Mycotoxins in Children's Food: Problem and Halal Management

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ABSTRACT

Mycotoxins are ubiquitous compounds found in the natural life cycle of food- producing plants. They have a range of diverse chemical and physical properties and toxicological effects on man and animal. Mycotoxins are considered the most important contaminants of the food chain due to their chronic adverse effects on health and the economy. Mycotoxins are known as the 21th century "Great Masquerader" due to its complex natural history involving different tissues and resembling different diseases at each stage in its evolution. Mycotoxins can induce a variety of clinical symptoms including epistaxis, conjunctivitis, coughing, apnea, wheezing, vomiting and nausea. Some mycotoxins induce acute pulmonary hemorrhage, bone marrow failure and pneumonia. Knowledge about these symptoms enables the clinician to ask questions for possible exposure to the main classes of mycotoxins to protect children from sources of such exposure. These sources may include food, clothes, furniture and indoor air at home. Early childhood exposure to mycotoxins may be critical determinants of later health effects. Exposure in utero and through early infancy may additionally be important. Several well-known diseases such as neural tube defects, liver and esophageal cancers are associated with the consumption of mycotoxin-contaminated food. Knowledge of previous short or long term exposure to mycotoxins may help paediatricians to more accurately diagnose and provide treatment options to children and their families. The current review discusses the problems associated with the occurrence of different common mycotoxins in children's food and the possible halal strategies to counteract these problems.

1. Introduction

Recently, there has been much interest in paediatricians to understand the link between exposure to fungi and health problems in children and infants. The most at- risk and important target group in this focus are children who suffer from immune deficiency and those living in developing countries in Asia and Africa. Several studies on immunodeficiency disease in children in industrialized countries including the USA have identified allergic symptoms from exposure to fungi and/or their toxic metabolites. Primary care paediatricians are unaware of the toxic properties of fungi and many find themselves confused and somewhat puzzled by the often contradictory information in the literature.

Mycotoxins comprise a structurally diverse family of naturally occurring, fungal-elaborated toxins, many of which have been strongly implicated as chemical precursors for toxicity in humans and animals (Pereira et al. 2014; Sun et al. 2017). The significance of mycotoxin- induced health effects derives from the natural occurrence of mycotoxins as contaminants of crops and food, and the possibility of exposure across all ages. Consumption of foods heavily contaminated with mycotoxins has resulted in acute intoxication episodes in many human populations. Chronic health conditions from exposure to minute amounts of mycotoxins are varied and principally include cancer. Human exposure to mycotoxins is difficult to avoid because fungal growth in foods is difficult to prevent (CAST, 2003).

From a system perspective, mycotoxins can be addressed in three interacting subsystems: metabolism and toxicology; health and productivity; and wealth. These subsystems significantly interact. After exposure to mycotoxins by inhalation, ingestion or skin contact, metabolism of the mycotoxins leads to several sequential events that determine toxicity. These events include administration, absorption, transformation, pharmacokinetics, molecular interaction, distribution, and excretion of these toxins and their metabolites. Thus, mycotoxin toxicity affects human and animal health, which affects the production of wealth related to human endeavour, agriculture and livestock production (FAO, 2001). The Food and Agriculture Organization (FAO) of the United Nations estimated in 1996 that 25% of the world's grain supply would be contaminated with mycotoxins (FAO, 1996). However, the exact economic cost of mycotoxins on crops and livestock is impossible to accurately determine because of the lack of sufficient data (CAST, 2003).

Exposure to mycotoxins is mostly via ingestion, however; other routes such as inhalation, contact and passive exposure resulting from mycotic infection by toxigenic fungi, have been recognized (CAST, 2003). Humans can be exposed to mycotoxins directly via consumption of contaminated commodities or indirectly via the consumption of animal products (milk, meat, eggs) derived from animals that have consumed contaminated feeds. A widely studied example is the carry-over of aflatoxins from feed into milk and milk products, where they appear mainly as aflatoxin M_1 or other secondary contaminated animal products (FAO, 2001; Marin et al., 2013). Mycotoxins also are relatively stable to heat; therefore, food preparation processes and procedures using heat such as cooking cannot be expected to remove mycotoxins safely (Bullerman, 2002; Hisako et al., 2013; Kaushik, 2015).

Animal studies, observational and epidemiological evidence indicate involvement of fungal metabolites in human disease as toxic or carcinogenic etiological agents (IRAC, 1993a,b,c,d,e; Marin et al., 2013). Human disease caused by mycotoxins may be a larger public health problem than anticipated because a long period is elapsed before the illness is recognized unless large amounts of mycotoxins are consumed, resulting in acute symptomology (Alshannaq and Yu, 2017). With advances in research, the significance of mycotoxins to human health is increasingly being recognized (CAST, 2003; Fung and Clark, 2004; Williams et al, 2004). Still, as with pesticides, lifelong consequences of exposure to chemicals in early life are just beginning to be observed (Forrest and Riley 2004; NAS, 2004).

The impact of hazardous mycotoxin exposure on human health can take numerous shapes, levels of severity and clinical significance. Generally, the degree of toxicity of different chemicals tested on laboratory animals is affected by differences in species, age (foetus, young or old), and sex. In humans, mycotoxins can cause important health problems evidenced by occasional outbreaks of acute human mycotoxicoses (CDCP, 2004; Zain, 2011). Carcinogenicity is the most recognized late-onset disease from exposure to mycotoxins in humans. In exposed populations in Asia and West Africa, hepatitis B virus infection (and also hepatitis C virus infection) may confound the relationship between aflatoxin ingestion and liver cancer (Wogan, 1999; Magnuson et al., 2013). There have been some cases of infant death linked to presence of mold in living conditions (CDCP, 2000; Jarvis, 2002).

Among the many responses attributed to mycotoxin exposure is disturbed growth development in children, several types of cancer, reduced fertility and stillbirths (Barrett, 2000; Gong et al., 2016). Immuno-modulation caused by chronic exposure to mycotoxins is likely an important aspect of

their adverse health effects. In animal studies, consumption of sufficient amounts of mycotoxins leads to immuno-suppression involving specific classes of immunoglobulins or antibodies. However, the major effects appear to involve cellular immune phenomena and non-specific humoral factors associated with immunity. Immune-suppression is a likely major health effect of mycotoxins (CAST, 2003).

