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Reproductive, gestational, and fetal alterations induced by dietary mycotoxins: A systematic review[1]

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ABSTRACT.- Silva P.O., Ramalho L.N.Z., Oliveira C.A.F. & Ramalho F.S. 2024. **Reproductive, gestational, and fetal alterations induced by dietary mycotoxins: A systematic review.** *Pesquisa Veterinária Brasileira 44:e07481, 2024.* Departamento de Patologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes 3900, Ribeirão Preto, SP 14049-900, Brazil. E-mail: framalho@fmrp.usp.br

Mycotoxins are low molecular weight secondary metabolites produced by some fungi genera, such as *Aspergillus*, *Penicillium*, *Alternaria*, *Fusarium*, and *Claviceps*, during their growth in foods. These molecules share several common characteristics, including toxicity, carcinogenesis, and teratogenesis in animals and humans. This review addresses the reproductive, gestational and fetal changes induced by ochratoxin A, fumonisins, zearalenone, patulin, deoxynivalenol, and T-2 toxin. A systematic evaluation of scientific articles was conducted on research portals PubMed and Google Scholar using keywords related to the topic. The research articles revealed all the characteristics of toxicity, carcinogenesis, and teratogenesis available in the literature, indicating a growing academic and scientific concern in the deposition of information about these mycotoxins.

INDEX TERMS: Mycotoxin-induced gestational alterations, mycotoxin-induced fetal alterations, mycotoxin-induced reproductive alterations, deoxynivalenol, fumonisins, ochratoxin A, patulin, T-2 toxin, zearalenone.

RESUMO.- [**Alterações reprodutivas, gestacionais e fetais induzidas por micotoxinas alimentares: uma revisão sistemática.**] Micotoxinas são metabólitos secundários de baixo peso molecular produzidos por alguns gêneros de fungos, como *Aspergillus, Penicillium, Alternaria, Fusarium* e *Claviceps*, durante seu crescimento em alimentos. Estas moléculas partilham várias características comuns, incluindo toxicidade, carcinogênese e teratogênese em animais e humanos. Esta revisão aborda as alterações reprodutivas, gestacionais e fetais induzidas pela ocratoxina A, fumonisinas, zearalenona, patulina, desoxinivalenol e toxina T-2. Foi realizada uma avaliação sistemática de artigos científicos nos portais de pesquisa PubMed e Google Scholar utilizando palavras-chave relacionadas ao tema. Os artigos de pesquisa revelaram todas as características de toxicidade, carcinogênese e teratogênese disponíveis na literatura, indicando uma crescente preocupação acadêmica e científica na deposição de informações sobre essas micotoxinas.

TERMOS DE INDEXAÇÃO: Alterações gestacionais induzidas por micotoxinas, alterações fetais induzidas por micotoxinas, alterações reprodutivas induzidas por micotoxinas, deoxinivalenol, fumonisinas, ocratoxina A, patulina, toxina T-2, zearalenona.

INTRODUCTION

Mycotoxins are substances produced by various genera of fungi that cause significant toxic effects in animals and humans exposed to them, usually through contaminated foods. These molecules are just a product of secondary metabolism, with low molecular weight, naturally produced by fungal filaments known as hyphae, which grow in different climatic conditions and on various substrates, especially those containing high levels of carbohydrates (Marin et al. 2013). There are other fungal metabolites that, similarly, have low molecular weight but do not offer the same toxic potential (Bennett & Klich 2003).

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Several genera of fungi, mainly *Penicillium*, *Alternaria*, and *Claviceps*, produce specific mycotoxins (Zöllner et al. 2006, Marin et al. 2013). However, others can produce more than one type of mycotoxin, such as *Aspergillus* and *Fusarium* (Hussein & Brasel 2001).

The signs of exposure to mycotoxins are related to reduced feed intake and growth retardation (Fung & Clark 2004). Besides showing proven toxicity to various organs (especially the liver, kidneys, and intestines) and the immune and reproductive systems, these substances also exhibit potent mutagenic effects, leading to carcinogenesis and teratogenesis (González-Arias et al. 2014, Abdallah et al. 2015, Ülger et al. 2020).

In different species of domestic and wild animals, mycotoxins produce clinical and pathological changes to varying degrees, mainly due to distinct metabolism among species (Duarte et al. 2011). Additionally, clinical signs can vary depending on the dose and duration of exposure (Cheli et al. 2014). Moreover, various intrinsic factors can interfere with the impact of mycotoxins on the body, such as overall health, body weight, age, and sex (Wei et al. 2024).

Based on the incidence and severity of harmful effects on animal and human health, the main known mycotoxins are the aflatoxins (AF) B_1, B_2, G_1 and G_2, fumonisins (F) B_1 and B_2, ochratoxin A (OTA), zearalenone (ZEN), patulin (PAT), and trichothecenes such as deoxynivalenol (DON) and T-2 toxin (Afsah-Hejri et al. 2013, Jahanian 2016, Ülger et al. 2020).

The consumption of mycotoxin-contaminated foods, in general, can result in immunodeficiency against infectious agents (Bondy & Pestka 2000, Turner et al. 2003). However, the toxicogenic activity of mycotoxins has specific effects on organs and systems. For example, DON, ZEN, FB_1 and OTA are considered hematologically toxic (Yu et al. 2017), while OTA exhibits nephrotoxicity in humans and animals (Hussein & Brasel 2001).

Certain toxicity mechanisms of some mycotoxins have already been elucidated. DON, in particular, has the ability to inhibit ribosomal protein synthesis, depress the immune response, and induce endocrine changes, especially in growth hormone production and stress response signaling (Pestka & Smolinski 2005, Pestka 2010, Karlovsky 2011).

Another toxic effect of mycotoxins is eryptosis (erythrocyte apoptosis), which can cause a reduction in red blood cell levels, resulting in hypoxia and inflammation. This event may be responsible for the mechanism involved in fetal toxicity to DON, with premature birth induced by hypoxia (Yu et al. 2017, Gönenç et al. 2020).

In addition to adversely affecting organs and systems, mycotoxins can induce carcinogenesis due to their genotoxic and carcinogenic properties (Becit et al. 2017). Among mycotoxins, OTA, FBs, and AFs, in particular, can inhibit protein synthesis as well as the synthesis of nucleic acids (Longobardi et al. 2022). Cumulative DNA damage due to chronic ingestion of these mycotoxins can result in tumorigenesis in various organs.

