaling pathway-mediated cytotoxicity of DON

DON could induce cell apoptosis, and the underlying mechanism has very close relationship with the cellular signaling pathways. Normally, the MAPK and JAK/STAT signaling pathways are highly interested by the researchers. Today, more researchers are searching for the upstream signalings, which could induce the downstream events.

The studies of toxic mechanism of trichothecenes are well studied by the working group of Prof. Dr. Pestka in Michigan State University. The MAPKs were reported to correlate with and preceded apoptosis (Yang et al. 2000). Trichothecenes activated not only stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) and p38 but also ERK. This mechanism was termed the "ribotoxic stress response," and PKR and Hck are two critical upstream mediators of the ribotoxic stress response induced by DON (Zhou et al. 2003; Pestka et al. 2004; Gray et al. 2008). Moreover, p38 and ERK activation contribute to DON-induced transcriptional up-regulation of TNF-α, whereas JNK plays an important role in increasing mRNA stability (Chung et al. 2003). However, DON's effects on apoptosis and cytokine production are differentially regulated by MAPKs (Pestka et al. 2005). DON could induce the high expression of cyclooxygenase-2 (COX-2) gene in macrophages mediated by ERK and p38, but not JNK (Moon and Pestka 2002). In addition, DON could highly induce IL-6 expression, and this induction is CAMP response element-binding protein (CREB) mediated and PKR dependent.

DON could activate apoptotic (p38/p53/Bax/Mitochondria/caspase-3) and survival (ERK/AKT/p90Rsk/Bad) pathways in the RAW264.7 macrophages (Zhou et al. 2005). A prominent of DON exposure in macrophages is ribosomal RNA (rRNA) cleavage, which is closely linked to apoptosis. The DON-induced rRNA cleavage appears to involve the sequential activation of PKR/Hck-p38-p53-caspase8/9-caspase-3 (He et al. 2012). However, PKR is not an essential signaling molecular for DON's anorectic and weight effects (Flannery et al. 2013). Recently, Hirano and Kataoka (2013) have reported that DON induces the TNF-α-converting enzyme-dependent ectodomain shedding of TNF-receptor 1 via the activation of ERK and p38 MAP kinase, and thereby inhibits the TNF-α-induced NF-κB signaling pathway.

DON could trigger intestinal inflammation and impair intestinal barrier function. A chronic exposure to DON-contaminated foods may negatively affect human health by altering the intestinal mucosa integrity and by inducing the MAPKs implicated in inflammation (Sergent et al. 2006). MAPK activation is involved in claudin-4 protein expression, and claudin-4 is involved in the maintenance of the intestinal epithelial cell barrier function (Pinton et al. 2010). In the in vivo and ex vivo models of intestine, DON

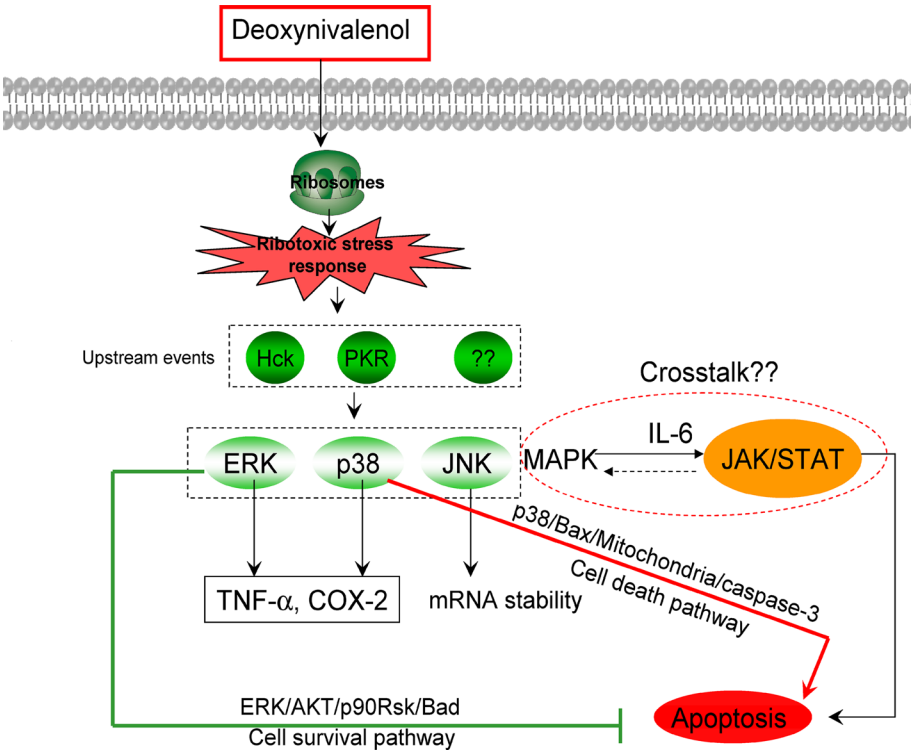

Fig. 2 Deoxynivalenol (DON)-mediated signal transduction in the apoptotic process

significantly enhanced the phosphorylation of ERK1/2 and p38, whereas the increased phosphorylation of JNK was nonsignificant (Lucioli et al. 2013), which strongly suggest that intestinal toxicity of DON involves MAPK activation.

