Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Occurrence and co-occurrence of mycotoxins and their modified forms in children food and risk assessment

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ARTICLE INFO

Article history:
Received 22 May 2024
Received in revised form 18 September 2024
Accepted 16 December 2024

Keywords:
Mycotoxins
Modified mycotoxins
Children's health
Risk assessment
Risk chracterizatioon
Children food

ABSTRACT

Mycotoxins are the toxic metabolites produced by the fungi that grow in food crops; however, the modified mycotoxins are the undetectable metabolites during testing for the parent mycotoxin. Although more than 300 mycotoxins were discovered and identified, little is known about the effects of most of them or their modified forms on child health. Aflatoxins are well known to induce liver cancer and play a significant role in the impairment of child growth. Fumonisin also are known to induce esophageal cancer and neural tube defects. However, deoxynivalenol and the other trichothecenes are well known as immunotoxic and induce gastroenteritis. In this review, the adverse health hazards in children associated with the major mycotoxins as well as the modified forms of fusarium mycotoxins were described. Additionally, the global burden of the health ghazards resulted from the exposure of children to dietary mycotoxin. The risk assessment, risk characterization and the challenges in risk characterization of multiple mycotoxins in children food were discussed.

1. Introduction

Mycotoxins are low molecular weight (mostly below 700 Da), toxic secondary metabolites produced by fungi and contaminate various grains and agricultural commodities at different stages, including before harvest, post-harvest, during processing, packaging, distribution and storage[1]. The Food and Agriculture Organization of the United Nation (FAO) reported that one third of all foodstuffs produced for the world's population are lost from field to consumer, reaching nearly 1.3 billion metric tons each year[2]. The Council for Agricultural Science and Technology (CAST) reported that 25% of the crops in the world are damaged by mold or fungal growth[3-4]. More than 100 fungi that belong to *Aspergillus*, *Penicillium* and *Fusarium* genera are well known to produce mycotoxins[5].

In laboratory animals and human, mycotoxins demonstrate acute toxic properties[6], they are mutagenic[7], carcinogenic[8], teratogenic[9] and estrogenic (zearalenone (ZEN)) properties[10]. Mycotoxins vary considerably in their chemical structure, from simple heterocyclic rings with molecular weights of up to 50 Da, two groups with 6−8 irregularly arranged heterocyclic rings with a molecular weight of over 500 Da[11] that determines their resistance to environmental factors and the absence, or traces of immunogenic properties[12].

The growth of fungi is mainly depending on the environmental factors, including the substrate structure, water activity, relative humidity, microbial competition, nutrient availability, rodents and

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Peer review under responsibility of Beijing Academy of Food Sciences.

SciOpen Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2024.9250426

insect damage[13]. These factors can influence the growth of fungi consequently; mycotoxins formation with different degrees. However, these factors strongly affect the mycotoxins production much more than their effects on the growth of fungi[14]. So, it is not easy to determine the particular environmental conditions that can enhance the production of mycotoxins or encourage the growth of fungi[3].

More than 200 million children all over the world suffer from the impaired the growth and about 2 million children die each year before the age 5[15]. So it was necessary to identify the overall contributing factors that lead to these health problems and to develop better intervention strategies[16]. Clinical symptoms induced by mycotoxins are diverse depending upon the ingested dose, exposure duration, mechanisms of action, physiological condition, metabolism, defense mechanisms and toxin species[17]. Some mycotoxins affect immune systems and enhance the sensitivity to different pathogens consequently, contribute to the occurrence of the infectious diseases[18]. Children and infants are more sensitive to mycotoxins compared to the adults, since they have higher metabolic rates, lower body weights, lower ability for detoxification and incomplete development of different organs and tissues, especially the central nervous system[19-20]. Among the most known and toxicological common mycotoxins that have wide public health importance are aflatoxins (AFs), ochratoxins (OTs), ZEN, fumonisins (FBs), patulin (PAT), trichothecenes (TRCs) and their derivatives[21]. The major fungi and their related mycotoxins are summarized in Table 1 are considered of primary significance for children[3,19-20]. Nevertheless, there are gaps in the data about the co-occurrence patterns of parent mycotoxins, metabolites, and their modified forms; consequently, no toxicological data were found to indicate the health risks associated with this co-occurrence[4]. Furthermore, because a single fungus species may produce many mycotoxins and fungi from different genera can infect the same crops, the coexistence of multiple mycotoxins and simultaneous exposure in the overall diet is more possible. Exposure to a combination of mycotoxins can have the same or different harmful effects, therefore this should be addressed when calculating the cumulative risk of co-occurring mycotoxins[22]. Table 2 provides an overview of the prevalence, data sources, and presence of multiple mycotoxins in various food items. This review focuses on major mycotoxins and the key modified fusariotoxins that represent a health risk to children as well as the risk assessment, risk characterization and the challenges in risk characterization of multiple mycotoxins in children food.

2. Major mycotoxins that affect child health

2.1 AFs

AFs are mainly elaborated by *Aspergillus* spp. mainly *A. parasiticus*, *A. flavus*, and rare *A. nomius*[23]. They are commonly contaminated grains (rice, maize, wheat, sorghum and barley) and nuts (peanuts, almonds, walnuts, Brazil nuts and pistachios) which are usually used in the manufacture of children's food[24]. AFs are known as the most relevant mycotoxins worldwide for their widespread occurrence, their high toxicity and their economic implications[25]. Moreover, AFs are considered a problem with processed foods, especially roasted nuts and bakery products because they are very stable and resistant to quite heavy processing like roasting, baking, extrusion and cooking[26]. AFs have several biological effects, including the carcinogenicity, mutagenicity, teratogenicity, immunosuppressive effects in laboratory

Table 1
Fungi and mycotoxins of primary importance to children's health[20].

Fungus	Mycotoxins	Associated health effects	Food commonly contaminated
A. flavus	AFs	Vomiting, hepatitis	All grains, dried fruit
A. parasiticus		Liver cancer	
F. verticillioides	FBs	Vomiting	
F. proliferatum		Neural tube defects	Maize
A. ochraceus		Esophageal cancer	
	TRCs, nonmacrocyclic		
F. culmorum	DON	Vomiting	
F. graminearum			
F. cerealis			Cereals (wheat, barley, maize, rice)
F. sporotrichiodes	T-2 toxin	Alimentary toxic aleukia	
		Vomiting, hemorrhage	
	TRCs, macrocyclic		
Stachybotrys chartarum	Satratoxins	Protein synthesis inhibition	
Trichoderma viridi		Hemorrhage	Cereals (wheat, barley, maize, rice)
Trichothecium roseum			
A. ochraceus	OTs	Balkan nephropathy	
A. niger		Renal cancer	Coffee, cocoa
A. alliaceus			
P. verrucosum			
P. expansum	PAT	Vomiting, cancer (suspect)	Apple
F. graminearum	ZEN	Estrogenic effects, cervical cancer (suspect)	Maize
Claviceps purpurea	Ergot alkaloids	Ergotism	

Table 2
Presence of multiple parent mycotoxins in food items-literature summary[156].