Hepatotoxic and carcinogenic AF metabolites produced by fungal species of the genus *Aspergillus*, mainly *A. flavus*, *A. parasiticus*, and *A. nomius*, are commonly identified in grains and cereals such as corn, wheat, and peanuts, among other foods (Afsah-Hejri et al. 2013). Twenty different types of AF have been identified, although AFB_1 is the most toxic mycotoxin. The carcinogenic activity of AFB_1 occurs through the formation of bonds with guanine in the DNA molecule, causing damage to genetic material. Thus, AFs are classified in Group 1 (human carcinogen) by the International Agency for Research on Cancer (IARC) (Ostry et al. 2017). Other mycotoxins, such as OTA and FB_1, are categorized in Group 2B (possible human carcinogen), while ZEN belongs to Group 3 (not yet classified as a human carcinogen) (Ostry et al. 2017).

Due to the ability to cross the placenta, mycotoxins can have a deleterious effect on the fetus, leading to malformations and intrauterine growth restriction (IUGR), thus representing a potential teratogenic agent. Detectable levels of mycotoxins in maternal and fetal blood samples demonstrate the possibility of intrauterine exposure to these metabolites during pregnancy (Castelino et al. 2014, Tesfamariam et al. 2019).

Furthermore, protein synthesis inhibition can result in morphological and physiological changes in the intestine, leading to nutrient malabsorption and damaging intestinal barrier function, similar to cases of environmental enteropathies (Smith et al. 2012). Some mycotoxins, especially FB1, apparently act directly or indirectly as embryotoxic or fetotoxic teratogens, causing growth retardation, delayed or incomplete organogenesis, malformations, and ultimately fetal death in various species, mainly in a dose-dependent manner (Lumsangkul et al. 2019).

Maternal anemia can also be a critical outcome of dietary mycotoxins, as several studies have demonstrated an association between exposure to these toxins and anemia (Shuaib et al. 2010a, Shuaib et al. 2010b, Smith et al. 2017). Maternal health can also suffer from the consequences of other toxic effects of mycotoxins, especially on immunity (González-Arias et al. 2014, Abdallah et al. 2015, Ülger et al. 2020).

Due to the vast number of review studies mainly focused on AF (Fetaih et al. 2014, Dai et al. 2017, Smith et al. 2017, Silva et al. 2021), this review reports the toxic effects of other mycotoxins of interest to health. Thus, this study aimed to address the cellular and/or tissue changes induced by mycotoxins OTA, FBs, ZEN, PAT, DON, and T-2 toxin, focusing on their deleterious effects on different organs, fetal development, and sexual development in animals and humans.

MATERIALS AND METHODS

Ethical approval. Since all the data were obtained from database literature searches, this study did not perform any animal experiments. It was not necessary to submit to the Ethics Committee on Animal Use (CEUA).

Searching strategy. A systematic literature search in PubMed and Google Scholar databases was conducted using the following key terms: Mycotoxin fetal exposure or mycotoxin pregnancy or ochratoxin A or fumonisins or zearalenone or patulin or deoxynivalenol or T-2 toxin to retrieve all relevant articles published from 2000 to 2024, that investigated the effects of mycotoxins on different organs, fetal development, and sexual development in animals and humans. Additionally, the reference lists of included articles were also manually searched to identify other suitable studies.

Data collection, inclusion and exclusion criteria. The following information was extracted from each study: Changes in reproductive physiology, alterations in maternal metabolism during pregnancy, adverse outcomes during gestation such as miscarriage or stillbirth, and changes in fetal tissues, including malformations. During the primary screening, the full texts of potentially eligible articles were downloaded after excluding unsuitable articles due to irrelevant content. Then, downloaded citations were examined

twice for the inclusion and criteria of final eligibility. Inclusion criteria were: (1) Full-text article available, (2) Original research studies, (3) Expression of exact experimental details, and (4) Articles published in the English language. The citations that did not meet these criteria were excluded. Considering the above criteria, 178 articles were included in this review.

RESULTS AND DISCUSSION

Table 1 presents a summary of available data regarding reproductive, gestational and fetal alterations induced by mycotoxins OTA, FBs, ZEN, PAT, DON, and T-2 toxin in animals and humans. Figure 1 shows the main pathogenic mechanisms of these mycotoxins in animals and humans.

Ochratoxin A (OTA)

The OTA is a mycotoxin produced mainly by ubiquitous strains of *Aspergillus* and *Penicillium*, with the main species producers being *A. ochraceus*, *A. carbonarius*, *A. melleus*, *A. sclerotiorum*, *P. verrucosum*, and *P. nordicum*. It is considered the most common and toxic substance among ochratoxins (Reddy et al. 2010, Zain 2011) and can be found as a contaminant in cereals and pork (Schwartz 2002).

The effects of OTA vary among species. Monogastric animals, such as dogs and pigs, are more susceptible to ochratoxicosis than chickens, while ruminants are more resistant (Yiannikouris & Jouany 2002, Zain 2011, Martins et al. 2012). On the other hand, the teratogenicity and toxicokinetics of OTA are similar in rats and humans, allowing experimental rat models to be considered suitable for assessing the deleterious effects of OTA in humans (Petzinger & Ziegler 2000, Zepnik et al. 2003, Patil et al. 2006).

Structurally, OTA is formed by a molecule of L-β-phenylalanine (Phe) associated with dihydro-isocoumarin through an amide bond. Due to the presence of Phe in its structure, OTA inhibits all biological processes involving Phe, particularly Phe-tRNA synthetase. Characteristics such as lipophilicity, efficient absorption through the gastrointestinal tract, high affinity for serum albumin, and low biotransformation into water-soluble metabolites result in greater persistence of these compounds in the human body (Patil et al. 2006).

The teratogenic effects of OTA have been documented in various animal models, including mice (Stove 2022), rats, hamsters, quails, and rabbits (Wangikar et al. 2005, Malir et al. 2013). Craniofacial abnormalities and reduced birth weight were the most commonly observed alterations. Additionally, the oral exposure of pregnant Wistar rats to OTA results in maternal toxicities, causing maternal deaths, embryo resorptions, and abortions (Patil et al. 2006).

Table 1. Summary of available data regarding reproductive, gestational and fetal alterations induced by mycotoxins OTA, FBs, ZEN, PAT, DON, and T-2 toxin in animals and humans

