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Review or Mini-review

Zearalenone as an endocrine disruptor in humans

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ABSTRACT

Zearalenone (ZEA), a fungal mycotoxin, is present in a wide range of human foods. Many animal studies have found ZEA to possess a disruptive effect on the hormonal balance, mainly due to its similarity to naturally-occurring estrogens. With increasing consciousness of the adverse effects of endocrine disruptors on human health, it is becoming more important to monitor ZEA concentrations in food and identify its potential effects on human health. Based on a review of recent studies on animal models and molecular pathways in which ZEA is reported to have an influence on humans, we postulate that ZEA might act as an endocrine disruptor in humans in a similar way to animals. Moreover, its endocrine-disrupting effect might be also a causative factor in carcinogenesis. This review article summarizes the latest knowledge about the influence of ZEA on the human hormonal balance.

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1. Introduction

1.1. Endocrine disruptors

Chemicals are becoming ever more present in everyday life, with some being implicated in dysregulation of the endocrine system (Bergman et al., 2013). In response to this recognition, in 2002, the World Health Organization (WHO), the United Nations Environment Programme (UNEP) and the International Labour Organization (ILO) developed the "Global Assessment of the State of the Science of Endocrine Disruptors" (IPCS, 2002), this work concluded that scientific knowledge at that time provided evidence that certain effects observed in wildlife can be attributed to chemicals that function as endocrine-disrupting agents (Bergman et al., 2013). In 2012, the UNEP and WHO presented an update of the IPCS 2002 document, entitled "State of the Science of Endocrine Disrupting Chemicals 2012", detailing the global status of scientific knowledge on exposure to and the effects of endocrine-disrupting chemicals (Bergman et al., 2013). According to the European Commission, an endocrine-disrupting chemical (EDCs) is an "exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function" (Trasande et al., 2015).

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The term endocrine-disrupting chemical encompasses a wide range of agents from natural compounds such as hormones, plants and fungal constituents to artificial products including drugs, pesticides and synthetic compounds used in plastics and the construction industry. They can be grouped in broad classes based on their physical and chemical characteristics, their origin or application, or their lifetime (persistent and short-life compounds) (Bergman et al., 2013). Some EDCs are persistent in the environment, and bioaccumulate through food webs to high concentrations in wildlife and humans, others with shorter half-lives are less persistent in the environment and do not remain in humans and wildlife for very long: they are not bioaccumulative. However, as exposure to them can be continual, they still represent a concern (Bergman et al., 2013; Li et al., 2012). Endocrine disruptors affect hormonal actions in different ways, they may directly influence hormone biosynthesis, metabolism, transport and mechanism of action on both receptor and post-receptor levels. Moreover, they are engaged in feedback mechanisms characteristic of the endocrine system. Some endocrine disruptors may also interfere with the developmental processes in humans (Bergman et al., 2013). At the genome level they can have an impact on gene expression and genomic imprinting via epigenetic mechanisms, and some might interact with natural hormones and have a complex effect on a variety of tissues (Hampl et al., 2016).

1.2. Zearalenone

Zearalenone (ZEA) is secondary metabolite synthesized by selected fungi of the genus *Fusarium: Fusariumgraminearum, Fusariumculmorum, Fusariumcerealis, Fusariumequiseti, Fusariumcrookwellense*, and *Fusariumsemitectum* (mostly *F. graminearum* and *F. culmorum*) (Gadzala-Kopciuch et al., 2011). ZEA is a non-steroidal estrogenic mycotoxin, chemically described as [6-(10-hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcyclic acid lactone. This chemical compound is stable, does not degrade at high temperature and exhibits fluorescence under ultraviolet (UV) light (Kong et al., 2013).The structure and shape of zearalenone and its metabolites resembles endogenous estrogen, the 17β-estradiol. Because of this similarity, ZEA activates the estrogen gene and causes alterations in the reproductive system (Wang et al., 2014a).

2. Zearalenone exposure in human

ZEA is produced by fungi of the genus *Fusarium*, which attacks crops during its growth in the field as well as its time in storage. Humans can be exposed to ZEA directly by contaminated food or indirectly through products derived from animals exposed to mycotoxins. As it is not removed by the manufacturing process, ZEA affects the entire human food chain through a range of food products including cereals, meat, milk, wine, beer, dried fruits and spices (Kriszt et al., 2012). After ingestion, ZEA metabolites accumulate in various tissues (Brera et al., 2014). Moreover, ZEA might be also delivered with water contaminated with the fungus *Fusarium Graminearum* (Pfeiffer et al., 2011).

The European Food Safety Authority (ESFA) established the daily exposure limit for zearalenone as 0.25 ppb (~0.8 nM). Limits to human consumption of ZEA have also been established by the European Commission (Table 1) (European Commission, 2007) as well as for animal feed (Table 2) (European Commission, 2006).

Table 1
Limits related to human consumption of zearalenone (European Commission, 2007); ppb-parts per billion.

Source	Maximum level [ppb]
Unprocessed cereals without maize	100
Unprocessed maize	350
Cereals intended for direct human consumption, cereal flour, bran and germ as end product for direct human consumption	75
Maize intended for direct human consumption, maize based snacks and maize based breakfast cereals	100

Table 2
Limits of zearalenone related to animal feed (European Commission, 2006); ppm-parts per million.

Source intended for animal feed	Guidance level [ppm]
Cereals and cereal products with exception of maize by-products	2
Maize by-products	3
Complementary and complete feeding stuff for:	
–piglets and gilts	0.1
–sows and fattening pigs	0.25
–calves, dairy cattle, sheep and goat	0.5

The average daily exposure of ZEA differs between countries. For instance, the average daily exposure of people in France is around 0.006 ppb (parts per billion) (Wang et al., 2014c). Due to the increasing consciousness of mycotoxin risks, some countries have already defined maximum limits for ZEA in cereals ranging from 20 to 1000 μg/kg. The maximum limit for ZEA is established at 60 μg/kg in wheat and corn in China (Kong et al., 2013). It should be emphasized that the LD_{50} values for oral administration in mice, rats and guinea pigs is 2000–20000 mg/kg body weight, which is relatively low acute toxicity (Kriszt et al., 2012). In addition to food and animal feed, another route of exposure to ZEA is by inhalation: ZEA and toxigenic spores have been found in the nasal cavity, and air-born ZEA has also been reported. The maximum level of ZEA was 2.4 mg/kg, which means that exposure through dust inhalation was estimated to be 0.1% of the tolerable daily intake (So et al., 2014).

Only a few mycotoxins, (aflatoxins, ochratoxin A, zearalenone, deoxynivalenol and fumonisins) are considered to have an economic impact, and legal regulations dictate their permitted concentrations (Streit et al., 2013). Table 3 provides summarized data from the study concerning occurrence of mycotoxins in different samples collected between 2004 and 2011. This study suggests that the incidence of mycotoxins might be distributed differentially worldwide, nevertheless, more studies are needed to confirm this (Streit et al., 2013):

Ferrigo et al. also showed that both mycotoxin distribution and zearalenone contamination levels vary worldwide (Table 4) (Ferrigo et al., 2016).

Table 3
Summarized results from the study conducted by Streit E. et al. (Streit et al., 2013).

Mycotoxin	Positive samples [%]	Average [μg/kg]	Type of sample	Origin of the highest concentration
aflatoxins	27	16	Corn	Vietnam
zearalenone	36	101	Silage	Australia
deoxynivalenol	55	535	Wheat	Central Europe
fumonisins	54	914	Finished feed	China
ochratoxin A	25	4	Finished feed	China