REVIEW

Mycotoxins and child health: The need for health risk assessment

Sherif O. Sherif\(^a\), Emad E. Salama\(^b\), Mosaad A. Abdel-Wahhab\(^c\),* 

\(^a\)Department of Child Health, National Research Center, Dokki, Cairo, Egypt  
\(^b\)Department of Pediatrics, National Research Center, Dokki, Cairo, Egypt  
\(^c\)Food Toxicology & Contaminants Department, National Research Center, Dokki, Cairo, Egypt

Received 7 July 2007; received in revised form 5 June 2008; accepted 11 August 2008

Abstract

The occurrences of mycotoxins as food contaminants in different localities particularly in developing countries and the inevitable exposure of populations and children to these toxins with probable adverse outcomes need be scientifically and systematically assessed. Health risk assessment developed in the 1980s is separate from risk management, both with risk communication form the risk analysis framework adopted by the World Health Organization. The process contributes increasingly to policy development, public health decision making, the establishment of mycotoxin regulations and research planning. However, the exercise of the risk assessment structured approach is not simple and is faced up to lack of data, capable infrastructure facilities and need for trained personnel and resources. Furthermore, adopted methodologies need be developed focusing on child characteristics and health concerns. © 2008 Elsevier GmbH. All rights reserved.

Keywords: Mycotoxins; Aflatoxins; Risk analysis; Child health; Risk assessment

Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>348</td>
</tr>
<tr>
<td>Major mycotoxins and child health</td>
<td>349</td>
</tr>
<tr>
<td>Aflatoxins</td>
<td>350</td>
</tr>
<tr>
<td>Ochratoxin A</td>
<td>352</td>
</tr>
<tr>
<td>Fumonisins</td>
<td>352</td>
</tr>
<tr>
<td>Patulin</td>
<td>353</td>
</tr>
<tr>
<td>Trichothecenes</td>
<td>353</td>
</tr>
<tr>
<td>Deoxynivalenol</td>
<td>353</td>
</tr>
<tr>
<td>T-2 toxin</td>
<td>353</td>
</tr>
<tr>
<td>Zearalenone</td>
<td>354</td>
</tr>
<tr>
<td>Ergot</td>
<td>354</td>
</tr>
<tr>
<td>Measurement of mycotoxins in food</td>
<td>354</td>
</tr>
<tr>
<td>Risk analysis</td>
<td>354</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>355</td>
</tr>
<tr>
<td>Risk assessment comprises four interrelated steps</td>
<td>355</td>
</tr>
</tbody>
</table>

*Corresponding author. Tel.: +202 2283 1943; Fax: +202 337 0931. 
E-mail address: mosaad_abdelwahhab@yahoo.com (M.A. Abdel-Wahhab).
Introduction

Mycotoxins are fungal metabolites which when ingested, inhaled or absorbed through the skin; cause lowered performance, sickness or death in man or animals including birds (Pitt, 1996). Mycotoxins are an extremely diverse group of biological compounds. Generally, mycotoxins are of low molecular weight (mostly below 700 Da) and their chemical structure and physical properties are widely varied. They are found in different chemical groups (e.g. pyrones, anthracinones, coumarines, macrolides, steroids and cyclic polypeptides) and their biological conversion products of mycotoxins are also referred to as mycotoxins (Weidenborner, 2001; van Egmond and Speijers, 1999).

Mycotoxins are produced by fungi and contaminate various agricultural commodities either before harvest or under post-harvest conditions (FAO, 1991). Among the thousands of species of fungi, only about 100 belonging to genera Aspergillus, Penicillium and Fusarium are known to produce mycotoxins (Barrett, 2000). Mycotoxins also are relatively stable to cooking and processing therefore, food preparation procedures cannot be expected to remove mycotoxins safely (Rutledge, 1976; Rao et al., 1982; Bullerman, 2002).

The global occurrence of toxigenic fungi and the world crop trade are responsible for the widespread occurrence of mycotoxins in various localities (Smith, 1997). Crops in tropical and subtropical areas are more susceptible to contamination than those in temperate regions, since the high humidity and temperature in these areas provide optimal conditions for toxin formation. Poor harvesting practices, improper storage and less than optimal conditions during transportation, marketing and processing can also contribute to fungal growth and increase the risk of mycotoxin production (Thomson and Henke, 2000; Bhat and Vasanthi, 2003). According to the Food and Agriculture organization (FAO) of the United Nation, 25% of the world grain supply is contaminated with mycotoxins (FAO, 1996). However, the economic costs of mycotoxins on crops and livestock are impossible to accurately determine because of lack of sufficient data (CAST, 2003).

Aflatoxins (AFs) were isolated and characterized after the death of more than 100,000 Turkey poult (Turkey-x-disease) was traced to the consumption of a mold-contaminated peanut meal (Blount, 1961; Bennett and Klitch, 2003). The veterinary literature has been a rich source of information on known and potential mycotoxin problems. In animals, mycotoxins are capable of producing acute toxic, carcinogenic, mutagenic teratogenic and estrogenic effects on animals at normal levels of exposure and young animals are more sensitive to mycotoxins than matures. Mycotoxins are known to cause animal intoxications and adversely affect growth and reproduction in animals causing serious economic losses (Goldblatt, 1969; Fink, 1999; WHO, 1979; CAST, 2003).

Mycotoxins may affect many diverse cellular processes and have a wide spectrum of toxicological effects. This complexity is reflected in the very diverse range of responses by different animal species and it is likely that there will be also differences in response amongst different races of humans that bear on genetic basis and even amongst different individuals of the same race (Kuiper-Goodman, 2004).

These toxins may affect the reproductive system, affect the immune system, exhibit hormonal activity, affect specific target organs and may be neurotoxin. 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, cause skin irradiation, have hematological effects and reduce growth (Richard, 1991; Sharma, 1993; CAST, 2003; Kuiper-Goodman, 2004).

Meanwhile there is ample scientific evidence of mycotoxins producing acute and chronic adverse health effects in animals definite evidence of these cause-effect relationships in humans is meager (Hendricks, 1997; Fink, 1999; CAST, 2003). Involvement of these fungal metabolites in human disease derives animal
studies, observational and epidemiological evidence (Goldblatt, 1969; WHO, 1979; CAST, 2003).

In humans, mycotoxins can cause outbreaks of acute human mycotoxicoses (Peraica et al., 1999; CDC, 2004). Carcinogenicity is the most recognized late adverse health effects of exposure to mycotoxins in humans. With advancement of research, the significance of mycotoxins to human health is increasingly being recognized. Species of Stachybotrys rarely pathogenic for man, have earned a considerable notoriety in recent years due to their production of potent toxins. They have been linked to some cases of infant death in moldy buildings (CDC, 2000; Jarvis, 2002).