	Alterations		
	Reproductive	Gestational	Fetal
OTA	Ovarian follicular atresia Interference with oocyte maturation	Maternal deaths Embryo resorptions and abortions Teratogenicity	Reduced birth weight Clastogenicity Impaired brain development and craniofacial abnormalities Visceral anomalies, especially urinary system Skeletal anomalies
FBs	Delayed puberty Imbalances in the endocrine regulation of the developing ovarian follicle Impairment of spermatogenesis	Disruption of maternal and fetal sphingolipid metabolism Embryo resorptions Teratogenicity	Severe fetal abnormalities, such as neural tube closure defects Suppression of fetal growth and death Interference with folate transport to the developing fetus
ZEN	Early puberty Delayed pre-ovulatory follicular maturation and ovarian atrophy Impairment of testosterone production and spermatogenesis Hyperestrogenic syndromes	Impairment of placental development Embryo resorptions	Interference in sexual development Decrease of primordial ovarian follicles Anomalies in testicular development
PAT	Interference in the production of steroid hormones	Embryotoxicity Teratogenicity	Structural chromosomal aberrations and fetal malformations
DON	Degeneration of testicular germ cells and a higher percentage of deformed sperm Decrease in testosterone levels and increase in serum concentrations of FSH and LH	Increase in levels of glucocorticoids and cardiovascular risk factors during pregnancy Premature birth Teratogenicity	Induction of anomalous gene expression Impairment of fetal development Skeletal deformities
T-2 toxin	Rupture of seminiferous tubules with impairment of spermatogenesis Decrease in testosterone levels Impairing oocyte maturation with the production of defective eggs Inhibition of ovarian granulosa cell proliferation and steroidogenesis	Maternal and fetal deaths Placental hemorrhage Embryo resorptions Teratogenicity	Meiotic aberrations in female fetuses Skeletal anomalies

OTA = ochratoxin A, FBs = fumonisins, ZEN = zearalenone, PAT = patulin, DON = deoxynivalenol, FSH = follicle-stimulating hormone, LH = luteinizing hormone.

Regarding visceral anomalies, the main malformations observed were related to the urinary system, such as renal pelvis dilation, renal hypoplasia, hydronephrosis, and ureteral dilation (Patil et al. 2006). OTA also induces damage to various regions of the mesencephalon and hippocampus in mice, compromising brain development and potentially causing hydrocephalus and microphthalmia (Hsuuw et al. 2013, González-Arias et al. 2014).

In rats, skeletal changes were also noted, including reduced size and ossification failure with agenesis of the metacarpals, metatarsals, and phalanges of the forelimbs and hindlimbs. Other skeletal anomalies involving the skull, ribs, sternum, and vertebrae were also observed. Such skeletal changes can be attributed to the effect of OTA on calcium homeostasis, an essential mineral for osteogenesis (Wangikar et al. 2004, Patil et al. 2006, Pietsch et al. 2020).

It has been demonstrated that the location of ^{14}C-labeled OTA in fetal organs of mice confirmed that this substance could more easily cross the placenta in the early stages of gestation and thereby interfere with fetal development. Additionally, the transport of OTA through maternal-fetal circulation played a significant role in inducing malformations in the offspring of mice (Stoev 2022).

The results of a study with mice conducted by Jia et al. (2020) showed that OTA induced follicular atresia in the ovaries, indicating that OTA promotes changes in ovarian morphology and oocyte growth environment. In this case, mitochondrial damage and insufficient energy supply led to the meiotic failure of oocytes. Additionally, OTA was able to disrupt epigenetic modifications throughout oocyte development. These results demonstrated that OTA can decrease oocyte maturation and fertility induced by oxidative stress and epigenetic changes (Jia et al. 2020).

At micromolar levels, OTA is capable of reducing mitochondrial activity and stimulating the generation of reactive oxygen species (ROS), inducing alterations in the bioenergetic state and functional damage to cells (Dell Dell'Aquila et al. 2021). Indeed, oxidative stress is the central basis of the cytotoxic pathways caused by OTA. OTA interferes with lipid peroxidation by impairing the endoplasmic reticulum and associated membranes, causing oxidative stress and mitochondrial damage (Fung & Clark 2004, Abrunhosa et al. 2010).

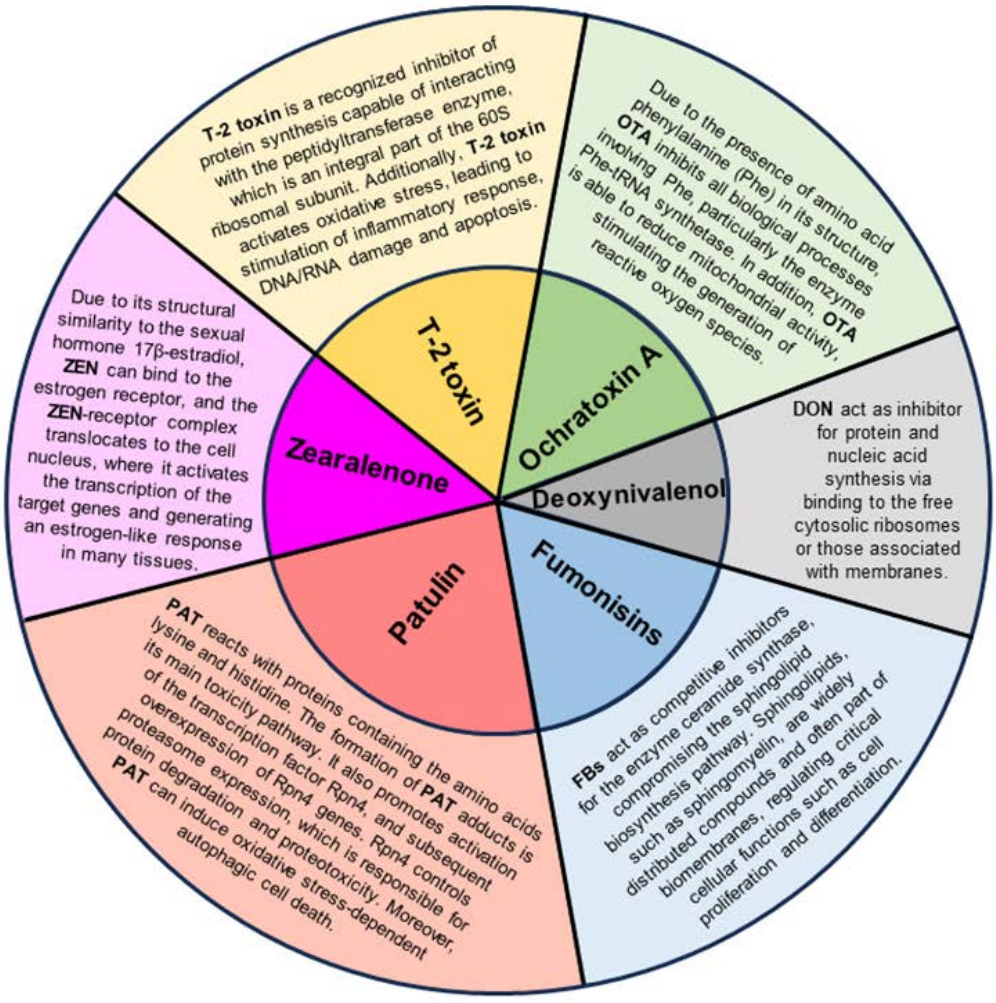

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Fig.1. Main pathogenic mechanisms of mycotoxins ochratoxin A (OTA), fumonisins (FBs), zearalenone (ZEN), patulin (PAT), deoxynivalenol (DON), and T-2 toxin in animals and humans.