DON could cause significant slowdown of cell proliferation and increase of apoptotic cells in blood cell lines (Baltriukine et al. 2007). In blood-derived REH and Jurkat cells, DON-induced apoptotic changes were preceded by an increase in JNK and P38 phosphorylation, as well as in c-Jun expression. However, the authors stated that p38 but not JNK was needed for DON-induced apoptosis in REH cells. Moreover, DON was observed to induce a DNA fragmentation followed by p53 and caspase-3 activations in human colon carcinoma cells. Thus, DON could be considered to be a genotoxic agent inducing cell death via an apoptotic process (Bensassi et al. 2009, 2012). p53 signaling pathway induced by DON also plays an important role in the inhibition of the proliferation of mouse thymic epithelial cell line 1 (Li et al. 2013). The activation of caspases is regulated by Bcl-2 family proteins (Ma et al. 2012).

In addition to induce apoptosis, DON could also arrest epithelial cell cycle at G_2/M phase via elevated p21 gene expression. Signaling pathways associated with DON-induced p21 gene expression included PI3 kinase and ERK1/2 MAP kinase cascade. Particularly, ERK1/2 signal was associated with DON-induced p21 mRNA stability in the human epithelial cells (Yang et al. 2008).

Most studies focused on MAPK signal pathway to uncover the underlying toxic mechanism of DON. But the role of JAK/STAT signal pathway in DON toxicity is rarely reported. Recently, Wang et al. (2012) have reported that JAK/STAT signaling pathway plays a critical role in the cell apoptosis induced by trichothecenes. STAT1 and STAT3 might be the downstream targets for the regulation of proinflammatory response, cell proliferation, and apoptosis induced by trichothecenes. Thus, a potential cross talk between MAPK and JAK/STAT signaling pathways should be studied in the future.

In summary, MAPK and JAK/STAT are important signaling pathways for the toxic mechanism of DON. PKR and Hck are two uncovered upstream kinases for the induction of the downstream events induced by DON. DON can cause cell survival and cell death signaling pathways and shows us more complicated face of its toxic mechanism. We suspect that besides PKR and Hck, there are other important upstream events which are able to active MAPK signaling pathway and induce cell apoptosis. Currently, the cross talk of the JAK/STAT and MAPK induced by trichothecenes is never elucidated. DON-mediated signal transduction in the apoptotic process is present in Fig. 2.

Assessment of DON and its metabolite profiles in humans

Currently, a series studies are focusing on the metabolic fates of DON after the human exposure and the fates of DON in the people from different regions or from different

work positions show very different profiles. These differences are possibly due to the DON levels in cereal-based foods and are correlated with cereal intake in different countries and regions.

In order to establish a urine-based human biomarker, urine samples were collected from female inhabitants of Linxian County, China, a high risk region for esophageal cancer and an area of potentially high DON exposure, and Gejiu, a low risk region in China. The mean levels of DON from the suspected high and low exposure regions of China were 37 ng/mL (range 14–94 ng/mL) and 12 ng/mL (range 4–18 ng/mL), respectively (Meky et al. 2003). The urinary levels of DON in human are positively correlated with cereal intake. Turner et al. (2008a) used the UK adult National Diet and Nutrition Survey to compare 24-h urinary DON excretion with cereal intake, and DON was detected in 98.7 % of the urine samples. Cereal intake was significantly associated with urinary DON (Turner et al. 2009). But the exposure of DON in humans can be markedly reduced by avoiding wheat in the diet (Turner et al. 2008b). In the women from Shanghai, China, DON + DON-glucuronide combined was detected in 96.7 % urine samples (mean 4.8 ng DON/mL), which was much lower than that found in UK women (Turner et al. 2011a). DOM-1 was not detected in any urine samples in Shanghai women. The reason for the lower levels of DON in women in Shanghai than in UK is possibly due to the diet habit, since in Shanghai, maize and barley are rarely consumed, but rice consumption is by far the predominant cereal consumed, and rice is not a major source of DON (CAST 2003).

Besides DON (98.7 %), the de-epoxy metabolite DOM-1 was firstly detected in 34 % (range 0.2–2.8 ng/mL) of urine samples from French farmers. But interestingly, DOM-1 was not detectable in UK adults (Turner et al. 2010). Similarly, in another study, DON (2.4 ng/mL) was detected in 68 % of the UK adults, but urinary DOM-1 was detected only in 1/34 of individuals (Turner et al. 2011b). The potential reasons for this difference could be the accidental transmission of animal microbiota to French farm workers, which has the capacity for DON conversion to DOM-1.