Exposure to mycotoxins is mostly by ingestion; however, other routes such as inhalation, contact, and passive exposure resulting from a mycotic infection by a toxigenic fungus have been recognized (CAST, 2003). Directly contaminated commodities as cereals or indirectly contaminated animal products (milk, meat and eggs) with converted small amounts of mycotoxins derived from animals that have consumed contaminated feeds are the main source of human exposure to these toxins. A widely studied example is the carry over of AFs from feed into milk and milk products, where they appear mainly as aflatoxin M₁ or other secondarily toxigenic animal products (WHO, 1979; Watson, 1985; FAO, 2001).

The degree of toxicity of different chemicals in laboratory animals generally, has been found to be affected by differences in species, age (fetus, young or old), and sex (Goldblatt, 1969). Infants and children are considered to be more susceptible to different toxins than adults, because of their lower body weight, higher metabolic rate, lower ability to detoxify and because of incomplete development of some organs and tissues such as the central nervous system (WHO, 1986; NAS, 1993).

The hazardous impact of human exposures to mycotoxin can take numerous shapes of various severity and clinical significance. Consumption of foods heavily contaminated with mycotoxin has resulted in acute intoxication episodes in human populations. A characteristic feature of mycotoxicoses is their protean symptoms and the wide array of signs shared by other disease states. Consequently, it is likely that the diagnosis of mycotoxicoses is covered up unless kept in mind and get properly investigated (Kuiper-Goodman, 2004; Etzel, 2006). Late adverse health effects of exposure to minute amounts of mycotoxins are widely varied and principally include cancer. Nonetheless, human illnesses caused by mycotoxins may be a larger public health problem than anyone realizes because a long period elapse before an illness is recognized unless large amounts of mycotoxins are consumed resulting in acute symptomology (Hesseltine, 1985). Still, as with pesticides, lifelong consequences of exposures to chemicals in early life are beginning to be observed (Forrest and Riley, 2004; NAS, 2004).

The significance of mycotoxins-induced adverse health effects derives from natural occurrence of mycotoxins as contaminants of crops and food, the possibility of exposure in all age of exposed communities. Alas, after decades of research on mycotoxins, still missing are critical evaluations of the actual human health impacts of these inevitable food contaminants in many parts of the world. Meanwhile, available literature includes incriminating statements blaming mycotoxins for child diseases without complete scientific evidence (Denning, 1987; CAST, 2003; Kuiper-Goodman, 2004).

Health risk assessment is structured scientific approach widely used in environmental settings (NAS, 1983) and food safety appraisal (FAO/WHO, 1995; CAST, 1999). The purpose of health risk assessments is to predict, as much as scientifically possible, the health implications of exposure to certain contaminants (e.g., mycotoxins) over time (NAS, 1983; Paustenbach, 1989; FAO, 1998). It also includes a comparison to other risks as well as socioeconomic factors (Rodricks, 1994). The output of risk assessment should provide the risk manager with sufficient information and advice on the predicted incidences and natures of the adverse health effects that would result from exposure to mycotoxins. Its credibility depends to a large extent on the strength of the scientific evidence on which it is based. The expected outcome of health risk assessment should help determine what actions, if any, are needed to reduce health risk in the community and which actions would be the most effective in reducing risks and to set control regulations. It also often plays an important role in cost-benefit analysis and risk communication (WHO, 2000a; Rodricks, 2002).

However, a special approach that take into account child/adult biological differences is needed for assessment of the hazardous impact of environmental toxicants on child health (WHO, 1986, 2001a, 2006a; Larsen and Pascal, 2001; Kyle et al., 2006). The aim of this review is to address the importance of developing child-based health risk assessments for exposure to mycotoxins. Also, called for are research efforts to build a comprehensive data set from which to evaluate the extent and severity of child exposures to mycotoxins.

**Major mycotoxins and child health**

Several mycotoxins in agricultural products and food cause health hazards to people and animals although there are many species of toxigenic molds, only a few mycotoxins, particularly those affecting cereals and groundnuts, are considered to be significant for humans. Mycotoxins of worldwide public health importance are: AFs, ochratoxins (OAs), fumonisins, zearalenone
Mycotoxins can be dealt in a system perspective comprising three interacting subsystems: metabolism and toxicology; health and productivity and wealth. These subsystems significantly interact. After exposure (by ingestion, inhalation or skin contact), the toxicity of a mycotoxin is determined by a sequence of events (metabolism) involving the administration, absorption, transformation, pharmacokinetics (PK), molecular interactions, distribution and excretion of the toxin and its metabolites. In turn, the toxicity of a mycotoxin will be manifested by its effect on the health and productivity of crops, humans and animals and these effects will influence the production of wealth associated with human endeavour and agricultural and livestock products (FAO, 2001).

### Aflatoxins

AFs are difuranocoumarin derivatives produced by a polyketide pathway by many strains of *Aspergillus flavus*, *Aspergillus parasiticus* and the rare *Aspergillus nomius*, which contaminate agricultural commodities. They have toxic, carcinogenic, mutagenic and teratogenic effects in laboratory animals (Abdel-Wahhab et al., 1998, 1999b, 2005, 2006). AFs are one of the most potent toxic substances 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 (Goldblatt, 1969; Jarvis, 1976; IARC, 1993a; CAST, 2003).

The liver is the main target organ for aflatoxin toxicity and carcinogenicity (Abdel-Wahhab et al., 2007). Early symptoms of hepatotoxicity from aflatoxicosis are protean and may masquerade many other forms of toxaeamias. It can manifest as anorexia, malaise, and low-grade fever. Aflatoxicosis can progress to potentially lethal acute hepatitis with vomiting, abdominal pain, hepatitis, and eventually death (Krishnamachari et al., 1975; Etzel, 2002). Recently, acute aflatoxicosis outbreaks affecting a large geographical area and causing over 123 deaths were reported in Kenya (CDC, 2004; Azziz-Baumgartner et al., 2005; Lewis et al., 2005). For the diagnosis of sporadic cases of aflatoxicosis cognisance of geographical location, past events, staple diet and clinical features to exclude other infections; high index of suspicion and importantly serum levels of aflatoxin are required (Mwanda et al., 2005).

The human gastrointestinal tract rapidly absorbs AFs after consumption of contaminated food and the circulatory system transports the AFs to the liver (Fung and Clark, 2004). From 1% to 3% of ingested AFs irreversibly bind to proteins and DNA bases to form adducts such as aflatoxin B1-lysine in albumin (Skipper and Tannenbaum, 1990). Depending upon the genetic predisposition of animal species, aflatoxin is metabolized by microsomial mixed function oxygenase (MFOs) to form metabolites as aflatoxin M1, aflatoxin Q1, aflatoxin P1 and aflatoxin B1-8,9-epoxide. Moreover, in the liver cells, cytoplasmic reductase acts on AFB1 to form aflatoxicol (Campbell and Hayes, 1976). Disruption of proteins and DNA bases in hepatocytes causes liver toxicity (Tandon et al., 1978). The metabolism of AFs plays a major role in deciding the degree of its carcinogenicity and toxicity (Patterson, 1978). In all species and tissues tested to date, mutagenicity, carcinogenicity and DNA-binding activity of aflatoxin B1 appear to result from its activation by cytochrome P450 enzymes to produce aflatoxin B1-8,9-epoxide (WHO, 2002).
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). In Qidong, China, an area of both high aflatoxin exposure and endemic hepatitis B infection – mutations in the p53 tumor suppressor gene were observed in tumor tissues from residing patients with hepatocellular carcinoma (HCC). Many of the point mutations observed were G T or G C transversion events (Hsu et al., 1991). Also, in patients residing in sub-Saharan Africa, where high exposure to aflatoxin B1 and high rates of hepatitis B infections prevail, occurring in liver cancer from people exposed to aflatoxin and infected with hepatitis B.