Co-occurring mycotoxins	Food matrix	Percent of incidence of multiple contamination (%)
FBs, DON, ZEN, nivalenol (NIV), T-2/HT-2	Maize, wheat, barley, oats, etc.	54.9
Ochratoxin A (OTA), ZEN, deoxynivalenol (DON)	Cereals	75
ZEN, DON, NIV	Wheat	74
DON	Wheat	12
NIV	Market foods	49
FBs, DON, NIV, ZEN	Commercial cereals	3 for quadruple, 22 for triple, 30 for double
DON + AFs AFs + FBs + DON AFs + FBs + ZEN + DON	Maize	100 for double, 87 for triple and more
AFs + FBs + ZEN + DON T-2, citrinin, DON	Market cereals	50 for triple and more
DON, ZEN	Cereals	42

animals[8,27]. AFs were reported to play an important role in childhood stunting at the age of 2 years[28].

They induce oxidative stress and decrease the enzymatic activities and non-enzymatic antioxidant agents[29-30]. In spite of the fact that 20 AFs were identified, the main 4 AFs: B_1, B_2, G_1 and G_2 are being the most significant and directly contaminated diets. AFB_1 display acute and/or chronic toxicity, including carcinogenic, mutagenic (Fig. 1), immunosuppressive and teratogenic effects on different organisms[31], and it was classified as Group 1 human carcinogen by the International Agency for Research on Cancer (IARC) [32]. However, the modified form AFM_1 was classified in Group 2B[33].

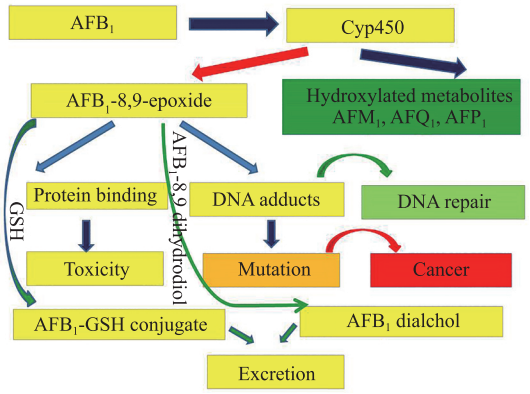

Fig. 1 Summary of the toxicity and carcinogenicity of AFB_1. GSH, glutathione.

In general, the early symptoms of AFB_1-induced hepatotoxicity in human are anorexia, malaise and low-grade fever and it can progress with vomiting, abdominal pain and even may be associated with diarrhea[20,27]. It was reported that AFB_1 caused an epidemic affect the Eastern province in Kenya resulting in more than 125 death cases during 2004 – 2005[34]. There are several evidences that AFB_1 cause the degeneration of fats of the encephalopathy and viscera in the children which is known as Reye's syndrome. The symptoms including sore throat, fever, vomiting, coughing, earache, rhinorrhea, convulsions, disturbances in respiratory cadence beside the muscle tone loss[35].

AFB_1 may contribute to growth stunting during early childhood and it was suggested by Khlangwis et al.[36] that AFB_1 together with other mycotoxins are playing a role in the development of edema in the malnourished people beside the pathogenesis of the kwashiorkor frequent condition in African children. Generally, it was reported that two main children's diseases with undefined etiology were linked to the exposure to AFB_1 in contaminated foods: Reye's syndrome and kwashiorkor. The kwashiorkor was reported to be geographically and is associated with the distribution and occurrence of AFB_1 in food seasonally. Moreover, malnutrition can affect the metabolism of AFs leading to their detection in children with Reye's syndrome patients in New Zealand, Thailand, USA and the former Czechoslovakia[37].

The exposure of pregnant (Fig. 2) or lactating (Fig. 3) women to AFB_1 might induce adverse pregnancy outcomes *via* 3 main pathways: i) induction of environmental dysfunction in the intestine, including impaired barrier function, intestinal inflammation and systemic immune activation; ii) up-regulate the pro-inflammatory cytokines and down regulation of anti-inflammatory cytokines and iii) the potential toxic effects on the maternal and fetal organs after the absorption of the toxins cause the systemic immune activation and impaired the fetal and placental development[38-39]. The cross-sectional studies performed in humans suggested that exposure to AFs impairs the intrauterine growth of the fetus and in some cases, it causes pregnancy loss. In spite of the rarely conclusive studies on humans, there are some evidences from the *in vivo* or *in vitro* studies indicating that exposure to AFB_1 or its metabolite form (AFM_1) sometimes cause intestinal damage[40], anemia and increase the pro-inflammatory cytokines. However, the effect of AFB_1 on the placenta is poorly studied; the ability of the placenta to metabolize and transport AFB_1 should be considered[41].

In-utero exposure to AFB_1 can be detected by assaying the maternal venous peripheral blood and cord blood for AFB_1-lysine adducts. A previous report indicated that there was a correlation between the levels of adducts in the maternal venous and matched cord sera in the Gambia. This report concluded that the maternal food intake is an important determinant factor of the carcinogenicity and fetal damage. Turner et al.[42] reported that no positive correlations between the levels of AFB_1-albumin adduct in the mother's blood and the weight and the height gain during the first year of life in Gambian children. The analysis of 64 samples of cord blood from the pregnant women in Sierra Leone showed the occurrence of AFs in 58% of the samples, although no relationship was observed between AFB_1 in the maternal venous and cord blood[43]. Exposure to AFB_1 can reduce the adequacy of immunization in the children with the resultant increase the susceptibility to infections[44]. Additionally, it exerts synergistic effects with hepatitis B virus resulting in

