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Review

Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearalenone: An oestrogenic mycotoxin

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Abstract

Zearalenone (ZEA) is a mycotoxin produced mainly by fungi belonging to the genus *Fusarium* in foods and feeds. It is frequently implicated in reproductive disorders of farm animals and occasionally in hyperoestrogenic syndromes in humans. There is evidence that ZEA and its metabolites possess oestrogenic activity in pigs, cattle and sheep. However, ZEA is of a relatively low acute toxicity after oral or interperitoneal administration in mice, rat and pig. The biotransformation for ZEA in animals involves the formation of two metabolites α-zearalenol (α-ZEA) and β-zearalenol (β-ZEA) which are subsequently conjugated with glucuronic acid. Moreover, ZEA has also been shown to be hepatotoxic, haematotoxic, immunotoxic and genotoxic. The exact mechanism of ZEA toxicity is not completely established. This paper gives an overview about the acute, subacute and chronic toxicity, reproductive and developmental toxicity, carcinogenicity, genotoxicity and immunotoxicity of ZEA and its metabolites. ZEA is commonly found on several foods and feeds in the temperate regions of Europe, Africa, Asia, America and Oceania. Recent data about the worldwide contamination of foods and feeds by ZEA are considered in this review. Due to economic losses engendered by ZEA and its impact on human and animal health, several strategies for detoxifying contaminated foods and feeds have been described in the literature including physical, chemical and biological process. Dietary intakes of ZEA were reported from few countries from the world. The mean dietary intakes for ZEA have been estimated at 20 ng/kg b.w./day for Canada, Denmark and Norway and at 30 ng/kg b.w./day for the USA. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional maximum tolerable daily intake (PMTDI) for ZEA of 0.5 μg/kg of body weight.

Keywords: Zearalenone; Toxicity; Occurrence; Food; Metabolism; Detoxification

Contents

Abbreviations: ZEA, zearalenone; α-ZEA, α-zearalenol; β-ZEA, β-zearalenol; α-ZAL, α-zearalanol; β-ZAL, β-zearalanol; ZAN, zearalanone; DON, deoxynivalenol; 3-ADON, 3-acetyldeoxynivalenol; 15-ADON, 15-acetyldeoxynivalenol; NIV, nivalenol; OTA, ochratoxin A; AFB1, aflatoxin B1; aluminosilicates, HSCAS.

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1. Introduction

Zearalenone (previously known as F-2 toxin) is a non-steroidal oestrogenic mycotoxin biosynthesized through a polyketide pathway by a variety of *Fusarium* fungi, including *F. graminearum* (*Gibberella zeae*), *F. culmorum, F. cerealis, F. equiseti*, *F. crookwellense* and *F. semitectum*, which are common soil fungi, in temperate and warm countries, and are regular contaminants of cereal crops worldwide (Bennett and Klich, 2003). Zearalenone (ZEA) is a resorcyclic acid lactone, chemically described as 6-[10-hydroxy-6-oxo-*trans*-1-undecenyl]-B-resorcyclic acid lactone (Fig. 1). ZEA was given the trivial name zearalenone as a combination of *G. zeae*, resorcylic acid lactone, -ene (for the presence of the C-1′ to C-2 double bond), and -one, for the C-6′ ketone (Urry et al., 1966). In mammals, the keto group at C-8 is reduced to two sterioisomeric metabolites of ZEA (α- and β-isomers). These metabolites are also produced by the fungi, but at much lower concentrations than for ZEA (CCFAC, 2000).

Fungi-producing ZEA contaminate corn and also colonize, to a lesser extent, barley, oats, wheat, sorghum, millet and rice. In addition, the toxin has been detected in cereals products like flour, malt, soybeans and beer. Fungi of the genus *Fusarium* infect cereals in the field. Toxin production mainly takes place before harvesting, but may also occurs post harvest if the crop is not handled and dried properly (CCFAC, 2000). The ZEA derivatives (α-zearalenol (α-ZEA), β-zearalenol (β-ZEA), α-zearalanol (α-ZAL), β-zearalanol (β-ZAL), zearalanone (ZAN)) can be detected in corn stems infected with *Fusarium* in the field (Bottalico et al., 1985) and in rice culture (Richardson et al., 1985). Recently, Schollenberger et al. (2006) have reported the occurrence of α-ZEA and β-ZEA in corn by-products, corn silage and soya meal at low levels.

2. Occurrence of ZEA in foods and feeds

Many of the toxigenic species of *Fusarium* are major pathogens of cereal plants, causing head blight in wheat and barley and ear rot in maize. According to Placinta et al. (1999), it is possible that fungi may be spread from one country to another with increases in global grain trade. However, in respect of *Fusarium* fungi this risk is likely to be minimal since these phytopathogens are field rather than storage organisms. Although *Fusarium*-infected cereals

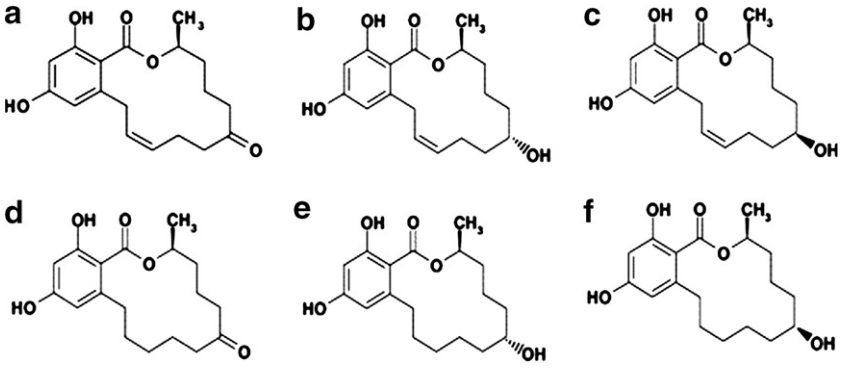

Fig. 1. Chemical structures of ZEA and its derivatives: (a) zearalenone (ZEA), (b) α-zearalenol (α-ZEA), (c) β-zearalenol (β-ZEA), (d) zearalanone (ZAN), (e) α-zearalanol (α-ZAL) and (f) β-zearalanol (β-ZAL).

standing in the field may accumulate ZEA before harvest time, numerous experiments tend to indicate that the high levels of ZEA reported to occur naturally in some samples of corn-based animal feeds result from improper storage rather than development in the field (Kuiper-Goodman et al., 1987). On the other hand, there is now overwhelming evidence of global contamination of cereals and animals with *Fusarium* mycotoxins particularly ZEA. Trade of these commodities may contribute to the worldwide dispersal of this mycotoxin. The worldwide contamination of foodstuffs and animal feeds with ZEA is reported in Table 1. The predominant feature of ZEA distribution in cereal grains and animal feed is its occurrence with other *Fusarium* toxins including trichothecenes and fumonisins. This observation is consistent with the confirmed production of ZEA by virtual all toxigenic and plant pathogenic species of *Fusarium* (D'Mello et al., 1997).

2.1. Europe

Available data in Europe indicate that maize is the most prominent cereal at risk with high incidence and high levels of contamination with ZEA, however wheat, oats, as well as soybean products have been found to be contaminated occasionally with ZEA (EC, 2004).

In 1988, Tanaka et al. published an overview on data about the occurrence of ZEA from 19 countries including some European countries (Germany, Italy, Poland and UK). The paper reported the contamination of wheat, barley, maize, oat, sorghum, rye and rice by ZEA. Placinta

Table 1
Worldwide contamination of foods and feeds by ZEA

Country	Commodity	Range (mg/kg)	References
Europe			
Bulgaria	Wheat	Up to 0.12	Vrabcheva et al. (1996)
Croatia	Maize grain	Mean of 1.70	Domijan et al. (2005)
Finland	Feeds and grains	0.022–0.095	Hietaniemi and Kumpulainen (1991)
Germany	Wheat	0.001–8.04	Müller et al. (1997a)
Germany	Barley	0.002–0.311	Müller et al. (1997b)
Germany	Wheat	0.017–0.104	Schneweis et al. (2002)
Germany	Wheat, corn, oat products	0.002–0.018	Schollenberger et al. (2005)
Germany	Wheat	Mean of 0.015	Schollenberger et al. (2006)
Germany	Corn	Up to 0.860	Schollenberger et al. (2006)
Germany	Oats	Up to 0.021	Schollenberger et al. (2006)
Germany	Corn by-products	Up to 1.362	Schollenberger et al. (2006)
Germany	Corn plants	Up to 0.553	Schollenberger et al. (2006)
Germany	Corn silage	Up to 1.790	Schollenberger et al. (2006)
Germany	Soya meal	Up to 0.211	Schollenberger et al. (2006)
Hungary	Mouldy stored corn	0.01–11.8	Fazekas et al. (1996)
Italy	Corn	0.004–0.15	Visconti and Pascale (1998)
Italy	Maize	Mean of 0.453	Pietri et al. (2004)
The Netherlands	Wheat	0.020–0.231	Tanaka et al. (1990)
The Netherlands	Corn feed	Up to 3.1	Veldman et al. (1992)
Poland	Wheat	0.01–2	Perkowski et al. (1990)
Scotland	Barley stored (3 month–1 year)	2.1–26.5	Gross and Robb (1975)
Slovakia	Poultry feed mixture	0.003–0.086	Labuda et al. (2005)
Switzerland	Wheat	0.01–0.121	Bucheli et al. (1996)
Switzerland	Wheat	0.01–0.018	Noser et al. (1996)
UK	Corn feeds	0.02–1.8	Scudamore et al. (1998)
UK	Corn	0.04–1.8	Scudamore et al. (1998)
Yugoslavia	Oats	0.03–0.086	Hietaniemi and Kumpulainen (1991)
Yugoslavia	Barley	0.021–0.03	Hietaniemi and Kumpulainen (1991)
Yugoslavia	Corn	0.043–10	Balzer et al. (1977)
Yugoslavia	Dairy cattle feed	0.14–0.96	Skrinjar et al. (1995)
Africa			
Egypt	Cereals	0.005–0.045	Abd Alla (1997)
Egypt	Corn	9.8–38.4	El-Maghraby et al. (1995)
Morocco	Maize	0.0135–0.0165	Zinedine et al. (2006)
Nigeria	Mouldy acha	0.2–0.6	Gbodi et al. (1986a)
Nigeria	Maize	Up to 17.5	Gbodi et al. (1986b)
Nigeria	Beer	0.245–1.32 mg/l	Okoye (1987)
Zambia	Maize for beer brewing	0.1–0.8	Lovelace and Nyathi (1977)
Zambia	Corn malt	Up to 4	Lovelace and Nyathi (1977)
Zambia	Beer	0.09–4.6 mg/l	Lovelace and Nyathi (1977)
South Africa	Cereal/animal feed	0.05–8.0	Dutton and Kinsey (1996)

(*continued on next page*)

Table 1 (*continued*)

Country	Commodity	Range (mg/kg)	References
South America			
Argentina	Grains and food	0.2–0.75	Lopez and Tapia (1980)
Argentina	Cow feeding stuffs	1.2–3.06	Cavaglieri et al. (2005)
Argentina	Poultry feeds	0.03–0.28	Dalcero et al. (1997)
Argentina	Poultry feeds	0.327–5.85	Dalcero et al. (1998)
Argentina	Corn	0.005–2.0	Resnik et al. (1996)
Brazil	Wheat	0.04–0.21	Furlong et al. (1995)
Brazil	Corn	0.653–9.83	Sabino et al. (1989)
Brazil	Corn	0.0467–0.719	Silva and Vargas (2001)
Brazil	Corn	0.0368–0.719	Vargas et al. (2001)
Uruguay	Dried fruits and vegetables	0.1–0.2	Pineiro et al. (1996a)
Uruguay	Barley and malt	0.1–0.2	Pineiro et al. (1996b)
North America			
Canada	Corn	0.005–0.647	Scott (1997)
Canada	Barley	0.004–0.021	Scott (1997)
Canada	Wheat and barley	Up to 0.3	Stratton et al. (1993)
Canada	Feed corn	<0.01–141	Funnell (1979)
USA	Mouldy corn	0.1–21.4	Park et al. (1996)
USA	Wheat	0.36–11.05	Shotwell et al. (1977)
USA	Corn	0.114–3	Bennett et al. (1985)
USA	Shelled corn	0.021–0.48	Bagneris et al. (1986)
	Unshelled corn	0.019–3.656	
USA	Sorghum	0.047–1.48	Bagneris et al. (1986)
USA	Moldy corn	Up to 13.2	Abbas et al. (1988)
USA	Beets and beet fibers	0.012–0.391	Bosch and Mirocha (1992)
Asia			
China	Wheat	0.005–1.4	Li et al. (2002)
China	Corn	0.014–0.169	Luo et al. (1990)
China	Corn	0.01–0.04	Janardhana et al. (1999)
India	Straw	Mean of 0.422	Phillips et al. (1996)
India	A mixed concentrate sample	0.843	Phillips et al. (1996)
India	Maize	0.01–0.04	Janardhana et al. (1999)
India	Wheat and rice	Up to 600	JECFA (2000)
Indonesia	Corn and poultry feeds	0.0055–0.526	Nuryono et al. (2005)
Iran	Corn flour	Up to 0.889	Reza Oveisi et al. (2005)
Iran	Maize	0.1–0.212	Hadiani et al. (2003)
Iran	Cheese snacks	Up to 1.471	Reza Oveisi et al. (2005)
Japan	Wheat	0.002–0.025	Sugiura et al. (1993)
Japan	Barley	0.010–0.658	Sugiura et al. (1993)
Japan	Wheat	0.053–0.51	Yoshizawa (1997)
Japan	Barley	11–15	Yoshizawa (1997)
Japan	Barley	0.105–15.3	Yoshizawa and Jin (1995)
Korea	Barley	0.04–1.416	Kim et al. (1993)
Korea	Corn	0.04–0.386	Kim et al. (1993)
Korea	Barley	0.014–0.171	Park et al. (2002)
Korea	Barley foods	0.0034–0.120	Park et al. (2002)
Korea	Corn	0.0034–0.0058	Park et al. (2002)
Korea	Rice	0.0217–0.047	Park et al. (2005)
Korea	Corn foods	0.0036–0.084	Park et al. (2002)
Philippines	Maize	0.059–0.0505	Yamashita et al. (1995)
Qatar	Rice	0.00018–0.0014	Abdulkadar et al. (2004)
Qatar	Wheat	0.00021–0.0021	Abdulkadar et al. (2004)
Qatar	Cornflakes	0.0038–0.00681	Abdulkadar et al. (2004)
Thailand	Maize	0.923	Yamashita et al. (1995)
Oceania			
Australia	Wheat	0.04–0.43	Blaney et al. (1987)
Australia	Maize	>1	Blaney et al. (1984)
New Zealand	Maize	2.7–10.5	Lauren et al. (1996)
New Zealand	Maize	0.1–16	Hussein et al. (1989)
New Zealand	Maize plants	8–75	di Menna et al. (1997)
New Zealand	Corn germ, fiber and glutten	2.2–4.8	Lauren and Ringrose (1997)

et al. (1999) reported the contamination of samples of wheat, barley, oat, rye and feeds from Bulgaria, Germany, Finland, Netherlands, Norway and Poland by ZEA at levels from few μg/kg to 8 mg/kg.