Aflatoxin-related mutations with a hot spot at codon 249 of the p53 gene were observed in HCC tumors (Bressac et al., 1991). The p53 gene mutations can be measured in DNA from blood and has been shown to be a biomarker of aflatoxin exposure and effect (Eaton and Groopman, 1994; Eaton and Gallagher, 1994; Groopman et al., 1996; Semenza and Weasel, 1997; Wild and Turner, 2001; Groopman and Kessler, 2005).

AFs can cross placental barrier, and thus can adversely affect fetal systems, to increase still-births and neonatal mortality (Wild et al., 1991; Hendricks, 1997; Maxwell, 1998). In-utero exposure to AFs could be detected on assaying maternal venous peripheral blood and cord blood For AFB1-lysine adducts. In the Gambia, there was a highly significant correlation between adduct levels in maternal venous and matched cord sera indicating maternal dietary intake to be important determinant of the carcinogenic-induced damage in the fetus (Wild et al., 1991). Analysis of 64 cord blood samples from pregnant women in Sierra Leone revealed the presence of AFs in 58% of samples. However, there was no relationship between aflatoxin in maternal and cord blood. The effect these toxins might have had on the birth weight of infants need be assessed (Jonsyn et al., 1995).

In UAE, Abdulrazzaq et al. (2003b) performed a study on AFs in cord blood in relation to birth weight. Aflatoxin B1, M1 and M2 were measured using high performance liquid chromatography. AFs were detected in 110 (54.7%) samples, 27 of which were positive for B1, 106 for M1 and 31 for M2. There was a significant negative correlation ($p<0.001$) between birth weight and levels of aflatoxin. A significant number of infants in the UAE are exposed to these toxins which reflect maternal ingestion of aflatoxin-containing food.

Maternal consumption of aflatoxin contaminated food whilst breast-feeding can result in the accumulation of AFs and their metabolites in breast milk. In exposed communities, AFs have been detected in breast milk (Coulter et al., 1984; Saad et al., 1995; Navas et al., 2005). Estimated carryover of aflatoxin from dietary intake to milk in animals is around 1%, and similar estimates were made from studies measuring intakes versus excretion in individual women in The Gambia. However, Breast-feeding likely provides a period of relatively low aflatoxin exposure in a population whose primary weaning foods, particularly maize, are at high risk of contamination (Zarba et al., 1992). Approximately 95% of AFB1 metabolites excreted in milk are in the form of AFM1, though AFM2, AFG1 and AFB1 are also reported (Zarba et al., 1992; El-Nezami et al., 1995; Abdulrazzaq et al., 2003a; Turconi et al., 2004). Recently, Polychronaki et al. (2006, 2007, 2008) reported that breast milk samples obtained from 388 Egyptian women were shown to have detectable AFs M1 with levels in nearly 36% of samples (13.5 pg/ml, interquartile range 10.27–21.43).

The IARC (1993a) classified AFM1 as a proven animal carcinogen, but as yet there is insufficient data to be classified a human carcinogen, and thus is regarded as a possible human carcinogen (group 2B). AFM1 although less carcinogenic than AFB1, it is reportedly as cytotoxic (Neal et al., 1998) and is being consumed by infants that are rapidly developing and thus highly susceptible to toxic insult (CAST, 2003).

Mycotoxin-induced adverse effects on the immune status of human adults and children have been reported (Turner et al., 2003; Jiang et al., 2005). A reduced level of salivary sIgA has been associated with aflatoxin exposure in Gambian children (Turner et al., 2003). It is hypothesized that early and repeated exposures to AFs in-utero and through childhood might predispose to cancer liver later in life. Moreover, immunosuppression due to consumed AFs is another contributing factor (Wild et al., 1991; Maxwell, 1998). AFs thus, may increase child susceptibility to infections and may cause failure of immunizations (Hendricks, 1997).

Mycotoxin-induced adverse effects on the immune status in animals are well documented. Meanwhile there is insufficient evidence for counterpart effects in humans. Denning et al. (1995), addressed the potentially contributory role in the poor outcome of acute lower respiratory infections in children in the Philippines and came to the conclusion that a potentially immunosuppressive role of AFs in the context of pneumonia cannot be excluded. Oyelami et al. (1997) demonstrated that all children died with pneumonia had detectable levels of AFs in their lungs. In this concern, the review of Williams et al. (2004) “Human aflatoxicosis in developing countries” covers in depth, possible roles of AFs in child malnutrition and infections covering zinc, iron and vitamin A deficiencies and HIV infections and liver cancer.

Neonatal jaundice (NNJ) of obscure cause is a major problem in many tropical developing countries. Recently, AFs have been identified as a risk factor in newborn jaundice. Many recent epidemiologic studies show inconclusive evidence of the association between
NNJ and exposure to AFs (Hendricks, 1997; Ahmed et al., 1999; Hadhoud et al., 2001; Galal et al., 2006). G6PD deficiency and/or the presence of serum AFs are risk factors for NNJ in Nigeria (Sodeinde et al., 1995). In another study, the frequency of detection of AFs in peripheral blood was not significantly different in jaundiced and non-jaundiced babies. AFs were detected in the blood of over 50% of neonates with jaundice of ‘unknown’ aetiopathology. There was no correlation between severity of hyperbilirubinemia and serum aflatoxin levels (Ahmed et al., 1995; Galal et al., 2006).

AFs may contribute to early childhood growth faltering (Turner et al., 2003). A probable consequence of early exposure to AFs is growth faltering. Epidemiological evidence derived from cross-sectional studies comprising West African young children < 5 yr, where a dose–response relation between aflatoxin exposure and the degree of stunting and underweight has been observed (Gong et al., 2002, 2003). A longitudinal study on infants in Benin showed a strong negative correlation (p < 0.0001) between AF-alb and height increase over the 8-month follow-up after adjustment for age, sex, height at recruitment, socioeconomic status, village and weaning status (Gong et al., 2004) and in a study on urinary biomarkers of aflatoxin exposure in young children from Egypt and Guinea (Polychronaki et al., 2008).