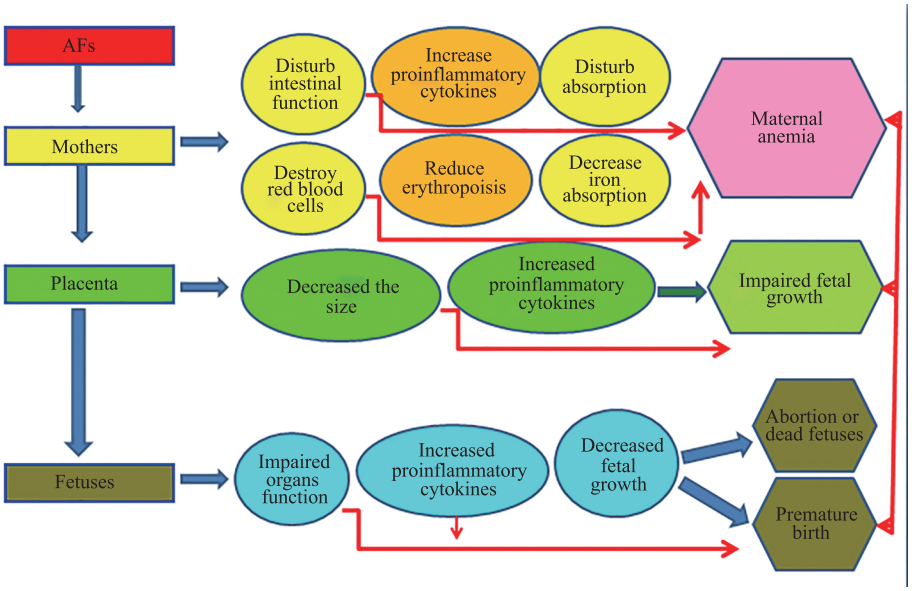

Fig. 2 Summary of the direct and indirect effect of AFs exposure on maternal, placenta and fetal health.

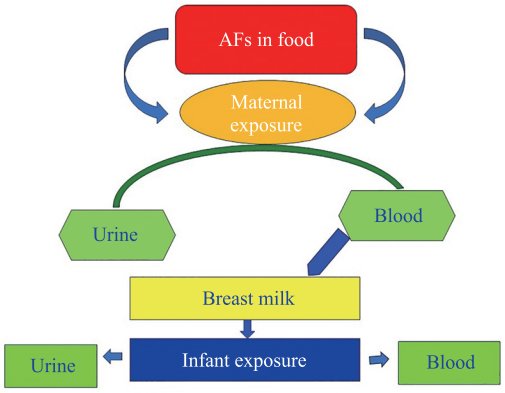

Fig. 3 Exposure of maternal and infants' to AFs in contaminated food.

hepatocelular carcinoma through the integration of x gene of hepatitis B virus, affects methylation of genes, induces DNA mutations and interferes with the nucleotide excision repair[45]. Furthermore, El-Sayed et al.[14] reported that the frequency of AFs positive urine and blood samples of African children was high especially during the summer. In Gambian children, the levels of AFB_1-albumin adduct in the winter were recorded twice as low as in the summer[46]. Additionally, it was shown that environmental enteropathy and dietary AFs exposure are important variables influencing childhood stunting[47].

2.2 OTA

OTA is produced by *Aspergillus ochraceus* and *Penicillium verrucosum* in the temperate climates, the tropical and warm countries[48], and it was discovered after AFs. OTA was classified by IARC[49] as group 2B carcinogen which mean probable carcinogen to human. OTA and its modified metabolites (ochratoxin α, 4-hydroxyochratoxin A) were reported to be found in breast milk and affect the function of the kidney and develop urinary tumors in young children and infants[50]. High levels of OTA (200−337 ng/mL) were found in 35% of breast milk samples collected from Sierra Leone[42]. Wangikar et al.[51] reported that simultaneous prenatal exposure to AFB_1 and OTA in rabbits caused different gross, visceral and skeletal anomalies. Additionally, new manifestations mainly syndactyly and gastroschisis were found to accompany with incidence of cardiac defects in the fetuses following co-treatment with AFB_1 and OTA. However, long-term exposure to OTA, particularly during the period of organogenesis resulted in mutations and histopathological alterations in fetuses[51].

In spite of these toxic potential of OTA, the suggested daily intake and the regulations of this mycotoxin may differ from country to another due to the eating habits and the consumption of contaminated foods. In Italy, Meucci et al.[52] found that 72% of 185 samples of the milk-based infant formula were positive for OTA with a level between 35.1 and 689.5 ng/L. Moreover, OTA level was detected in pasta prepared for children in the range of 0.09−0.52 mg/kg, which is considered below the European limit[53]. These authors reported that 51.85% of the samples contained OTA below 0.2 mg/kg and 40.74% were contaminated by OTA at a level of 0.2−0.5 mg/kg. The European Regulation 1881/2006 fixed the limits of 0.5 mg/kg OTA in the processed cereal-based foods intended for baby foods, infants and young children[54]. This mycotoxin is found to be a contaminant in different agricultural crops such as cocoa, cereals coffee and grapes[55].

OTA was reported to induce a teratogenic effect[56], immunosuppressive properties and apoptosis[57], hepatonephrotoxic[58] and the enhancement of oxidative stress[32]. In-utero transfer of OTA was reported in rats and mice[58]; however, in human, the mechanism of transfer across the placenta is not totally confirmed. Woo et al.[59] reported that reduced metabolism, the presence of transporters and the low ability of fetus elimination are responsible for the bioaccumulation of OTA in fetal circulation. Previously, Gökmen et al.[60] reported that the outbreaks of fatal chronic renal disease known as Balkan Endemic Nephropathy were widespread in South Eastern European countries. This disease was associated with the exposure to OTA and the patients have higher levels of OTA in their blood than of those unaffected people[61]. WHO reported that the exposure to OTA was associated with the formation of tumors in the upper urinary tract[62]. Additionally, the exposure of fetuses to OTA was also documented

as the active placental transfer sometimes occur in the pregnant women and it was reported that the levels of OTA in the umbilical cord blood were twice the umbilical cord blood of maternal blood at delivery time[63].

The mechanisms suggested for the adverse health effects of OTA including the genotoxicity[64], the inhibition of histone acetyltransferase and the cytoskeleton destabilization. Moreover, OTA suppresses nuclear factor erythroid 2-like (Nrf2), the responsible for the major oxidative stress response and regulates the transcription of the genes implied into the reduction of reactive oxygen species (ROS), glutathione synthesis and quinines[65]. Additionally, the exposure to OTA was reported to be related to the congenital defects of fetus in rats[66] but its potential malformation and the mechanism of action by which OTA induced its teratogenicity in humans are not understood.

2.3 FBs

FBs are mycotoxins produced by the *Fusarium* species, mostly *F. proliferatum* and *F. verticillioides*[67] and have a chemical structural similar to sphinganine which is the backbone of sphingolipids. Hydrolyzed fumonisins (HFB) are the modified form of FBs which is resulting from the alkali treatment of FBs[68]. FBs contaminate corn and sorghum, which are the main sources of the exposure to FBs in human[69]. Children and infants who consume maize-based foods are considered at high risk of FBs and there is a strong association between the exposure of FBs in maize and the growth retardation among Tanzanian infants who exposed to FBs at a concentration exceeded the provisional maximum tolerable daily intake (PMTDI) of 2 mg/kg bw[70]. Shirima et al.[71] detected urinary FB_1 in 96% of Tanzanian children in concentrations of 82.8, 211.7 and 327.2 in Kikelelwa, Nyabula and Kigwa, respectively. Assessment of FBs in different age groups in Japan revealed that children and toddlers were the highest exposed groups, although the PMTDI percentage was less than 10%[72]. However, in the Netherlands, FBs exposure recorded 28 ng/(kg·day), which was below the corresponding tolerable daily intake (TDI)[73].