Germany seems to be the European country where more data can be found about ZEA in cereals are more available in Europe. Surveys of cereals and derivatives for several years confirmed their contamination with ZEA (Müller et al., 1997a,b ; Schneweis et al., 2002; Schollenberger et al., 2005, 2006). In Yugoslavia, ZEA was found at high levels (up to 10 mg/kg) in corn (Balzer et al., 1977) and in dairy cattle feeds (Skrinjar et al., 1995). In Poland, the contamination of wheat by ZEA was confirmed by Perkowski et al. (1990). Zakharova et al. (1995) reported a low contamination of cereal crop from Russia in 1993 and 1994 by ZEA. The contamination of wheat by ZEA was also found in Bulgaria (Vrabcheva et al., 1996). In Hungary, Fazekas et al. (1996) reported the contamination of mouldy and stored corn with ZEA that ranged between 0.01 and 11.8 mg/kg. Cereals from Finland (oats, barley) have been found to contain ZEA together with deoxynivalenol (DON) and 3-acetyldeoxynivalenol (3-ADON) (Hietaniemi and Kumpulainen, 1991). In the Netherlands, the occurrence of ZEA was reported in wheat (Tanaka et al., 1990) and in feed ingredients (Veldman et al., 1992). In the United Kingdom, ZEA was detected in corn and ingredients of animal feeding stuffs (maize and maize products) by Scudamore et al. (1998). In Scotland, according to Gross and Robb (1975), high contamination of barley stored (for 3 month to about one year) with ZEA was detected and levels varied between 2.1 and 26.5 mg/kg. In Italy, the contamination of corn was found with ZEA was reported from studies of Pietri et al. (2004) and Visconti and Pascale (1998). In Slovakia, Labuda et al. (2005) reported the contamination of poultry feed mixtures with ZEA with the co-occurrence of DON, 3-ADON, 15-acetyldeoxynivalenol (15-ADON), T-2 and HT-2 toxins.

Concerning recent data on human exposure in Europe to ZEA, the occurrence of the toxin was reported in 32% of mixed cereal samples ($n = 4918$) from nine European countries. The distribution showed that much of this contamination was in maize cereal grains and wheat cereal grain. A high incidence of ZEA was found in samples of oat from Finland (47% of samples containing >0.2 mg/kg with a maximum level of 1.31 mg/kg being reported) and high incidence of ZEA in wheat from France (16% of samples containing >0.2 mg/kg with a maximum level of 1.817 mg/kg being reported). Raw maize was the food commodity with the highest level of ZEA, results reported the contamination of 14% of maize with a levels >0.2 mg/kg, the highest level (6.492 mg/kg) was reported in a sample of maize from Italy (SCOOP, 2003).

2.2. Africa

Even though most African countries have a climate characterized by high humidity and high temperature which favor growth of moulds, little information is available on the occurrence of *Fusarium* toxins particularly ZEA in foods and feeds. High contaminations of the raw material is an ongoing problem. Regulatory issues are not available in the field of food exhibition and retailing, and mycotoxin problems have already been associated with some food contamination in some areas in Africa.

An earlier investigation from Zambia reported the contamination of maize for beer brewing, beer and corn malt by ZEA (Lovelace and Nyathi, 1977). In Nigeria, Gbodi et al. (1986a) reported that ZEA was the most prevalent mycotoxin in mouldy acha samples. A high level of ZEA (17.5 mg/kg) was also found in maize (*Zea mays*) from Nigeria (Gbodi et al., 1986b). Beer from Nigeria was also found contaminated with ZEA (Okoye, 1987).

In Egypt, several commodities were reported to contain ZEA especially corn, wheat and rice (Abd Alla, 1997) and walnut (Abdel-hafez and Saber, 1993). Corn from Egypt was also found contaminated with high levels of ZEA that ranged from 9.8 to 38.4 mg/kg (El-Maghraby et al., 1995). In South Africa, samples of cereals, animal feeds and brewed beers were found to be contaminated with ZEA (Dutton and Kinsey, 1996; Odhav and Naicker, 2002). In North African countries, there is a lack of investigations on the occurrence of *Fusarium* toxins in foods and feeds. The first report from Morocco has reported the co-occurrence of ZEA with fumonisin B1 and ochratoxin A (OTA) in corn (Zinedine et al., 2006).

2.3. Asia

In Japan, the contamination of cereals (barley and wheat) with ZEA was reported by Yoshizawa and Jin (1995) and Yoshizawa (1997). The 1990 barley and corn crops in Korea were reported to be heavily contaminated with ZEA because of the high rainfall and humidity (Park et al., 1992; Kim et al., 1993). Park et al. (2002) reported the contamination of barley, barley-based foods, corn and corn-based foods from Korea with ZEA. In a recent investigation, rice collected from Korea was also found contaminated with ZEA with the co-occurrence of OTA, aflatoxin B1 (AFB1), DON and nivalenol (NIV) (Park et al., 2005). Co-contamination of maize with ZEA, NIV, Fumonisins and aflatoxins is an emerging issue in Philippines and Thailand (Yamashita et al., 1995). In India, cereals including maize, wheat and rice, were reported to contain ZEA (Phillips et al., 1996; Janardhana et al., 1999; Luo et al., 1990). Co-occurrence of ZEA with AFB1, OTA, T-2 toxin, DON and citrinin was also reported in Indian maize (Janardhana et al., 1999).

Foodstuffs available in Qatar including cereals and cereals products (rice, wheat, oats and cornflakes) were reported to contain ZEA at low levels with the co-occurrence of OTA, aflatoxins and DON in rice (Abdulkadar et al., 2004). The contamination of maize-based food and poultry feeds with ZEA was reported in Indonesia (Nuryono et al., 2005). In Iran, ZEA was found in pre-harvest

maize (Hadiani et al., 2003), in corn flour and in a cheese snacks (Reza Oveisi et al., 2005).

2.4. North America

In Canada, high concentrations of ZEA (up to 141 mg/kg) were reported in corn for animals (Funnell, 1979). Monitoring of Canadian foods (wheat, barley, soybeans, corn, corn-based foods and grain crops) by Stratton et al. (1993) and Scott (1997) reported also the presence of ZEA at different levels. Recently, ZEA was detected in infant cereal foods from the Canadian retail market (Lombaert et al., 2003).

In the USA, an earlier investigation by Shotwell et al. (1977) showed the contamination of wheat with ZEA. Corn from USA was found to be contaminated with ZEA (Bennett et al., 1985; Bagneris et al., 1986; Hooshmand and Klopfenstein, 1995). High level values of ZEA related to mouldy corn samples were reported by Abbas et al. (1988) and Park et al. (1996). The contamination of sorghum and mouldy sugar beet root was also reported by Bagneris et al. (1986) and by Bosch and Mirocha (1992) respectively. On some occasions, phenomenally high concentrations of ZEA have been reported, e.g. 2900 mg/kg in a food sample from the USA (Pittet, 1998).

2.5. South America

In Brazil, the occurrence of ZEA was reported in corn by Sabino et al. (1989), Silva and Vargas (2001) and Vargas et al. (2001). The Contamination of wheat by ZEA was also reported by Furlong et al. (1995). In Uruguay, a pilot study for monitoring mycotoxin contamination of foods and feeds showed the contamination of corn, barley, malt, dried fruits and dried vegetables with ZEA (Pineiro et al., 1996a,b).

In Argentina, ZEA was found in grain (Lopez and Tapia, 1980), wheat (Quiroga et al., 1995), corn-based foods (Resnik et al., 1996) and poultry feeds (Dalcero et al., 1997, 1998). New data reported the contamination of cow feeding stuffs from Argentina with ZEA at levels that ranged from 1.2 to 3.06 mg/kg (Cavaglieri et al., 2005).

2.6. Oceania

In New Zealand, ZEA was detected in maize at high levels (up to16 mg/kg) (Hussein et al., 1989 ; Lauren et al., 1996), in corn germ, in fiber and in glutten (Lauren and Ringrose, 1997). In an other survey, di Menna et al. (1997) reported also that ZEA was found in leaf axils and blades (8–75 mg/kg) and in rachis fractions with high levels (up to 417 mg/kg).

In Australia, a survey for mycotoxins and fungal damage in maize (*Zea mays* L.) reported that ZEA contaminated four samples with concentrations that exceeded 1 mg/kg (Blaney et al., 1984). While in samples of wheat, ZEA was detected with aflatoxins and 4-DON (Blaney et al., 1987).

3. Dietary intakes of ZEA

Due to the rapid biotransformation and excretion of ZEA in animals, the dietary intake from meat and products thereof is probably of little significance (Creppy, 2002). ZEA can be excreted into milk after lactating cows are fed it in high doses. According to Prelusky et al. (1990), the maximum concentrations (6.1 μg/L ZEA, 4 μg/L α-ZEA, and 6.6 μg/L β-ZEA) were found in the milk of one cow given an oral dose of 6000 mg ZEA (equivalent to 12 mg/kg b.w.), but neither ZEA nor its metabolites were found in the milk (<0.5 μg/L) of three lactating cows fed 50 or 165 mg ZEA (equivalent to 0.1 and 0.33 mg/kg b.w.) for 21 days. Nor has ZEA been reported in eggs from commercial production. The main sources of ZEA are wheat, rye and oats in European countries, and corn, corn products and wheat products in Canada and the USA. Considering the mean levels of ZEA in the principal foods and their consumption, the average daily intakes of ZEA ranged among adults from 0.8 to 29 ng/kg b.w., while small children have the highest average daily intakes ranging from 6 to 55 ng/kg b.w./day (Minervini et al., 2005). Few reports are available on human dietary intake of ZEA probably due to the lack of data on the ZEA contents of consumed foods and to the lack of studies in countries from different parts of the world. Reviews of Canadian and Scandinavian data have concluded that the risk to human populations is minimal (Kuiper-Goodman et al., 1987; Eriksen and Alexander, 1998). It has been estimated that the mean dietary intakes of ZEA are 20 ng/kg b.w./day for Canada, Denmark and Norway and 30 ng/kg b.w./day for the USA.

The theoretical maximum daily intake of α-ZAL from food when used as a veterinary drug was calculated to be 1.6 μg/day (0.02 μg/kg b.w./day) on the basis of the recommended maximum residue limits of 10 μg/kg in cattle liver and 2 μg/kg in cattle muscle. Studies of the pharmacokinetics and metabolism of ZEA indicate that it is extensively metabolized by intestinal tissue in pigs, and possibly in humans, during its absorption, with the formation of α-ZEA, β-ZEA and β-ZAL, which are subsequently conjugated with glucuronic acid. The existence of this pathway limits the value of studies conducted by parenteral administration for assessing the risk associated with dietary intake (JECFA, 2000). A provisional maximum tolerable daily intake (PMTDI) for ZEA of 0.5 μg/kg of body weight is now established by the Joint Committee FAO/WHO, based on the NOEL of 40 μg/kg b.w./day obtained in a 15 day study in pigs. The committee recommended that the total intake for ZEA and its metabolites (including α-ZEA) should not exceed this value (CCFAC, 2000).

4. Metabolism of ZEA

ZEA is rapidly absorbed after oral administration. Although the degree of absorption is difficult to measure owing to extensive biliary excretion, it appears to be exten-

sively absorbed in rats, rabbits and humans (Kuiper-Goodman et al., 1987). The uptake in a pig after a single oral dose of 10 mg/kg b.w. was estimated to be 80–85% (Biehl et al., 1993). According to Olsen et al. (1981), two major biotransformation pathways for ZEA in animals have been suggested. These are:

1. Hydroxylation resulting in the formation of α-ZEA and β-ZEA, assumed to be catalyzed by 3α- and 3β-hydroxysteroid dehydrogenases (HSDs).
2. Conjugation of ZEA and its reduced metabolites with glucuronic acid, catalyzed by uridine diphosphate glucuronyl transferases (UDPGT).