Mycotoxins affect diverse cellular processes and have a wide spectrum of toxicological effects. This complexity is reflected in the diversity of responses in different animal species. This is likely to translate into differences in human response depending on race and even in individuals of the same race. These toxins may affect the reproductive system, immune system, hormonal activity, target organs and the nervous system. Developmental defects including birth defects are another possible adverse effect following exposure to mycotoxins. In addition to these diverse organ or site-specific actions, mycotoxins may affect the gastrointestinal system, have haematological effects and reduce growth (Weidenborner, 2001; Kuiper-Goodman, 2004).

Worldwide, large numbers of vulnerable children are exposed to food contaminated with mycotoxins. In communities exposed to mycotoxins, the hazardous impact of mycotoxins can affect pregnancy, lactation and child growth (Williams et al, 2004; Smith et al., 2017). Children are a nutritionally vulnerable group and they are behaviorally (naughty, defiant and impulsive from time to time, oppositional defiant disorder, conduct disorder and attention deficit hyperactivity disorder) and physiologically different from adults. Their susceptibility to the adverse health effects of mycotoxins is also likely different from adults (WHO; 1986, 2006). The disproportionate impact of exposure to toxic substances on children compared to adults has led to much- deserved research efforts. Exposure to chemical agents such as pesticides at the child developmental stage produces effects that differ qualitatively and quantitatively from those in adult exposure, and represents a major empirical and conceptual foundation for child health risk assessment (NAS, 1993). Because their organ systems are growing and developing, they may be more susceptible to toxins and respond differently to environmental challenges at various stages of development. The manifestations of developmental toxicity will vary depending on the time of exposure and the underlying developmental processes at that growth stage (Scheuplein et al, 2002; Tamburlini et al. 2002; Thompson, 2004).

The risks associated with mycotoxin exposure in children depend on the degree of exposure and the degree of toxicity of the mycotoxin. It has been found, consistently, that naturally contaminated grains are more toxic than known pure mycotoxins. This is due presumably to the presence of and interaction with other identified or as yet unidentified mycotoxins or metabolites. These additional substances need to be considered in the overall exposure assessment for children, and in hazard and risk assessments for children (Kuiper-Goodman, 1991). Infants and children are more susceptible to different toxins compared to adults because of their lower body weight, higher metabolic rate, lower detox capabilities, and on-going development of essential organs and tissues, such as in the central nervous system.

The Acceptable Daily Intake of any chemical (ADI) is defined as the amount of chemicals that can be ingested daily over a lifetime without appreciable health risk. However, there has been ongoing debate on the question of whether the limits afford protection to all sectors of the human population (Bellisle and Rolland-Cachera, 2000). Focus has been particularly centred on whether infants (from birth to 12 months) and children (1 to 12 years of age) are adequately protected by the ADI, because of hypothetical concerns that:

- Infants and children may differ in their capacity to detoxify and eliminate chemicals from the body (toxicokinetics).
- Infants and children may be more sensitive to toxicity (toxicodynamics)

In addition, different dietary requirements and habits may result in intake of chemicals exceeding the ADI. Although derivation from the ADI allows for assessment of possible effects on neonatal animals, the values are considered inappropriate to apply in infants below the age of 12 weeks.

There are two reasons for this: **(1)** Insufficient data is available with respect to the effects of chemicals on very young infants. It is known that enzyme levels responsible for biotransformation are generally much lower in the newborn, particularly in the pre-term infant. Lower levels of enzyme activity can potentially lead to impaired detoxification or to decreased formation of toxin metabolites. There are also some types of toxic effects to which the neonate is more sensitive, as a result of its rapidly changing physiology. These factors increase the uncertainty in establishing safe intake levels for the infant in the first few weeks of life. **(2)** Exposure to suckling animals via the mother's milk mimics the situation of the breast-fed infant, but routine studies do not simulate direct exposure to additives in infant milk formula (Benford, 2001).

The available scientific data supports suggestions that older infants and children are at greater risk from toxin than adults. As already noted, a large number of biochemical and physiological changes occur in the early stages of life. These may influence the rates of absorption, distribution, metabolism and excretion from the body (Worm et al., 2000). In particular, the various enzymes involved in metabolism of toxic compounds develop at different rates in the first few weeks after birth. However, although large differences are present in enzyme levels and physiological functions between infants and adults, these differences do not seem to have major implications for the fate of the toxic compounds ingested into the body. Studies on a wide range of drugs have shown that the rate of elimination in infants was similar to, or in some cases higher than that in adults (Sohn, et al., 2000). This means that variation between infants and adults is covered under the "toxicokinetic safety factor".

2. Mycotoxins

2.1. Mycotoxins in breast milk

2.1.1. Aflatoxins

Aflatoxins are highly toxic secondary fungal metabolites produced by *Aspergillus flavus and A. parasiticus*. When lactating women ingest an aflatoxin-contaminated diet, a major aflatoxin metabolite, aflatoxin M_1 (AFM_1) is secreted into the milk (Polychronaki et al., 2006; Prandini et al., 2009). AFM_1 has been reported as carcinogenic (Luongo et al., 2014) and mutagenic (IARC, 2015). Young infants are more sensitive to AFM_1 compared to adults. The symptoms are identical to that of Reye's syndrome and Kwashiorkor, both of which have been conjecturally associated with aflatoxins (Shank, 1997; WHO, 1999).

2.1.2. Ochratoxin (OA)

Humans are exposed to OA via consumption of foods directly contaminated with fungus growth and food by-products derived from exposed animals. OA is reported as nephrotoxic, carcinogenic, teratogenic and immunosuppressive (Abdel-Wahhab et al., 2005, Ringot and Chango, 2010, Heussner and Bingle 2015). In human milk samples, the highest concentrations of OA have been found in Sierra Leone (Table 1), where 35% of the samples contained OA at levels from 200 to 337 ng/ml (Miraglia et al., 1995; Jonsyn et al., 1999). OA in breast-milk was reported to affect kidney function and led to the development of urinary tumours in infants and young children (Skaug et al., 1998).