Several reports from South Africa and China suggested that this mycotoxin interfere with the uptake of cellular folate[74]. According to Huffman et al.[75], there are 28 members of FBs were isolated and characterized; however, FB_1 was reported to be the most widespread toxin and was classified by the IARC[49] as a Group 2B carcinogen which mean possibly carcinogenic in humans. This mycotoxin is resistant to the conditions that used in the processing of food; consequently, it poses a great health hazard to the human and the animal. It was suggested that the mechanism of FB_1-induced its toxicity is through the inhibition of an enzyme called ceramide synthase. This enzyme is responsible for the conversion of sphingoid bases to the sphingolipids complex[76]. On the other hand, the epidemiological reports suggest that there is a connection between consumption of corn contaminated by FB_1 and the esophageal cancer in human in Iran, China, Zimbabwe, Kenya, Italy, Brazil and South East USA[77]. Moreover, several epidemiologists reported that the exposure to FB_1 is considered a causative factor for development of neural tube defect in newborn babies occurred in the Southern area in Texas state, USA[78].

Previous reports suggested that FB_1 induced DNA damage through the histone demethylation and hypomethylation in human hepatocytes resulting in the instability of chromatin; consequently, induced liver tumor formation[8,79]. Moreover, Hassan et al.[80] reported that the mechanism of cytotoxicity of FB_1 is mainly due to the disruption of sphingolipid metabolism. The principal mechanisms of FB_1-initiate or promote cancer formation was suggested by Abdel-Wahhab et al.[8] who stated that FB_1 induced lipid peroxidation and consequently destroy the cell membrane and change its morphology, promote the fragmentation of DNA and differentiation of cell, disturbs the cell function and apoptosis[81].

2.4 PAT

PAT is a mycotoxin produced by *Pencillium* and *Aspergillus, Byssochlamys* species, although *P. expansum* is the most known fungal species to produce PAT[82]. PAT is a common contaminate to grains, moldy fruits and other food; however, the primary source is apple and apple products[83]. It can be found in a concentration reached several mg/kg in some infected apples and a concentration of $10-170 \times 10^{-9}$ mg/kg was reported in commercial apple food prepared for children and apple juice[84]. Children and young infants usually consume large amounts of the fruit juices thus they are susceptible to the risk of PAT[85]. The maximum limit of PAT was suggested by EC Regulation 1881/2006 to be 50 μg/kg for the fruit juices and the other products made from apples; however, the regulation was 25 μg/kg in solid apple products prepared for young children. On the other hand, 10 μg/kg was suggested in the cereals and apple products prepared for infants.

The toxicity of PAT was reported to involve the cellular glutathione level as well as the mitochondrial function beside its direct or indirect effect on the plasma membrane[85]. PAT was reported to inhibit the synthesis of DNA and destroy the body immunity[86]. Although the IARC has not identified any carcinogenic effect of PAT on humans, there is some indication that it can cause cancer in laboratory animals, since it has been shown to promote mutagenicity in rats and mice[87]. PAT also caused acute symptoms in several organs, such as kidney function changes, lung ulceration and congestion, convulsions, intestinal bleeding, edema, vomiting, and inflammation[88]. The chronic health hazards of PAT are associated with neurotoxicity, immunosuppressive, genotoxicity, teratogenicity and carcinogenic effects[89]. Moreover, it was suggested that PAT may induce damage in the structure of DNA through the cross-linking resulting in the formation of micronucleus[90]. de Melo et al.[91] investigated the genotoxic mechanism of PAT through the determination of GSH levels and the thiobarbituric acid-reactive species (TBARS) and they developed a relationship between prooxidant and genotoxic properties of PAT. Moreover, these authors confirmed a positive correlation between the depletion of GSH by PAT and DNA damage. On the other hand, the production of ROS is increased by the interaction between PAT and sulfhydryl groups, thus these ROS play an important role in the mechanism of apoptosis[92].

The exposure of infants to PAT was reported to be greater than the age-adjusted TDI; consequently, it induced risks to the gastrointestinal tract, toxicity to the kidney, neurotoxicity and genotoxicity resulting in the negative impact of this mycotoxin in the infant's development[93]. A propagation of diarrhea was spread in the Swedish children after the consumption of PAT-contaminated fruits. It was reported that PAT increases the permeability across the

monolayers of intestinal Caco-2. However, PAT was proposed as an effective drug for colon cancer and was applied as *in vitro* anticancer therapy due to the cytotoxic effects against colon cancer cell lines[94].

2.5 ZEN

ZEN, the estrogenic mycotoxin, is produced mainly by *F. graminearum*[95]. It is a known soil fungi found in the temperate and all warm countries. This mycotoxin is a regular contaminant for cereal crops all over the world, including corn, oats, barley, wheat, rice, sorghum, barley and sesame[96]. ZEN also can contaminate cereals directly as well as indirect contaminate certain products such as meat, eggs and milk derived from animals fed contaminated feed[20,97]. Based on the level of ZEN in the main food for human, it was found that the average daily intake in adults was 0.8−29 ng/(kg · day); however, a higher average was reported in infants and young children ranged from 6−55 ng/(kg · day) suggesting that these categories are at risk[98]. There are limited evidences about the carcinogenic effects of ZEN in laboratory animals so, the IARC[49] classified ZEN in Group 3, the agent that not classifiable as to its carcinogenicity in humans. The current reports speculate that this mycotoxin is associated with early puberty onset and may increase the risk of the cervical cancer[99]. On the other hand, previous report suggested that the reproductive system is the main system affected by ZEN because of its effects on the function and structure of the respective; consequently, leading to the hyperestrogenism symptoms including the enlargement of uterus vulva swelling and enlargement of breasts in young children[20].

The structure of ZEN is similar to the estrogen, so it is competing with 17 β-estradiol to bind the receptors of cytosolic estrogen[100] causing reproductive problems and infertility in female[101] and male[102]. The signs of clinical poisoning of ZEN are related to its role in hyper stimulating of the estrogen-dependent cells[103]. Consequently, the mechanisms of toxicity of ZEN received extensive interest because of the risk of its toxicity in animals and human as well as its economic[104]. A lot of anecdotal studies of the pestilence of the precocious of puberty suggested that this phenomenon is due to using zeranol as anabolic estrogen supplements in animal feeds[105]. In this concern, ZEN level was assessed in some clinical precocious puberty investigations in Italy and the results showed that the ZEN-positive young girls were proportionally heavier and taller than the ZEN-negative girls[106]. In spite of the enlargements in the breast in boys and girls and the precocious puberty in girls exposed to ZEN, Wolff et al.[107] reported that ZEN delay the development of breasts and uterine in girls at the age of 9−10 years. Furthermore, Christian et al.[108] concluded that the girls who were positive to ZEN tended to become shorter and did not reach the onset the development of their breast.