Warth et al. (2012) conducted a pilot survey to investigate the level of DON exposure in Austrian adults. The average concentration of total DON (free DON + DON-GlcA's) was estimated to be 20.4 ± 2.4 μg/L urine. Moreover, the in vivo metabolism of DON in humans was performed for the first time, and DON-15-GlcA was tentatively identified as a major DON metabolite in human urine while DON-3-GlcA accounted for approximately 25 %. In another study from this group, an in vivo metabolism of DON in human was carried out through the analysis of urine samples (Warth et al. 2013). The average rates of DON excretion and glucuronidation were determined to be 68 and 76 %, respectively. The investigation of formed glucuronides revealed DON-15-GlcA was accounted for 73 % of total DON-glucuronides. DON-3-GlcA was the conjugate with lower amounts detected (mean 27 %, range 24–31 %), which is in excellent agreement with Warth et al. (2012). In addition, a third DON-GlcA was also detected but was not identified due to the lack of reference standard.

In Spain, Rubert et al. (2011) analyzed the levels of DON in the urines from 27 volunteers during 2010 in Valencia. T-2 and HT-2 toxin were not detected in any of these samples analyzed, but DON was confirmed in 33.3 % of the urine samples, which was much lesser than the occurrence in UK populations (98.7 %) (Turner et al. 2008a). In South Africa, the level of DON in fifty-three female participants was analyzed in the high esophageal cancer region, Transkei. A single biomarker method detected 100 % DON (mean 20.4 ± 49.4 ng/mg creatinine) after hydrolysis with β-glucuronidase and DON-15-GlcA was predominantly present (Shephard et al. 2013). The DON levels in pregnant women from eastern Croatia were analyzed (Sarkanj et al. 2013). First-void urine samples were collected and analyzed, and DON, DON-15-GlcA, and DON-3-GlcA were detected in 97.5 % of the studied samples. DON exposure was primarily reflected by the presence of DON-15-GlcA with a mean concentration of 120 μg/L, while free DON was detected with a mean concentration of 18.3 μg/L. Several highly contaminated urine samples contained a third DON conjugate, tentatively identified as DON-7-glucuronide.

Human exposure of DON from food and water

Cereals

Cereals, including maize, wheat, oats, and barely, are important food and feed sources for humans and animals. However, DON contamination may occur in the field and during storage due to weather conditions. Each year, a large number of cereals are contaminated by fungal invasion, which causes considerable financial losses and impaired health in animals and humans. These fungi produce various mycotoxins, which are highly toxic to animals and humans. Throughout the world, DON is the major member of the trichothecenes that causes widespread contamination of cereals. Cereals are the most important sources of food and feeds; thus, contamination by mycotoxins, including DON, is a global problem.

DON, 3-acetyl-DON, and 15-acetyl-DON were analyzed in breakfast cereal samples (corn, wheat, and rice) collected from Spanish retail markets (Montes et al. 2012), and DON was detected frequently and at a high concentration (468 μg/kg), whereas 3- and 15-acetyl-DON were

not detected in these samples. Wheat and oat bran samples were also analyzed from shops and supermarkets in two different Spanish cities (Vidal et al. 2013), which demonstrated the frequent co-occurrence of DON and zearalenone (ZON). Sixty-two percent of wheat samples were contaminated with DON (1,308 μg/kg) and 17 % of the oat bran samples contained DON (230 μg/kg). Bran accounts for an important proportion of DON exposure in the total diet. Rodríguez-Carrasco et al. (2013) studied contamination with DON, 3-acetyl-DON, and other mycotoxins, including T-2, HT-2, and nivalenol (NIV), in wheat-, maize-, and rice-based products from Spanish markets. The wheat-based samples had the highest level of mycotoxin contamination, where DON (79.8 %) was the most frequent mycotoxin detected, followed by HT-2 toxin (16.8 %) and NIV (3.4 %). However, the levels of mycotoxin contamination, including DON, in cereal-derived products from Spain were lower than the levels permitted by the EU for safe consumption.

In the Czech Republic, the DON content of wheat intended for human consumption was monitored during 2003–2005 (Polišenská and Tvarůžek 2007), and DON was detected at maximum levels of 5,090, 18,300, and 4,437 μg/kg in 2003, 2004, and 2005, respectively. In addition to wheat, other cereals harvested in the Czech Republic were also analyzed, such as barley and rye (2000–2006) (Polišenská et al. 2008), where 1.6 % of the barley samples analyzed exceeded the maximum limit for DON (1,250 μg/kg), which was set by the European Commission (2006a). In Slovakia, the DON content was analyzed in wheat samples from maize, sugar beet, and potato growing areas (2004–2006) (Šliková et al. 2008). The highest mean DON content was found in the potato growing area and the lowest in the maize growing area. However, 9.3, 5, and 14.3 % of the samples from the maize, sugar beet, and potato growing areas, respectively, exceeded the limit of 1,250 μg/kg specified by the EU.

Velić et al. (2007) monitored DON contamination in malt barley during 2004 in eastern Croatia, where DON was detected in 57.14 % of the samples. The contamination level was 0.1–3.9 mg/kg, with an overall mean of 0.78 mg/kg. High humidity and low temperatures lead to increased contamination of maize with *Fusarium* molds and the production of its secondary metabolites. Pleadin et al. (2012) investigated DON contamination in Croatian maize samples harvested in 2010 after a growth period that was characterized by extremely high rainfall and low temperatures. DON was detected in 85 % of the samples with a maximum concentration of 17.92 mg/kg. Similarly, in cereal samples (maize, wheat, barley, and oats) collected during 2011, maize was the most contaminated cereal, and DON was the most frequent *Fusarium* mycotoxin (52.5 %).