2.2. Mycotoxins in bottle-fed infants:

Contaminated water supply, poor bottle cleaning procedures, poor storage facilities, and having only one bottle, teat and funnel for the preparation of bottled milk make the preparation of uncontaminated, bacteriologically safe milk extremely difficult, if not impossible, in real-life circumstances faced in tropical homes. This was true even when attempted by trained health staff for trial purposes (Gursky, 2000). Johnston and Monte (2000) summarized the situation as follows: Bottle-fed infants are particularly prone to diarrheal diseases, which are almost unavoidable under the poor hygiene conditions of households of modest income. A vicious circle sets in diarrheal disease, reduced intake (due to semi-starvation or starvation diet), early malnutrition, reduced

appetite, reduced resistance, and further diarrhoea (Baskaran et al., 1999). Cow's milk-based infant formulas may be contaminated by different contaminant residues i.e. mycotoxins (Skaug, 1999), especially AFM_1 (Galal-Gorchev, 1993; Oliveira, et al., 1997). These contaminant residues induce health hazards in small children who consume large quantities of milk.

2.3. Mycotoxins in children's food:

As mentioned above, mycotoxins comprise a structurally diverse family of naturally occurring, fungal-elaborated toxins, many of which have been strongly implicated as chemical precursors of toxicity in humans and animals. Exposure to mycotoxins is difficult to avoid because fungal growth in foods is not easy to prevent (Bellisle and Rolland, 2000). Consumption of foods heavily contaminated with mycotoxins has resulted in acute intoxication episodes in children. Table (1) summarizes selected mycotoxin-producing fungi of relevance to children's health.

Table 1. Selected mycotoxin-producing fungi of relevance to children's health.

Fungus	Mycotoxins	Associated health effects
Aspergillus flavus, A. Parasiticus	Aflatoxins	Vomiting, hepatitis, Liver cancer
Fusarium verticillioides	Fumonisins	Vomiting, Neural tube defects, Esophageal cancer
Fusarium culmorum	Deoxynivalenol	Vomiting
Fusarium sporotrichiodes	T-2 toxin	Alimentary toxic aleukia, Vomiting, hemorrhage
Aspergillus ochraceus, A. niger	Ochratoxins	Balkan nephropathy, Renal cancer
Penicillium expansum	Patulin	Vomiting, cancer (suspect)
Fusarium graminearum	Zearalenone	Estrogenic effects, cervical cancer (suspect)
Claviceps purpurea	Ergot alkaloids	Ergotism

Generally, the degree of toxicity of different chemical compounds on laboratory animals is found to be affected by differences in species, age, and sex. In humans, children are considered to be more susceptible than adults. The mycotoxins that are highly toxic to children are described as the following:

2.3.1. Aflatoxin

Aflatoxin refers to a group of potent toxins that are found in a wide range of agricultural crops especially grains and nuts which are commonly used for the preparation of children's food (Kensler et al., 2011; Bhatnagar-Mathur et al., 2015; Verheecke et al., 2016). Up to now, several aflatoxins have been discovered and the most important, naturally-occurring are B_1, B_2, G_1, and G_2. Aflatoxins have continued to receive attention as the most carcinogenic and toxic mycotoxin (IRAC, 1993a, CAST, 2003; Ostry et al. 2017; El-Nekeety et al., 2017) with mutagenic and teratogenic properties when tested in laboratory animals (Abdel-Wahhab et al., 2010, 2015, 2016; Milićević et al. 2016; Kumar 2017). For this reason, they may be hazardous to humans and especially children and infants. In many species, the major target for acute and chronic toxicity due to aflatoxin exposure is the liver.

The human gastrointestinal tract rapidly absorbs aflatoxins after consumption of contaminated food, and the circulatory system transports the aflatoxins to the liver (Fung and Clark, 2004). 1 to 3% of ingested aflatoxins irreversibly bind to proteins and DNA bases to form adducts such as aflatoxin B_1-lysine in albumin (Skipper and Tannenbaum, 1990). Because aflatoxin B_1-lysine adducts are not repaired, their half-life in human serum is approximately 20-60 days (Azziz-Baumgartner et al., 2005). In 1993, the International Agency for Research on Cancer determined

that aflatoxin B_1 (the most potent of the aflatoxins) was a human carcinogen (IARC, 1993a; Ostry et al. 2017). Epidemiologic studies clearly document that ingestion of aflatoxin B_1 is a risk factor for hepatocellular carcinoma in humans (Liu and Wu, 2010). Figure (1) shows that hepatocellular cancer follows many years after the acute symptoms of aflatoxin ingestion (vomiting, abdominal pain, hemetemesis, fever, diarrhea, dizziness, and seizures) have occurred.