Earlier investigations of Ueno et al. (1983) showed that α-ZEA was a major metabolite in cultured hepathocytes of the rat, mouse, pig, cow and rabbit at pH 4.5 with either NADH or NADPH and at pH 7.4 with NADH, although at pH 7.4 with NADPH, β-ZEA was the predominant metabolite. In guinea pigs, both α- and β-ZEA were produced in roughly similar amounts irrespective of the pH and cofactor, while in hamsters β-ZEA was the major metabolite. These findings indicated that there are two types of ZEA reductase differing in optimum pH. Olsen et al. (1987) reported also that ZEA was metabolized to α-ZEA and β-ZEA by sow intestinal mucosa *in vitro* with the predominance of β-isomer.

Recently, Malekinejad et al. (2006) has reported differences between species in hepatic biotransformation of ZEA. The authors demonstrated that pigs seem to convert ZEA predominantly into α-ZEA, whereas in cattle β-ZEA is the dominant hepatic metabolite, while the sheep liver post-mitochondrial fraction converted ZEA mainly into α-ZEA.

Even though significant differences were found in the metabolic profile of ZEA among animal species, very limited data are available for man. In pigs and probably in humans, ZEA is rapidly adsorbed after oral administration and can be metabolized in intestinal cells. In these cells, ZEA is degraded into α-ZEA, β-ZEA, α-ZAL and β-ZAL, which are subsequently conjugated with glucuronic acid (JECFA, 2000). High levels of some of these forms may be excreted in the urine as glucuronides by grazing sheep (Cheeke, 1998). ZEA would be significantly eliminated in bile and urine (Döll et al., 2003). The ZEA, α-ZEA and β-ZEA concentrations in the urine of a male volunteer 6, 12, and 24 h after a single oral dose of 100 mg ZEA were 3.7 and 3 μg/ml and not detected after 6 h; 6.9, 6, and 2.7 μg/ml after 12 h; and 2.7, 4 and 2 μg/ml after 24 h (Mirocha et al., 1981). In ruminants, ZEA and its metabolites are detected in bile at respective rates of 68% β-ZEA, 24% α-ZEA and 8% ZEA (Danicke et al., 2002). ZEA and its metabolite concentrations in liver and bile increases with administered dose (Döll et al., 2003). Neither ZEA nor its metabolites are detected in muscles, kidneys, liver, bladder, dorsal fat of male bovine ingesting 0.1 mg ZEA/day/kg feed (Danicke et al., 2002).

Metabolism of mycotoxins by animals may affect the manifestation of adverse effects. There may also be additional implications for carcass and milk quality if extensive transformation occurs within the digestive tract or within the tissues of animals (D'Mello et al., 1999). The ovine metabolism of ZEA has been proposed to include the synthesis of at least five metabolites including ZEA, α-ZEA, β-ZEA, α-ZAL and β-ZAL (Miles et al., 1996). The adverse effects of ZEA will be partly determined by the process of elimination. In pigs, as in sheep, ZEA is conjugated with glucoronic acid and in addition may be metabolized to α-ZEA. However, Biehl et al. (1993) indicated that biliary excretion and enterohepatic cycling are important processes affecting the fate of ZEA. It was suggested that the glucuronide of ZEA was substantially excreted in bile to be re-absorbed and metabolized further by intestinal mucosal cells, ultimately entering the liver and the systemic circulation via the portal blood supply. The reduced form of ZEA, zearalenol, has increased oestrogenic activity. A synthetic commercial formulation called zeranol (Ralgro) has been marketed successfully for use as an anabolic agent for both sheep and cattle. In 1989, zeranol was banned by the European Union, but it is still used in other parts of the world (Hagler et al., 2001).

5. Toxicity of ZEA

Prior to the discovery and implementation of modern milling practices, *Fusarium* species have been implicated in several human outbreaks of mycotoxicoses (Hussein and Brasel, 2001). Both DON and ZEA from toxic *Fusaria* have been linked to scabby grain toxicoses in the USA, China, Japan, and Australia, symptoms included nausea, vomiting, and diarrhea (Bilgrami and Choudhary, 1998).

5.1. Acute toxicity

It is acknowledged that ZEA is of a relatively low acute toxicity (oral LD 50 values of >2000–20 000 mg/kg b.w.) after oral administration in mice, rats and guinea pigs (Flannigan, 1991). It is more toxic by intraperitoneal injection. Table 2 gives results of some studies of acute toxicity (LD50) of ZEA in animals according to JECFA (2000).

5.2. Subacute and subchronic toxicity

In oral toxicity studies of up to 90 days, the effects seen in experimental as well as in domestic animals appeared to be dependant on interactions of ZEA or its metabolites with the estrogen receptors. Pig and sheep appear to be more sensitive than rodents; in controlled studies with well-defined exposure to multiple does, the NOEL in pigs was 40 μg/kg of body weight per day compared with the NOEL of 100 μg/kg of body weight in rats (Kuiper-Goodman et al., 1987; JECFA, 2000).

Table 2
Acute toxicity (LD50) of ZEA in different animal models

Species	Sex	Route of administration	LD_{50} (mg/kg b.w.)	References
Mouse	M/F	Oral	>2000	NTP (1982)
Mouse	F	Oral	>20000	Hidy et al. (1977)
Mouse	F	Intraperitoneal	>500	Hidy et al. (1977)
Rat	M/F	Oral	>4000	NTP (1982)
Rat	M/F	Oral	>10000	Hidy et al. (1977)
Rat	M	Intraperitoneal	5500	Hidy et al. (1977)
Guinea-pig	F	Oral	>5000	Hidy et al. (1977)
Guinea-pig	F	Intraperitoneal	2500	Hidy et al. (1977)

5.3. Chronic toxicity and carcinogenicity

First data were reported on the capability of ZEA to induce adverse liver lesions with subsequent development of hepatocarcinoma (NTP, 1982). B6C3F1 mice were fed diets containing various concentrations of ZEA (0, 50 or 100 mg/kg) for 103 weeks (corresponding to 0, 8 or 17 mg/kg b.w./day in males and 0, 9 or 18 mg/kg b.w./day in females:). No significant difference in survival or changes in body weight gain was observed between groups. Treatment-related non-neoplastic lesions were not found in male mice. In females, estrogen-related, dose dependent effects were seen in several tissues (fibrosis in the uterus, cystic ducts in mammary glands), as well as myelofibrosis in the bone marrow. Hepatocellular adenomas were found in 8%, 6% and 14% and 0%, 4% and 14% in males and females, respectively. The increase was statistically significant in the high-dose females. A statistically significant trend was observed in the incidence of pituitary adenomas in both males (0%, 9%, and 14%) and females (7%, 5%, and 31%). Pituitary carcinomas were found in one male in the low-dose group and in two females in the high-dose group. However, the incidence of pituitary carcinomas in treated and control animals was not significantly different statistically (NTP, 1982).

Fischer 344/N rats were fed diets containing 0, 25 or 50 mg/kg ZEA for 103 weeks (0, 1, or 2 mg/kg b.w./day). Mean body weight gains of treated rats were lower than those of controls, and the depression in mean body weight (by 19% in males and 11% in females in the high-dose group after 44 weeks of exposure) was dose-related. No significant difference in survival was observed between groups. The following non-neoplastic lesions were observed: inflammation of the prostate gland, testicular atrophy, cysts or cystic ducts in mammary glands of males, increased incidence of hepatocellular cytoplasmic vacuolization in males, and an increased incidence of chronic progressive nephropathy in both sexes at both doses. Retinopathy and cataracts were observed in increased incidence in low- and high-dose males, and in low-dose females. No treatment-related increase in tumour incidence was found in the study (NTP, 1982).

FDRL Wistar rats were fed dietary ZEA for 104 weeks (0, 0.1, 1 or 3 mg/kg b.w./day). Significantly increased liver weights were found in males and females exposed to 3.0 mg/kg b.w., and uterine weights were increased in females in the two highest treatment groups. In rats receiving the highest dose of ZEA, increased trabeculation of the femur was noted. A part from that, no biologically significant changes were seen, and no treatment-related tumours were found (Becci et al., 1982a). Survival rates and tumour incidences were not reported. A NOEL of 0.1 mg/kg b.w./day can be taken from this study.

ZEA was also shown to be haematotoxic. According to Maaroufi et al. (1996), dysfunction of the blood coagulation process in rats and some blood parameters changes (hematocrit, MCV, the number of platelets and WBC) as well as some biochemical markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum creatinine, bilirubin, were observed *in vivo* indicating liver toxicity. ZEA was also found to be hepatotoxic. The effects of low (10 μg/kg b.w.) and high (100 μg/kg b.w.) doses of ZEA on selected blood serum enzyme activities of AST, ALT, ALP, gamma-glutamyltransferase (GGT), and total lactatedehydrogenase (LD) of rabbits were studied by ČonKová et al. (2001). Results from this study reported a significant increase in ALP activity at 168 and 336 h during the experiment with the first group (10 μg/kg b.w.). In the second 100 μg ZEA sera group, significant increases in activities of AST, ALT, ALP, GGT, and LD were observed at 168 and 336 h, indicating possible liver toxicity due to chronic effects of the toxin. ZEA and derivatives were evaluated by IARC and are classified, in the group 3 (IARC, 1999).

Recent studies have demonstrated the potential for ZEA to stimulate growth of human breast cancer cells containing estrogen response receptors (Ahamed et al., 2001). Oestrogenic effects of ZEA, in combination with the temporal concordance of its high concentrations present in foodstuffs worldwide with increasing age-adjusted incidence rates of breast cancer, stimulated the hypothesis that exposure to ZEA may contribute to the increasing occurrence of breast cancer (Yu et al., 2005) (Table 3).

5.4. Genotoxicity

ZEA has been shown to be genotoxic, and to induce DNA-adduct formation in *in vitro* cultures of bovine lymphocytes (Lioi et al., 2004), DNA fragmentation and micronuclei production in cultured DOK, Vero and

Table 3
Some reproductive and disorders effects induced by ZEA in animals

Animal type	Dosage and ZEA source	Duration	Effects	References
Mouse (CBA/Ca)	Gavage of 20 mg ZEA/kg b.w.	9 days	No malformation, increased late fetal deaths	Arora et al. (1983)
Rat (wistar)	Diet 0.1, 1, 10 mg ZEA/kg b.w.	10 months	Maternal toxicity, decreased fertility, Medullary trabeculation increased	Becci et al. (1982a,b)
Guinea-pig	Diet 7, 14, 21 mg ZEA/kg b.w.	8 days	Reduced incidence of pregnancy (21 mg/kg b.w.), altered levels of progesterone	Long and Diekman (1989)
Chicken	Diet 0.7–59 mg ZEA/kg b.w.	56 days	No effect on egg production	Allen et al. (1981)
Turkey	Diet 4 mg ZEA/kg b.w.	56 days	20% of decreased egg production	Allen et al. (1983)
Sows	Natural contamination or addition of pure ZEA	–	Vulvovaginitis, anestrus, decreased luteinising hormone and progesterone secretion	Etienne and Dourmad (1994)
Sows, gilts and piglets	*Fusarium*-contaminated feed	–	Reduced conception rates, litter size, enlargement of ovaries and uterus, swelling of vulva in piglets	Vanyi et al. (1994)
Piglets	Naturally contaminated fed	–	Endematous swelling and reddening of vulva, congenital lesions of the external genitalia	Dacasto et al. (1995)
Boars	Natural contamination or addition of pure ZEA	–	Depression of serum testosterone, feminization and suppression of libido	Diekman and Green (1992)
Cows	250 mg of 99% purified ZEA	1 day	Infertility and reduced milk production	Weaver et al. (1986)
Cattle	Diet 20 mg ZEA/kg feed for	72 days	Degeneration of germinal epithelium, 75% incidence of sperm degeneration	Vanyi et al. (1980)
Mink	20 mg ZEA/kg	–	Hyperplasia of uterus, atrophy of ovarian follicles	Yamini et al. (1997)
Mink	Fed diets containing 20 ppm ZEA	30 days	Increased gestation length, ovarian follicular atrophy	Yang et al. (1995)
Rabbits	Fed diets containing 1 and 4 ppm ZEA	18 days	Histopathological changes in liver, kidneys, lungs, heart, adrenal glands, spleen and uterus	Abdelhamid et al. (1992)
Rats	1.5, 3 and 5 mg/kg ZEA i.p.	48 h	Changes in some blood and biochemical parameters indicating liver toxicity	Maaroufi et al. (1996)
Rats	Pure ZEA	–	Reduced serum testosterone levels and sperm counts	Kaliamurthy et al. (1997)
Mice	5–30 micrograms of pure ZEA/animal	1–10 days	Mimic oestrogen actions, delayed vaginal opening, persistent oestrus and sterility	Ito and Ohtsubo (1994)
Mice	2 mg/kg i.p. or orally	1 time	Genotoxicity, ability to induce hepatocellular adenomas	Pfohl-Leszkowicz et al. (1995)
Pig	Fed diet containing 180 μg ZEA/kg	3 reproduction cycles	Disturbances expressed in an elevated return to oestrus rate, abortions and symptoms of hyperoestrogenism in newborn piglets occurred already after a short period of exposure during the first reproduction cycle	Jadamus and Schneider (2002)
Pig	0.2 and 0.4 ZEA mg/kg b.w./day	7 days	Ovarian follicle atresia and apoptoso-like changes in granule cells, intensified cell proliferation in uterus and oviduct	Obremski et al. (2003)
Pig	0.35 mg ZEA/kg b.w./day in presence and in absence of inorganic adsorbent	35 days	No effect of the weight of the uterus in the absence of adsorbent, increased uterus weight in the presence of adsorbent	Döll et al. (2003)
Gilts	200 μg ZEA/kg b.w.	8 days	Disturbances in the process of development and maturation of some of the ovarian follicles	Zwierzchowski et al. (2005)