In Germany, 89 % of the durum wheat harvested during 2001 was positive for DON contamination with a median concentration of 790 μg/kg, which clearly exceeded the EU action level of 500 μg/kg (Brockmeyer and Thielert 2004). In 2002, 85 % of the durum wheat in Germany was DON-positive, but the median concentration was only 215 μg/kg, thereby demonstrating the efforts of food producers to decrease the DON contamination levels in wheat (Brockmeyer and Thielert 2004).

In Serbia, DON contamination in crops was first reported by Jajić et al. (2008a). Crops were collected during 2004–2005, and sunflower (47.4 %) had the highest rate of DON contamination, followed by maize (44.7 %), wheat (37.5 %), and barley (25 %). In the positive samples, the level of DON contamination was 0.04–2.46 mg/kg. The presence and concentration of DON in maize and wheat samples obtained from the 2005–2007 harvest were also monitored by this group (Jajić et al. 2008b). In the 2005–2007 harvest, the average rate of DON contamination in maize was 32.4 % (0.027–2.21 mg/kg), whereas that in wheat was 34.5 % (0.057–0.423 mg/kg). Moreover, DON co-occurred with fumonisins in wheat and maize harvested in Serbia during 2010 (Jakšić et al. 2012). Approximately 65.3 % of the samples contained DON contamination in the range of 0.064–1.604 mg/kg and 50.7 % contained fumonisins in the range of 0.027–0.614 mg/kg. In Tunisia, a survey was performed to study the occurrence of DON in a durum wheat area (North of Tunisia) during the harvest of 2007 (Bensassi et al. 2010), and 83 % of the samples had DON contamination, which ranged from 12.8 ± 5 to 30.5 ± 13.3 % mg/kg.

Australian researchers have focused on the occurrence of conjugated DON in cereals. A survey of free and conjugated DON in cereal crops was performed in several Australian states during 2009, 2010, and 2011 (Tran and Smith 2013) when conjugated DON (0.1–7.31 mg/kg) was detected in 61, 87, and 68 % of the contaminated grain samples, respectively. The highest level of DON contamination was found in New South Wales, whereas no samples from South or Western Australia contained this compound. Free DON could not be detected in almost half of the samples collected during this 3-year survey. Cross-reactivity to DON-3-glucoside and DON acetates may contribute to false-positive results and the overestimation of DON.

Contamination with free and conjugated DON was also analyzed in corn samples collected from the 2008 harvest in Ontario, Canada (Tran et al. 2012). Conjugated DON was detected in 83.7 % of the samples, and higher contamination levels were found mainly in corn from the east-central region. The levels of free DON ranged from 0.17 to 14 mg/kg. The southern and southwestern region of Ontario had more severe DON contamination than the eastern regions. Subsequently, Tittlemier et al. (2013)

monitored the occurrence of DON, 3-, and 15-acetyl-DON, NIV, T-2, and HT-2 toxins in shipments of Canadian wheat, durum wheat, barley, corn, rye, and oats transported during 2010–2012, which showed that DON was the most frequent trichothecene (2.34 mg/kg), and the concentrations of DON were associated significantly with the wheat class and grade.

Apparently, DON is not prevalent in rice from South Korea based on an analysis of harvested rice collected from six locations in South Korea during 2010 (Ok et al. 2014), where ZON was the major mycotoxin contaminant, followed by NIV in brown rice and white rice. DON was not detectable in white rice samples, and its level was very low in brown rice.

In China, a survey was conducted to determine the incidence of DON in *Fusarium*-infected wheat from the Yangtze–Huaihe river basin region (Cui et al. 2013), where 89.3 % of the samples were contaminated by DON at concentrations of 259–4,975 μg/kg. Approximately 44 % of the samples exceeded the European Commission limits for unprocessed wheat (1,750 μg/kg). The samples that exceeded this limit came mainly from the Eastern and Central Anhui region, where very high rainfall was recorded during the flowering season with high humidity.

In India, DON was detected in 30 % of cereals (wheat, maize, and barley), and the contamination levels ranged from 0.01 to 4.73 mg/kg (Mishra et al. 2013). Chronic exposure to high levels of DON in the Indian population could be a potential factor that contributes to gastrointestinal disorders in the district of Uttar Pradesh.

A survey of the occurrence of DON in wheat, rye, barley, and maize harvested in 1989–2001 was conducted in Russia (Tutelyan 2004). DON was detected in 69 % of the food grain wheat samples (1989–1992) from the Krasnodar region. The highest rate of DON contamination was found in the North-Caucasian region where the levels were 0.1–8.6 mg/kg. The DON occurrence and contamination levels were much lower in wheat.

Morocco has a climate that is characterized by high humidity and high temperatures, which favors the growth of molds. Ennouari et al. (2013) first reported the occurrence of DON in durum wheat from Morocco, where 11.1 % of the samples were contaminated with DON (65–1,310 μg/kg). The mean DON level in positive samples was 502.1 ± 40.4 μg/kg. The maximum DON contamination level was found in the Rabat-Salé area.