There is a clear interface between oxidative stress and the genotoxic activity of OTA on neural stem cells (Sava et al. 2006). Maternal exposure to OTA irreversibly disrupts neurogenesis in the offspring of rats, reducing the number of type 2 progenitor cells in the subgranular zone and the subpopulation of cholinergic and GABAergic hilar interneurons. Suppression of cholinergic and GABAergic signals and increased oxidative stress may be responsible for the decrease in the number of type 2 progenitor cells (Tanaka et al. 2016).

The presence of ROS produced by OTA in various regions of the mesencephalon and hippocampus of mice can lead to multifocal hemorrhages, compromising cerebral development (Richard 2007, Duarte et al. 2011, Afsah-Hejri et al. 2013, Marin et al. 2013). Additionally, previous studies have reported that the generation of OTA-induced ROS activates mitochondria-dependent apoptotic processes in mouse blastocyst cells, leading to malformations in the central nervous system (Hsuuw et al. 2013).

Zhu et al. (2017) reported that OTA is an effective inducer of DNA damage, with the potential to compromise intracellular calcium homeostasis and cause actin fiber breakage, revealing that OTA has a predominantly clastogenic characteristic in its mode of action (González-Arias et al. 2014). Kuroda et al. (2014) demonstrated that exposure to OTA increases the expression of γ-H2AX, indicating the presence of double-strand DNA breaks in an experimental rat model (Kuroda et al. 2014).

Fumonisins

Fumonisins are secondary metabolites first isolated in South Africa in 1988 through cultures of *Fusarium verticillioides* strain MRC 826, followed by the elucidation of the structures of the prevalent isoforms FB_1 and FB_2 (Marasas et al. 2004). They are water-soluble, non-fluorescent mycotoxins produced mainly by the fungi *F. verticillioides* and *F. proliferatum* and, more rarely, by other species of the *Fusarium* genus, such as *F. napiforme, F. dlamini, and F. nygamai* (Domijan et al. 2005, Lino et al. 2007, Marin et al. 2013).

FBs contain two chains of propane-1,2,3-tricarboxylic acid, esterified in the central core of aminopolyol. They are commonly identified as contaminants in corn and corn-based foods worldwide. Interference with cellular lipid metabolism represents the primary mechanism of toxicity for these mycotoxins (Riley et al. 2001).

FB_1 act as a competitive inhibitor for the ceramide synthase enzyme, compromising the sphingolipid biosynthesis pathway. Inhibition of sphingolipid formation is considered the main pathway of FB_1 teratogenesis (Fung & Clark 2004, Theumer et al. 2008).

Ceramide synthase inhibition seems to occur due to the characteristic structural properties of FB_1 resembling co-substrates (sphingoid bases and fatty acyl-CoA). This inhibition has been characterized *in vitro* in various cell lines from animals, plants, and fungi (Gönenç et al. 2020).

Sphingolipids, such as sphingomyelin, are widely distributed compounds, and often part of biomembranes, regulating critical cellular functions such as cell proliferation, differentiation, and apoptosis (Merril Jr. et al. 2001, Lumsangkul et al. 2019). According to Brown et al. (2014), the toxic effects of FB_1 result in the disruption of lipid messenger-mediated signal transduction pathways through the cytoplasmic membrane. These effects include changes in cell adhesion, intercellular communication, cell proliferation and apoptosis rates, as well as generating oxidative stress and modulating gene expression (Brown et al. 2014).

Besides disrupting sphingolipid biosynthesis through ceramide synthase inhibition, the mechanism of action of FB_1 appears to involve the modification of cell proliferation through changes in cell cycle regulators and increased cytokine expression, such as TNFα.

Some authors have reported adverse outcomes in the exposure of pregnant mice to FB_1, such as neural tube closure defects and suppressed fetal growth (Gelineau-van Waes et al. 2012). In another study, pregnant mice exposed to a semipurified extract of FB_1 had fetuses with neural tube formation defects, showing an increase in the number of embryo resorptions and fetal abnormalities in a dose-dependent manner (Theumer et al. 2008). Liao et al. (2014) also demonstrated that fetuses of pregnant mice fed with FB_1 exhibited fetal abnormalities, such as neural tube formation defects (Liao et al. 2014).

It was observed that administering FB_1 to pregnant rabbits caused fetal mortality and disrupted maternal sphingolipid metabolism (Ewuola & Egbunike 2010). High rates of embryonic mortality and compromised fetal development due to disruption or interruption of sphingolipid metabolism were not evident in rabbit fetuses, suggesting that the effect of FB_1 on rabbits could be secondary to maternal toxicity (Lumsangkul et al. 2019). Aqueous extracts of corn contaminated with *F. verticillioides* provided to pregnant hamsters demonstrated that FB_1 was also toxic to fetal development (Missmer et al. 2006, Nesic et al. 2014).

In addition to dysfunction in sphingolipid metabolism, interference with folate transport may also be related to the toxic effects of FB_1, leading to insufficient transfer of folates to the developing fetus, causing syndromes secondary to this deficiency during embryogenesis (Marasas et al. 2004, Gelineau-van Waes et al. 2005, Lumsangkul et al. 2019). Thus, FB_1 disrupts folic acid metabolism through the high-affinity folate transporter, which may also contribute to the incidence of neural tube closure defects in mice and humans related to folate deficiency (Voss et al. 2006, Chandrasekhar & Sreelakshmi 2012, Lumsangkul et al. 2019, Gönenç et al. 2020).

Based on histopathology and sphingolipid profile evaluation in mothers, fetal toxicity secondary to maternal toxicity is prominent (Gelineau-van Waes et al. 2009). FB_1 exposure results in a significant increase in sphinganine concentrations in the liver, kidney, and maternal placenta, as well as in embryonic tissue, suggesting that the toxin crosses the placenta and inhibits de novo sphingolipid biosynthesis within the developing embryo (Gelineau-van Waes et al. 2005, 2012). Additionally, exposure to purified FB_1 has been shown to cause fetal toxicity in rats and mice (Van de Bor 2019).

Early fetal abnormalities, including hydrocephalus, enlarged beaks, and elongated necks, were also observed in animals exposed to FB_1 as embryos. Pathological changes were evident in livers, kidneys, hearts, lungs, musculoskeletal systems, intestines, testicles, and brains in these toxin-exposed embryos, according to Lumsangkul et al. (2019).

Previous studies indicate that FB_1, as previously observed for DON, ZEN, and T-2 toxin, has the potential to negatively influence the steroidogenic capacity of ovarian granulosa cells in pigs, demonstrating the ability of these mycotoxins

to cause disruptions to the endocrine regulation of the developing ovarian follicle, an essential factor for achieving the pre-ovulatory stage (Cortinovis et al. 2013). Similarly, male rabbits exposed to FB_1-contaminated diets also showed testicular and epididymal depression, as well as reduced sperm reserves, sperm production, and potentially impaired male reproduction (Ewuola & Egbunike 2010).