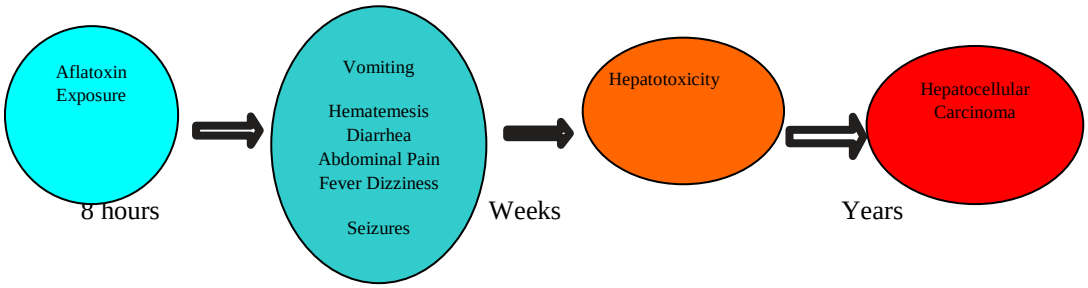

Fig 1. Time course of adverse events preceding hepatocellular carcinoma

A disease of children in Thailand with symptoms identical to that of Reye's syndrome was conjecturally associated with aflatoxicosis (Van Rensburg, 1977). This disease was characterized by vomiting, convulsions, coma, and death with cerebral oedema and fatty involvement of the liver, kidney, and heart (Bourgeois et al., 1971; Lucarelli et al., 2000). Shank (1997) found significant levels of aflatoxins (1-4 µg/kg) in livers of 23 Thai children who had died of Reye's syndrome. In New Zealand and Czechoslovakia, aflatoxins were found in the liver of children who died due to Reye's syndrome at autopsy. Kwashiorkor, a disease of children in Northern Africa and in undernourished populations, is usually attributed to nutritional deficiencies and may also be related to aflatoxin intake (Etzel, 2014). The liver damage induced by aflatoxins prevented the children from coping with high protein diets which are usually recommended for the treatment of Kwashiorkor (Newell, 1983; Afsah-Hejri et al., 2013).

In many species, the major target for acute and chronic toxicity due to aflatoxin exposure is the liver; however, limited information is available associating this risk with outbreaks of aflatoxin toxicity. In addition, only a few animal studies have measured aflatoxin concentrations because unbound aflatoxins remain in the blood for a very short period of time after exposure (i.e., 13-120 min) (Wong and Hsiech, 1978; Zain 2011; Alshannaq and Yu 2017). In all species and tissues tested to date, the mutagenicity, carcinogenicity and DNA-binding activity of aflatoxin B_1 appear to result from its activation by cytochrome P450 enzymes to produce aflatoxin B_1-8,9-epoxide (WHO, 2002; Josse et al. 2012). Microsomial mixed function oxygenase (MFOs) form AFM_1, AFQ_1, AFP_1 and AFB_1-8, 9-oxide**.** Moreover, in the liver cells, AFB_1 is altered by cytoplasmic reductase to form aflatoxicol (Monson et al., 2015). The 8,9-epoxide binds covalently to DNA, forming mutagenic adducts; there is a positive correlation between risk of tumor formation and levels of AFB_1-DNA adducts in the liver in animal models (Josse et al.,2012). Mutations of p53 are a relevant marker in the molecular epidemiology of liver cancer, as some 20% of cases show mutations of this oncogene. Moreover, a mutation at the third base of codon 249 (a GC to TA transversion leading to a change from arginine to serine) has been described in geographical correlation studies of aflatoxin B_1 intake (WHO, 2001 Josse et al., 2012). The question of whether aflatoxin is a human carcinogen or not has been difficult to resolve due to the presence of several confounding factors, including hepatitis B virus infection. However, results of epidemiological studies have shown that aflatoxin exposure is an important determinant of the variations in human liver cancer incidence (IARC, 1987; Sohn et al., 2000; Mokhles et al., 2007).

Aflatoxins are now believed to increase neonatal mortality and still-births, increase susceptibility to neonatal jaundice (Galal et al., 2006), play a role in the pathogenesis of Kwashiorkor, and increase child susceptibility to infection and malignant disease. Early and repeated exposure to aflatoxins in-utero and throughout childhood might predispose the child to liver cancer later in life. Immuno-

suppression due to aflatoxin consumption is another contributing factor (Williams et al., 2004; Gong et al., 2016).

Aflatoxins have been reported to adversely affect the outcome of lower respiratory tract infections in children (Denning et al., 1995). In one study on Gambian children, evidence of a reduced level of salivary immunoglobulin A (IgA) was found in individuals exposed to aflatoxins. No effect on antibody titer to pneumococcal and rabies vaccines was noted. In Africa, the aggressive nature of HIV infection might be partially attributed to aflatoxin-induced immune-suppression. Aflatoxins may also contribute to failure of protective immunizations (Gong et al., 2016).

2.3.2. Ochratoxin A

Ochratoxin (OA) is a secondary fungal metabolite of some toxigenic species of *Aspergillus* and *Penicillium* growing on cereal grains (barley, oats, rye, corn, and wheat) and other food items including coffee, milk powder, wine, and beer (Njobeh et al., 2010, Reddy and Bhoola, 2010; Cremer et al., 2011). OA is reported to be hepatotoxic, nephrotoxic, teratogenic (Abdel-Wahhab et al., 2005, 2008,2016; Costa et al., 2016), and carcinogenic to single-stomached animals (Kuiper-Goodman and Scott, 1989). Of greatest concern in humans is its implicated role in an irreversible and fetal kidney disease referred to as Balkan Endemic Nephropathy (BEN) (Pavlovic et al., 1999, Ringot et al., 2006; Pfohl-Leszkowicz et al., 2007). Increased incidence of renal disease is accompanied by a high risk of urinary tract tumors. In addition to OA, very low selenium levels of the population could also be a risk factor for BEN and urinary tract tumors (Miraglia et al., 1995, Miletiĉ-Medved et al., 2005; Ringot et al., 2006). OA is heat stable. El-Banna and Scott (1984) report that cooking Fava beans and polished wheat spiked with OA at 125 ng/g resulted in destruction of only 16-20% and 6% of OA, respectively. This indicates that complete destruction of OA via heat processing is not possible. Generally, no children aged 4-14 years were affected by endemic nephropathy (Akkmeteli, 1977; Breilholtz et al., 1993). Because of the long-term effects, a direct relationship is difficult to establish. Table (2) summarizes a comparison of mean dietary intake estimates for an average person calculated from occurrence and consumption data in human blood plasma.