In summary, DON is the most frequent mycotoxin that contaminates cereals in most countries. For the countries mentioned above, wheat appears to be the major DON-contaminated cereal in Spain and the Czech Republic, whereas maize is the most DON-contaminated cereal in Croatia. Sunflower and maize are the most contaminated cereals in Serbia. Conjugated DON (also called masked DON) may be difficult to determine experimentally because of its increased polarity, but it can also release toxic precursors after hydrolysis in animals and it is an additional risk. At present, Australian and Canadian researchers are focusing on the detection of masked DON in different cereals. A dietary transition from maize to less-contaminated cereals would reduce the likelihood of exposure. The occurrence of DON in the cereals from different countries is summarized in Table 1.

Cereal-based food

DON is highly resistant to food cooking and processing; thus, food preparation procedures do not guarantee its removal (Wu et al. 2011). DON is frequent in snacks, beer, bread, soy sauces, and noodles. Humans may experience potential health risks by consuming DON-contaminated cereal-based food products.

To evaluate the occurrence of DON in samples of the corn-based food products (breakfast cereals and snacks) consumed by the Spanish population, a total of 175 commercially available samples were collected randomly in Valencia during 2005 (Castillo et al. 2008). The occurrence of DON was detected in 25.5 % (26.1–80.4 μg/kg), 27.6 % (36.4–131.7 μg/kg), and 46.8 % (30.1–121.1 μg/kg) of fried snacks, baked snacks, and breakfast cereals, respectively. The highest level of DON was found in the baked snacked samples (131.7 μg/kg), but no samples exceeded the legally established limit for DON (500 μg/kg) (European Commission 2005). In Valencia, DON was also detected in 28.0 and 62.6 % of bread and pasta samples, respectively (González-Osnaya et al. 2011). The average DON contents in the bread and pasta samples were 42.5 and 137.1 μg/kg, respectively. However, none of the samples exceeded the maximum permitted level for DON established by the EU for specific food products (500 and 750 μg/kg for bread and pasta, respectively) (European Commission 2006a). In the Catalonia region of Spain, DON was also the major trichothecene detected in wheat flakes, corn flakes, corn snacks, pasta, and bread, where the proportions of positive samples ranged from 1.4 to 100 % (Cano-Sancho et al. 2011), and the median DON content was 0.012–0.242 mg/kg. Despite the high incidence of DON, only a very small number of samples exceeded the EU limits (European Commission 2006b).

Recently, Rodríguez-Carrasco et al. (2014) monitored the occurrence of trichothecenes in milled grain-based products from supermarkets and smaller shops in different regions of Spain. Over 60 % of the samples contained DON contamination, followed by HT-2 toxin (12.1 %) and NIV (10.4 %), and mycotoxins also co-occurred in the major cereals. Wheat-based samples had the highest frequency of DON contamination, i.e., 79.8 % (12.7 μg/kg), although

Table 1 The occurrence of DON in cereals from different countries

Country	Year	Samples (*n*)	Positive	Average/range (μg/kg)	Greatest level (μg/kg)	Analysis method	References
Spain	2009	Corn, wheat, and rice (148)	25.7 %	74.4	468 (wheat)	GC–MS	Montes et al. (2012)
Spain	2012	Wheat (37), oat (30)	62 % (wheat), 17 % (oat)	1,308 (wheat), 230 (oat)	6,178 (wheat), 276 (oat)	HPLC	Vidal et al. (2013)
Spain	2012	Wheat (119)	79.8 %	10.5–19.5	43.2	GC–MS	Rodríguez-Carrasco et al. (2013)
Czech Republic	2003–2005	Wheat (1,000, 1,063, 987)	6.9, 4.7, 8.5 %		5,090, 18,300, 4,437	ELISA	Polišenská and Tvarůžek (2007)
Czech Republic	2000–2006	Wheat (345), barley (498), and rye (113)		203, 379, 211	4,590, 3,770, 1,100	ELISA	Polišenská et al. (2008)
Slovakia	2004–2006	Maize (139)		510		ELISA	Šliková et al. (2008)
Croatia	2004	Barley	57.14 %	780	3,930	HPLC	Velić et al. (2007)
Croatia	2010	Maize	85 %	2,150 ± 2,290	17,920	ELISA, TLC	Pleadin et al. (2012)
Germany	2001	Wheat (53)	89 %	790		HPLC	Brockmeyer and Thielert (2004)
Germany	2002	Wheat (60)	85 %	215		HPLC	Brockmeyer and Thielert (2004)
Serbia	2004–2005	Maize (76), wheat (16), soybean (24), sunflower (19) and barley (4)	8.3–47.4 %	100–2,091	2,460 (maize)	HPLC	Jajić et al. (2008a)
Serbia	2005–2007	Maize (226), wheat (59)	32.4 % (maize), 34.5 % (wheat)	223 (maize), 1,235 (wheat)	423 (wheat), 2,210 (maize)	HPLC	Jajić et al. (2008b)
Tunisia	2007	Wheat (65)	83 %	12.8–30.5	54,000	HPLC	Bensassi et al. (2010)
Canada (Ontario)	2008	Corn (86)	100 %	700–1,400	2,630	GC–MS	Tran et al. (2012)
China	2010	Wheat (56)	89.3 %	1,962	4,975	HPLC	Cui et al. (2013)
India	2013	Wheat, maize, and barley (total 100)	30 %	10–4,370		HPLC–MS	Mishra et al. (2013)
Russia	1989–2001	Wheat, rye, barley and maize (total 5,562)	69 %	100–8,600		HPLC, TLC	Tutelyan (2004)
Morocco	2013	Wheat (81)	11.1 %	502.1 ± 40.4	1,310	LC	Ennouari et al. (2013)

none of the samples exceeded the maximum levels established in the EU legislation.