In addition, different authors have demonstrated that mycotoxins, especially FB_1, can induce erythrocyte lysis, inhibit hematopoiesis, disrupt and reduce iron absorption, affect hemoglobin levels, and initiate microcytic hypochromic anemia, thus initiating a series of events with the potential to generate hypoxia, oxidative stress, and widespread inflammation related to preeclampsia (Yousef et al. 2003, Kumar & Balachandran 2005, Docan et al. 2011, Gönenç et al. 2020).

The preponderance of evidence suggests that FB_1 can also be potent promoters of liver cancer, as demonstrated by their ability to induce pre-neoplastic foci with high expression of the enzymes γ-glutamyl transpeptidase and glutathione-S-transferase in rat liver (Voss et al. 2002).

Zearalenone (ZEN)

ZEN is a mycotoxin produced by fungi of the genus *Fusarium*, primarily by *F. graminearum, F. culmorum,* and *F. sporotrichioides*, known for its ability to exert hyperestrogenic effects. Corn, wheat, oats, barley, and rye are the main food items infected with ZEN-producing fungi (De Saeger et al. 2003). ZEN mycotoxin is a common food contaminant in parts per billion (ppb) and parts per million (ppm), and contamination of milk by ZEN and its metabolites have also been reported (Signorini et al. 2012, Huang et al. 2014).

Swine are frequently affected by this mycotoxin (Hussein & Brasel 2001). In humans, the exposure of pregnant women to ZEN-contaminated foods may also be associated with maternal health risks and compromise female development due to transgenerational toxicity (Gao et al. 2017).

After ingestion, ZEN is predominantly metabolized into α- and β-zearalenol (ZOL) by 3α- and 3β-hydroxysteroid dehydrogenases in the liver. α-ZOL has been shown to be the dominant derivative of ZEN in pigs, humans, rats, and mice (Fink-Gremmels & Malekinejad 2007, Deng et al. 2012). It is a macrocyclic lactone that, due to its ability to bind to estrogen receptors, is included in the group of phytoestrogens (Coffey 2001). As a result, it stimulates protein synthesis in specific reproductive system cells, leading to increased cell proliferation or decreased aromatase and dehydrogenase activity in the steroidogenesis process (Coffey 2001). Although not common in humans, hyperestrogenic syndromes can be observed.

In animals, ZEN is a weak estrogen and inhibits the secretion of follicle-stimulating hormone (FSH), thus delaying pre-ovulatory follicle maturation in the ovaries and exerting reproductive toxicity (Zinedine et al. 2007, Marin et al. 2013). Due to its structural similarity to 17β-estradiol (E2), ZEN can bind to the estrogen receptor, and the ZEN-receptor complex translocates to the nucleus, where it binds to estrogen response elements, activating the transcription of the target gene and generating an estrogen-like response in many organs (Metzler et al. 2010, Patubicki et al. 2021).

In humans, prepubertal ZEN consumption has been linked to the occurrence of early puberty, with females being more sensitive than males (Massart & Saggese 2010). Similarly, several *in vivo* studies have reported the toxicological effects of ZEN, including functional changes in reproductive organs, increased embryo resorption, reduced fertility, and abnormal hormone levels in the female reproductive system in both laboratory and farm animals (Yousef et al. 2023, Collins et al. 2006a).

ZEN can be excreted in the milk of sows and cows due to exposure to high doses in feed (Abdallah et al. 2015). Birds have shown some resistance to ZEN, with only highly contaminated foods leading to infertility and reduced spermatogenesis (Fung & Clark 2004, Richard 2007, Zain 2011).

In vitro studies have demonstrated that ZEN and its metabolites disrupt the function of Leydig cells due to impaired mitochondrial function, inducing apoptosis of such cells (Li et al. 2019).

The *Esr1* gene, related to the estrogen receptor, is a known target of ZEN exposure, leading to impairment in *Esr1* signaling pathways. Thus, its decrease may indicate a decrease in the ability to mediate the biological effects of estrogens and result in deficient reproductive processes. The results also showed a significant decrease in GnRHr mRNA expression in fetuses and newly weaned animals, indicating impaired GnRHr activation (Zhang et al. 2014).

In sexually mature sows, ZEN induces various reproductive dysfunctions, including pseudopregnancy, endometrial changes such as squamous metaplasia, ovarian atrophy, and inhibition of follicular maturation during the preovulatory stage (Cortinovis et al. 2013). Cortinovis et al. (2013) also reported a negative effect of ZEN and its derivatives α-ZOL and β-ZOL on the meiotic progression of bovine oocytes *in vitro*. Oocyte maturation to metaphase II was inhibited in oocytes cultured in the presence of ZEN or α-ZOL, with a significant increase in chromatin abnormalities, particularly after the addition of α-ZOL (Cortinovis et al. 2013).

In young boars, ZEN was responsible for reducing testicular weight, spermatogenesis, serum testosterone, and libido. ZEN and its derivatives, α-ZOL and β-ZOL, promote a decrease in sperm viability and motility. Moreover, ZEN and α-ZOL were also associated with a reduction in the ability of boar sperm to bind to the zona pellucida and to affect the integrity of sperm chromatin, which is important not only for fertilization but also for normal embryonic development. ZEN also inhibited testosterone production by mouse Leydig cells *in vitro* (Benzoni et al. 2008, Tsakmakidis et al. 2008, Cortinovis et al. 2013).

ZEN and its metabolites are also transferred to the fetus through the placenta, and associations have been identified between maternal exposure to ZEN and adverse pregnancy outcomes, such as developmental impairments and reduced litter size. After maternal exposure, comparatively greater susceptibility was observed in female newborns than in males (Kippler et al. 2012, Schoevers et al. 2012). Fetal exposure to ZEN can cause damage to ovarian follicles and, therefore, poses a health risk to young women due to premature oocyte depletion (Schoevers et al. 2012, Gao et al. 2017).

Prenatal exposure to ZEN also affected the expression of genes and proteins related to hormones in various organs of rats. A decrease in *Esr1* mRNA expression was observed in the placenta, as well as in the brains of fetuses and newly weaned rats. There was also a significant decrease in *Esr1* mRNA and the expression of other proteins in mature ovaries (Zhao et al. 2013, Zhang et al. 2014). This may indicate a feedback

mechanism involving transcriptional and translational repression of *Esr1* (Hofmeister & Bonefeld-Jørgensen 2004, Gao et al. 2017).

A notable decrease in 3β-HSD was observed in adult rats' uteruss and ovaries at both the mRNA and protein levels. Reproductive toxicity induced by ZEN may be related to the regulation of genes related to hormonal synthesis (Esr1 and 3β-HSD) and crucial ABC transporter isoenzymes (Abcc1 and Abcc5) involved in ZEN efflux clearance in the ovaries and uterus. Dysregulation of this hormonal axis can result in transgenerational toxicity (Knapczyk-Stwora et al. 2014).