Table 2. Comparison of estimates of mean dietary intake of OA for an average person calculated from occurrence and consumption data and from mean human blood plasma levels (SCOOP, 1996)

Country	Average concentration in blood plasma (ng/ml)	Estimated daily intake calculated from blood plasma concentration (ng/kg bw)	Estimated daily intake based on occurrence data and consumption data (ng/kg bw)
Denmark	1.8	2.4	2.0
France	0.4	0.5	1.5
Germany	0.45	0.6	0.9
Italy	0.53	0.7	4.6
Netherlands			2.0
Spain			0.7
Sweden	0.18	0.24	1.5
United Kingdom			1.4

2.3.3. Fumonisins

Fumonisins are structurally related mycotoxins produced by *Fusarium moniliform* and *F. proliferatum* which are found worldwide in corn and corn-based human foods (Rodrigues and Naehrer, 2012). Fumonisins have been associated with human esophageal cancer in regions in South Africa, Northeastern Italy, Northern China and Southeastern United States (Chu and Li, 1994; Doko and Viscinti, 1994; Hopmans and Murphy, 1993; Rheeder et al., 1992; Sydenham et al., 1991). In these regions corn is a dietary staple, and preliminary data indicate that corn and corn-based food products from these and other regions may be significantly contaminated with fumonisins.

Thiel et al. (1992) analyzed samples of commercially available corn or corn-based products obtained from retail stores in the USA, South Africa, Egypt and Peru for fumonisin content (Table 3). Fumonisin levels detected in samples from South Africa and Peru were relatively low, while samples obtained from Egypt and the USA contained high levels of fumonisin. Analyses of corn-based children's food products collected from different areas indicated the presence of fumonisins in all samples (Table 4).

Table 3. Fumonisin levels in commercial corn products for human consumption[a]

Source	**No. of samples**	**Fumonisins (ng/g)**	
		FB_1	**FB_2**
South Africa	68	0 - 457	0 - 120
		(105)	(21)
Egypt	2	1780 - 2980	410 - 780
		(2380)	(595)
USA	29	0 - 2790	0 - 1070
		(711)	(190)
Peru	4	0 - 660	0 - 135
		(165)	(34)

[a] Values in parentheses = means.

Table 4. Total fumonisins content in corn-based children food products determined by ELISA and HPLC

Food product	**Total no. of samples**	**Fumonisin (ng/g of food)**	
		Total by ELISA	**Total by HPLC**
Cornflakes	2	ND – 400	ND
Corn pops cereal	1	200	ND
Corn starch	1	500	< 75
Infant cereal	1	200	ND
Infant cream corn	1	200	ND

ND, none detected

2.3.4. Patulin

Patulin is a mycotoxin produced by several *Pencillium* and *Aspergillus, Byssochlamys* species, with *Pencillium expansum* being the most commonly encountered species. This fungus is the principal cause of apple rot (Davis and Diener, 1987, Steinman et al., 1989 Boussabbeh et al., 2016). Patulin was found in commercial apple juice and apple foods for children at concentrations ranging between 10 and 170 ppb (Prieta et al., 1994; Battilani et al., 2008). Sharma (1993) stated that the toxicity of patulin may directly affect cellular glutathione levels, mitochondrial function and integrity of the plasma membrane. Patulin also has an immunosuppressive effect and inhibits DNA synthesis (Glaser and Stopper, 2012). WHO (1996) reviewed the acute toxicity of patulin and reported that the toxic signs include agitation, convulsion, dyspnea, pulmonary congestion and edema, ulceration, hyperemia, and distension of the gastrointestinal tract. WHO recommended a maximum concentration of 50 ppb for patulin in apple juice and apple products, whereas, some countries state a limit of 10 ppb in baby-foods (Stoloff et al., 1991; FAO, 2005).

2.3.5. Zearalenone

Zearalenone is a mycotoxin produced by *Fusarium* species growing on corn, wheat, barley, oats, sorghum, sesame, and hay and has estrogenic and anabolic activity. When livestock was fed moldy feeds containing zearalenone, the milk and milk products produced from the animals contained estrogenic substances (Frizzell et al., 2011). Estrogenic agents can increase the plasma levels of cholesterol and triglycerides in females. An association between oral-estrogen use and myocardial infection and stroke has been described (Wallace et al., 1977). Zearalenone also causes cytogenetic effects and chromosomal aberrations (Ben Salah-Abbès et al., 2010; Ismaiel et al., 2015). The major effects of zearalenone in children are on the reproductive system, leading to hyperestrogenism and affecting reproductive organ structure and function (Kuiper-Goodman, 1991 Sherif et al., 2009; Zheng et al., 2016).

2.3.6. Ergot

Ergot alkaloids are produced by *Claviceps purpurea* and are known to be more of a problem on cereal grains (Coufal-Majewski et al., 2016). There are three main modes of action of Ergot alkaloids: peripheral, neurohormonal, and adrenergic blockage (Cordell, 1981). The most important peripheral effect is smooth-muscle contraction typified by vasoconstriction and uterotonic effects. The neurohormonal effects of ergot are observed in serotonin and adrenaline antagonism. Adrenergic blocking agents prevent the stimulation of sympathetic nerves by antagonizing the effects of other drugs such as epinephrine.

2.3.7. Sterigmatocystin

Sterigmatocystin (Stg) is a mycotoxin produced by *Aspergillus* genera and causes mammalian liver cancers (Adamson, 1989; Versilovskis and De Saeger, 2010). Stg was found in foods including peanuts, corn, tree nuts, cheese, milk, and meat (Diener et al., 1987; Northolt et al., 1980, Almeida et al., 2012), and has genotoxic effects in non-mammalian species (Abdel-Wahhab et al., 2005b). Stg is a major secondary metabolite of *Aspergillus versicolor* and *A. nidulans* (Sivakumar et al., 2001), is closely related to aflatoxins and is a precursor in aflatoxin biosynthesis (Barnes et al., 1994). However, the chronic or acute toxicities of Stg are considerably lower than aflatoxin (Scudamore et al., 1997). Stg is one of the predominant contaminating mycotoxins in food and grains in high-incidence malignant tumor areas in China (Huang et al., 2002). Stg is carcinogenic in mice (pulmonary adenocarcinomas) and rats (hepatocellular carcinomas) following oral administration (IARC, 1976, 1987) and is classified as an IARC Group-2B carcinogen (i.e., possibly carcinogenic to humans). The toxicity of Stg is mainly confined to the hepatic and renal tissues. However, lung tumors were also observed in newborn mice injected by a single subcutaneous dose of 5 mg/kg bw of Stg (Gujii et al., 1976).