In 2010, the occurrence of DON and DON-3-glucoside was monitored in white flour, mixed flour, breakfast cereals, snacks, and flour in Czech retail markets (Malachova et al. 2011), and DON was detected in 75 % of the samples, with concentrations of 13–594 μg/kg. The highest rate of contamination (94 %) was observed in bakery products made from white flour, followed by 89 % in mixed flour products and 73 % in flour. The masked form, DON-3-glucoside, was found in 80 % of samples (5–72 μg/kg). Subsequently, this research group also monitored the occurrence of DON in malt, beer, and bread samples collected in the Czech Republic (Zachariasova et al. 2012). In addition to the most common DON-3-glucoside, an oligoglycosylated DON with up to four hexose units was detected in cereal-based products (Zachariasova et al. 2012). Thus, the establishment of total daily intake amounts or maximum limits for masked DON should be reviewed urgently.

A survey of South African commercial products was conducted to determine the DON levels in maize meal and wheat flours (Shephard et al. 2010). Brown and whole-wheat flours contained a maximum of 20 μg/kg DON, whereas refined white bread and cake flours contained a maximum of 100 μg/kg DON. In contrast to European countries, maize is the main cereal consumed in South African. However, there was a higher frequency of positive maize meal samples (89 %), and their maximum level was higher than that of the combined wheat flour samples (frequency of 50 % and maximum of 100 μg/kg). In Brazil (state of Rio Grande Do Sul), a 3-year (2006–2008) survey of commercial wheat grain quantified the levels of DON and NIV (Del Ponte et al. 2012), which showed that co-contamination was common (59/66) in all samples, and the overall mean levels of DON and NIV were 540 and 337 μg/kg, respectively.

However, not all countries have reported high levels of DON contamination in cereal-based food. In Portugal, DON was not detected in any of the samples analyzed (corn meal, sweet corn, and corn flakes), although high levels of fumonisin B1 (100 %) and fumonisin B2 (70.7 %) contamination were found in the cereal samples (Martins et al. 2008a, b). In Turkey, 50 commercially available beer samples were collected from markets and analyzed by high performance liquid chromatography (HPLC) (Omurtag and Beyoğlu 2007), but none of the samples contained detectable levels of DON. In Malaysia, a low frequency of DON in commercial noodle products was reported by Moazami and Jinap (2009). High variations in the DON concentrations among all types of noodles and brands were also reported. Only one sample each of instant and yellow alkaline noodles was contaminated with DON, with concentrations of 1.003 and 1.243 μg/kg, respectively. This study suggests that the human risk of DON exposure due to the consumption of noodles is very low in Malaysia. In China, the average frequency of DON contamination in domestic soy sauce was shown to be 97.1 %, but with a range of 4.5–1,245.6 μg/L and an average level of 141.5 μg/L, which suggests that the intake of DON from soy sauce is very low in China (Zhao et al. 2013).

In summary, Spanish and Turkish populations are exposed to relatively low DON levels in cereal-based food. In Portugal, no DON was detectable in corn-based food products. In Malaysia, the human risk of DON exposure due to the consumption of noodles is very low. However, a high frequency of DON contamination was detected in bakery products from the Czech Republic. Very high DON contamination levels were detected in maize meal from South Africa, where it is the major food source. In addition, very high DON levels were reported from Brazil due to the hot and humid weather in this region. The intake of DON from soy sauce is very low in China. The DON contamination levels in Africa and South America are much higher than those in Europe and Asia.

Water

Mycotoxins can contaminate rivers from fields cultivated with fungi-infected cereals, as well as from farm animals and human excretion via sewerage systems (Schenzel et al. 2012b). In rivers, DON is toxic to aquatic species. DON (5 mg/kg) can reduce the body weight of carp, as well as causing cell degeneration and necrosis, and loss of the intestinal mucosa and villous atrophy in the intestinal tract (He et al. 2010).

The presence of mycotoxins in food and feeds has been studied widely, whereas environmental contamination with mycotoxins has been analyzed only rarely. At present, DON contamination of water systems has been reported only from Switzerland (2008–2012), where Bucheli et al. (2008) monitored the occurrence of DON in Swiss surface waters during July and August 2007. DON was detected in 60 % of all samples, and the concentrations ranged from not detected to 22 ng/L. The runoff from agricultural fields was a significant source of mycotoxins in surface waters, but DON was not detected in rivers that were not located in wheat-growing areas. This group also analyzed contamination with 30 mycotoxins in drainage, rivers, and waste water treatment plant (WWTP) effluent waters in Switzerland between January and June 2010 (Schenzel et al. 2010). DON was detected in 17 % of drainage water samples, with a maximum concentration of 22.5 ng/L. In river waters and WWTP effluents, DON was detected in 16.6 % (maximum = 11.9 ng/L) and 100 % (maximum = 38.8 ng/L) of the samples, respectively.