Caco-2 cells (Abid-Essefi et al., 2003, 2004), in Vero monkey kidney cells and in bone marrow cells of mice (Ouanes et al., 2003). According to Creppy (2002), ZEA did not induce mutations in *Salmonella typhimurium* (Ames test) or mitotic crossing over in *Saccharomyces cerevisiae*. It induced sister chromatid exchanges, chromosomal aberrations and polyploidy in Chinese hamster ovary cells *in vitro* in the absence of exogenous metabolic activation. It also induced SOS repair in bacteria (Ghedira-Chekir et al., 1998, 1999). Experiments with female Balb C mice, treated i.p. with a single dose of ZEA (2 mg/kg b.w.) revealed DNA-adducts identified by the ^{32}P-post-labeling

method in the kidney and the liver (Pfohl-Leszkowicz et al., 1995). This was confirmed by another study, in which ZEA also formed DNA-adducts in mouse liver and kidney after a single i.p. dosage of 2 mg/kg using the 32P-labelling method (Grosse et al., 1997). Co-administration of α-tocopherol (4 mg/kg b.w.) significantly decreased DNA-adduct formation (Grosse et al., 1997; Ghedira-Chekir et al., 1999). A recent report showed that ZEA target mitochondria and/or lysosomes, induces lipid peroxidation, cell death and inhibits protein and DNA syntheses (Kouadio et al., 2005). Cetin and Bullerman (2005a) reported that ZEA showed less cytotoxicity to mammalians cells cultures in the *in vitro* models tested (C5-O, Caco-2, V79 and CHO-K1 cell lines).

5.5. Reproductive and developmental toxicity

During pregnancy, ZEA reduces embryonic survival when administered above a threshold and sometimes decreases foetal weight (D'Mello et al., 1999). ZEA may affect the uterus by decreasing LH and progesterone secretion and by altering the morphology of uterine tissues (Etienne and Dourmad, 1994). In male pigs, ZEA can depress serum testosterone, weights of testes and spermatogenesis, while inducing feminization and suppressing libido. In cows, infertility, reduced milk production and hyperestrogenism have been associated with ZEA or with *Fusarium* producing this mycotoxin (D'Mello et al., 1999). ZEA causes alterations in the reproductive tract of laboratory animals (mice, rat, guinea pigs, hamsters, rabbits) and domestic animals. Various oestrogenic effects like decreased fertility, increased embryolethal resorptions, reduced litter size, changed weight of adrenal, thyroid and pituitary glands and change in serum levels of progesterone and estradiol have been observed but no teratogenic effects were found in mice, rats, guinea pigs and rabbits (Kuiper-Goodman et al., 1987; Bacha et al., 1993; JECFA, 2000). Pigs and sheep appear to be more sensitive than rodents.

ZEA was measured in endometrial tissue from 49 women. There were 27 endometrial adenocarcinomas, 11 endometrial hyperplasis and 11 normal proliferative endometria with ZEA values of 47.8 ± 6.5, 167.0 ± 17.7 ng/ml and below detection limit in the groups, respectively. In 8 cases of hyperplastic and 5 cases of neoplastic endometrial tissue, ZEA was not detected (Tomaszewski et al., 1998). Increased incidence of early telearche has been reported from the southeast region of Hungary, ZEA was found in concentrations from 18.9 to 103.5 μg/ml in serum sampled from the patients and ZEA was also present in samples of surplus food collected from the patients (Szuetz et al., 1997).

5.6. Effect on the endocrine system

ZEA and some of its metabolites have been shown to competitively bind to oestrogen receptors (ERα and ERβ) in a number of *in vitro* or *in vivo* systems (Kuiper et al., 1998). In an immortalized pituitary cell line, ZEA bound to the ER with an affinity of 0.01 relative to 17β-estradiol and induced prolactin excretion (Stahl et al., 1998).

Male 70-day-old rats treated orally with ZEA at 20 mg/kg b.w. per day for five weeks had increased serum prolactin values, but other parameters such as body and testis weights, serum luteinizing hormone and follicle stimulating hormone concentrations and volume fractions of Sertoli cells, spermatogonia, early and late primary spermatocytes, and long and round spermatids were not affected (Milano et al., 1995). Neonatal Charles River CD rats received 100 and 1000 μg of ZEA by subcutaneous injection on days 1–10 of life, were castrated on day 21, and received gonadotropin-releasing hormone on day 42, when luteinizing hormone was determined. Males and females exposed to either dose of ZEA had decreased pituitary responsiveness to gonadotropin-releasing hormone. The highest dose of ZEA increased the volume of the sexually dimorphic nucleus of the preoptic area in females, whereas no changes were seen in males (Faber and Hughes, 1991).

In ovariectomized Charles River CD rats, subcutaneous injection of ZEA at 8 mg/kg b.w. did not inhibit tonic luteinizing hormone secretion and did not provide oestrogenic priming for progesterone-induced luteinizing hormone secretion, but it did block gonadotropin-releasing hormone-induced luteinizing hormone secretion (Hughes et al., 1991). Daily injection of pregnant mice with 20 ng of 17β-estradiol or 2 μg of ZEA (equivalent to 10 μg/kg b.w.) on days 15–20 of gestation increased the density of terminal end buds in the mammary glands. ZEA also increased epithelial differentiation and density (Hilakivi-Clarke et al., 1998).

Kuiper-Goodman et al. (1987) based a risk assessment on a study on a "no hormonal effect level" (NHEL) for α-ZAL in ovariectomized monkeys in which vaginal cornification was used as the end point. In rhesus monkeys treated orally for 10 days, the NHEL was 225 μg/kg b.w./day, whereas a NHEL of <50 μg/kg b.w./day was found in a 90-day study with cynomolgus monkeys. Kuiper-Goodman et al. (1987) suggested that ZEA is less oestrogenic than α-ZAL and that the NHEL for ZEA is probably higher. The relative binding affinities to the rat uterine cytoplasmic receptor for ZEA and derivatives are in decreasing order α-ZAL > α-ZEA > β-ZAL > ZEA > β-ZEA (Kuiper-Goodman et al., 1987; Eriksen and Alexander, 1998). Recently, Minervini et al. (2005) have reported that ZEA and derivatives showed similar oestrogenic proprieties, with the exception of α-ZEA that induced a higher oestrogenic activity.

5.7. Immunotoxicity

In female B6C3F1 mice fed a diet supplemented with 10.0 mg/kg ZEA (1.5 mg/kg b.w./day) for 6 weeks, no differences from the control group could be seen in serum

concentration of IgG, IgM or IgA or in white blood cell count or in differential counts (lymphocytes, polymorphonuclear neutrophils, monocytes and eosinophils) (Forsell et al., 1986). B6C3F1 mice were fed a diet supplemented with 10 mg/kg ZEA (1.5 mg/kg b.w./day) for 2 weeks. After i.v. infection with *Listeria monocytogenes* the splenic bacterial count showed an increasing trend on days 1 and 4 compared with the control animals (11 animals). No negative effects were seen after 8 weeks of feeding. The exposure did not affect the splenic plaqueforming response to sheep red blood cells or the delayed hypersensitivity response to keyhole limpet haemocyanine after either 2 nor 8 weeks (Pestka et al., 1987).

Recent investigations have reported that several alterations of immunological parameters were found *in vitro* associated with ZEA concentrations in mice (Marin et al., 1996) and humans (Berek et al., 2001). According to Eriksen and Alexander (1998), alterations of immunological parameters such as the inhibition of mitogen stimulated lymphocyte proliferation, the increase IL-2 and IL-5 production were found at high ZEA concentrations *in vitro*.

6. Detoxification and biodegradation of ZEA

Detoxification strategies for contaminated foods and feeds to reduce or eliminate the toxic effects of ZEA by chemical, physical, and biological methods are crucial to improve food safety, prevent economic losses, and reclaim contaminated products. Data reported on binding, detoxification and biodegradation processes of ZEA are summarized in Table 4.

Degradation and detoxification of common mycotoxins in the presence of high concentrations of ozone (O_3) have been investigated by McKenzie et al. (1997), authors reported that ZEA was degraded at 15 s, with no by-products detectable by HPLC. Additionally, the toxicity of these compounds (measured by a mycotoxin-sensitive bioassay) was significantly decreased following treatment with O_3 for 15 s. Efficiency of H_2O_2 for destruction of ZEA in contaminated corn was studied at different concentrations (3, 5 and 10%) by Abd Alla (1997). Results revealed that the percentage of destruction of ZEA was found to be dependent upon the concentration of H_2O_2, temperature and period of exposure. The highest amount of degradation was 83.9%, with 10% H_2O_2 at 80 °C for 16 h, followed by 75% at the same conditions for 8 h (Abd Alla, 1997). However, there is no information about the metabolites of ZEA and their potential toxicity.

Extrusion cooking of cereal products is being used increasingly in the food industry to convert cereals into breakfast foods, snack foods, and pet foods. Extrusion cooking is one of the fastest growing food-processing operations in recent years due to several advantages over

Table 4
Processes described for binding, detoxification or degradation of ZEA

Process	Observation	References
Biological process		
Mannan-oligosaccharides derived from the cell wall of *S. cerevisiae* 1026	Binding capacity of about 80% of ZEA	Devegowda et al. (1996)
Mixed bacterial culture	Total degradation of ZEA. No ZEA or ZEA-like products were detected	Megharaj et al. (1997)
Ruminants protozoa	90–100% of ZEA metab to α-ZEA and to a lesser degree to β-ZEA	Kiessling et al. (1984)
Lactonohydrolase from *Clonostachys rosea* IFO 7063	Conversion of ZEA to less toxic compounds	Takahashi-Ando et al. (2002)
L. rhamnosus GG and *L. rhamnosus* LC705	Binding of ZEA	El-Nezami et al. (2002)
Lactic acid bacteria	Reduction of 68–75% in 4 days of fermentation in maize	Mokoena et al. (2005)
Trichosporon mycotoxinivorans	Degradation of ZEA to non-toxic metabolites	Molnar et al. (2004)
Gliocladium roseum	Metabolization of 80–90% ZEA to two isomeric compounds that are less toxic than ZEA	El-Sharkawy and Abul-Hajj (1988)
Physical process		
Montmorillonite	Adsorption of 108 mg/g	Lemke et al. (1998)
Montmorillonite	Adsorption of 0.19 mg/g	Ramos et al. (1996)
Bentonite	Adsorption of 0.11 mg/g	Ramos et al. (1996)
Sepiolite	Adsorption of 0.07 mg/g	Ramos et al. (1996)
Mg trisilicate	Adsorption of 0.02 mg/g	Ramos et al. (1996)
Cholestyramine	Adsorption of >0.3 mg/g	Ramos et al. (1996)
Crospovidone	Adsorption of 0.3 mg/g	Ramos et al. (1996)
Cross-linked polyvinylpyrrolidone	Adsorption of 0.5–2.1 mg/g	Alegakis et al. (1999)
Activated carbon	Binding 100% ZEA (pH 3 and 7.3)	Bueno et al. (2005)
Extrusion Cooking	Reduction of 83% of ZEA	Ryu et al. (1999)
Chemical process		
Ozone (O_3)	Total degradation of ZEA	McKenzie et al. (1997)
H_2O_2 (10%) at 80 °C for 16 h	83.9% of degradation of ZEA	Abd Alla (1997)

traditional methods. In addition to improving the quality of intermediate and final processed products, it may also improve food safety because of having the potential to reduce mycotoxin levels in cereals (Cetin and Bullerman, 2005b). The levels of ZEA in cereal-based foods were reduced significantly by extrusion processing, and reduction of 83% of ZEA in corn-based foods was obtained with this process (Ryu et al., 1999). However, there remains a need to demonstrate that the toxicity or biological activity of ZEA has been reduced or completely eliminated in cereal-based foods using extrusion processing (Cetin and Bullerman, 2005b).

Addition of nutritionally inert sorbents is one of the most recent approaches that have been proposed to reduce ZEA toxicity. Most studies related to the alleviation of mycotoxicosis by the use of adsorbents are focused on aluminosilicates (HSCAS), and aluminosilicates containing clays. The use of HSCAS for the adsorption of ZEA was tested, but with little success except for a chemically modified montmorillonite with a binding capacity 108 mg/g (Lemke et al., 1998). This clay derivatized with cetylpyridinium or hexadecyltrimethylammonium resulting in an increased hydrophobicity of the clay surface following a high affinity to the hydrophobic ZEA (Huwig et al., 2001). Cholestyramine, a bile acid-binding resin, was tested and confirmed as protective agent against mycotoxins. It was reported that activated carbon and cholestyramine are good candidates for ZEA detoxification and could be used as feed additives to prevent hyperestrogenism in pigs (Avantaggiato et al., 2004). However, its high cost would make its commercial use economically prohibitive (Galvano et al., 2001).