2.3.8. Vomitoxin (VT)

Vomitoxin, one of the most common mycotoxins causing vomiting among children, frequently contaminates wheat and corn. The estimated tolerable daily intake of vomitoxin is 1.5 µg/kg body weight and 3.0 µg/kg body weight for infants and adults, respectively (Kuiper-Goodman, 2004). Multiple outbreaks of vomiting illness between 1961 to 1985 in China were linked to consumption of foods made with grains contaminated with vomitoxin (Luo, 1988). In 1987, nearly 100 persons in India became ill after they consumed wheat products from which vomitoxin and other trichothecene mycotoxins were recovered (Luo et al., 1988). In 1997 and 1998, approximately 1700 school children in the United States developed vomiting, nausea, headache, and abdominal cramps after eating burritos (CDCP, 1999). Vomitoxin was identified as a contaminant in the burritos and might have caused the outbreaks, which subsided within 24 hours of onset (CDCP, 1999).

2.4. Mycotoxin Legislation

Limits for contaminants such as mycotoxins in foods are set in EC Regulation 466/2001 setting maximum limits for certain contaminants in foodstuffs and its amendments. Further amendments to this legislation are currently being implemented to include infant foods as described below.

EC Regulation 1425/2003 set a limit of 10 µg/kg of patulin for the following categories of foods:

- Apple juice or apple products prepared for young children and infants.
- Other non-cereal based baby food

This limit applies directly in the UK although provisions for the enforcement of the limit are currently being implemented into UK law. The limits apply to the product “as sold”.

EC Regulation 683/2004 sets the following limits which came into force on 1 November 2004 and are set on a dry-matter basis:

- 0.5 µg/kg for aflatoxin B_1 for baby foods and processed cereal-based foods for infants and young children, and dietary foods for special medical purposes intended specifically for infants;
- 0.025 µg/kg for aflatoxin M_1 for infant formulae and follow-on formulae, including infant milk and follow-on milk and dietary foods for special medical purposes intended specifically for infants; and
- 0.5 µg/kg for ochratoxin A for baby foods and processed cereal-based foods for infants and young children, and dietary foods for special medical purposes intended specifically for infants.

2.5. Halal strategies for the prevention of mycotoxin contamination

The prevention of fungal contamination and mycotoxin production in agricultural commodities generally may be divided into three levels:

2.5.1. Primary prevention

Primary prevention is the most effective method to reduce the growth of fungi and production of mycotoxins. Several methods are recommended to prevent favourable conditions for the growth of fungi, including:

- Development of halal crop varieties resistant against fungal infection;
- Control of plant infection in the field using halal fungicides;
- Development of a suitable pre- and post-harvest schedule;
- Reducing moisture content in seeds of plants post-harvest or during storage;
- Storing commodities at low temperatures whenever possible;
- Using halal fungicides and preservatives against fungal growth during storage;

- Control of insect infestation in stored bulk grains using approved insecticides.

2.5.2. Secondary prevention

This level of prevention is required when early phase fungal invasion has started in commodities. The occurrence of toxigenic fungi should be reduced or their growth stopped in order to prevent further decay and contamination with mycotoxins. Several measures are suggested as follows:

- Growth of the infested fungi should be stopped by re-drying the products;
- Contaminated seeds should be removed;
- Mycotoxin contamination should be inactivated or detoxified;
- Stored products should be protected from any favourable conditions which enhance the growth of fungi.

2.5.3. Tertiary prevention

If the commodities are heavily infested with toxic fungi, neither the primary nor secondary preventions are feasible. None of the primary or secondary prevention measures would be effective to stop the growth of toxic fungi and the formation of their toxins. However, several measures have to be carried out to avoid the transfer of toxic fungi and mycotoxins to food or the environment; these include detoxification or destruction of the mycotoxins to a minimal level.

2.6. Halal decontamination strategies

The mycotoxin-contaminated food and feed should be removed, detoxified or inactivated by chemical, physical and biological means following the Islamic view. Each treatment may have its own limitations because the treated products should be halal, safe and not affect the essential nutritive value of the product. The suggested methods for effective decontamination of some mycotoxins can be summarized as the following:

2.6.1. Physical strategies

Density segregation, mechanical separation, colour sorting and screening bulk grain and nut shipments significantly reduced possible mycotoxin contamination of grains. Washing using water or sodium carbonate solution reduces the presence of FB_1 and ZEN in grains. Gamma irradiation is used successfully to control ochratoxin levels (Refai et al., 1996).

2.6.2. Chemical strategies

Several chemicals have been found to be effective (to different extents) against different mycotoxins. These chemicals fall into the following categories: acids, bases (e.g. ammonia, sodium hydroxide), oxidising reagents (e.g. hydrogen peroxide, ozone), reducing agents (e.g. bisulphite, sugars), chlorinating agents (e.g. chlorine), salts and miscellaneous reagents such as formaldehyde (Table 5).

Table 5: Chemical treatments used in the removal of mycotoxins from contaminated commodities

a- Acetic acid (C_2H_5OH).	**b**- Ammonia gas (NH_3) or NH_4OH or ammonium salts, 3-5%.
c- Acetic acid (C_2H_5OH).	**d**- Calcium hydroxide ($Ca(OH)_2$).
e- Formaldehyde.	**f**- Hydrogen peroxide (H_2O_2).
g- Methylamine (CH_3-NH_2).	h- Ozone gas (O_3).
i- Phosphoric acid (H_3PO_4).	**j**- Phosphine gas (PH_3), very highly toxic!

k-Sodium bicarbonate ($NaHCO_3$).	**l**- Sodium bisulfite ($NaHSO_3$).
m- Sodium bisulfite (NaOH).	**n**- Sodium hypochlorite (NaOCI).