Negative effects on female offspring can affect conception and reproduction. Recent findings support that α-ZOL and β-ZOL mediate cell death via mitochondrial stress without caspase activation in these cells. The mode of cell death induced by these metabolites has been predominantly apoptotic rather than necrotic (Lu et al. 2013). A previous study demonstrated that a ZEN diet blocked embryo implantation in mice (Zhao et al. 2013). In fact, ZEN at relevant environmental levels may adversely affect placental development (Watson & Cross 2005).

According to observations by Li et al. (2019), an increase in resorption of embryonic implantation sites was evident. All implantation sites that were not reabsorbed showed placental hemorrhage foci, demonstrating the toxicity of a diet containing ZEN on placental development in mice (Zinedine et al. 2007, Zhao et al. 2014, Li et al. 2019).

In pregnant sows exposed to ZEN in the diet, the passage of the toxin through the placenta was noted due to its presence in the bile of newborn piglets, where ZEN and its metabolites were detected in varying concentrations. Female piglets also showed a significant decrease in the percentage of normal primordial ovarian follicles at all tested ZEN doses (Schoevers et al. 2012).

Bo et al. (2015) reported that exposure of pregnant mice to α-ZOL caused anomalies in fetal testicular development. Through its influence on the endocrine system, ZEN is potentially capable of interfering equally with sexual development in males (Bo et al. 2015).

It has also been demonstrated that oral exposure to ZEN can result in various other deleterious effects in mammals, including cancer induction, neurotoxicity, genotoxicity, and immunotoxicity (Obremski et al. 2003).

Patulin (PAT)

PAT is a mycotoxin found in fruits, primarily in apples and their derivatives, produced by some species of fungi from the genera *Aspergillus, Penicillium, Paecilomyces,* and *Byssochlamys* (Ioi et al. 2017). It was first isolated from *Penicillium griseofulvum* in 1943, and currently, *Penicillium expansum* is considered the main food-contaminating microorganism known to produce PAT (Ioi et al. 2017).

PAT is a polyketide lactone, classified as a heat-stable lactone, and its notable feature is that it cannot be thermally denatured (Puel et al. 2010). PAT is a potentially proteotoxic molecule, and studies confirm that its toxic effects can affect animals at the proteomic level, generally in a sex-dependent manner (Guerra-Moreno & Hanna 2017). The sex-dependent adverse effect of mycotoxins should not be overlooked, with evidence suggesting that males may be more sensitive to PAT than females (Andretta et al. 2012). Male sensitivity to PAT effects was demonstrated in a study involving intramuscular injection of PAT in rabbits, where male rabbits exhibited more intense bone remodeling (Duranova et al. 2015).

The toxicity of PAT has been extensively explored through experimental models, including rats, hamsters, chickens, and monkeys. The most common exposure route is ingestion, either added to the animals' feed or water, while other studies used gavage to simulate natural intoxication. PAT pathogenesis begins inside the cell, where this mycotoxin targets cysteine and causes its depletion. It can also react with proteins containing the amino acids lysine and histidine. The formation of PAT adducts is its main toxicity pathway (Song et al. 2014). PAT affinity for thiol groups has been widely described, explaining its inhibitory effect on many enzymes (ATPase, lysosomal enzymes, RNA polymerase, among others) (Puel et al. 2010).

PAT can also promote activation of the transcription factor Rpn4 and subsequent overexpression of Rpn4 genes. Rpn4 controls proteasome expression, responsible for protein degradation and proteotoxicity (Guerra-Moreno & Hanna 2017).

Exposure to PAT compromises the intestinal mucosal barrier, causing gastrointestinal, immunological, neurological, and developmental problems, posing risks to human health, especially in more vulnerable populations such as children (Saleh & Goktepe 2019).

Regarding cytotoxicity, *in vivo* toxicity assessment shows damage to vital organs and systems, including the liver, kidneys, intestines, and the immune system (Wichmann et al. 2002). It has also been proven that PAT can impair the endocrine system activity in both males and females (Soler & Oswald 2018).

In terms of teratogenesis, it has been demonstrated that in mice, oral administration causes loss of offspring with hemorrhages in the brain, lungs, and epidermis. Intraperitoneal administration increases the incidence of cleft palate and renal malformations. PAT exposure can also increase the frequency of defective embryos, including anomalies such as growth retardation, mesencephalic and telencephalic hypoplasia, and mandibular development process hyperplasia. Furthermore, in a study using chicken eggs, PAT was embryotoxic and teratogenic, with embryos not surviving beyond 40 hours of incubation after PAT administration. PAT also induced a significant reduction in protein and DNA content, altering the yolk sac diameter and the somite count (Puel et al. 2010).

Excessive ROS levels can induce cell autophagy and damage genetic material. Oxidative stress plays a crucial role in PAT-induced cell death in renal embryonic cells (Zhang et al. 2015). Higher levels of ROS were observed in cells exposed to PAT, along with overexpression of autophagy markers (LC3-II and LC31). PAT exposure led to p62 protein accumulation, which functions as a pro-survival signal, ultimately leading to cell cycle arrest mediated by oxidative stress (Pal et al. 2017).

Autophagy activation involves mass degradation of some cytoplasmic proteins and selective degradation of cytoplasmic organelles. This mechanism was observed in human hepatoma G2 (HepG2) cells exposed to PAT, and treating cells with an autophagosome inhibitor (3-methyladenine) reduced PAT toxic effect, indicating that the PAT toxicity pathway may involve autophagy and oxidative stress (Sun et al. 2018). Moreover, PAT can induce ROS-dependent autophagic cell death in HepG2 cells (Yang et al. 2018).

On the other hand, accumulation of p62 mediated by PAT-induced autophagy inhibition provides increased cell

survival and may lead to a disruption in the balance between cell death and growth, considered an early and crucial event in the carcinogenic process (Guo et al. 2013).

There is a close interaction between oxidative stress pathways and PAT genotoxic potential. A study conducted on two types of cell lines, wild-type p53 embryonic kidney cells and p53 knockout mouse embryonic fibroblasts, demonstrated that p53 plays an important role in increasing the generation of ROS and oxidative stress related to PAT (Zhong et al. 2017). Also, using two types of human cell lines, Boussabbeh et al. (2015a) demonstrated that PAT-induced apoptosis is mediated by increased ROS production involving ER stress and activation of mitochondrial apoptotic pathways. The treatment of cells with the ROS scavenger N-acetyl cysteine inhibited the ER stress response and prevented mitochondrial apoptosis (Boussabbeh et al. 2015b).