Kwashiorkor, a disease of children in Northern Africa and elsewhere in undernourished populations, which is usually attributed to nutritional deficiencies, may also be related to aflatoxin intake based on observational studies. AFs and/or probably other mycotoxins are incriminated in the pathogenesis of edema in malnourished infants and children and in the pathogenesis of kwashiorkor (Hendrickse, 1982, 1985; Coulter et al., 1986; Hendrickse and Maxwell, 1989; Golden and Ramadath, 1987). A multifactorial consensus of the etiology of kwashiorkor does not exclude the hypothesized role of mycotoxins in some cases of kwashiorkor, rather it mandates consideration of all relevant nutritional factors (Househam and Hundt, 1991; Jelliffe and Jelliffe, 1992).

AFs can induce liver lesions identical to those seen in cases of Indian childhood cirrhosis (Amla et al., 1971; Shank, 1978). It is hypothesized that in children with Indian childhood liver cirrhosis, excessive intake of copper may be acting in synergy with a hepatotoxicity of AFs (Tanner, 1998). The hepatopathic pathology of Rye and alike have been linked to AFs (Lucarelli et al., 2000). Shank (1977) found significant levels of AFs (1–4 mg/kg) in livers of 23 Thai children who had died of Rye’s syndrome. Children who have died from Rye’s syndrome in Czechoslovakia and in New Zealand have also been found to have had AFs in their livers at autopsy (WHO, 1979; Hendricks, 1997).

Ochratoxin A

The ochratoxins were the first group of mycotoxins to be found after the discovery of the AFs. OA is a secondary fungal metabolite of *Aspergillus* and *Penicillium*. In European countries OA is probably the most ubiquitous mycotoxin, in particular, in Central Europe (Sweden, Germany, Denmark and the UK) and it can be revealed at levels greater than 0.1 ppb in more than 90% of human and swine blood samples (Petzinger and Weidenbach, 2002). Main food carriers of OA are considered beer, cereals, coffee and pork meat (Petzinger and Weidenbach, 2002) and cocoa products (Tafuri et al., 2004; Wanigasuriya et al., 2008). Outbreaks of Balkan nephropathy, a fatal chronic renal disease occurring in limited areas of Bulgaria, the former Yugoslavia, and Romania, have been associated with OA (Petkova-Bocharova and Castegnaro, 1985; Abid et al., 2003). Levels of OA are higher in the blood of patients with Balkan nephropathy than in the blood of unaffected people (International Agency for Research on Cancer (IARC), 1993b).

OA occurrence in food is widespread and it has been shown to be nephrotoxic, hepatotoxic, teratogenic in laboratory animals (Abdel-Wahhab et al., 1999a, 2005; Abdel-Wahhab, 2000) and carcinogenic to single-stomached animals (Kuiper-Goodman and Scott, 1989). Moreover, tumors of the upper urinary tract have been associated with exposure to OA (WHO, 2001b). Some researchers speculate that OA may be linked to testicular cancer. Epidemiologic information suggests a carcinogenic exposure in early life may play a role in the development of this cancer (Drew et al., 1983; Schwartz, 2002). IARC has determined that there is sufficient evidence in experimental animals for the carcinogenicity of OA and categorized it as possibly carcinogenic to humans (group 2B) (IARC, 1993b).

Experimental in-utero transfer of OA has been documented in mice (Fukai et al., 1987) and rats (Abdel-Wahhab et al., 1999a). In humans, OA levels were twice as high in umbilical cord blood as in maternal blood at the time of delivery suggesting that active placental transfer may be occurring in humans (Zimmerli and Dick, 1995; Jonsyn et al., 1995). In breast milk samples, the highest concentrations of OA have been found in Sierra Leone, where 35% of the samples contained OA at levels from 200 to 337 ng/ml (Jonsyn et al., 1995). OA in breast milk was found to affect the kidney function and the development of urinary tumors in infants and young children (Skauag, 1999).

Fumonisins

The fumonisins were discovered in 1988 following an outbreak of equine leukoencephalomalacia in South
Africa in 1970 (Marasas, 2001). Fumonisins are mycotoxins produced by at least 11 species of the fungus \textit{Fusarium}, including the maize pathogens \textit{Fusarium verticillioides} and \textit{Fusarium proliferatum}. Fumonisins can be divided into structurally distinct groups, four of which have been designated A, B, C and P fumonisins (Musser and Plattner, 1997; Rheeder et al., 2002). The fumonisins can disrupt sphingolipid metabolism (Missmer et al., 2001; Abdel-Wahhab et al., 2004; Marasas et al., 2004) which play a role in membrane and lipoprotein structure and in cell regulation as second messengers for growth factors, differentiation factors, and cytokines (Missmer et al., 2001). Epidemiologic studies suggest a link between exposure to fumonisin B₁ (FB₁) and esophageal cancer (Rheeder et al., 2002; Shephard, 2008).

In 1989 and 1990 corn grown in the United States had high levels of fumonisins; fatal outbreaks of equine leukomalacia and porcine prenatal and neonatal mortality and pulmonary edema occurred (Bane et al., 1992). FB₁ causes other fatal diseases in animals including pulmonary edema in pigs and developmental toxicity in rats (WHO, 2000a; Abdel-Wahhab et al., 2004). Epidemiologic studies of prevalence of neural tube defects in localities proved to have high occurrences of fumonisins suggest a link inbetween (Ncayiyana, 1986). A cluster of neural tube defects that occurred in South Texas in 1990 generated the hypothesis that ingestion of high levels of fumonisins in corn-based products is linked to birth defects such as anencephaly and spina bifida in humans (Hendrickse, 1999; Hendrickse et al., 1999; Missmer et al., 2000). Mexican Americans have neural tube defect rates that are much higher than those of non-Hispanic whites (Hendrickse et al., 1999; Missmer et al., 2006). A case-control study showed that increasing levels of the postpartum sphinganinetosphingosine ratio (a biomarker for fumonisin exposure) were associated with an increased odds ratio for neural tube defects (Missmer et al., 2006). Fumonisins was also found to interfere with cellular folate uptake (Stevens and Plattner, 1997). Studies in China and South Africa lend support to this association (Ncayiyana, 1986; Venter et al., 1995).

**Patulin**

Patulin is a mycotoxin produced by several \textit{Pencillium} and \textit{Aspergillus}, \textit{Bysschahlyans} species, but \textit{Pencillium expansum} is the most commonly encountered species. This fungus is the principal cause of apple rot (Davis and Diener, 1987; Steinman et al., 1989). Patulin was found in commercial apple juice and apple food for children at concentration ranged between 10 and 170 ppb (Prieta et al., 1994). Burghardt et al. (1992) stated that the toxic effects of patulin may involve directly cellular glutathione level and mitochondrial function in addition to its direct effects on the plasma membrane. Patulin also has an immunosuppressive effect and inhibits DNA synthesis (Sharma, 1993). Patulin is suspected to have carcinogenic properties, although IARC concluded that no evaluation could be made of the carcinogenicity of patulin to humans and that there was inadequate evidence in experimental animals (IARC, 1986).