2.6 TRCs

TRCs are considered the biggest family of mycotoxins produced mainly by *Fusarium* species, but they can be also produced by other genera such as *Trichoderma*, *Trichothecium*, *Stachybotrys* and *Myrothecium*[109]. These mycotoxins are potent inhibitors for protein, which is considered the basic mechanism of toxicity beside that, they are able to produce several effects in the experimental animal[3]. According to their chemical structures, they are classified based on the ring system designated 12,13-epoxytrichothec-9-ene with many possible functionality groups[110]. The most serious members in this group of mycotoxins are DON and T-toxin.

This group of mycotoxins induced severe toxicological effects in animal and humans, such as hematological abnormality, gastroenteritis, emesis and anorexia[3,111]. The immune system in children and young infants is very sensitive to TRCs and the low dose exposure can induce a rapid and transient up-regulation of the proinflammatory cytokines resulting in immune stimulation. Whereas, the high level of TRCs exposure induces apoptosis in the lymphoid tissues, leading to immunosuppression[3,111].

2.6.1 DON

DON belongs to type B TRC produced by the *Fusarium culmorum, F. crookwellense* and *F. graminearum*[112]. For human exposure, grains and grain-based products were main sources, whereas in farm and companion animals, cereal grains, cereal by-products and forage maize contributed most[113]. Corn, wheat and barley are the most infected crops by DON and bread, rolls, pasta and fine bakery wares are the main sources for DON exposure[113]. In 2015, a study undertaken in several European nations, including Norway, Italy, and the United Kingdom, found that the urine concentration of DON was 2.3−2.6 times greater in children than in adults[114]. This high concentration of urinary DON may be due to the immature liver function and the lower expression of uridine 5′-diphospho-glucuronosyltransferase (UGT)[115]. In animal experiments, ingestion of DON-contaminated food causes severe health risks such as disruptions in cell signaling differentiation, anorexia, vomiting, disturbances in body immunity and neuroendocrine system function, as well as gastrointestinal homeostasis due to impaired macromolecule synthesis[116].

In children, the ingestion of food heavily contaminated with DON induces vomiting within a few hours. During the period of 1961−1985, an outbreak of vomiting disease in China was attributed to the consumption of food prepared from DON contaminated grains[117]. Moreover, in the year 1978, more than 100 Indian persons were ill after the consumption of wheat contaminated with DON and other TRC. However, during 1997 and 1998, about 1 700 school children suffer from the headache, abdominal cramps and nausea, vomiting in the United States after the consumption of burritos diets[118]. Thus, DON appeared as burritos contaminant resulting in the appearance of this outbreak; however, it subsided after 24 h of its beginning[118]. It was reported that the major toxic effects of DON are the suppression of the synthesis of protein[119]. Nevertheless, the toxicity may depend on the dose, route and the duration of exposure and the purity of the toxin[120]. According to IARC[49], DON was not classified as a human carcinogenic (Group 3); however, it was suggested to be undesirable substance in animal feed be the European Commission[121].

The ingestion of DON was hypothesized that it generates free radicals resulting in the harm of cell membranes and the damage of DNA in rats[121]. Consequently, the oxidative stress should be considered as the major factor in DON toxicity. It was reported that DON reduces the viability of cell, damage the cell membrane, induces chromosomal aberration and DNA damage and increases the peroxidation of lipid and ROS production in human lymphocytes[122]. Additionally, it inhibits the synthesis of RNA, DNA and protein

through modifying cell membranes[120]. Pestka et al.[123] indicated that concentrations of DON as low as 5 mg/kg stimulated the immune system; however, the high concentrations suppressed the immune responses. Human consumption of a single DON-contaminated meal caused gastroenteritis with vomiting[124]. A large outbreak was reported in affected children consumed DON-contaminated bread in the Kashmir Valley (India) and the symptoms appeared within 15 min to 1 h. These symptoms included irritated throat and secondary infections of the upper respiratory tract[125].

2.6.2 T-2 toxin

T-2 toxin is the largest class of trichothecene mycotoxin and is produced by *F. sporotrichioides*[3,126], although there are a few strains produce similar mycotoxin known as HT-2 toxin. This mycotoxin is produced mainly on corn, barley, wheat, soybeans and millet[125]. Several reports worldwide have been suggested an association of T-2 toxin with the agricultural damage and its toxicity in animals. Prieto et al.[127] reported that T-2 toxin was a common contaminant in cereal samples from EU member states and these members are considered at risk of dietary exposure to this *Fusarium* toxin. Several reports showed that this mycotoxin can cross the placenta and induces severe developmental and reproductive toxicities. T-2 toxin was reported to be associated with leucopenia, cell depletion in the lymphoid organs and the inhibition of erythropoiesis in the bone marrow and spleen[128]. Moreover, exposure to this toxin resulted in the reduction of steroidogenesis and alters the expression of steroidogenic gene, suggesting its strong action of the endocrine activity[68]. T-2 toxin also regulates the secretion of steroid hormone by the ovarian granulosa cells *via* cAMP-PKA pathway[129] and it stimulates the secretion of GnRH in the hypothalamus neuronal cell line exposed to low dose[130]. Taken together, it is clear that T-2 toxin has potential effects on the development and pubertal onset.

3. Co-occurrence of mycotoxins in infant and children cereal-based foods

Cereals, a common constituent in many child-oriented items such as instant meals, breakfast cereals, and snacks, are especially susceptible to fungal contamination during cultivation, storage, or processing[131]. de Sá et al.[132] conducted a detailed investigation was undertaken on 148 processed cereal-based goods, which included breakfast cereals (n = 39), cereal bars (n = 25), cookies (n = 32), baby formulae (n = 25), and snacks (n = 27). They reported that all positive samples displayed AFB_1, OTA and ZEN concentrations far exceeding the EU regulatory threshold (AFB_1 exceeds it by more than 5 000 times in one case) established for such processed cereal-based products intended for infants and children, set at 0.10, 0.50 and 50 μg/kg, respectively[133]. In another study in Canada, 580 out of 954 cereal-based products samples were contaminated with OTA (61%), with a maximum concentration value of 6.95 μg/kg[134], lower than the maximum found in this study (11.6 μg/kg in a white label sample). In Morocco, Mahnine et al.[135] found 228 μg/kg of FBs in breakfast cereal samples, lower than de Sá et al.[132] who found 295.4 μg/kg. The concentration levels in citrinin (CIT) range from 1.2 to 4 415 μg/kg[136-137]; enniatin A1 (ENNA1) reported values that ranged from 0.5 to 688 000 μg/kg[136,138]; and enniatin B (ENNB) displayed values that ranged from 0.1 to 110 900 μg/kg[136,139]; beauvericin (BEA) was detected from less than 0.10 μg/kg[140] to a maximum value of 5 300 μg/kg[138].