Furthermore, some studies indicated that PAT impaired DNA synthesis. Such genotoxic effects may be related to its ability to react with thiol groups and induce oxidative damage. Studies have shown that PAT acts as a clastogenic factor in mammalian cells, inducing micronuclei without kinetochores and presenting structural chromosomal aberrations (Alves et al. 2000, Liu et al. 2007, Pal et al. 2017).

Trichothecenes

Trichothecenes are mycotoxins synthesized by fungi from different species of the genus *Fusarium*, such as *F. culmorum, F. sporotrichioides, F. tricinctum, F. roseum, F. graminearum, F. nivale,* and *F. sambucinum*, as well as some species from the genera *Myrothecium* and *Stachybotrys*. The target food items for contamination are usually corn, barley, wheat, oats, rye, soybeans, and fruits, as well as animal feeds.

They form a large family of chemically related toxins containing a common 12,13-epoxitricothec-9-ene sesquiterpenoid tetracyclic ring, with the 12,13-epoxy ring being responsible for their toxicological activity (Li et al. 2011). Despite their various forms, few trichothecenes have toxic potential, with DON and T-2 toxins considered the most important (Abdallah et al. 2015).

The mechanism of toxicity involves the inhibition of protein synthesis through interaction with a 60S ribosomal subunit and the peptidyl transferase enzyme (Sweeney et al. 2002, Zou et al. 2012). There is a disruption of DNA and RNA through the inhibition of the peptidyl transferase, consequently affecting actively mitotic cells such as intestinal epithelial cells, dermal cells, lymphoid cells, and erythroid cells.

Trichothecenes can also induce oxidative stress and a wide range of secondary consequences by modifying cell signaling proteins, such as DNA/RNA damage, apoptosis and activation of the inflammatory response (Ren et al. 2020).

Additionally, they can stimulate type-four hypersensitivity reactions simultaneously with the inhibition of suppressor T cells and, at low doses, disrupt glucose metabolism and calcium ions (Abdallah et al. 2015).

A significant increase in interleukin-6 (IL-6) mRNA levels was observed in a culture of human choriocarcinoma cells exposed to DON and T-2 toxin (Toutounchi et al. 2019). High stress response, insulin resistance, hypertension, and dysregulation of the hypothalamus-pituitary-adrenal axis during adulthood are among the consequences of prenatal exposure to IL-6, both early and late in gestation (Dahlgren et al. 2001, Samuelsson et al. 2004).

The main trichothecene mycotoxins DON and T-2 toxin will be discussed further in terms of their metabolism and physiological consequences in the body.

Deoxynivalenol (DON)

DON is a type B trichothecene mycotoxin, primarily produced by fungi of the *Fusarium* genus. At the molecular level, DON has been observed to inhibit DNA, RNA, and protein synthesis (Bensassi et al. 2012). Some studies indicate that the main targets are free cytosolic ribosomes or those associated with membranes (Nielsen et al. 2011).

Significant teratogenic alterations result from exposure to DON. Various studies have shown that fetal bone malformation is a universal phenomenon after DON exposure (Yu et al. 2017). Assessment of fetal skeletal malformations in pregnant mice exposed to DON revealed various skeletal abnormalities, including misalignment or fused vertebrae, split or fused ribs, polydactyly, hemivertebrae, short fingers, and tail anomalies.

Experimental study results showed that DON induced anomalous gene expression in 282 genes (148 negatively regulated and 134 positively regulated genes). Among them, six genes closely related to bone development, including fibrillin-1, alpha 2 (IX) collagen (Col9A2), 3'-phosphoadenosine 5'-phosphosulfate synthase 2 (PAPSS2), and (PAX1), were significantly upregulated. On the other hand, runt-related transcription factor 2 (RUNX2) and parathyroid hormone-related protein (PTHLH) were considerably downregulated after exposure to DON. The altered expression of these genes plays a critical role in fetal skeletal deformities (Yu et al. 2017).

The risks of acute or chronic exposure to DON for pregnant women should be carefully considered due to its high toxicity to fetuses (Piekkola et al. 2012). DON delayed fetal development in rats by inducing imperfect bone formation, as evidenced by a significant reduction in skeletal ossification or defects in the axial skeleton, dorsal arches, metacarpals, metatarsals, and vertebrae (Collins et al. 2006b, Zhao et al. 2012).

Transfer of DON through the placenta to the fetus has been observed in different species. After exposure to pregnant sows, DON was detected in fetal plasma, liver, and kidneys (Tiemann et al. 2008a, 2008b). In rats, relatively high doses of DON administered to pregnant females impaired fetal development (Collins et al. 2006b).

In a recent study, newly mated female rats were exposed to DON via gavage, and the exposure continued throughout gestation and lactation. DON concentrations were similar in the plasma of mothers and fetuses, demonstrating the transfer of this mycotoxin through the placenta (Silinski et al. 2020). This is consistent with the study by Nielsen et al. (2011), who, using an *ex vivo* dual perfusion model, demonstrated that DON could cross the human placenta, as DON concentrations in the plasma of mothers and offspring were similar. Dänicke et al. (2007) indicated a significant reduction in body weight, spleen weight, hemoglobin concentration, and hematocrit in piglets from exposed sows, indicating a significant passage of DON and its metabolites to piglets (Dänicke et al. 2007).

Even at low levels, DON ingestion can result in increased endogenous CO_2 and greater peroxynitrite generation, promoting membrane oxidation and eryptosis. This mycotoxin can also lead to the release of pro-inflammatory

cytokines throughout the systemic circulation, followed by the activation of the hormonal stress response, resulting in increased glucocorticoids and cardiovascular risk factors during pregnancy (Zhao et al. 2012).

Regarding cytotoxicity, DON can destabilize the immune system's functions in different animal species (Gray et al. 2008, Pestka 2010). It can also induce hematological disorders such as neutropenia, thrombocytopenia, and aplastic anemia in humans and animals. *In vivo*, the inhibition of protein synthesis has been demonstrated in bone marrow, spleen, and thymus cells (Yu et al. 2019).

In rats, DON has been described to adversely affect male reproductive function. DON exposure can result in degeneration of testicular germ cells, failure in sperm release, abnormal development of germ cells, decreased testosterone levels, and increased serum concentrations of FSH and luteinizing hormone (LH) (Cortinovis et al. 2013).

Observations of DON-induced lesions in male mice by Sprando et al. (2005) highlighted the potential toxicological effect on testicular and epididymal sperm count and testicular morphology. The authors found a significantly higher number of sperm with tail abnormalities and considerably lower sperm motility than the control group (Sprando et al. 2005).

In terms of toxicity mechanisms, it was demonstrated that DON-induced apoptosis via mitochondria-dependent pathways associated with the opening of the mitochondrial permeability transition pore, loss of mitochondrial transmembrane potential, ROS generation, and cytochrome C release (Dragan et al. 2001, Kamp et al. 2005, Wu et al. 2008, Bensassi et al. 2012).