**Trichothecenes**

The trichothecene mycotoxins are group of more than 200 structurally related sesquiterpenoid metabolites produced by food borne and environmental fungi that are characterized by the tetra cyclic 12,13-epoxytrichothec-9-ene ring system (Grove, 2007). Toxicological effects associated with trichothecene mycotoxin poisoning in humans and animals include anorexia, gastroenteritis, emesis and hematological disorders (Pestka and Casale, 1990). The immune system is extremely sensitive to trichothecenes. Exposure to low trichothecene doses induces rapid, transient upregulation of proinflammatory cytokines causing immune stimulation, whereas high doses of trichothecenes cause apoptosis in lymphoid tissues resulting in immunosuppression (Pestka et al., 2004; CAST, 2003).

**Deoxynivalenol**

Deoxynivalenol (DON, vomitoxin) belongs to the Type B non-macrocyclic trichothecenes commonly found in wheat, barley and corn that have been infected by the mold \textit{Fusarium graminearum} (Placinta et al., 1999; Schothorst and van Egmond, 2004). In children, ingestion of heavily DON-contaminated food results in vomiting within hours (Shiefer and Beasley, 1989; Pestka et al., 2004, Pestka and Smolinski, 2005). Multiple outbreaks of vomiting illness during 1961–1985 in China were linked to consumption of foods made with grain contaminated with vomitoxin (Luo, 1989). In 1987, nearly 100 persons in India became ill after they consumed wheat products from which vomitoxin and other trichothecene mycotoxins were recovered (Bhat et al., 1989). In 1997 and 1998, approximately 1700 school children in the United States developed vomiting, nausea, headache and abdominal cramps after eating burritos (CDC, 1999). Vomitoxin was identified as a contaminant in the burritos and might have caused the outbreaks, which subsided within 24 h of onset (CDC, 1999).

**T-2 toxin**

T-2 toxin is a representative of a large group of trichothecenes. It belongs to the Type A chemical class.
of non-macrocyclic trichothecenes. The principle fungus responsible for the production of T-2 toxin is *F. sporotrichioides* (CAST, 2003). Some strains of this fungus also produce some closely related mycotoxins (HT-2 toxin and diacetoxyscirpenol) belonging to the same chemical class. The major effect of T-2 toxin and other trichothecenes is that they inhibit protein synthesis which is followed by a secondary disruption of DNA and RNA synthesis. It affects the actively dividing cells such as those lining the gastrointestinal tract, skin, lymphoid and erythroid cells. It can decrease antibody levels, immunoglobulins and certain other humoral factors such as cytokines (Niyo et al., 1988; Richard, 1991)

### Zearalenone

A mycotoxin produced by *Fusarium* species, has estrogenic and anabolic activity. ZEN was found in corn, wheat, barley, oats, sorghum and sesame. It can adopt a conformation resembling 17-beta-estradiol that allows it to bind to the estrogen receptor in target cells (Pillay et al., 2002). Livestock fed moldy feeds containing ZEN may produce milk and milk products that contain these estrogenic substances (Schoental, 1977).

Estrogenic agents can increase the plasma levels of cholesterol and triglycerides in females, and an association between oral-estrogen use and myocardial infection and stroke has been described (Wallace et al., 1977). Its estrogenic properties make exposure a concern for human health. Although studies are ongoing, researchers speculate that the mycotoxin may be associated with precocious puberty and possibly cervical cancer (Bhatnager et al., 2002).

In children, the major effect of ZEN bears on the reproductive system affecting reproductive organ structure and function and leading to hyperestrogenism (Kuiper-Goodman, 1991). ZENs may affect steady child growth and development; exposure to these compounds can cause premature thelarche, pubarche, and breast enlargement and precocious puberty (Schoental, 1983; Kuiper-Goodman et al., 1987). ZEN was detected in blood samples of children with precocious puberty in Puerto Rico (Saenz de Rodriguez, 1984) and of those with premature telarche in the Southeast part of Hungary (Szuets et al., 1997).

### Ergot

Ergot alkaloids are mycotoxins produced by the *Claviceps purpurea* and are known to be more of a problem on cereal grains (Lorenz, 1979). There are three main actions 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. Ergot neurohormonal effects are observed in serotonin and adrenaline antagonism. Adrenergic blocking agents prevent the stimulation of sympathetic nerves by antagonizing the effects of other drugs like epinephrine.

Ergotism following ingestion of contaminated food is very rare today. It is important for clinicians to recognize the symptoms because they may occur as side effects following therapeutic administration of ergot alkaloids (Caballero-Granado et al., 1997; Rosenthal et al., 1999).

### Measurement of mycotoxins in food

A vast array of food commodities is liable to contamination with mycotoxin usually frequently at low nanogram (ng)/g levels, in the complex chemical mixture of natural organic material. Since mycotoxins display a wide diversity of chemical structures, there are no uniform methods of analysis either collectively or for specific mycotoxins on various foods and feeds (Smith et al., 1995). Appropriate sampling procedures and validated qualitative and quantitative data on representative food samples are required (CA-1A, 1999).

The utilization of validated analytical methods (e.g. thin layer chromatography, high performance liquid chromatography or immunoassay methods) is essential to ensure that the results of food surveys provide a reliable assessment of intake as well as biological sample analysis. Official methods will have usually been validated for analytical performance in collaborative studies in which characteristics such as accuracy, precision, specificity and practicality have been tested. Regardless of whether accredited methods are used to produce data, laboratories should undertake internal analytical quality assurance measures such as use of tests for recovery and use of tests to confirm the identity of mycotoxins detected in samples (Jones, 1987; Gilbert, 1999; Gilbert and Anklham, 2002; WHO, 2002).

### Risk analysis

Risk is the probability of injury, disease or death under specific circumstances. A hazard is a set of circumstances that may cause adverse effects and the likelihood that a hazard will cause such effects is the risk associated with it (Henry, 1997). Risk assessment is the estimation of likelihood magnitude and uncertainty of population health risks associated with exposures. In the context of food safety, risk is defined as an estimate of the likelihood/probability of the occurrence of an adverse health effect in humans, weighted for its severity that may result from exposure to a biological, chemical or physical agent in food. The importance of risk
assessment lies not only in its capacity for estimating human risk but also in its function as a framework for organizing data as well as for allocating responsibility for analysis (WHO, 2000b).

Risk analysis as a scientific tool applied to food safety concerns is made up of three separate parts: risk assessment, risk management and risk communication (NAS, 1983; FAO/WHO, 1995, 2002). These three components are interrelated and cannot function well in isolation. Risk analysis must be the foundation upon which food safety policy and consumer protection measures are based (FAO/WHO, 2002). These three elements are:

(a) **Risk assessment**: A process of systematic and objective evaluation of all information pertaining to food hazards (consisting of hazard identification, hazard characterization, exposure assessment, and risk characterization).

(b) **Risk management**: The process of weighing policy alternatives in light of risk assessment and if required, selecting and implementing appropriate control options and regulatory measures.

(c) **Risk communication**: The exchange of information and opinions concerning risk and risk management options and actions among risk assessors, risk managers, consumers and other interested parties.