2.6.3. Physicochemical strategies

Phyllosilicate clay is reportedly able to chemisorb mycotoxins from aqueous solutions (Phillips et al., 2008; Abdel-Wahhab et al., 2015). The *in vitro* binding of aluminosilicate to AFB_1 is reported to form complexes at varying strengths. Hydrated sodium calcium aluminosilicate (HSCAS) binds to AFB_1 and forms a more stable complex compared to other tested compounds (Phillips et al., 2008). The HSCASs bentonite and montmorillonite were found to protect laboratory animals from toxic and teratogenic effects of aflatoxins (Abdel-Wahhab et al., 1999b, 2002b, 2015). Montmorillonite (MTT) is the active ingredient in bentonites for AF binding (Marroquín-Cardona 2009). These clays have been effectively used to reduce the negative effects of AF exposure in dairy cows (Kutz et al., 2009), goats (Smith et al., 1994), and several other animal species (Leduox et al., 1999; Phillips et al., 1999). MTT has the ability to chemisorb AFB_1 and FB_1 from aqueous solutions to varying degrees and form complexes of varying strengths (Zhang et al., 2010, 2011). The ability of MMT to adsorb these mycotoxins is mainly due to its high surface area. MMT is able to adsorb organic substances on external surfaces and also in the internal structures in laminar spaces via interaction with or substitution of exchange cations present in their spaces (Aly et al., 2004).

2.6.4. Chemoprotection

Chemoprotection against aflatoxins has been demonstrated with the use of a number of halal compounds that either increase an animal's detoxification process or prevents the production of the epoxide that leads to chromosomal damage (Kensler et al., 1993). One technical solution is drug therapy, because several compounds such as oltipraz and chlorophyll, are able to decrease the biologically effective dose of aflatoxins (Wang and Shen, 1999). Long-term therapy is expensive and may result in side effects. This would not be feasible in most developing countries. Yeast extracts and esterified glucomanoses were suggested as novel approaches to chemoprotection for aflatoxin detoxification (Kensler et al., 1993).

2.6.5. Enterosorption

Enterosorption is a detoxification mechanism suggested for the adsorption of clay minerals to aflatoxins to prevent its absorption in the gastrointestinal tract (Phillips et al., 2008). Adsorption agents have different efficiencies when it comes to prevention of aflatoxicosis (Phillips et al., 1993). The risk with enterosorption is non- specificity: enterosoption is feared to also act against micronutrient uptake from food (Mayura et al., 1998). However, *in vitro* tests of hydrated sodium calcium aluminosilicates (HSCAS) suggest that there is little adsorption of micronutrients (Chung et al., 1990). The use of HSCAS as additives in contaminated feeds is reported to be effective in preventing aflatoxin toxicity in turkeys, chickens, lambs, cattle, pigs, goats, rats, and mice (CAST, 2003; Abdel-Wahhab et al., 1998; 2002b, 2005d) and ZER (Abbès et al., 2006). Bentonite and montmorillonite were also effective in removing AFB_1 and FB_1 from aqueous solution (Aly et al., 2004). Recently Abdel-Wahhab et al. (2015a) reported that the modification of montmorillonite surfactants with long-chain organic cations such as Cetyltrimethyl ammoniumbromide increased hydrophobicity of the mineral surface and resulted in excellent adsorption capability of AFs, ZEN and FB_1as well as ZEN and OTA (Abdel-Wahhab et al., 2015b) *in vitro* and *in vivo* (El-Nekeety et al., 2017).

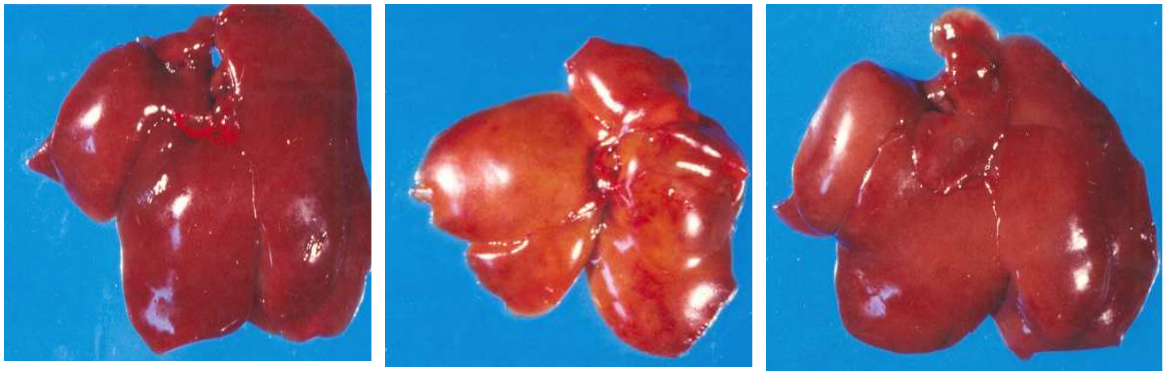

Fig. 2. Photograph showing livers of rats treated with aflatoxin alone and in combination with HSCAS or EM. Left: control (normal colour of the liver), Middle: aflatoxin treated (pale yellow liver typical of aflatoxicosis), Right: HSCAS or EM plus aflatoxin (normal comparable to the control liver) (Abdel-Wahhab et al., 2005c)

2.6.6. Biological

Biological detoxification can be defined as the enzymatic degradation or biotransformation of mycotoxins by either the whole cell or an enzyme system (Bata and Lásztity, 1999). For example, the mycotoxin AFB_1 is degraded by enzymes in *Flavobacterium aurantiacum* (Smiley and Draughon, 2000). Other microorganisms including *Rhizopus* sp., *Corynebacterium rubrum, Candida lipolytica, Aspergillus niger, Trichoderma viride, Mucor ambiguous, Neurospora* spp., *Armillariella tabescens* and lactic acid bacteria have been tested in *in vitro* systems with varying results (Jebali et al., 2018; Karlovsky, 1999). Several microorganisms were screened for their ability to degrade OTA and convert OTA to the less toxic form, ochratoxin α. *Aspergillus niger* was reportedly able to degrade ochratoxin α to another unknown compound. Two species of black yeast fungus *(Exophiala spinifera, Rhi-nocladiella atrovirens)* and a Gram-negative bacterium *(Caulobacter* spp.) isolated from mouldy corn kernels have been found to extensively metabolise fumonisins to CO_2 in liquid media (Blackwell et al., 1999; Duvick, 2001). Several microorganisms including yeasts, fungi and bacteria are able to convert ZEN to α - and β -zearalenol. However, this transformation cannot be regarded as detoxification since the oestrogenic activity of the resulting metabolites is similar to that of zearalenone (Everett et al., 1987).