All these last studies on emerging mycotoxins have shown maximum values significantly higher than those reported by de Sá et al.[132] who found that emerging mycotoxins were the predominant contaminants across most brand types. Specifically, FB_1 and BEA exhibited the highest prevalence at 33% each, followed by ENNB (15%) and FB_2 (4%). In a Turkish survey, FBs were found in 27 of 42 samples of maize snacks, with concentrations for FB_1 and FB_2 ranging from 18 to 4 313 μg/kg and 20 to 742 μg/kg, respectively[140]. According to de Sá et al.[141], ENNB was the most often discovered substance in this matrix, followed by BEA. The values ranged from 0.000 4 μg/kg[142] to 240 μg/kg[143] for ENNB and 0.1 μg/kg[144] to 31 μg/kg[142] for BEA.

In the USA, a review of 64 infant food items revealed that 5% were contaminated with AFB_1, 22% with AFB_2, and 14% with AFG_2, with amounts ranging from 2.4−5.9, 1.1−5.0, and 0.4−1.7 μg/kg, respectively[145]. According to this study, FBs were detected in 10% of the contaminated samples. FB_1 was found in one sample at a value of 6.2 μg/kg, while FB_2 was found in 5 samples at quantities ranging from 1.5 μg/kg to 15.8 μg/kg. Additionally, in Burkina Faso, only 3 out of 199 baby formula samples were found to be contaminated with FBs, with concentration levels ranging from < 5.0 μg/kg to 672.9 μg/kg[146]. In an Iranian survey, 93.4% of 30 cookie samples tested positive for FBs contamination, with levels ranging from 0.0−2 300 μg/kg[147]. The greatest result is 500 times greater than ours (FB_1 = 4.6 μg/kg) and almost 10 times higher than the EC's limit. Only ENNB was detected in cookies, with a maximum concentration lower than studies from the Netherlands (15−17 μg/kg) [131], Romania (43% of 23 samples contaminated, maximum value 9.7 μg/kg) [148], and Spain (100% contamination, values ranging from 6.66 to 39.88 μg/kg)[149].

In 2011, the EFSA analyzed 420 food samples designed for newborns and young children, including ready-to-eat meals and cereal-based foods. Infant formulas were the most common category, notably in the sub-group "Cereal-based food for infants and young children" (280 samples-67%). Only 4% of samples tested positive, with a highest result of 20 μg/kg[150], within the EC's 20 μg/kg limit for infant meals. The study evaluated 1 377, 541, and 121 breakfast cereals, biscuits (cookies), and snacks with positive percentages of 8.7%, 33%, and 16%, respectively, and reported maximum levels of 172, 98, and 50 μg/kg, respectively, exceeding the established maximum values for breakfast cereals and biscuits (50 μg/kg). Several reports suggest that newborns and children may be exposed to various mycotoxins[141,151-152]. As a result, there is increasing worry about the health consequences associated with such exposure[153-154]. Recent reviews have emphasized the global prevalence of mycotoxin co-occurrence, notably among AFs, FBs, OTA, ZEN, CIT, and ENNs[14,141]. These reviews underscore the need for more thorough toxicity studies that evaluate simultaneous exposure to numerous mycotoxins, especially in babies and children, to assess potential synergistic and additive effects and their implications for public health.

4. Modified mycotoxins

Modified mycotoxins include masked and bonded mycotoxins, as well as mycotoxin metabolites. The term "masked" refers to the fact that they were previously undetectable during normal feed and food

analysis, and there were no maximum limits in force, therefore they were only identified on rare occasions during the study of original forms of mycotoxins. Modified mycotoxins can be described as metabolites of the original mycotoxins produced by plant-specific enzymes in response to mold infestation, or they can be created by molds themselves. They may also be antibiotic-derived as a result of a chemical interaction between the original toxin and the matrix during the processing of food. Some study has also shown that modified mycotoxins are formed during metabolic processes in animals and humans, but these conjugates are exceedingly unlikely to have a function in feed or food and hence are not classified as masked mycotoxins[155]. The first modified mycotoxin found before they were known as "masked mycotoxins" was AFM_1 (excreted in milk), a metabolite of AFB_1 generated by hydroxylation in animals who ingest mycotoxin-contaminated feed[156] .

Following this finding, another ZEN-derived chemical was identified in the 1980s. However, the discovery of various types of mycotoxins has only increased in recent years[157]. Because Fusarium infestations often occur in the field, their mycotoxins are the most common candidates for conjugation with sugars, amino acids, or sulfate groups in the conversion process carried out by host plants. As a result, the most frequently modified mycotoxins are fusariotoxins, which are linked glucose-conjugates of DON (DON3G), ZEN (ZEN14G, zearalenol (ZEL) 14G, ZEL14G), ZEN-14 sulfate (ZEN14S), nivalenol (NIV3G), fumonisin esters, T-2/HT-2 (T-2 and HT-2), OTA with ochratoxin α; 4*S*-hydroxyochratoxin A; 4*R*-hydroxyochratoxin A; hydroxyochratoxin A-*β*-glucoside; OTA methyl ester; ochratoxin α amide; 14-decarboxyochratoxin A; OTA mono- and disaccharide esters; and a few others[158] (Table 2). Plants have been shown to alter additional toxins, including OTA, PAT, and destruxins[159]. The most modified forms of mycotoxins detected in the naturally contaminated grains used in baby foods are presented in Table 3.

Although the toxic effects of different modified mycotoxin in children are still unknown, several reports suggested a potential risk due to the release of the parent mycotoxins through the hydrolysis process during the processing of food or the digestion. Consequently, the Panel on Contaminants in the Food Chain of the EFSA (European Food Safety Authority) decided that modified mycotoxins should be considered as the same hazards of their parent mycotoxins during the risk assessment[160]. Therefore, the potential risk to the consumers is due to the possible hydrolysis forms of the modified mycotoxins to their toxic free parent forms during the mammalian digestion[161].