**Risk assessment**

The scientific process of risk assessment was formulated by the US National Academy of Science in 1983 (Fig. 1). The process is linked to research but is separate from the policy exercise of risk management (NAS, 1983).

**Risk assessment comprises four interrelated steps**

Identification of the hazard and comprehension of the danger it represents, the impact in terms of human health and the circumstances under which the danger is present (hazard identification).

1. Qualitative and/or quantitative evaluation of the adverse effects of the hazard on human health (hazard characterization).
2. Qualitative and/or quantitative evaluation of the likely degree of consumption or intake of the hazardous agent (exposure assessment).
3. Integration of the first three steps into an estimate of the likely adverse effect in the target population (risk characterization).

**Health risk assessment**

**Hazard identification**

Hazard identification is the process of determining whether exposure to an agent can lead to adverse health outcomes. It is based on analyses of a variety of data that may range from observations in humans and animal data to an analysis of mechanisms of action and structure–activity relationships. Each source of

---

**Fig. 1.** Diagram of elements of risk assessment and risk management (NAS, 1983; WHO, 2002).
information has its advantages and limitations which determine the weight of the evidence. The result of the hazard identification exercise is a scientific judgment as to whether the chemical evaluated can, under given exposure conditions, cause an adverse health effect in humans (WHO, 1999, 2006a).

Exposure assessment

Exposure assessment is to identify and define the exposures that occur, or anticipated to occur, in human populations (WHO, 1993). Risk of children from mycotoxins depends on the degree of exposure to and on the degree of hazard from individual mycotoxins. In regions that are at high risk for aflatoxin contamination, it is important to understand exposure patterns (Kuiper-Goodman, 2004). Key features of exposure assessment in children include marked variability with children of the same age often exhibiting tremendous differences in their exposure. Combined with the rapid growth that occurs during childhood, the variability in the population of children generally limits the extent to which fixed age ranges can be used for assessing children’s development, exposure and risk (Thompson, 2004). Timing of exposure is critical in early stages of life and delayed adverse effects require integration of intake estimates over long periods (Paustenbach, 2001).

A major component of risk assessment of chemicals in food is estimation of chemical exposure based on food consumption. This can be difficult since an individual’s diet contains a variety of items and the food composition and dietary intake or food consumption rate can vary in relation to individual variability, age, seasonal differences, and geographic, cultural and economical conditions (Rees and Tennant, 1994). Dietary exposure estimates for food contaminants as mycotoxins are limited by the availability of the database for food consumption rates, contaminant concentration in various food items and contributions from other sources of exposure, food preparation methods, bioavailability, bioactivity, monitoring data on chemical or reactive breakdown product and chemicals forms in food (Bullerman, 1979; CAST, 2003).

Three main methods are used to assess human exposures to chemical and biologic agents: questionnaires and other indirect means, environmental monitoring including personal monitoring and biomonitoring. All these methods seek to gain information on the concentrations of the agent(s) to which the person(s) may have been exposed, the duration and frequency of that exposure and an estimation of their internal dose. Other data that should be factored into the assessment especially when the human population being studied contains fetuses and children are the timing of the exposure (or when the exposure took place) during those critical susceptible periods of development (Needham et al., 2005).

Mycotoxin biomarkers and exposure assessment

Measures of contaminant in biological material (biomarkers) afford a direct measure of exposure modified by and integrated over sometime in the past which depends on physiological factors that control metabolism and excretion (WHO, 2001b). Also, biomarkers (Fig. 2) provide a valuable adjunct because they permit evaluation of the dose–response relationships and thus provide a bridge between measures of external exposure and internal effect (Moore, 2003).

Aflatoxin, metabolite or adducts may serve as biomarkers. A recent study investigated aflatoxin exposure in Egyptian children (n = 50, aged 1–2.5 years) by assessing urinary aflatoxin metabolite (AFM1, AFB1, AFB2, AFG1 and AFG2 levels). Samples from Guinean children (n = 50, aged 2–4 years) were analyzed in parallel providing a comparison to a region of established frequent aflatoxin exposure. Overall AFs were less frequently present in Egyptian (38%) than Guinean urine samples (86%) (p<0.001), which was particularly related to differences in detection rates of AFM1 (8% compared to 64%, respectively (p<0.001)). For AFM1, the geometric mean level in Guinea (16.3 pg/ml; 95% CI: 10.1, 26.6 pg/ml) was 6-fold higher (p<0.001) than in Egypt (2.7 pg/ml; 95% CI: 2.5, 2.8 pg/ml). Urinary AFs from healthy children in these two regions have not previously been reported, and exposure appears modest in Egypt compared to Guinea (Polychronaki et al., 2008).

Aflatoxin albumin adducts (Wild et al., 1991) and aflatoxin DNA adducts have been utilized in exposure assessment (Qian et al., 1994; Groopman, 1994; Perera, 1995; Azziz-Baumgartner et al., 2005). However, currently available biomarkers for aflatoxin (e.g., aflatoxin/albumin adducts in blood serum), as an individual measure of aflatoxin exposure, are still limited because they reflect aflatoxin exposure only for the lifetime of the marker (about 22 days for serum). A measure of aflatoxin exposure over a third to half a lifetime is still needed to more nearly reflect the probable induction time for human cancer (Henry et al., 2000).

FB1 is an inhibitor of sphinganine N-acyltransferase and the increase in the sphinganine/sphingosine (Sa/So) ratio in urine or serum. Sa/So ratio has been used as an indicator of fumonisin exposure in animals. In humans, efforts to evaluate sphingosine/sphinganine-1-phosphate as a serum biomarker of exposure are at its beginning. Monitoring of Sa and So in human urine and monitor the Sa/So ratio in urine of humans exposed to FB1 in corn diets over 1 month suggest that sphingolipid metabolism of humans could be affected by FB1 intake,
the urinary Sa/So ratio may be useful for evaluating FB₁ exposure when the contamination of FB₁ is high (Qiu and Liu, 2001).

Probabilistic exposure models

The use of probabilistic modeling techniques within the field of exposure assessment is a subject of increasing interest. Mathematical modeling is the process of combining quantitative data with a qualitative understanding to produce an explanatory and predictive tool (Pullan and Smith, 2004). Numerical simulation techniques provide powerful tools that will take advantage of all available knowledge (empirical data, expert judgments, etc.), in order to provide realistic estimates of exposure. In these approaches, various values can be introduced to ensure the representativeness of all possible outcomes. The results, however, are only as good as the input data, algorithms and assumptions (Arcella and Leclercq, 2004). Modeling for children is difficult as exposure data often have a wide array of age categories. The ability to model children’s exposure should improve over time with the collection of better information, but this depends on ensuring that research focuses on filling the existing gaps (Thompson, 2004).