2.6.7. Antioxidant strategies

Since some mycotoxins (i.e. AFB_1, FB_1, OTA, and zearalenone) are known to cause cell membrane damage through increased lipid peroxidation (Gautier et al., 2001; Abdel-Wahhab et al., 2004a, 2005c, 2006), the protective properties of antioxidant substances against mycotoxin damage were extensively reviewed by Galvano et al. (2001). Selenium, vitamins A, C and E and their precursors showed potential antioxidant effects and acted as scavengers for superoxide anion. Moreover, several natural (provitamins, carotenoids, chlorophyll and its derivatives and phenolics) as well as synthetic compounds (butylated hydroxyanisole and butylated hydroxyl toluene) showed effective antioxidant properties.

2.6.8. Diet and nutrients that support detoxification

Nutrition plays a significant role in the support of detoxification. Dietary interventions intended to reduce toxicity after mycotoxins have been absorbed, are an effective detoxification strategy. Dietary interventions include intake of choline, methionine, vitamins, protein, dietary fat, antioxidants and inducers of metabolizing enzymes. This can be added to animal feeds to lower toxicity caused by mycotoxins in maize (Abdel-Wahhab et al., 1999a).

2.6.9. Antioxidant and natural constituent defense against mycotoxins toxicity

Feed additives such as antioxidants, sulphur-containing amino acids, vitamins, and trace elements can be useful mycotoxin detoxicants (Huwig et al., 2001; Abdel-Wahhab et al., 2004a, 2005a,

2006; Abdel-Wahhab and Aly 2003, 2005, El-Nekeety et al, 2014). Several reports are now available that suggest that antioxidants are able to protect against chemical carcinogenesis if administered prior to/ or concomitantly with these carcinogens.

2.7. Future strategies for mycotoxin management

In spite of the large progress achieved in understanding the factors affecting mycotoxin production, detection and diagnosis in the past years, mycotoxins remain a food safety threat. The biggest challenges to develop and perfect strategies or technologies to guarantee food safety and ensure a healthy environment are changes in agricultural production and storage practices and food processing. This should be carried out parallel to changes in public and environmental policy

The areas of public policy and research required to ensure safe food and feed supply in the twenty-first century are listed below:

2.7.1. Critical Needs

For sustained management of mycotoxins along the food chain, the following procedures are recommended:

Public Policy

1. Develop uniform standards and regulations for mycotoxin contamination.
2. Support joint international cooperation (FAO/ WHO/UNEP) to adopt standardized regulations.
3. Develop a safe food supply for local populations.

Mycotoxin Detection

1. Develop new technologies for mycotoxin analysis, including multiple-toxin analysis, and improve detection of specific mycotoxins in prepared foods.
2. Develop biomarkers for human and animal exposure to mycotoxins, including multipanel arrays that can detect exposure to multiple toxins.

Human and Animal Interactions

1. Assess mycotoxins as virulence factors.
2. Research the effect of mycotoxins as immunosuppressors.
3. Evaluate toxicological interactions of toxins with the host (activation and detoxification of mycotoxins by host metabolism).
4. Examine population variation for sensitivity to mycotoxins
5. Assess interactions between mycotoxins and drugs, diet, and nutrition.
6. Assess the role of fumonisins on humans and their involvement in esophageal cancer.
7. Assess the risks of ochratoxin exposure due to its occurrence in a variety of foods and environmental locations.

Plant and Fungus Interactions

1. Establish a better understanding of the factors affecting mycotoxin formation in the field and in storage.
2. Improve understanding of the ecology and epidemiology of mycotoxin-producing fungi.
3. Develop sound agronomic-management practices to decrease mycotoxin contamination.
4. Develop host-plant resistance to mycotoxin-producing fungi and to mycotoxin occurrence.
5. Develop models to better forecast the potential of mycotoxin contamination.
6. Research genetic regulation and biosynthesis of mycotoxins by the producing organisms.

Indoor Air Quality

1. Determine mycotoxins responsible for indoor air-quality problems.
2. Develop sound sampling protocols for assessing fungal populations.

3. Establish limits for respiratory exposure to mycotoxins.

Defence against Mycotoxins

1- The first line of defence against mycotoxins is to avoid eating mouldy and rotten food.

2- The second line of defence is a properly functioning liver, the major organ that detoxifies harmful chemicals. Liver function can be improved by taking liver supplements such as herbs and by detoxifying the body with hyperthermia.

3- Plants and foods with high Brix readings will dehydrate before spoiling (getting mouldy). Therefore, high Brix readings are the third line of defence against mould and aflatoxin consumption.

4- The intake of antioxidant-rich foods that support the liver by helping to remove toxic chemicals from the body.

5- The intake of chlorophyll found in all green leafy vegetables.

6- Consumption of certain foods that are reported to provide defence against mycotoxins, such as coffee, strawberries, tea, pepper, grapes, turmeric, fava beans, garlic, cabbage, and onions as well as chemosorbent materials (Abdel-Wahhab, 2000; Abdel-Wahhab and Aly, 2003l Abdel-Wahhab et al., 1998, 1999a, 2005b, 2015b).

7- The use of electro-medicine that neutralizes mycotoxins in the blood.

2.7.2. Recommendations

1. Setup and coordinate research and monitoring programmes on different types of mycotoxins.
2. Standardize sampling, sample handling and analysis.
3. Test economic viability and acceptability of existing drying technologies.
4. Develop a field kit for analysis.
5. Improve on-farm storage facilities.
6. Improve coordination and streamlining of programs in African-Asian countries.

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