Increasing interest has been generated by the possibility of using microorganisms to reduce the bioavailability of mycotoxins to farm animals. Knowledge on interaction of yeasts with mycotoxins goes back more than three decades. In the early eighties, there were some reports on use of ZEA contaminated maize to produce ethanol by fermentation and it was found that the toxin was recovered in the residual solids (Bennett et al., 1981). In an *in vitro* study with the cell wall material, modified mannan-oligosaccharides derived from the *S. cerevisiae* 1026 cell showed considerably high binding to ZEA of about 80% (Devegowda et al., 1996).

Previously, in the 1980s, El-Sharkawy and Abul-Hajj published a series of important papers on ZEA transformation by fungi and actinomycetes. They characterized a non-oestrogenic substance: ZEA-4-O-β-glucoside, produced by *Thamnidium elegans* and *Mucor bainieri* (El-Sharkawy and Abul-Hajj, 1987a). In addition, the transformation products of *Streptomyces rimosus*and *Cunninghamella bainieri*, 8′-hydroxy-zearalenone and 2,4-dimethoxyzearalenone, respectively, did not bind to rat oestrogen receptor, indicating a loss of oestrogenicity (El-Sharkawy and Abul-Hajj, 1987b). The most significant detoxification was the cleavage of the lactone bond of ZEA by the mycoparasite *Gliocladium roseum*. El-Sharkawy and Abul-Hajj (1988) reported that preliminary screening with 150 fungal species showed that *Gliocladium roseum* NRRL 1859 was capable of metabolizing ZEA in 80–90% yields. The product, which is far less oestrogenic than ZEA, consisting of a mixture of two isomeric hydroxyketones, decarboxylated spontaneously, rendering the reaction irreversible.

A variety of microorganisms including bacteria, yeasts and fungi were found to be able to convert zearalenone to α- and β-ZEA. However, according to Karlovsky (1999), this transformation cannot be regarded as detoxification since the oestrogenic activity of these metabolites is similar to that of ZEA. Biehl et al. (1993) suggested also that the reduction of ZEA to α-ZEA occurred most actively in the intestinal mucosa. Evidence of ruminal microbial degradation of ZEA has been demonstrated in isolates cultures of rumen contents. Kiessling et al. (1984) reported that rumen protozoa were more active than bacteria in ZEA degradation and demonstrated that 90–100% of ZEA concentration was transformed to α-ZEA and to a lesser degree to β-ZEA. They concluded that protozoa were considered as the most important ruminal microbial population in ZEA biodegradation (Kiessling et al., 1984; Hussein and Brasel, 2001; Cavret and Lecoeur, 2006). However this degradation should not be regarded as a detoxification since α-ZEA (more oestrogenic than ZEA) was the major metabolite obtained.

The ability of a mixed culture of bacteria to degrade completely ZEA from culture media was also reported by Megharaj et al. (1997), HPLC and ELISA analysis of culture extracts revealed no ZEA or ZEA-like products. Takahashi-Ando et al. (2002) identified and characterized a lactonohydrolase enzyme in the fungus *Clonostachys rosea* which converts ZEA to a less oestrogenic compound. Recently, ZEA was found to be completely degraded by several *Rhizopus* isolates including *R. stolonifer*, *R. oryzae* and *R. microsporus* strains (Varga et al., 2005), but further studies are needed for the identification of ZEA-degrading enzymes in *Rhizopus* isolates. The interaction of ZEA and its derivative α-ZEA with two food grade strains of *Lactobacillus* (*L. rhamnosus* GG and *L. rhamnosus* LC705) was investigated by El-Nezami et al. (2002). *L. rhamnosus* strains LGG and LC 705 are shown to effectively bind ZEA and its derivative up to 55% (w/w) and when the two toxins were tested in combinations, binding of individual toxins were compromised indicating the possibility of the two toxins sharing similar surface binding sites. Molnar et al. (2004) described a new yeast strain, *Trichosporon mycotoxinivorans*, able to degrade ZEA to carbon oxide and other non-toxic metabolites, nether α- nor β-ZEA were detected, authors suggested that this yeast strain can be used for the detoxification of the respective mycotoxins in animal feeds. Recently, Mokoena et al. (2005) reported that lactic acid bacteria fermentation can significantly reduce the concentration of ZEA in maize by 68–75% in fourth days of fermentation. However, such a reduction may not significantly alter the possible toxic effects of the toxin.

7. Maximum limits for ZEA

According to Van Egmond (1993), there are various factors that may influence the establishment of tolerances for certain mycotoxins, such as the availability of toxicological data, the availability of data on dietary exposure, the distribution of mycotoxins over commodities, legislation of other countries with which trade contacts exist, and the availability of methods of analysis. According to FAO (2004), ZEA was regulated in 1996 by 6 countries, but by the year 2003 the toxin ZEA was regulated in foods and animal feeds by 16 countries. Limits for ZEA in maize and other cereals, currently vary from 50 to 1000 μg/kg. Current regulations of ZEA in foods and feeds set by countries from Europe, Asia, Africa and America and reported by FAO (2004) are represented in Table 5.

Table 5
Maximum limits for ZEA in foods and feeds in various countries (FAO, 2004)

Country	Maximum limit (μg/kg)	Commodity
Armenia	1000	All foods
Austria	60	Wheat, rye/durum wheat
	50	Feed for breeding-pigs
Belarus	1000	Barley, wheat, maize
Bulgaria	200	Cereals and processed products thereof intended for direct human consumption or as an ingredient in foodstuffs
Canada	3000	Feed for gilts and sows
Chile	200	All foods
Colombia	1000	Sorghum
Cyprus	2000	Feed materials
	1500	Complete feedingstuffs for piglets
	3000	Complete feedingstuffs for swine other than piglets
France	50	Cereals and cereal products
France	200	Vegetable oils
Estonia	1000	Wheat, barley, maize, cereal flours (wheat, barley, maize), cereal groats and flakes (wheat, barley, maize), pasta products, ordinary baker's wares, fine baker's wares, confectionery products, legume vegetables, fats, oils; isolates, concentrates and hydrolysates of cereals protein
	200	Complementary feedingstuffs for cattle, pigs and other farm animals
	100	Feedingstuffs of vegetable origin, complete feedingstuffs for cattle, pigs and other farm animals
	50	Complete feedingstuffs for young cattle, young pigs and other young farm animals
Hungary	100	Milled products, cereal-constituent of muesli
Indonesia	Not detectable	Maize
Iran	400	Barley
	200	Maize, wheat, rice
Italy	20	Baby foods
	100	Cereals and derived products
Japan	1000	Compound feeds
Latvia	1000	Cereals
	1000	Bread
Lithuania	300	Feed for piglet
	100	Feed for pig
Moldova	1000	Wheat and wheat flour, barley and barley flour, maize and maize flour
Morocco	200	Cereals, vegetable oils
Romania	20	Feeds
Russia	1000	Wheat, barley, maize, corn
Serbia and Montenegro	1000	Corn
	500	Feed for pigs (until 50 kg)
	1000	Feed for other type of swine
	3000	Feed for cow, sheep and goat
	5000	Feed for ox
	100,000	Feed for egg laying hen
Slovenia	1000	Feedstuffs for pigs
Ukraine	40	Grain-based babyfood products
	1000	Grains, beans; sunflower press; flour, bread; all nuts; all seeds to be used for immediate human consumption and for processing into the products for human consumption; vegetable oil; wheat middlings
	40	Combined feed for sows (pregnant, feeding), breeding boars, piglets younger than 2 months
	1000	Soya press for feed
	2000	Combined feed for pigs fed for pork lighter than 50 kg
	3000	Combined feed for pigs fed for pork over 50 kg of weight
Uruguay	200	Corn, barley

8. Risk assessment of ZEA

Hepatocellular adenomas and pituitary tumours were observed in long-term studies of carcinogenicity in mice. However, these tumours were observed only at doses greatly in excess of the concentrations that have hormonal effects i.e. at levels 8–9 mg/kg of body weight or more. JECFA (2000) concluded that these tumours are a consequence of the ZEA oestrogenic effects. ZEA did not induce gene mutations in bacteria or recombination in yeast. However, ZEA induced sister chromatid exchanges and chromosomal anomalies *in vitro*, and DNA-adducts as measured by 32P-postlabelling in mice. Data available on genotoxicity of ZEA do not allow an adequate evaluation of its genotoxic potential and its mechanism of action in inducing chromosomal anomalies and DNA-adducts in mice. JECFA (2000) concluded that the safety of ZEA could be evaluated on the basis of the dose that had no hormonal effects in pigs, the most sensitive species, and established a Provisional Maximum Tolerable Daily Intake for ZEA of 0.5 μg/kg of body weight. This decision was based on the NOEL of 40 μg/kg of body weight per day obtained in a 15-day study in pigs and the lowest observed effect level of 200 μg/kg body weight per day in this study.

Risk assessment, based on exposure and hazard evaluation, needs to take into account ZEA transfer in the organism, and has to evaluate all contamination sources (Kuiper-Goodman, 1990). Although ZEA is ubiquitous and toxic, it globally presents a potential danger for animal and human health only when it is absorbed in high amounts or over a long time of exposure. It is thus of great interest to develop studies focusing on ZEA absorption, metabolism, or eventual storage and elimination, in order to better understand its bioavailability and also its transfer rate to animal products. More data on occurrence of ZEA in feed materials (as opposed to cereals intended for human consumption) and bedding are needed to improve exposure assessment for farm animals. Studies in farm animals should be initiated that allow the establishment of a safe level of ZEA in feed materials and compounded feeds, particularly for pigs of different age groups, as they are considered to be the most sensitive animal species, followed by dose-effect studies in other (farm) animals.

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References

Abbas, H.K., Mirocha, C.J., Meronuck, R.A., Pokorny, J.D., Gould, S.L., Kommedahl, T., 1988. Mycotoxins and *Fusarium* spp. associated with infected ears of corn in Minnesota. Appl. Environ. Microbiol. 54, 1930–1933.

Abd Alla, E.S., 1997. Zearalenone: toxigenic fungi and chemical decontamination in Egyptian cereals. Nahrung 41, 362–365.

Abdel-hafez, A.I., Saber, S.M., 1993. Mycoflora and mycotoxin of hazelnut (*Corylus avellana* L.) and walnut (*Juglans regia* L.) seeds in Egypt. Zentralbl Mikrobiol. 148, 137–147.

Abdelhamid, A.M., Kelada, I.P., Ali, M.M., El-Ayouty, S.A., 1992. Influence of zearalenone on some metabolic, physiological and pathological aspects of female rabbits at two different ages. Arch. Anim. Nutr. 42, 63–70.

Abdulkadar, A.H.W., Al-Ali, A.A., Al-Kildi, F.M., Al-Jedah, J.H., 2004. Mycotoxins in foods available in Qatar. Food Control 15, 543–548.

Abid-Essefi, S., Baudrimont, I., Hassen, W., Ouanes, Z., Mobio, T.A., Anane, R., Creppy, E., EBacha, H., 2003. DNA fragmentation, apoptosis and cell cycle arrest induced by zearalenone in cultured DOK, Vero and Caco-2 cells: prevention by Vitamin E. Toxicology 192, 237–248.

Abid-Essefi, S., Ouanes, Z., Hassen, W., Baudrimont, I., Creppy, E.E., Bacha, H., 2004. Cytotoxicity, inhibition of DNA and protein syntheses and oxidative damage in cultured cells exposed to zearalenone. Toxicol. In Vitro 18, 467–474.

Ahamed, S., Foster, J.S., Bukovsky, A., Wimalasena, J., 2001. Signal transduction through the ras/Erk pathway is essential for the mycoestrogen zearalenone-induced cell-cycle progression in MCF-7 cells. Mol. Carcinog. 30, 88–98.

Alegakis, A.K., Tsatsakis, A.M., Shtilman, M.I., Lysovenko, D.L., Vlachonikolis, I.G., 1999. Deactivation of mycotoxins. I. An in vitro study of zearalenone adsorption on new polymeric adsorbents. J. Environ. Sci. Healt. B34, 633–644.

Allen, N.K., Mirocha, C.J., Aakus-Allen, S., Bitgood, J.J., Weaver, G., Bates, F., 1981. Effect of dietary zearalenone on reproduction of chickens. Poultry Sci. 62, 1165–1174.

Allen, N.K., Peguri, A., Mirocha, C.J., Newman, J.A., 1983. Effects of *Fusarium*cultures, T-2 toxin and zearalenone on reproduction of turkey females. Poultry Sci. 62, 282–289.

Arora, R.G., Frolen, H., Fellner-Feldegg, H., 1983. Inhibition of ochratoxin and teratogenesis by zearalenone and diethylstilboestrol. Food Chem. Toxicol. 21, 779–783.

Avantaggiato, G., Havenaar, R., Visconti, A., 2004. Assessing the zearalenone binding activity of adsorbent materials during passage through a dynamic in vitro gastrointestinal model. Food Chem. Toxicol. 41, 1283–1290.

Bacha, H., Chekir, L., Ellouz, F., Hadidane, R., Creppy, E.E., 1993. Effects of zearalenone on fertilization and gestation in rats. In: Scudamore, K.A. (Ed.), Proceedings of the UK Workshop, Occurrence and Significance of Mycotoxin, The University of West London, Central Sciences Laboratory, London, pp. 258–262.

Bagneris, R.W., Gaul, J.A., Ware, G.M., 1986. Liquid chromatographic determination of zearalenone and zearalenol in animal feeds and grains, using fluorescence detection. J. Assoc. Off. Anal. Chem. 69, 894–898.