4.1 Modified FBs

FB_1 can be modified to other derivatives by alkali to HFB during the chemical treatments[162]. Although, the toxicity of HFB is not well understood, several reports showed that the HFB is less toxic than the parent FB_1[163]. Dall'Asta et al.[164] reported that FB_1 can be modified also by other routes such as the formation of covalent bonds between the side chains of tricarballylic acid of FBs and hydroxyl groups in the sugar or the sulfidric or amino groups in the proteinsn[165]. Moreover, during thermal processing, bonds between the amine group of FB_1 and the reducing sugar molecules of food matrix can be formed resulting in the formation of *N*-(carboxymethyl) FB_1[162]. Although the toxicity of *N*-substituted FBs is not fully understood, some reports indicated the reduction of its toxic effects due to the blocking of amino groups which are bounded to the sugar molecule. On the other hand, *N*-Acyl HFB_1 was reported to induce more toxicity to the cells compared to HFB_1[166]. Although the processing methods play an important role in the content of FB_1 in the final product, some thermally processed food product prepared for infants and children, such as corn flakes was reported to contain bound FB_1 and the thermally and alkali processed food such as snacks was reported to have low contamination levels due to the binding between FB_1 and the fatty acids and its release in cooking oil[21].

4.2 Modified ZEN

ZEN is transformed into its modified form *α*-ZEL during the metabolism in the digestive tract of humans and animals. This derivative showed an estrogenic effect 3−4 times greater than the original ZEN[167]. Although several hydrolysis forms of ZEN such as (ZEN-14G, *α*-ZEL-14G and *β*-ZEL-14G) are synthesis by human fecal microbiota. The conversion of these modified forms to the parent ZEN by intestinal microbiota and serum albumin also suggested the ability of hydrolyzation of ZEN-14G to ZEN as well as the biotransformation to *α*-ZEL and *β*-ZEL[168]. Although the liver is the main organ responsible for ZEN bioactivation via the metabolism processes in several species of animals, the systemic circulation is considered responsible for the high levels of ZEN[169]. The modified ZEN is reconverted into the parent ZEN during the digestion in the stomach or the intestine.

Table 3
Most often identified modified mycotoxins[158].

Parent mycotoxin	Modified mycotoxin	Food matrix
DON	DON3G; DON 3-*D*-glucopyranoside; DON 3-acetyl; DON 15-acetyl; DON glutathione (DON-GSH); sulfo-conjugates	Corn, wheat, oats, rye, barley, beer, breakfast cereals and snacks
ZEN	ZEN14G; ZEN4-*D*-glucopyranoside; ZEA-14-*β*-*D*-glucopyranoside (ZEN14*β*DG); ZEN14*β*DGp; ZEN2,4-*O*-diglucoside; ZEN14S; palmitoyl ZEN	Wheat bran, corn-based food (grain bread, bakery products, breakfast cereals); vegetable oils
NIV	NIV3G; NIV 15-acetyldeoxy; NIV 3-acetyldeoxy; NIV4-acetyl; NIV 4,7-dideoxy	Wheat and corn
FBs	*N*-acyl-HFB_1, HFB_1	Corn
T-2/HT-2	T-2-3-glucoside; HT-2-3-glucoside	Oats and wheat
Neosolaniol (NEO)	Neosolaniol-glucoside (NEO-G)	Corn
Diacetoxyscirpenol (DAS)	Diacetoxyscirpenol-glucoside (DAS-G)	Corn
Fusarenon-X (FUSX)	Fusarenon-X-glucoside (FUSX-G)	Wheat

4.3 Modified TRCs

Although more than 200 compounds of TRCs were discovered and their chemical structure and biosynthesis pathways were identified[170], only DON and T-2 toxins were the most studied members due to their abundant and potential toxicity. These parent mycotoxins undergo several transformations by the fungi, the plant mechanisms, the microorganisms, during the digestion process or even during the food processing[171].

4.3.1 Modified DON

The co-occurrence of the free parent and modified DON forms, DON-3-glucoside, 3-acetyldeoxynivalenol (3-ADON) and 15-acetyldeoxynivalenol (15-ADON) are well documented in the raw wheat. However, the levels of DON-3-glucoside were variable and their concentrations may be considered high even they are similar to the parent DON in the processed cereals[172]. The compounds 15-ADON and 3-ADON were detected in the cereals and cereals-based products, but their frequently was lower than the DON-3-glucoside[172]. Heyndrickx et al.[173], and Vidal et al.[174] reported that the mean dietary exposure to these forms of DON is higher than the group-TDI (group tolerable daily intake) which was set as 1 μg/(kg·day) (DON, DON-3-glucoside, 3-ADON and 15-ADON) in toddlers, infants and other children, adolescents and adults in Europe resulting in a potential health concern[112]. The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) has considered an additional uncertainty factor of three and established the health-based guidance values (HBGV) of 300 ng/(kg·day) for children[175].

4.3.2 Modified T-2 toxin

T-2 toxin may be biotranformed into several modified forms including HT2 toxin-3-glucoside; T-2 toxin-α-glucoside; T-2 toxin-β-glucoside; 15-acetyl-T2-tetraol-glucoside; hydroxy-HT2-glucoside; hydroxy-HT2-malonyl-glucoside; T2-triolglucoside; dehydro-HT2-glucoside; HT2-diglucoside; HT2-malonyl-glucoside; 3-acetyl-HT2; 3-acetyl-T2; feruloyl-T2; HT2-sulfate[130]. The parent T-2 and its modified forms are well known as an inhibitor for the synthesis of protein and suppressor of the function of mitochondria as well as its cytotoxic and immunosuppressive effects *in vivo* and *in vitro*[176] and can induce severe toxicity to mucous membranes and skin.

5. Risk assessment

Despite numerous studies conducted over the last few decades on the global prevalence of mycotoxins, limited data exists regarding population exposure to these chemical hazards, particularly the emerging ones. Regarding each processed cereal-based matrix, infant formulas emerged as the primary contributor to the estimated daily intake of mycotoxins by Portuguese infants and children, exhibiting the highest values for FB_1, AFG_2, FB_2, and ENNB, followed by breakfast cereals. Similar results were found by Assunção et al.[151] reporting breakfast cereals and infant flours as the ones with the highest contribution to the estimated daily intakes. Regarding the risk assessment, de Sá et al.[132] revealed that several hazard quotient (HQ) values (higher values are mostly FBs and ZEN) and all hazard index (HI) values exceeded 1, indicating potential concerns regarding the safety of consuming these mycotoxins through food. Overall, the the margin of exposure (MoE) for AFs + OTA was less than 10 000 in both optimistic and pessimistic scenarios for all matrix types, underlining the need of prioritizing risk management[176]. Assunção et al.[178] found HQ valuesbelow 1 and MoE valueswell above 10 000 for all AFs, except for AFB_1 for the highest percentages of intake (P90, P95, and P99), but much higher than our results, where values reached the thousands. Assunção et al.[151] reported similar findings. However, it is crucial to highlight that this study only examined certain processed cereal-based items, which account for a small fraction of the average diet of Portuguese newborns and children.