At the cellular level, a major toxic effect is related to the inhibition of protein and nucleic acid synthesis (Gab-Allah et al. 2023, Vörösházi et al. 2024) via binding to the ribosome and activation of cellular kinases involved in signal transduction, resulting in decreased cell proliferation (Bensassi et al. 2012, Gab-Allah et al. 2023).

Yu et al. (2019) also investigated DON hepatotoxicity during pregnancy and the role played by induced oxidative stress in the process. Oxidative stress and the antioxidant system were activated, marked by increased ROS and malondialdehyde levels and decreased glutathione consumption.

T-2 toxin

T-2 toxin is a type A trichothecene molecule produced by various *Fusarium* species, with hepatotoxic (Yang et al. 2017, Song et al. 2023), hematotoxic (Ficheux et al. 2012), immunotoxic (Wu et al. 2017, Huang et al. 2018), and reproductive toxic properties (Yang et al. 2010, Escrivá et al. 2015, Zhang et al. 2018, 2019).

T-2 toxin is considered the most cytotoxic member of the T-2 toxin family, with oral, parenteral, and cutaneous exposure to this mycotoxin shown to induce lesions in lymphoid, hematopoietic, and gastrointestinal tissues, as well as suppress reproductive functions (Sehata et al. 2004, Doi et al. 2008, Zhang et al. 2024). Emerging evidence has revealed the effects of T-2 toxin on reproduction, including impaired meiotic maturation, abnormal meiotic spindle formation, deficiency in oocyte cytoskeleton formation (Zhu et al. 2016), disturbance of spermatogenesis (Yang et al. 2019), abnormal testicular structure, changes in testosterone synthesis (Shen et al. 2019, Yang et al. 2022), impaired steroidogenesis, and reduced vitality of ovarian granulosa cells (Li et al. 2020).

The toxicity mechanism of the T-2 toxin is directly related to its proteotoxic potential, as it is a recognized inhibitor of protein synthesis capable of interacting with the peptidyltransferase enzyme, which is an integral part of the 60S ribosomal subunit (Vörösházi et al. 2024). Another major mechanism of T-2 toxin cytotoxicity is the activation of oxidative stress. ROS can induce lipoperoxidation of cellular membranes, oxidative damage to DNA, RNA and proteins, cell cycle arrest, apoptosis and stimulation of the inflammatory response through activation of the NF-□B signaling pathway (Sokolović et al. 2008). T-2 toxin activates the ROS/ NF-□B pathway to upregulate the expression of proinflammatory factors interleukin-1β, interleukin-6, and tumor necrosis factor-alpha as well as the proinflammatory induction enzyme cyclooxygenase-2, and promotes inflammatory reactions (Ren et al. 2020).

Maternal exposure to T-2 toxin during gestation and lactation disrupts the structure of seminiferous tubules and testosterone synthesis in male animals due to increased oxidative stress and apoptosis (Shen et al. 2019). Unfavorable findings in semen quality can be attributed to the compromise of the blood-testis barrier formation, leading to apoptosis of spermatogenic lineage cells and consequent impairment of spermatogenesis (Faisal et al. 2008, Yang et al. 2010, 2014, 2022, Karacaoglu & Selmanoğlu 2017).

T-2 toxin exposure impairs meiotic spindle assembly in females, reducing phosphorylated MAPK levels, resulting in abnormal oocyte cytoskeleton, increased oxidative stress, and cell apoptosis, further affecting oocyte maturation (Zhu et al. 2016).

Insufficient repair of DNA damage compromises meiotic prophase I and activates checkpoints that trigger apoptosis (Bolcun-Filas et al. 2014). Therefore, due to weak meiotic checkpoints in oocytes, unrepaired DNA damage can lead to the production of defective or even aneuploid eggs, resulting in spontaneous abortion or teratogenicity (Susiarjo et al. 2007, Reichman et al. 2017).

In a recent study, pregnant mice exposed to T-2 toxin exhibited meiotic aberrations in female fetuses, including delayed progression of meiotic prophase I, unmatched DNA damage in oocytes, and increased homologous recombination. Additionally, excessive increases in oxidative stress and mitochondria-related apoptosis were observed in the fetal ovary exposed to T-2 toxin (Hong et al. 2021).

The effect of oral exposure to low doses of T-2 toxin on ovarian function was evaluated in ewes and heifers, showing that the oral ingestion of this mycotoxin can significantly delay the maturation of ovarian follicles, postpone subsequent ovulation, delay consecutive luteinization, and impair conception in inseminated animals (Huszenicza et al. 2000). T-2 toxin strongly inhibits FSH and IGF-I-induced progesterone, leading to increased production of estradiol and a higher number of ovarian follicles. These direct ovarian effects could be a mechanism by which the presence of T-2 toxin in animal feed could impact the reproductive performance of livestock (Cortinovis et al. 2013).

An *in vitro* study investigated the potential impact of T-2 toxin on the reproductive activity of female pigs, focusing on the effects of this mycotoxin on the functions of granulosa cells. T-2 toxin showed potent direct inhibitory effects on

the proliferation of granulosa cells and on steroidogenesis in female pigs in a dose-dependent manner (Caloni et al. 2009).

The effects of high doses of T-2 toxin on sperm, seminal plasma, and testosterone production were also investigated in adult male rabbits, and exposure to T-2 toxin resulted in decreased motility and an increase in the number of sperm with morphological abnormalities, a drop in citric acid concentration in seminal plasma, and a decrease in testosterone levels (Kovacs et al. 2011, Cortinovis et al. 2013).

The oral exposure of pregnant CD-1 mice to T-2 toxin resulted in maternal toxicities causing placental hemorrhage, maternal death, embryotoxicity, and fetal loss. Defective fetal development was also observed, with a greater frequency of skeletal anomalies (Yang et al. 2020).

T-2 toxin can induce apoptosis in basal keratinocytes when applied to the dorsal skin of rats. The expression of the oncogenes c-fos and c-jun and the pro-inflammatory cytokines TNF-α and IL-1β was markedly increased in apoptotic cells, indicating an important role of these molecules in T-2-induced apoptosis in keratinocytes (Albarenque & Doi 2005).

CONCLUSIONS

Mycotoxins OTA, FB_1, ZEN, PAT, DON, and T-2 toxin can cause adverse effects based on their overall toxicity (cytotoxicity).

OTA and FB_1 cause genetic damage and produce cancer cells. At the same time, all of them have the potential to cross the placental barrier in mammals, leading to fetal malformations and/or intrauterine growth retardation (teratogenesis). Thus, cumulative and acute damage in these mycotoxins' toxicity, carcinogenesis, and teratogenesis can be attributed to their metabolism and the duration of ingestion, whether chronic or acute.

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