Balzer, I., Bogdanic, C., Muzic, S., 1977. Natural contamination of corn (*Zea mays*) with mycotoxins in Yugoslavia. Ann. Nutr. Aliment. 31, 425–430.

Becci, P.J., Voss, K.A., Hess, F.G., Gallo, M.A., Parent, R.A., Stevens, K.R., Taylor, J.M., 1982a. Long-term carcinogenicity and toxicity study of zearalenone in the rat. J. Appl. Toxicol. 2, 247–254.

Becci, P.J., Johnson, W.D., Hess, F.G., Gallo, M.A., Parent, R.A., 1982b. Combined two-generation reproduction-teratogenesis study of zearalenone in the rat. J. Appl. Toxicol. 2, 201–206.

Bennett, J.W., Klich, M., 2003. Mycotoxins. Clin. Microbiol. Rev. 16, 497–516.

Bennett, G.A., Lagoda, A.A., Shotwell, O.L., Hesseltine, C.M., 1981. Utilization of zearalenone-contaminated corn for ethanol production. J. Am. Oil Chem. Soc. 58, 974–976.

Bennett, G.A., Shotwell, O.L., Kwolek, W.F., 1985. Liquid chromatographic determination of alpha-zearalenol and zearalenone in corn: Collaborative study. J. Assoc. Off. Anal. Chem. 68, 958–961.

Berek, L., Petri, I.B., Mesterhazy, A., Teren, J., Molanr, J., 2001. Effects of mycotoxins on human immune functions in vitro. Toxicol. In Vitro 15, 25–30.

Biehl, M.L., Prelusky, D.B., Koritz, G.D., Hartin, K.E., Buck, W.B., Trenholm, H.L., 1993. Biliary excretion and enterohepatic cycling of zearalenone in immature pigs. Toxicol. Appl. Pharmacol. 121, 152–159.

Bilgrami, K.S., Choudhary, A.K., 1998. Mycotoxins in preharvest contamination of agricultural crops. In: Sinha, K.K., Bhatnagar, D. (Eds.), Mycotoxins, Agriculture, and Food Safety. Marcel Dekker Publishers, New York.

Blaney, B.J., Moore, C.J., Tyler, A.L., 1984. Mycotoxins and fungal damage in maize harvested during 1982 in Far North Queensland. Austr. J. Agric. Res. 35, 463–471.

Blaney, B.J., Moore, C.J., Tyler, A.L., 1987. The mycotoxins dash 4-deoxynivalenol, zearalenone and aflatoxin dash in weather-damaged wheat harvested 1983-1985 in south-eastern Queensland. Austr. J. Agric. Res. 38, 993–1000.

Bosch, U., Mirocha, C.J., 1992. Toxin production by *Fusarium* species from sugar beets and natural occurrence of zearalenone in beets and beet fibers. Appl. Environ. Microbiol. 58, 3233–3239.

Bottalico, A., Visconti, A., Logrieco, A., Solfrizzo, M., Mirocha, C.J., 1985. Occurrence of zearalenols (diastereomeric mixture) in corn stalk rot and their production by associated *Fusarium* species. Appl. Environ. Microbiol. 49, 547–551.

Bucheli, B., Diserens, P., Rychener, M., Tieche, J.D., Trenkner, N., 1996. Untersuchungen zum Fusarienbefall und zur mykotoxinbelastung des schweizerischen Brotgetreides des Ernten 1992–1994. Mitt. Gebiete. Lebensm. Hyg. 87, 84–102.

Bueno, D.J., Di Marco, L., Oliver, G., Bardon, A., 2005. In vitro binding of zearalenone to different adsorbents. J. Foot Prot. 68, 613–615.

Cavaglieri, L.R., Gonzalez Pereyra, L.M., Pereyra, C.M., Magnoli, C.E., Chulze, S.N., Dalcero, A.M., 2005. Fungal and mycotoxin contamination of cow feeding stuffs in Argentina. In: International Conference. Fifth Framework Program. European Union Myco-Globe Project. European commission, 13–16 September, Accra, Ghana.

Cavret, S., Lecoeur, S., 2006. Fusariotoxin transfer in animal. Food Chem. Toxicol. 44, 444–453.

CCFAC, 2000. Codex Committee on Food Additives and Contaminants. Posting date. Joint FAO/WHO Expert Committee on Food Additives: Position paper on zearalenone. Publication CCFAC 00/19. Codex Alimentarius Commission, Rome, Italy.

Cetin, Y., Bullerman, L.B., 2005a. Cytotoxicity of *Fusarium* mycotoxins to mammalian cell cultures as determined by the MTT bioassay. Food Chem. Toxicol. 43, 755–764.

Cetin, Y., Bullerman, L.B., 2005b. Evaluation of reduced toxicity of zearalenone by extrusion processing as measured by the MTT cell proliferation assay. J. Agric. Food Chem. 16, 6558–6563.

Cheeke, P.R., 1998. Mycotoxins in cereal grains and supplements. In: Cheeke, P.R. (Ed.), Natural Toxicants in feeds, forages and Poisonous plants. Interstate Publishers, Inc., Danville, IL, pp. 7–136.

ČonKová, E., Laciakova, A., Pastorová, B., Seidel, H., Kováč, G., 2001. The effect of zearalenone on some enzymatic parameters in rabbits. Toxicol. Lett. 121, 145–149.

Creppy, E.E., 2002. Update of survey, regulation and toxic effects of mycotoxins in Europe. Toxicol. Lett. 127, 19–28.

Dacasto, M., Rolando, P., Nachtmann, C., Ceppa, L., Nebbia, C., 1995. Zearalenone mycotoxicosis in piglets suckling sows fed contaminated grain. Vet. Hum. Toxicol. 37, 359–361.

Dalcero, A., Magnoli, C., Chiacchiera, S., Palacios, G., Reynoso, M., 1997. Mycoflora and incidence of aflatoxin B1, zearalenone and deoxynivalenol in poultry feeds in Argentina. Mycopathologia 137, 179–184.

Dalcero, A., Magnoli, C., Luna, M., Ancasi, G., Reynoso, M.M., Chiacchiera, S., Miazzo, R., Palacio, G., 1998. Mycoflora and naturally occurring mycotoxins in poultry feeds in Argentina. Mycopathologia 141, 37–43.

Danicke, S., Ueberschar, K.H., Halle, I., Matthes, S., Valenta, H., Flachowsky, G., 2002. Effect of a detoxifying agent to laying hen diets containing uncontaminated or *Fusarium* toxin-contaminated maize on performance of hens and carryover of zearalenone. Poultry Sci. 81, 1671–1680.

Devegowda, G., Arvind, B.I.R., Morton, M.G., 1996. *Saccharomyces cerevisiae* and mannanoligosaccharides to counteract aflatoxisis in broilers. Proc. Aust. Poult. Sci. Symp. 8, 103–106.

Diekman, M.A., Green, M.L., 1992. Mycotoxins and reproduction in domestic livestock. J. Anim. Sci. 70, 1615–1627.

di Menna, M.E., Lauren, D.R., Hardacre, A., 1997. Fusaria and *Fusarium* toxins in New Zealand maize plants. Mycopathologia 139, 165–173.

D'Mello, J.P.F., Porter, J.K., Macdonald, A.M.C., Placinta, C.M., 1997. *Fusarium* mycotoxins. In: D'Mello, J.P.F. (Ed.), Handbook of Plant and Fungal Toxicants. CRC Press, Boca Raton, FL, pp. 287–301.

D'Mello, J.P.F., Placinta, C.M., Macdonald, A.M.C., 1999. *Fusarium* mycotoxins: a review of global implications for animal health, welfare and productivity. Anim. Feed Sci. Technol. 80, 183–205.

Döll, S., Danicke, S., Schnurrbusch, U., 2003. The effect of increasing concentrations of *Fusarium* toxins in the diets of piglets on histological parameters of uterus. Mycotox. Res. 19, 73–76.

Domijan, A.M., Peraica, M., Cvjetkovic, B., Turcin, S., Jurjevic, Z., Ivic, D., 2005. Mould contamination and co-occurrence of mycotoxins in maize grain in Croatia. Acta Pharm. 55, 349–356.

Dutton, M.F., Kinsey, A., 1996. A note on the occurrence of mycotoxins in cereals and animal feedstuffs in Kwazulu Natal, South Africa 1984–1993. S. Afr. J. Anim. Sci. 26, 53–57.

EC, European Commission, 2004. Opinion of the scientific panel on contaminants in the food chain in a request from the commission related to zearalenone as undesirable substance in animal feed. EFSA J. 89, 1–35.

El-Maghraby, O.M., El-Kady, I.A., Soliman, S., 1995. Mycoflora and *Fusarium* toxins of three types of corn grains in Egypt with special reference to production of trichothecene-toxins. Microbiol. Res. 150, 225–232.

El-Nezami, H., Polychronaki, N., Salminen, S., Mykkänen, H., 2002. Binding rather than metabolism may explain the interaction of two food-grade lactobacillus strains with zearalenone and its derivative α-zearalenol. Appl. Environ. Microbiol. 68, 3545–3549.

El-Sharkawy, S., Abul-Hajj, Y., 1987a. Microbial transformation of zearalenone. 1. Formation of zearalenone 4-O-b-glucoside. J. Nat. Prod. 50, 520–521.

El-Sharkawy, S., Abul-Hajj, Y., 1987b. Microbial transformation of zearalenone. 2. Reduction, hydroxylation, and methylation products. J. Org. Chem. 53, 515–519.

El-Sharkawy, S., Abul-Hajj, Y.J., 1988. Microbial cleavage of zearalenone. Xenobiotica 18, 365–371.

Eriksen, G.S., Alexander, J., 1998. In: Nordic Council of Ministers (Ed.), *Fusarium* Toxins in Cereals – A Risk Assessment, vol. 502. Tema Nord, Copenhagen, pp. 7–58.

Etienne, M., Dourmad, J.Y., 1994. Effects of zearalenone or glucosinolates in the diet on reproduction in sows: a review. Livest. Prod. Sci., 99–113.

Faber, K.A., Hughes Jr., C.L., 1991. The effect of neonatal exposure to diethylstilbestrol, genistein, and zearalenone on pituitary responsiveness and sexually dimorphic nucleus volume in the castrated adult rat. Biol. Reprod. 45, 649–653.

FAO, 2004. Worldwide regulations for mycotoxins in food and feed in 2003. FAO Food and Nutrition paper No. 81. Food and Agriculture Organization of the United Nations, Rome, Italy.

Fazekas, B., Kis, M., Hajdu, E.T., 1996. Data on the contamination of maize with fumonisin B_1 and other fusariotoxins in Hungary. Acta Vet. Hung. 44, 25–37.

Flannigan, B., 1991. Mycotoxins. In: D'Mello, J.P.F., Duffus, C.M., Duffus, J.H. (Eds.), Toxic Substances in Crop Plants. The Royal Society of Chemistry, Cambridge, pp. 226–257.

Forsell, J.H., Witt, M.F., Tai, J.-H., Jensen, R., Pestka, J.J., 1986. Effects of 8-week exposure of the B6C3F1-mouse to dietary deoxynivalenol (vomitoxin) and zearalenone. Food. Chem. Toxicol. 24, 213–219.

Funnell, H.S., 1979. Mycotoxins in animal feedstuffs in Ontario, 1972 to 1977. Can. J. Comp. Med. 43, 243–246.

Furlong, E.B., Soares, L.M.V., Lasca, C.C., Kohara, E.Y., 1995. Mycotoxins and fungi in wheat harvested during 1990 in test plots in the state of Sao Paulo Brazil. Mycopathologia 131, 185–190.

Galvano, F., Piva, A., Ritlen, A., Galvano, G., 2001. Dietary strategies to counteract the effects of mycotoxins: a review. J. Food Prot. 64, 120–131.

Gbodi, T.A., Nwude, N., Aliu, Y.O., Ikediobi, C.O., 1986a. The mycoflora and some mycotoxins found in acha (Digitaria exilis Stapf.) in Plateau State, Nigeria. Food Chem. Toxicol. 24, 339–342.

Gbodi, T.A., Nwude, N., Aliu, Y.O., Ikediobi, C.O., 1986b. The mycoflora and some mycotoxins found in maize (*Zea mays*) in the Plateau State of Nigeria. Vet. Hum. Toxicol. 28, 1–5.

Ghedira-Chekir, L., Zakhama, A., Ellouz, F., Dhouib, S., Creppy, E.E., Bacha, H., 1998. Induction of SOS repair system in lysogenic bacteria by zearalenone and its prevention by vitamin E. Chem. Biol. Interact. 113, 15–25.

Ghedira-Chekir, L., Maaroufi, K., Creppy, E.E., Bacha, H., 1999. Cytotoxicity and genotoxocity of zearalenone: prevention by vitamin E. J. Toxicol. Toxin Rev. 18, 355–368.

Gross, V.J., Robb, J., 1975. Zearalenone production in barley. Ann. Appl. Biol. 80, 211–216.

Grosse, Y., Ghedira-Chekir, L., Huc, A., Obrecht-Pflumio, S., Dirheimer, G., Bacha, H., Pfoh-Leszkowicz, A., 1997. Retinol, ascorbic acid and alpha tocopherol prevent DNA adduct formation in mice treated with the mycotoxins ochratoxin A and zearalenone. Cancer Lett. 114, 225–229.