The DON contamination levels were monitored continuously during 2009–2011 in Swiss drainage waters and rivers (Schenzel et al. 2012a, b), which showed that T-2 and HT-2 toxins were not detectable in the drainage water samples, but DON was detected at a high frequency of 54 % with a mean concentration of 14.9 ng/L, followed by 3-acetyl-DON with 19 % (mean 25.2 ng/L). The maximum concentrations of DON and 3-acetyl-DON were 1.1 μg/L and 367.5 ng/L, respectively (Schenzel et al. 2012a). In another study (Schenzel et al. 2012b), DON (36 %) and NIV (37 %) were the most frequent mycotoxins detected in rivers in Switzerland between January 2010 and October 2011. The maximum concentrations of DON, NIV, and 3-acetyl-DON were 19.0, 24.1, and 19.2 ng/L, respectively. In general, rivers with higher water discharge rates had lower mycotoxin concentrations. The occurrence of these mycotoxins was highly seasonal because of the spatial variability of different *Fusarium* species and their infection rates.

With the exception of these reports by Swiss researchers, no other information is available from other countries. In China, however, the level of type A trichothecene T-2 toxin was reported for drinking water in Qinghai province (Sun et al. 2012), where a low mean concentration of 0.156 μg/L was detected.

In summary, the DON contamination levels in rivers are much lower compared with those in cereal-based food and feed, although the ecotoxicological risk should be assessed comprehensively in the future.

Animal-derived food

Trichothecenes can be carried over into meat, milk, and eggs after livestock and poultry animals are fed with trichothecene-contaminated feed. Thus, trichothecenes can enter human and animal food chains via these sources, although the exposure risk to humans due to the consumption of animals exposed to trichothecenes is minor compared with the direct consumption of grain products (Seeling et al. 2006; Zou et al. 2012).

Meat

Dänicke et al. (2007) have analyzed DON and DOM-1 residues in the plasma, liver, and breast meat of turkeys, but the concentrations were low, and even lower than the detection limits of 2 ng/mL (plasma) and 4 μg/kg, respectively. DON was not detected in pig dorsal muscle and chicken muscle in samples collected from markets in Chongqing, China (Zou et al. 2012), whereas 30 % of the pig back fat samples were contaminated with DON (0.1232–0.4265 μg/kg). Recently, Xu et al. (2014) have determined the DON contamination levels in chicken tissues from Guangzhou, China, where one muscle (2.1 μg/kg) and two kidney (1.3 and 2.0 μg/kg) samples were confirmed as containing traces of DON. After feeding DON (0.24 mg/kg diet)-contaminated wheat to pigs, however, only trace amounts of DON were carried over into the liver (0.0057 mg/kg), muscle (0.0016 mg/kg), and back fat (0.0002 mg/kg) (Goyarts et al. 2007). Thus, the DON contamination levels in meat products are far lower than those in cereal-based food and feeds, but they may still give cause for concern.

Eggs

A study (El-Banna et al. 1983) showed that DON was not detectable in eggs after chickens were fed a diet contaminated with DON (4–5 μg/kg feed) for 28–190 days. The detection limit of the method used was 10 pg of DON/kg of tissue. Similar results were also reported by Valenta and Dänicke (2005), where laying hens were fed a maize-based diet with a DON concentration of 11.9 mg/kg dry matter (DM) for 16 weeks, but DON, DOM-1, or glucuronide conjugates of both substances were not detected in any of the samples. These results suggest that eggs do not contribute significantly to the dietary intake of DON by humans.

However, low levels of DON were detected in eggs in several studies. Prelusky et al. (1987) studied the transmission of [^{14}C]-DON (2.2 mg of DON, 2.4 μCi/bird) to eggs following oral administration to laying hens. A maximum radioactivity of 1.9 μg DON-equivalents/60-g egg was detected in the first eggs laid after dosing for 24 h, but the DON levels dropped rapidly in subsequent eggs. The levels did not persist after the contaminated feed source was withdrawn. In another study, laying hens were provided with a 5.5 mg/kg ^{14}C-DON-spiked diet (0.55 mg DON; 0.825 μCi/bird/day) for a 65-day period (Prelusky et al. 1989), and maximum radioactivity levels of 1.7 μg DON or metabolites per 60-g egg were detected. The yolk, albumen, and shell membrane contributed 70, 29, and 1 % to the total amount, respectively. Furthermore, laying hens were fed a diet that included different amounts of naturally contaminated wheat-containing DON (ca 20 mg/kg) (Sypecka et al. 2004), and very low transmission rates of 15,000:1, 18,000:1, and 29,000:1 were detected with treatment levels of 5, 7.5, and 10 mg/kg DON feed, respectively. In Belgium, low levels of DON (2.6–17.9 μg/kg) and DOM-1 (2.4–23.7 μg/kg) were detected in home-produced eggs collected during 2006–2007 (Tangi et al. 2009). These findings suggest that the DON levels in eggs are very low, and the potential health risk to humans is likely to be minimal.