Dose–response assessment

Dose–response assessment determines the relationship between changes in exposure levels and specific effects that result. A range of different approaches may be needed to determine the relationship between dose to the target tissue and adverse effects in human depending on the relevant data available. Inherent in this process are many uncertainties. Animal model is still the most widely used method for assessing potential toxicity risks to humans. Nonetheless, animal-to-human extrapolation has its problems. There are a variety of difficulties faced by regulatory agencies that attempt to use results of animal studies to predict human risks (Sexton et al., 1995; WHO, 2000b; Edler et al., 2002).

A prime tenet of toxicology is that it is the dose that makes the poison. Mycotoxins can be dealt with as carcinogens or toxigenic agents. With regard to carcinogens, it is generally presumed that there is no threshold dose below which there is no induction of cancer initiation and thus there would always be some risk even at very low doses (Fan and Tomar, 1999).

For quantification of toxicity LD₅₀ and lowest-observed-adverse-effect-level (LOAEL) are two extremes. For non-carcinogens or genotoxic chemicals threshold dose for LOAEL and NOAEL for a toxicity endpoint specific to a chemical are determined. These levels are then divided by an uncertainty factor (UF) to account for one or more of the following: quality of data, intra-species differences and inter-species differences. The value obtained represents the total health protective reference exposure level (REL) with a reasonable safety margin at which no appreciable adverse health effects are anticipated (Fan and Tomar, 1999).
The range of UFAs applied in the derivation of tolerable intakes (TIs) has been wide (1–10,000) although a value of 100 has been often used. The value of 100 has been regarded as comprising two factors of 10 each allow inter-species and inter-individual (intra-species) variations. Further improvements of extrapolation process allow subdivision of each 10-fold factor to incorporate appropriate data on toxicokinetics or toxidynamics where these exist. Thus, the default inter-individual 10 \times factor can be seen as comprising equally a half-log (3.16 ×) PK and a similar half-log (3.16 ×) pharmacodynamics (PD) component. The range of neonate/adult half-life ratios exceeds the 3.16-fold factor commonly ascribed to inter-individual PK variability. Furthermore, UF may not be adequate for certain chemicals in the early postnatal period (WHO, 1987; Renwick, 1993, 1998; Ginsberg et al., 2002).

Risk characterization

Risk characterization is the process of estimating the probable incidence of an adverse health effect to humans under various conditions of exposure including a description of the uncertainties involved. Risk characterization has to be an iterative process in which information on hazard and exposure are peer reviewed, matched and any discrepancy taken into account where necessary by the generation of additional data (Paustenbach, 2001). The demonstration of specific patterns of association can provide strong support for causal interpretations if patho-physiological models agree with them. In such cases, more complex, and hence less implausible, patterns of confounding or bias are required as counter-explanations (Hill, 1965). Associations can be demonstrated most clearly if it is possible to compare groups exposed to several levels of the agent in question, but, in the last resort, hypotheses about the exact form of exposure/effect relationships can be tested effectively in experimental situations, where the research worker has some control over exposures (WHO, 2000a).

Current state of mycotoxins risk assessment

Risk assessment considers scientific principles related to human and animal health and there is enormous variability in the extent and nature of different data bases for risk assessment. Adequate human data are the most relevant data for assessing risk to humans. Most environmental epidemiology data are necessarily of an observational nature, that is, they are observations based on existing situations (WHO, 1983). Such studies are generally conducted in countries where there is known to be high exposure to a particular mycotoxin. Different conditions such as those related to dietary patterns, prevalence of infections or lifespan may influence the outcome of such studies (Kuiper-Goodman, 2004). These epidemiological studies are also not sufficient because exposure is unusually uncontrolled (Rodricks and Park, 1983).


The notion of uncertainty and natural variability must be taken into account in risk analysis (Randell, 2002; Hoffman and Hammonds, 1992, 1994). The assessment of uncertainty is a critical part of the risk assessment process. Much of the limitations and uncertainty is associated with the database or paucity of data. As the database is strengthened, the findings will become more relevant (GAO, 2006).

It has been found, consistently, that naturally contaminated grains are more toxic than would expect from the presence of 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 the hazard assessment and risk assessment for children (Kuiper-Goodman, 1991).

At present, toxicological studies are being directed at the combined and possible synergistic effects that some of the mycotoxins may have on human and animal life. Clearly, if an accurate prediction of the possible health impact of individual mycotoxins in foods is difficult; possible additive or synergistic effects of multiple mycotoxins make the task far more complex (Tapia and Seawright, 1985; Kuiper-Goodman, 1999; van De Venter, 2000; Tessari et al., 2006).

Cancer risk assessment methods currently assume that children and adults are equally susceptible to exposure to chemicals. However, there is evidence that suggest increased susceptibility to cancer from early-life exposure, particularly for chemicals acting through a mutagenic mode of action (e.g. AFs). Further analysis is warranted to determine whether early-life exposure results in increased susceptibility to cancer compared with adult exposures (NAS, 1993; Anderson et al., 2000; Barton et al., 2005).

Considerable international efforts have been expended in assessing the health risks from just a few mycotoxins. In 1997, the JECFA Committee of the
Codex Alimentarius Commission considered that the weight of scientific evidence, which introduced epidemiological data, studies in laboratory animals and in vivo and in vitro studies of metabolites, supported the conclusion that AFs should be treated as carcinogenic food contaminants, the intake of which should be reduced to as low as reasonably achievable levels (ALARA levels) (WHO/FAO, 1997; Herrmann and Walker, 1999). Other assessed mycotoxins include aflatoxin M1, fumonisins B1, B2, B3, OA A, deoxynivalenol, and T-2 and HT-2 toxins and ZEN that may contaminate food commodities (IARC, 1993a–d; WHO/FAO, 2001; WHO, 2000a, 2002). However, these evaluations need to be re-examined from time to time with respect to new information on exposure, toxicology as well as a better understanding of the mechanism and mode of action (Kuiper-Goodman, 2004).

Strengthening the scientific basis for setting regulations is only one aspect of risk assessment outcomes with the aim of consumer protection and not only for trade considerations. Current regulations for mycotoxins world wide (FAO, 2004) show that nearly 20 countries have set regulations for permissible levels of mycotoxins in baby foods (22 countries) and feeds for young animals (39 countries) (FAO, 2004; Sherif, 2006). However, the wide variations in setting permissible levels in food and feeds for mycotoxins in foods and feeds might reflect irrationality and calls for scientific judgment. Based on risk assessment the European community (EC) has set forth the following regulation for mycotoxins in baby foods: EC Regulation 683/2004 which came into force on 1 November, 2004 (EC, 2004) sets the following limits and are set on a dry-matter basis:

- 0.1 µg/kg for AFB1 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 AFM1 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 OA for baby foods and processed cereal-based foods for infants and young children, and dietary foods for special medical purposes intended specifically for infants.

**Approaching risk assessment for children**

Children are reared in different communities where exposure to mycotoxins is likely different. Children have unique exposure possibilities to chemical hazards. Because children have more future years of life than do most adults, they have more time to develop chronic diseases that may be triggered by early environmental exposures. That overpopulation is more a feature of developing countries; millions of children are thus prone to be exposed to these toxins in developing communities (Williams et al., 2004; FAO, 2005).