Hadiani, M.R., Yazdanpanah, H., Ghazi-Khansari, M., Cheraghali, A.M., Goodarzi, M., 2003. Survey of the natural occurrence of zearalenone in maize from northern Iran by thin-layer chromatography densitometry. Food Addit. Contam. 20, 380–385.

Hagler Jr., W.M., Towers, N.R., Mirocha, C.J., Eppley, R.M., Bryden, W.L., 2001. Zearalenone: mycotoxin or mycoestrogen? In: Summerell, B.A., Leslie, J.F., Backhouse, D., Bryden, W.L., Burgess, L.W. (Eds.), *Fusarium.* Paul E. Nelson Memorial Symposium. APS Press, St. Paul, Minn.

Hidy, P.H., Baldwin, R.S., Greasham, R.L., Keith, C.L., McMullan, J.R., 1977. Zearalenone and some derivatives: Production and biological activities. Adv. Appl. Microbiol. 22, 55–82.

Hietaniemi, V., Kumpulainen, J., 1991. Contents of *Fusarium* toxins in Finnish and imported grains and feeds. Food Addit. Contam. 8, 171–182.

Hilakivi-Clarke, L., Cho, E., Clarke, R., 1998. Maternal genistein exposure mimics the effects of estrogen on mammary gland development in female mouse offspring. Oncol. Rep. 5, 609–616.

Hooshmand, H., Klopfenstein, C.F., 1995. Effects of gamma irradiation on mycotoxin disappearance and amino acid contents of corn, wheat, and soybeans with different moisture contents. Plant Foods Hum. Nutr. 47, 227–238.

Hughes Jr., C.L., Chakinala, M.M., Reece, S.G., Miller, R.N., Schomberg Jr., D.W., Basham, K.B., 1991. Acute and subacute effects of naturally occurring estrogens on luteinizing hormone secretion in the ovariectomized rat: Part 2. Reprod. Toxicol. 5, 133–137.

Hussein, H.S., Brasel, J.M., 2001. Toxicity, metabolism, and impact of mycotoxins on humans and animals. Toxicology 167, 101–134.

Hussein, H.M., Franich, R.A., Baxter, M., Andrew, I.G., 1989. Naturally occurring *Fusarium* toxins in New Zealand maize. Mycopathologia 6, 49–57.

Huwig, A., Freimund, S., Käppeli, O., Dutler, H., 2001. Mycotoxin detoxification of animal feed by different sorbents. Toxicol. Lett. 122, 179–188.

IARC, 1999. Overall evaluations of carcinogenicity to humans. International Agency for Research on Cancer. IARC Monographs, vols. 1–73, pp. 1–36.

Ito, Y., Ohtsubo, K.I., 1994. Effects of neonatal administration of zearalenone on the reproductive physiology of female mice. J. Vet. Med. Sci. 56, 1155–1159.

Jadamus, A., Schneider, D., 2002. Long term effect of fusariotoxins on the reproductive performance on sows testing effectiveness of detoxifying feed additives 700. Feed Mag. 10, 396–405.

Janardhana, G.R., Rabeas, K.A., Shekar Shetty, H., 1999. Mycotoxin contamination of maize grains grown in Karnataka (India). Food Chem. Toxicol. 37, 863–868.

JECFA, 2000. Zearalenone. In: Joint FAO/WHO Expert Committee on Food Additives (Ed.), Safety evaluation of certain food additives and contaminants. WHO/FAO Food additives Series 44. IPCS – International Programme on Chemical Safety. WHO, Geneva.

Kaliamurthy, P., Geraldine, P., Thomas, P.A., 1997. Effects of zearalenone on food consumption, growth, organ weight and serum testosterone level in male rats. J. Environ. Biol. 18, 115–120.

Karlovsky, P., 1999. Biological detoxification of fungal toxins and its use in plant breeding, feed and food production, Nat. Toxins 7, 1–23.

Kiessling, K.H., Pettersson, H., Sandholm, K., Olsen, M., 1984. Metabolism of aflatoxin, ochratoxin, zearalenone, and three tricothecenes by intact rumen fluid, rumen protozoa, and rumen bacteria. Appl. Environ. Microbiol. 47, 1070–1073.

Kim, C., Kang, H.J., Lee, D.H., Lee, Y.W., Yoshizawa, T., 1993. Natural occurrence of *Fusarium* mycotoxins (trichothecenes and zearalenone) in barley and corn in Korea. Appl. Environ. Microbiol. 59, 3798–3802.

Kouadio, J.H., Mobio, T.H., Baudrimont, I., Moukha, S., Dano, S.D., Creppy, E.E., 2005. Comparative study of cytotoxicity and oxidative stress induced by deoxynivalenol, zearalenone or fumonisin B1 in human intestinal cell line Caco-2. Toxicology 213, 56–65.

Kuiper, G.G.J.M., Lemmen, J.G., Carlsson, B., Corton, J.C., Safe, S.H., Van der Saag, P.T., Van der Burg, B., Gustafsson, J.A., 1998. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β. Endocrinology 139, 4252–4263.

Kuiper-Goodman, T., 1990. Uncertainties in the risk assessment of three mycotoxins: aflatoxin, ochratoxin, and zearalenone. Can. J. Phys. Pharmacol. 68, 1017–1024.

Kuiper-Goodman, T., Scott, P.M., Watanabe, H., 1987. Risk assessment of the mycotoxin zearalenone. Regul. Toxicol. Pharmacol. 7, 253–306.

Labuda, R., Parich, A., Berthiller, F., Tančinová, D., 2005. Incidence of trichothecenes and zearalenone in poultry feed mixtures from Slovakia. Int. J. Food Microbiol. 105, 19–25.

Lauren, D.R., Ringrose, M.A., 1997. Determination of the fate of three *Fusarium* mycotoxins through wet-milling of maize using an improved HPLC analytical technique. Food Addit. Contam. 14, 435–443.

Lauren, D.R., Jensen, D.J., Smith, W.A., Dow, B.W., Sayer, S.T., 1996. Mycotoxins in New Zealand maize: a study of some factors influencing contamination levels in grain New Zealand. NZ. J. Crop Hortic. Sci. 24, 13–20.

Lemke, S.L., Grant, P.G., Phillips, T.D., 1998. Adsorption of zearalenone by organophilic montmorillonite clay. J. Agric. Food Chem. 46, 3789–3796.

Li, F.Q., Li, Y.W., Luo, X.Y., Yoshizawa, T., 2002. *Fusarium* toxins in wheat from an area in Henan Province, PR China, with a previous human red mould intoxication episode. Food Addit. Contam. 19.

Lioi, M.B., Santoro, A., Barbieri, R., Salzano, Ursini, M.V., 2004. Ochratoxin and zearalenone: a comparative study on genotoxic effects and cell death induced in bovine lymphocytes. Mutat. Res. 557, 19–24.

Lombaert, G.A., Oellaers, P., Roscoe, V., Mankotia, M., Neil, R., Scott, P.M., 2003. Mycotoxins in infant cereal foods from the Canadian retail market. Food Addit. Contam. 20, 494–504.

Long, G.G., Diekman, M.A., 1989. Effect of zearalenone on early pregnancy in guinea pigs. Am. J. Vet. Res. 50, 1220–1223.

Lopez, T.A., Tapia, M.O., 1980. Identification of the mycotoxin zearalenone in Argentina. Rev. Argent. Microbiol. 12, 29–33.

Lovelace, C.E., Nyathi, C.B., 1977. Estimation of the fungal toxins, zearalenone and aflatoxin, contaminating opaque maize beer in Zambia. J. Sci. Food Agric. 28, 288–292.

Luo, Y., Yoshizawa, T., Katayama, T., 1990. Comparative study on the natural occurrence of *Fusarium* mycotoxins (trichothecenes and zearalenone) in corn and wheat from high- and low-risk areas for human esophageal cancer in China. Appl. Environ. Microbiol. 56, 3723–3726.

Maaroufi, K., Chekir, L., Creppy, E.E., Ellouz, F., Bacha, H., 1996. Zearalenone induces modifications in haematological and biochemical parameters in rats. Toxicon 34, 534–540.

Malekinejad, H., Maas-Bakker, R., Fink-Gremmels, J., 2006. Species differences in the hepatic biotransformation of zearalenone. Vet. J. 172, 96–102.

Marin, L., Murtha, J., Dong, W., Pestka, J.J., 1996. Effects of mycotoxins on cytokine production and proliferation in EL-4 thymoma cells. J. Toxicol. Environ. Health 48, 379–396.

McKenzie, K.S., Sarr, A.B., Mayura, K., Bailey, R.H., Millar, D.R., Rogers, T.D., Corred, W.P., Voss, K.A., Plattner, R.D., Kubena, L.F., Phillips, T.D., 1997. Oxidative degradation and detoxification of mycotoxins using a novel source of ozone. Food Chem. Toxicol. 35, 807–820.

Megharaj, M., Garthwaite, I., Thiele, J.H., 1997. Total biodegradation of the oestrogenic mycotoxin zearalenone by a bacterial culture. Lett. App. Microbiol. 24, 329–333.

Milano, G.D., Becú-Villalobos, D., Ofelia Tapia, M., 1995. Effects of long-term zearalenone administration on spermatogenesis and serum luteinizing hormone, follicle stimulating hormone, and prolactin values in male rats. Am. J. Vet. Res. 56, 954–957.

Miles, C.O., Erasmuson, A.F., Wilkins, A.L., 1996. Ovine metabolism of zearalenone to α-zearalanol (zeranol). J. Agric. Food Chem. 44, 3244–3250.

Minervini, F., Giannoccaro, A., Cavallini, A., Visconti, A., 2005. Investigations on cellular proliferation induced by zearalenone and its derivatives in relation to the estrogenic parameters. Toxicol. Lett. 159, 272–283.

Mirocha, C.J., Pathre, S.V., Robison, T.S., 1981. Comparative metabolism of zearalenone and transmission into bovine milk. Food Cosmet. Toxicol. 19, 25–30.

Mokoena, M.P., Chelule, P.K., Gqaleni, N., 2005. Reduction of fumonisin B1 and zearalenone by lactic acid bacteria in fermented maize meal. J. Food Prot. 68, 2095–2099.

Molnar, O., Schatzmayr, G., Fuchs, E., Prillinger, H., 2004. *Trichosporon mycotoxinivorans* sp. nov., a new yeast species useful in biological detoxification of various mycotoxins. Syst. Appl. Microbiol. 27, 661–671.

Müller, H.M., Reimann, J., Schumacher, U., Schwadorf, K., 1997a. *Fusarium* toxins in wheat harvested during six years in an area of southwest Germany. Nat. Toxins 5, 24–30.

Müller, H.M., Reimann, J., Schumacher, U., Schwadorf, K., 1997b. Natural occurrence of *Fusarium* toxins in barley harvested during 5 years in an area of southwest Germany. Mycopathologia 137.

Noser, J.R., Wenk, P., Sutter, A., 1996. Deoxynivalenol, zearalenone and ochratoxin A in wheat from Canton Basel-Landschaft. Mitt. Gebiete. Lebensm. Hyg. 87, 574–586.

NTP, 1982. Carcinogenicity bioassay of zearalenone in F344/N rats and F6C3F1 mice. National Toxicology Program Technical Reports Series 235. National Toxicology Program. Research Triangle Park, NC, USA.

Nuryono, N., Noviandi, C.T., Böhm, J., Razzazi-Fazeli, E., 2005. A limited survey of zearalenone in Indonesian maize-based food and feed by ELISA and high performance liquid chromatography. Food Control 16, 65–71.

Obremski, A., Gajecki, M., Zwierzchowski, W., Bakula, T., Apoznaniski, J., Wojciechoeski, J., 2003. The level of zearalenone and alpha-zearalenol in blood of gilts with clinical symptoms of toxicosis fed diets with a low zearalenone content. J. Anim. Feed Sci. 12, 529–532.

Odhav, B., Naicker, C., 2002. Mycotoxins in South African traditionally brewed beers. Food Addit. Comtam. 19, 55–61.

Okoye, Z.S., 1987. Stability of zearalenone in naturally contaminated corn during Nigerian traditional brewing. Food Addit. Contam. 4, 57–59.

Olsen, M., Pettersson, H., Kiessling, K.H., 1981. Reduction of zearalenone to zearalenol in female rat liver by 3 alpha-hydroxysteroid dehydrogenase. Acta Pharmacol. Toxicol. (Copenh) 48, 157–161.

Olsen, M., Pettersson, H., Sandholm, K., Visconti, A., Kiessling, K.H., 1987. Metabolism of zearalenone by sow intestinal mucosa in vitro. Food Chem. Toxicol. 25, 681–683.

Ouanes, Z., Abid, S., Ayed, I., Anane, R., Mobio, T., Creppy, E., Bacha, H., 2003. Induction of micronuclei by zearalenone in Vero monkey kidney cells and in bone marrow cells of mice: protective effect of vitamin E. Mutat. Res. 538, 63–70.

Park, K.J., Park, A.R., Lee, Y.W., 1992. Natural occurrence of *Fusarium* mycotoxins of the 1990 barley crop in Korea. Food Addit. Contam. 9, 639–645.

Park, J.J., Smalley, E.B., Chu, F.S., 1996. Natural occurrence of *Fusarium* mycotoxins in fields samples from the 1992 Wisconsin corn crop. Appl. Environ. Microbiol. 62, 1642–1648.

Park, J.W., Kim, E.K., Shon, D.H., Kim, Y.B., 2002. Natural co-occurrence of aflatoxin B1, fumonisin B1 and ochratoxin A in barley and corn foods from Korea. Food Addit. Contam. 19, 1073–1080.