Animal dose-response data is often derived from trials in which the drug is administered daily for the course of the investigation. Therefore, long-term average intake should ideally be included in human exposure data used to calculate the MoE. Average consumption levels are frequently overestimated by short-term human intake data. Because short-term intake data yields a lower MoE than long-term average intake data, it is likely to produce a more cautious estimate[179]. Furthermore, the study evaluated exposure by an indirect method, incorporating mycotoxin incidence and intake data. This common methodology has limitations in mycotoxin exposure assessment, such as the uneven distribution of mycotoxins in food, potential exposure *via* routes other than ingestion, the presence of masked mycotoxins, the impact of food processing, interindividual variations in absorption, distribution, metabolism, and excretion, and potential under- and overestimation in food consumption data[180].

6. Risk characterization from exposure to multiple mycotoxins in children food

Numerous studies have been conducted to assess dietary exposure to mycotoxins, however the characterization of risk associated with such exposure is not often done. In recent years, a few studies have been published that use risk assessment procedures that take into account concurrent exposure to several mycotoxins. Assunção et al.[178] assessed the risk of single and 12 mycotoxins in breakfast cereals ingested by children (1−3 years old) from Lisbon region (Portugal). The daily exposure of children to AFs, OTA, FBs, and TRCs was calculated using deterministic and probabilistic methods. For non-carcinogenic mycotoxins, the authors employed the hazard index (HI) to describe the risk of mycotoxins from the same family group. MoET was used to assess the risk associated with AFs, which are carcinogenic chemicals. García-Moraleja et al.[181] used a deterministic technique to determine the daily intake of 21 mycotoxins in coffee consumed by Spanish adults and adolescents under varied food consumption scenarios. The risk was assessed in contrast to the TDI or the provisional tolerable weekly intake (PTWI) suggested by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Han et al.[182] studied the cumulative health hazards of dietary exposure to various mycotoxins, including DON and its acetyl derivatives 3-acetyldeoxynivalenol and 15-acetyldeoxynivalenol. Sirot et al.[183] explored the overall French population's exposure to 25 mycotoxins as part of the second French total diet research. The health risk assessment was carried out by comparing dietary exposure to international health-based guidance levels (TDI, PMTDI, or PTWI), and the population rate of exceeding the health-based

guidance value was also determined for adults and children. Cano-Sancho et al.[184] studied the exposure of the Catalan (Spain) population to AFs (AFB_1, AFB_2, AFG_1, and AFG_2), and individual AF risk characterisation was obtained by estimating the MoEs, dividing the benchmark dose lower confidence limit ($BMDL_{10}$) by the average and percentile 95 of the exposure estimations. de Boevre et al.[185] investigated the quantitative dietary exposure to mycotoxins and their modified or masked forms (13 in total) through cereal-based food items consumed by the Belgian population. The outcome of exposure (individual and family groups) was compared to the mycotoxin TDI.

7. Main challenges in risk characterization of multiple mycotoxins

As previously stated, humans are naturally and frequently exposed to a wide range of mycotoxins, yet health risk assessments are typically conducted on individual mycotoxins, which may underestimate the overall risks. This might be explained by the fact that evaluating all conceivable combinations of mycotoxins found in food, as well as their potential combined harmful effects, is nearly difficult[186]. One of the most significant problems to risk characterization of various mycotoxins is a lack of toxicological data that may be utilized to quantify the risk. The utilization of toxicological data is required for risk categorization, and regardless of the mechanisms of combined effects or interactions, data for numerous mycotoxins are not yet comprehensive for all possible toxins in food. The adoption of harmonized language is an essential step toward a shared understanding of the fundamental phrases and ideas used when dealing with combined exposure to several chemicals for risk assessment reasons[187]. This presents additional issue for assessing the danger of various mycotoxins in food. It is clear that researchers took comparable techniques, but not necessarily using the same nomenclature. A standardized approach and technique for risk categorization is intended to improve the quality of the results obtained.

8. Conclusion and recommondations

The current review discussed the occurrence of free and modified mycotoxins with special interest in their effects on children's health. These metabolites cannot be avoided since it is not easy to prevent the growth of fungi in food, although their occurrence varies between the localities as well as at different seasons in the same location. Modified mycotoxins are the undetected metabolites during the determination of parent mycotoxins and can be produced by the fungi, the infected plants as part of their defense mechanism or during food processing and digestion. More than one mycotoxin can be found and even combined with different environmental contaminants in very low concentrations under the strict control. Children are very sensitive to mycotoxins or their their modified forms due to their incomplete development of some organs, their high food requirement and incomplete ability to detoxify. Moreover, the mechanism of toxicity is varied from one mycotoxin to another and they are linked to a variety of adverse health hazards in children, such as growth retardation and the suppression of child immune system. Based on the existing evidence, the glycosidic forms of the mycotoxins designated as priority (e. g., DON, ZEN) should be considered when assessing dietary exposure to these mycotoxins and determining the suitability of food for consumption. All modified and unmodified mycotoxins, as well as their combinations, should now be studied. To avoid the health hazards of mycotoxins or their modified forms on children, several strategies were applied, including the control of the environmental factors, the storage conditions, the use of resistances plant varieties, the use of physical, chemical and biological control as ell as the innovative approaches such as the use of natural products as fungal growth inhibitors, nanoparticles and magnetic materials as a major future challenge to control fungal growth and mycotoxins production. Despite several research on mycotoxins and their modified forms indicating the necessity for a comprehensive strategy to protecting against the hazardous consequences of exposure to the original and modified mycotoxin, the situation has remained unchanged to date. Increased lobbying is required to engage farmers, researchers, food processors, government officials, physicians, stakeholders, and policymakers. Extensive research should be conducted on mycotoxins and their modified forms in foods for newborns and young children, including exposure. The use of biomarkers in exposure assessments should also be encouraged since they estimate true levels of exposure while accounting for all possible routes. More epidemiological research are needed to identify additional health concerns associated with mycotoxin exposure and improve our understanding of the link between exposure to original and modified mycotoxins and health consequences. While further research is necessary, it is critical to stress the need for raising awareness of mycotoxin prevalence, exposure, and potential health effects in all communities. Furthermore, regional collaborative efforts in specific endamic areas are necessary to develop policies and programs to counteract the threat posed by mycotoxin contamination. Additionally, To achieve the 2030 agenda, policymakers and non-governmental organizations working on child nutrition and maternal health must commit to improving farmer knowledge, attitudes, and practices to reduce dietary mycotoxins exposure in low-income countries.

Conflict of interest

Wenyi Kang is an associate editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. There are no conflicts to declare.

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