Children are uniquely vulnerable to environmental toxicants because of their greater relative exposure, less developed metabolism, and higher rates of cell production, growth, and change. The environmental insults of childhood may manifest themselves over a lifetime of growth to adulthood and senescence. In addition to physiologic vulnerabilities, children may have great social vulnerabilities as well poverty, malnutrition (NAS, 1993; Carlson and Sokoloff, 1995). The disproportionate impact of exposure to toxic substances on children as compared to adults has deserved much research efforts. The fact that developmental exposure to agents as pesticides or other toxins produces effects that differ qualitatively and quantitatively from those produced by adult exposure requires a major empirical and conceptual foundation for child health risk assessment (NAS, 1993).

Developmental toxicology studies, though badly needed are difficult to perform. Though, epidemiologic evidence – whenever attained – is often difficult to draw in many situations whenever risk is low, number of people exposed is small, latency period is long and exposures are mixed and multiple (Hill, 1965; WHO, 2000b). The extrapolation of animal models to critical stages of human development is a real difficulty in determining counterpart adverse effects in humans (Bearer, 1998).

The manifestations of developmental toxicity will vary depending on the timing of exposure and the underlying processes that are occurring (NAS, 1993; EPA, 1991, 1996, 1997; Scheuplein et al., 2002; Tamburlini et al., 2002; Thompson, 2004). Comparing child to adult situations, many factors are considered: (i) exposure may be greater in young children due to a greater food ingestion rate (particularly for certain foods) per body weight and also greater inhalation rate and contact with soil, house dust, and other media which may contain contaminants (NAS, 1993; EPA, 1997); (ii) once exposure has occurred, the pharmacokinetic (PK) handling of xenobiotics is likely to differ from that in adults with respect to their metabolisms, clearance, protein binding and volume of distribution and (iii) pharmacodynamic (PD) differences in which the sensitivity of rapidly developing tissues/systems in neonates and young children may differ from that in adults (Besunder et al., 1988; Morselli, 1989; Kearns and Reed, 1989).

It is not yet known the extent to which mycotoxins, as environmental agents can adversely affects the health of the developing individual. Recent developments in information technology, molecular biology and...
instrumentation have provided new tools for use in environmental health research and biologically based risk assessment (WHO, 2001b). Biomarkers have the potential to be quantitative dosimeters of exposure and biologic effective dose, as well as early warning signals of biologic effect. Exposure biomarkers as aflatoxin adducts can reflect individual exposures, and they also focus exposures on key toxicological targets within the cell. Adducts can provide evidence for metabolic steps in the exposure–response continuum (Bearer, 1998; Schmidt, 2006). Biomarkers may document interindividual susceptibilities, as well as defining critical windows of exposure (Bearer, 1998). Studies to better understand inter- and intraspecies differences with respect to dose–response, especially the difference between adults and children are obviously needed (Dorne et al., 2005). Scientific advances in the field of biomarkers and OMIC sciences are expected to give more insight into pathological processes and inter- and intraspecies differences (Dorne and Renwick, 2005; Schmidt, 2006). Expected improved methodologies, could allow for developing more precise data on intra-species and possibly adult/child differences (ILSI, 2003)

Still the exercise of risk assessment for children and mycotoxins is faced with many difficulties regarding, assessment of exposure, the long latency of many diseases induced by the mycotoxins, confounding exposures from natural co-occurrences of mycotoxins or other toxins, or the effect of other dietary elements (as vitamins, antioxidants or chlorophyllic ingrediants) on toxicity (CAST, 2003; Kuiper-Goodman, 2004; Abdel-Wahhab and Aly, 2003, 2005; Abdel-Wahhab et al., 2004; Abdel-Wahhab, 2000; Oliveira et al., 2006).

Mycotoxins and health risk assessment in developing countries

It is unfortunate that the less developed countries tend to have climatic conditions that encourage mold growth and mycotoxin formation and hence are faced with much greater problems while at the same time having fewer resources to detect, control and reduce the extent of contaminated food. Also, mycotoxin regulations are unlikely to be of health concern (Stoloff et al., 1991; Scudamore, 1998). There are wide variations in expertise and resources between developed and developing countries and the responsibility for protecting public health may conflict with obligations to facilitate trade (FAO, 2003; Sherif, 2003, 2004). In parts of the world where food supplies are limited drastic regulatory measures to lower mycotoxin standards would lead to food shortages and higher prices (Bahat and Vasanti, 2003). The consumption of traded food items is small and laboratories to test their foods are economically and financially inaccessible. Where trade does occur, the least contaminated foods and feeds are exported which may lead to enhanced exposure of the producers (Henry et al., 1999; Wu, 2004). Meanwhile strict control for mycotoxins in foods and feeds has minimized such exposures in developed countries. The Food standards agency of Britain is of the opinion that provided that the levels of mycotoxins are kept to the lowest levels that are reasonably achievable, the benefits of eating these foodstuffs as part of a healthy and varied diet outweigh any possible risk to health (FSA, 2004).

Epilogue

The natural occurrence of mycotoxins varies between localities and at different times in the same locality. It may be single, multiple or combined with other environmental toxins and the concentrations may be too low under strict control. Meanwhile, human exposure to mycotoxins is difficult to avoid because fungal growth in foods is not easy to prevent (Scudamore, 1998; Lombart et al., 2003; CAST, 2003). Mycotoxins have been linked to a wide range of adverse health effects in children including poor growth and development and suppressed immune. In developing countries, mycotoxin interactions with malnutrition and infection are particularly significant in terms of coincidence and outcomes that need more scientific evaluations (Williams et al., 2004).

The protection of children against toxic chemicals in the environment will require fundamental and far-reaching revisions of current approaches to surveillance, toxicity testing, and risk assessment. The acquisition of better information on children’s exposure patterns and sources, and the undertaking of basic research both on mechanisms of underlying development and on chemical interactions of environmental agents with developing organ systems (Landrigan and Carlson, 1995; Carlson, 1998; Landrigan et al., 1998). International cooperation, research funding and training of personnel’s are essential to achieve a reliable scientific appraisal of the hazardous impact of exposure to mycotoxins on child health (FAO, 2004; Sherif, 2006).

References


IARC (International Agency for Research on Cancer), 1986.


ILSI, 2003. Trichotheccenes with a special focus on DON. Summary report of a workshop held in September 2003 in Dublin, Ireland organized by the ILSI Europe natural toxin task force.


Luo, X.Y., 1989. Outbreaks of moldy cereal poisonings in China. In: Toxicology Forum and the Chinese Academy of


Pillay, D., Chuturgoonm, A.A., Nevines, E., Manickum, T., Deppe, W., Dutton, M.F., 2002. The quantitative analysis of...


WHO, 1986. Principles for evaluating health risks from chemicals during infancy and early childhood; the need...
...for a special approach, IPCS, Environmental Health Criteria 59, WHO, Geneva.