Park, J.W., Shoi, S.Y., Hwang, H.J., Kim, Y.B., 2005. Fungal mycoflora and mycotoxins in Korean polished rice destined for humans. Int. J. Food Microbiol. 103, 305–314.

Perkowski, J., Plattner, R.D., Golinski, P., Vesonder, R.F., 1990. Natural occurrence of deoxynivalenol, 3-acetyl-deoxynivalenol, 15-acetyl-deoxynivalenol, nivalenol, 4,7-dideoxynivalenol and zearalenone in Polish wheat. Mycotoxin Res. 6, 7–12.

Pestka, J.J., Tai, J.H., Witt, M.F., Dixon, D.E., Forsell, J.H., 1987. Suppression of immune response in the B6C3F1 mouse after dietary exposure to the *Fusarium* mycotoxins deoxynivalenol (vomitoxin) and zearalenone. Food Chem. Toxicol. 25, 297–304.

Pfohl-Leszkowicz, A., Chekir-Ghedir, L., Bacha, L., 1995. Genotoxicity of zearalenone, an oestrogenic mycotoxin: DNA adduct formation in female mouse tissues. Carcinogenesis 16, 2315–2320.

Phillips, S.I., Wareing, P.W., Dutta, A., Panigrahi, S., Medlock, V., 1996. The mycoflora and incidence of aflatoxin, zearalenone and sterigmatocystin in dairy feed and forage samples from eastern India and Bangladesh. Mycopathologia 133, 15–21.

Pietri, A., Bertuzzi, T., Pallaroni, L., Piva, G., 2004. Occurrence of mycotoxins and ergosterol in maize harvested over 5 years in Northern Italy. Food Addit. Contam. 21, 479–487.

Pineiro, M., Dawson, R., Costarrica, M.L., 1996a. Monitoring program for mycotoxin contamination in Uruguayan food and feeds. Nat. Toxins 4, 242–245.

Pineiro, M.S., Scott, P.M., Kanhere, S.R., 1996b. Mycotoxin producing potential of *Fusarium* graminearum isolates from Uruguayan barley. Mycopathologia 132, 167–172.

Pittet, A., 1998. Natural occurrence of mycotoxins in foods and feeds- an update review. Rev. Méd. Vét. 149, 479–492.

Placinta, C.M., D'Mello, J.P.F., Macdonald, A.M.C., 1999. A review of worldwide contamination of cereal grains and animal feed with *Fusarium* mycotoxins. Anim. Feed Sci. Technol. 78, 21–37.

Prelusky, D.B., Scott, P.M., Trenholm, H., Lawrence, G.A., 1990. Minimal transmission of earalenone to milk of dairy cows. J. Environ. Sci. Health B 25, 87–103.

Quiroga, N., Resnik, S., Pacin, A., Martínez, E., Pagano, A., Riccobene, I., Neira, S., 1995. Natural occurrence of trichothecenes and zearalenone in Argentine wheat. Food Control 6, 201–204.

Ramos, A.J., Hernandez, E., Pla-Delfina, J.M., Merino, M., 1996. Intestinal absorption of zearalenone and in vitro study of non-nutritive sorbent materials. Int. J. Pharm. 128, 129–137.

Resnik, S., Neira, S., Pacin, A., Martinez, E., Apro, N., Latreite, S., 1996. A survey of the natural occurrence of aflatoxins and zearalenone in Argentine field maize: 1983–1994. Food Addit. Contam. 13, 115–120.

Reza Oveisi, M., Hajimahmoodi, M., Memarian, S., Sadeghi, N., Shoeibi, S., 2005. Determination of zearalenone in corn flour and a cheese snack product using high-performance liquid chromatography with fluorescence detection. Food Addit. Contam. 22, 443–448.

Richardson, K.E., Hagler, W.M., Mirocha, C.J., 1985. Production of zearalenone α- and β-zearalenol and α- and β-zearalanol by *Fusarium* spp. in rice culture. J. Agric. Food Chem. 33, 862–866.

Ryu, D., Hanna, M.A., Bullerman, L.B., 1999. Stability of zearalenone during extrusion of corn grits. J. Food Prot. 62, 1482–1484.

Sabino, M., Prado, G., Inomata, E.I., Pedroso Mde, O., Garcia, R.V., 1989. Natural occurrence of aflatoxins and zearalenone in maize in Brazil. Part II. Food Addit. Contam. 6, 327–331.

Schneweis, I., Meyer, K., Engelhardt, G., Bauer, J., 2002. Occurrence of zearalenone-4-beta-D-glucopyranoside in wheat. J. Agric. Food Chem. 50, 1736–1738.

Schollenberger, M., Müller, H.M., Rüfle, M., Suchy, S., Planck, S., Drochner, W., 2005. Survey of *Fusarium* toxins in foodstuffs of plant origin marketed in Germany. Int. J. Food Microbiol. 97, 317–326.

Schollenberger, M., Müller, H.M., Rüfle, M., Suchy, S., Planck, S., Drochner, W., 2006. Natural occurrence of 16 fusarium toxins in grains and feedstuffs of plant origin from Germany. Mycopathologia 161, 43–52.

SCOOP, 2003. Collection of occurrence data of *Fusarium* toxins in food and assessment of dietary intake by the population of EU Member States. Sub-task Zearalenone. SCOOP European Project. Task 3.2.10. In: Vidnes, A., Bergsten C., Paulsen B. (Eds.), pp. 241–481.

Scott, P.M., 1997. Multi-year monitoring of Canadian grains and grain based foods for trichothecenes and zearalenone. Food Addit. Contam. 14, 333–339.

Scudamore, K.A., Nawaz, S., Hetmanski, M.T., 1998. Mycotoxins in ingredients of animal feeding stuffs: II. Determination of mycotoxins in maize and maize products. Food Addit. Contam. 15, 30–55.

Shotwell, O.L., Goulden, M.L., Bennett, G.A., Plattner, R.D., Hesseltine, C.W., 1977. Survey of 1975 wheat and soybeans for aflatoxin, zearalenone, and ochratoxin. J. Assoc. Off. Anal. Chem. 60, 778–783.

Silva, C.M., Vargas, E.A., 2001. A survey of zearalenone in corn using Romer Mycosep 224 column and high performance liquid chromatography. Food Addit. Contam. 18, 39–45.

Skrinjar, M., Stubblefield, R.D., Stojanovic, E., Dimic, G., 1995. Occurrence of *Fusarium* species and zearalenone in dairy cattle feeds in Vojvodina. Acta Vet. Hung. 43, 259–267.

Stahl, S., Chun, T.Y., Gray, W.G., 1998. Phytoestrogens act as estrogen agonists in an estrogen-responsive pituitary cell line. Toxicol. Appl. Pharmacol. 152, 41–48.

Stratton, G.W., Robinson, A.R., Smith, H.C., Kittilsen, L., Barbour, M., 1993. Levels of five mycotoxins in grains harvested in Atlantic Canada as measured by high performance liquid chromatography. Arch. Environ. Contam. Toxicol. 24, 399–409.

Sugiura, Y., Fukasaku, K., Tanaka, T., Matsui, Y., Ueno, Y., 1993. *Fusarium poae* and *Fusarium crookwellense*, fungi responsible for the natural occurrence of nivalenol in Hokkaido. Appl. Environ. Microbiol. 59, 3334–3338.

Szuetz, P., Mesterhazy, A., Falkay, G.Y., Bartyok, T., 1997. Early telearche symptoms in children and their relations to zearalenone contamination in foodstuffs. Cereals Res. Commun. 25, 429–436.

Takahashi-Ando, N., Kimura, M., Kakeya, H., Osada, H., Yamaguchi, I., 2002. A novel lactonohydrolase responsible for the detoxification of zearalenone: enzyme purification and gene cloning. Biochem. J. 365, 1–6.

Tanaka, T., Hasegawa, A., Yamamoto, S., Li, U.-S., Sugiura, Y., Ueno, Y., 1988. Worldwide contamination of cereals by the *Fusarium* mycotoxins nivalenol, deoxynivalenol and zearalenone. 1. Survey of 19 countries. J. Agric. Food Chem. 36, 979–983.

Tanaka, T., Yamamoto, S., Hasegawa, A., Aoki, N., Besling, J.R., Sugiura, Y., Ueno, Y., 1990. A survey of the natural occurrence of *Fusarium* mycotoxins, deoxynivalenol, nivalenol and zearalenone, in cereals harvested in The Netherlands. Mycopathologia 110, 19–22.

Tomaszewski, J., Miturski, R., Semczuk, A., Kotarski, J., Jakowicki, J., 1998. Tissue zearalenone concentration in normal, hyperplastic and neoplastic human endometrium. Ginekol. Pol. 69, 363–366.

Ueno, Y., Tashiro, F., Kobayashi, T., 1983. Species differences in zearalenone-reductase activity. Food Chem. Toxicol. 21, 167–173.

Urry, W.H., Wehrmeister, H.L., Hodge, E.B., Hidy, P.H., 1966. The structure of zearalenone. Tetrahedron Lett. 27, 3109–3114.

Van Egmond, H.P., 1993. Rationale for regulatory programmes for mycotoxins in human foods and animal feeds. Food Addit. Contam. 10, 29–36.

Vanyi, A., Timar, I., Szeky, A., 1980. Fusariotoxicosis. The effect of F-2 toxin (zearalenone) on the spermatogenesis of rams and bulls. Magy. Allattorv. Lapja 35, 777–780.

Vanyi, A., Bata, A., Kovacs, F., 1994. Perinatal oestrogen syndrome in swine. Acta Vet. Hung. 42, 433–446.

Varga, J., Péteri, Z., Tábori, K., Téren, T., Vágvölgyi, C., 2005. Degradation of ochratoxin A and other mycotoxins by *Rhizopus* isolates. Int. J. Food Microbiol. 99, 321–328.

Vargas, E.A., Preis, R.A., Castro, L., Silva, C.M., 2001. Co-occurrence of aflatoxins B1, B2, G1, G2, zearalenone and fumonisin B1 in Brazilian corn. Food Addit. Contam. 18, 981–986.

Veldman, A., Borggreve, G.J., Mulders, E.J., van de Lagemaat, D., 1992. Occurrence of the mycotoxins ochratoxin A, zearalenone and deoxynivalenol in feed components. Food Addit. Contam. 9, 647–655.

Visconti, A., Pascale, M., 1998. Determination of zearalenone in corn by means of immunoaffinity clean-up and high-performance liquid chromatography with fluorescence detection. J. Chromatogr. A 815, 133–140.

Vrabcheva, T., Gebler, R., Usleber, E., Martlbauer, E., 1996. First survey on the natural occurrence of *Fusarium* mycotoxins in Bulgarian wheat. Mycopathologia 136, 47–52.

Weaver, G.A., Kurtz, H.J., Behrens, J.C., Robinson, T.S., Seguin, B.E., Bates, F.Y., Microcha, C.J., 1986. Effects of zearalenone on the fertility of virgin dairy heifers. Am. J. Vet. Res. 47, 1395–1397.

Yamashita, A., Yoshizawa, T., Aiura, Y., Sanchez, P.C., Dizon, E.I., Arim, R.H., Sardjono, 1995. *Fusarium* mycotoxins (fumonisins, nivalenol and zearalenone) and aflatoxins in corn from southeast Asia. Biosci. Biotech. Biochem. 59, 1804–1807.

Yamini, B., Bursian, S.J., Aulerich, R.J., 1997. Pathological effects of dietary zearalenone and/or tamoxifen on female mink reproductive organs. Vet. Hum. Toxicol. 39, 74–78.

Yang, H.H., Aulerich, R.J., Helferich, W., Yamini, B., Chou, K.C., Miller, E.R., Bursian, S.J., 1995. Effects of zearalenone and/or tamoxifen on swine and mink reproduction. J. Appl. Toxicol. 15, 223–232.

Yoshizawa, T., 1997. Geographic difference in trichothecene occurrence in Japanese wheat and barley. Bull. Inst. Compr. Agric. Sci. Kinki University 5, 23–30.

Yoshizawa, T., Jin, Y.Z., 1995. Natural occurrence of acetylated derivatives of deoxynivalenol and nivalenol in wheat and barley in Japan. Food Addit. Contam. 12, 689–694.

Yu, Z., Zhang, L., Wu, D., Liu, F., 2005. Anti-apoptotic action of zearalenone in MCF-7 cells. Ecotoxicol. Environ. Saf. 62, 441–446.

Zakharova, L.P., Obol'skii, O.L., L'vova, L.S., Bystriakova, Z.K., Kravchenko, L.V., Tutel'ian, V.A., 1995. *Fusarium* toxins in the cereal crop in Russia (situation in 1993 and 1994). Vopr. Pitan. 2, 26–29.

Zinedine, A., Brera, C., Elakhdari, S., Catano, C., Debegnach, F., Angelini, S., De Santis, B., Faid, M., Benlemlih, M., Minardi, V., Miraglia, M., 2006. Natural occurrence of mycotoxins in cereals and spices commercialized in Morocco. Food Control 17, 868–874.

Zwierzchowski, W., Przybylowicz, M., Obremski, K., Zielonka, L., Skorska-Wyszynska, E., Gajecka, M., Polar, M., Jakimiuk, E., Jana, B., Rybarczyk, L., Gajecki, M., 2005. Level of zearalenone in blood serum and lesions in ovarian follicles of sexually immature gilts in the course of zearalenone micotoxicosis. Pol. J. Vet. Sci. 8, 209–218.