Milk

The DON levels were quantified after a single oral dose of 920 mg DON in lactating cows (Prelusky et al. 1984),

and low amounts of free and conjugated DON (<4 ng/mL) were detected in the milk. In another study, dairy cows were exposed to DON (66 mg/kg feed) for 5 days (Côté et al. 1986), and DON was not detected in the milk, but its metabolite DOM-1 was found in milk at concentrations up to 26 ng/mL. Similarly, lactating German Holstein cows were fed with 5.3 mg DON/kg DM for 11 weeks (Keese et al. 2008), but no DON was detected in any of the milk samples, but DOM-1 was detected at levels between 0.6 and 2.2 μg/kg. The total carryover rate into milk for the ingested DON as DOM-1 ranged between 0.0002 and 0.0006.

Milk samples from German retail shops were analyzed by Curtui et al. (2005), but DON, DOM-1, and their glucuronides were not found in any samples, which indicated that DON and DOM-1 are mainly eliminated in the urine by lactating cows and that the carryover into milk is negligible. Similarly, the transfer of DON or DOM-1 into milk was not observed in a study by Charmley et al. (1993), where the concentrations of DON/DOM-1 were below the detection limits (1 mg/mL) according to HPLC-mass spectroscopy.

Dairy cows were exposed to DON (16.6–75.6 mg/kg/day DON feed) for 500–1800 hours, and the concentrations of DON and DOM-1 in the milk of cows ranged between 1.6 and 2.7 μg/kg. The total ingested DON carryover rates as DON and DOM-1 into milk were 0.0001–0.0002 and 0.0004–0.0024, respectively. The carryover rates of DON and DOM-1 increased with the milk yield, although the possible explanation for this effect is not clear (Seeling et al. 2006).

In summary, DON is preferentially biotransformed into DOM-1 and carried over into milk. The toxicity of DOM-1 is lower than that of DON, but risk assessments are required to ensure the safety of consumers.

Vegetables

There have been few studies of the occurrence of mycotoxins, including DON, in vegetables. In general, warm and humid weather conditions prevail during the dehydration of vegetables, and subsequent inadequate storage practices may facilitate the proliferation of mycotoxins.

In India, Sodhi and Sumbali (2012) analyzed the occurrence of DON in the most frequently consumed dried vegetables, including aubergine, tomato, cauliflower, bottle gourd, bitter gourd, and turnip, which showed that 25–40 % of the samples were contaminated by DON, and the highest concentration of DON was detected in dried cauliflower (2.12 mg/kg). In some samples of dried vegetables from markets, the co-occurrence of ZON and DON was detected. The fairly high level of DON detected in the dried vegetables tested in this study suggests that it is necessary to analyze more species of market vegetables in addition to dried vegetables, because the occurrence of DON needs to be determined in fresh vegetables.

Conclusions

MAPK and JAK/STAT are currently reported two important signaling pathways in the cytotoxicity of DON. PKR and Hck are the uncovered upstream kinases to induce the MAPK activation. But we suspect that, in addition to PKR and Hck, there should be other important upstream events in the toxic signaling pathways of DON. Another issue need to be elucidated in the future is the potential cross talk between MAPK and JAK/STAT signaling pathways. The biotransformation of DON in the human from different regions or from different work positions shows some different profiles. These differences are possibly due to the DON levels in cereal-based foods and are correlated with cereal intake in different countries and regions.

Human could expose DON from food and water, and DON contamination of food and water is a global issue. Different countries have very DON different contamination levels in cereals, which depend on the weather, climate, and storage conditions. Years that are characterized as humid and cool usually result in higher levels of DON in cereal crops. In some years, Spanish and Turkish populations are exposed to relatively lower DON levels in cereal-based food. However, the DON contamination levels in cereal-based foods in Africa and South America are much higher than those in Europe and Asia.

The DON contamination levels in water systems have only been reported from Switzerland; thus, further investigations are required urgently from other countries, especially regions with high DON contamination levels. Similarly, vegetables can be contaminated by DON, and analyses of vegetables should be performed in many countries. The co-occurrence of mycotoxins is very common in nature, and the combined effects of these toxins should be assessed.

More reports of human exposure of DON are available from European countries; thus, further information is required from the USA and Asian countries, and there is an urgent need to collect more epidemiological data and scientific evidence about possible interactions among mycotoxins, thereby allowing the definition of reliable tolerance and regulatory limits.

Mycotoxin reduction strategies, such as the addition of mycotoxin-deactivating products, should be considered based on different strategies, including adsorption, biotransformation, biodegradation, and bioprotection (Streit et al. 2013). Consumer awareness programs are also needed to minimize the risk. Many studies have been performed

since the original discovery of free and masked DON, but the significance of these mycotoxins for human and animal health remains to be determined.

Acknowledgments This work was financially supported by the projects of Excellence FIM UHK and MH CZ—DRO (UHHK, 00179906).

Conflict of interest The authors declare that they have no conflict of interest.

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