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Review

Invited review: Diagnosis of zearalenone (ZEN) exposure of farm animals and transfer of its residues into edible tissues (carry over)

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ABSTRACT

The aim of the review was to evaluate the opportunities for diagnosing the zearalenone (ZEN) exposure and intoxication of farm animals by analyzing biological specimens for ZEN residue levels. Metabolism is discussed to be important when evaluating species-specific consequences for the overall toxicity of ZEN. Besides these toxicological facts, analytics of ZEN residues in various animal-derived matrices requires sensitive, matrix-adapted multi-methods with low limits of quantification, which is more challenging than the ZEN analysis in feed.

Based on dose–response experiments with farm animals, the principle usability of various specimens as bio-indicators for ZEN exposure is discussed with regard to individual variation and practicability for the veterinary practitioner.

ZEN residue analysis in biological samples does not only enable evaluation of ZEN exposure but also allows the risk for the consumer arising from contaminated foodstuffs of animal origin to be assessed. It was compiled from literature that the tolerable daily intake of 0.25 μg ZEN/kg body weight and day is exploited to approximately 8%, when a daily basket of animal foodstuffs and associated carry over factors are assumed at reported ZEN contamination levels of complete feed.

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Abbreviations

α-ZAL	α-zearalanol
β-ZAL	β-zearalanol
α-ZEL	α-zearalenol
β-ZEL	β-zearalenol
AUC	area under the curve
b.w.	body weight
CEC	European Commission
COMT	catechol-*O*-methyltransferase
DAD	diode array detector
DM	dry matter
DON	deoxynivalenol
E2	estradiol
EFSA	European Food Safety Authority
ELISA	enzyme linked immunosorbent assay
F.	*Fusarium*
GC	gas chromatography
HPLC	high-performance liquid chromatography
HSD	hydroxysteroid dehydrogenase
IAC	immunoaffinity column
LC	liquid chromatography
LLE	liquid–liquid extraction
LOD	limit of detection
LOQ	limit of quantification
MIP	molecularly imprinted polymer
MS	mass spectrometry
NEL	net energy lactation
OTA	ochratoxin A
PBMC	peripheral blood mononuclear cells
RAL	resorcyclic acid lactone
RSD	residual standard deviation
SA	steroid sulfatase
SPE	solid phase extraction
TDI	tolerable daily intake
TLC	thin layer chromatography
TMR	total mixed ration
UV	ultraviolet
ZAN	zearalanone
ZEN	zearalenone
ZEN14G	zearalenone-14-β-D-glucopyranoside
ZEN16G	zearalenone-16-β-D-glucopyranoside

1. Introduction

The phytopathology, epidemiology and the genetic background of *Fusarium* infection and the consequences for the efficiency of crop production have been reviewed repeatedly and the economic impact of yield losses has often been addressed (e.g. Glenn, 2007; Miedaner, 1997; Parry et al., 1995). Not only the direct harvest losses, especially those of cereal grains, are important food security issues, but also the potential contamination by a number of chemically diverse *Fusarium* toxins with different toxicological effects might be of concern for food and feed safety. Especially adverse *Fusarium* toxin-related animal health effects might significantly compromise feed safety as some of these toxins frequently occur in feedstuffs at toxicological relevant concentrations. For this reason the Commission of the European Communities released recommendations for critical feedstuff concentrations for the most important *Fusarium* toxins and for ochratoxin A (OTA) to avoid animal health problems and foodstuff contamination (carry over aspect; CEC, 2006). Among the *Fusarium* toxins, deoxynivalenol (DON) and zearalenone (ZEN) are of special importance in animal nutrition as they often co-occur in feedstuffs (e.g., Döll and Dänicke, 2011; Binder et al., 2007; Placinta et al., 1999). Although their modes of action are different, they are relevant because especially pigs respond quite sensitively to both DON and ZEN (e.g., EFSA, 2004a,b; Döll and Dänicke, 2011). While the analysis of feed for mycotoxin contamination is an important prerequisite for risk evaluation and management to protect animals in general, it might be insufficient for diagnosing exposure and intoxication on an individual basis. The challenge for an intravital exposure diagnosis is that not only the parent toxin has to be considered and analyzed, but also the metabolites, which evolve at the pre-absorptive (i.e., gastro-intestinal or luminal-ingestive), the absorptive (i.e., intestine mucosal) and post-absorptive level with the liver as the most important site. Therefore, kinetics and metabolism are strongly inter-related and these aspects need to be considered when interpreting analyzed residue levels as a part of diagnostic procedures. The complex was recently reviewed for DON (Dänicke and Brezina, 2013) and will be addressed for ZEN in the current review.

ZEN is produced by various species of the genus *Fusarium* including *F. graminearum* (*Gibberella zeae*), *F. culmorum*, *F. cerealis*, *F. equiseti* and *F. semitectum* and is chemically defined as 6-(10-hydroxy-6-oxo-trans-1-undecenyl)-β-resorcyclic acid lactone ($C_{18}H_{22}O_5$, MW: 318.36, CAS 17924-92-4); (EFSA, 2004b). It is mainly formed pre-harvest but its synthesis might continue under poor storage conditions (Rohweder et al., 2011). Therefore, the climatic conditions during plant development prior to harvest are the major determinants for the ZEN contamination level of cereal grains used for food and feed. Further metabolites of ZEN are potentially possible as indicated by a detailed HPLC-DAD-MS analysis of an organic extract from a 40-day culture of *F. graminearum*, which resulted in the identification of novel metabolites such as an aliphatic epoxide of ZEN and the corresponding dihydrodiol. Moreover, several cyclization products of the dihydrodiol were characterized (Pfeiffer et al., 2010b).

In a recent publication (Metzler et al., 2010; Metzler, 2011) reviewed the discovery history of zearalenone, including the derivation of its common name which combines its frequent occurrence in maize (*Zea mays*) with chemical characteristics such as 'ral' for the resorcylic acid lactone, 'en' for the olefinic double bond, and 'one' for the keto group. They also discussed the nomenclature of related compounds including a suggestion for their abbreviation. Within the present review, we follow this suggestion and