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# Ochratoxin A: Potential epigenetic mechanisms of toxicity and carcinogenicity

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**Abstract**
Assessment of the significance to human health of ochratoxin A (OTA) in food is limited by a lack of human toxicity data. Therefore, OTA risk evaluation relies mainly on the use of animal data, with renal carcinogenicity in rat being considered as the pivotal effect. The elucidation of the mechanism of action would improve the use of the carcinogenicity data for risk assessment. Direct genotoxicity versus epigenetic mechanisms appears to be a key question. In this presentation, new biochemical and toxicogenomic results obtained in a recent European project (EU-Grant # QLK1-CT-2001-011614) will be summarized in the context of previously reported mechanisms of action including inhibition of protein synthesis, production of oxidative stress and alteration of cell signalling. Amongst others, the new data indicate that chronic administration of a carcinogenic dose of OTA affected cell-signalling pathways resulting in a significantly reduced renal antioxidant defence and increased oxidative DNA damage. These data confirm previous hypotheses involving oxidative stress as a possible key epigenetic mechanism of OTA toxicity and carcinogenicity.

**Keywords:** *Ochratoxin A, epigenetic mechanisms, oxidative stress, signal transduction, apoptosis, toxicogenomics*

## Introduction

Ochratoxin A (OTA) is a naturally occurring mycotoxin produced by several species of *Aspergillus* and *Penicillium*. Consequent to a widespread occurrence in food, a continuous human exposure to measurable levels has been observed. Although some data suggest a possible role for dietary OTA in the development of specific kidney diseases and urinary tract tumours, epidemiological studies do not allow the actual health impact of OTA in food to be assessed. Risk evaluation therefore relies mainly on the use of toxicological data obtained through animal experimentation (WHO 2001).

In animal models, OTA was shown to produce a wide array of toxicological effects, including nephrotoxicity and nephrocarcinogenicity, neurotoxicity and immunotoxicity (WHO 2001, O'Brien and Dietrich 2005). From a risk assessment perspective, it has been assumed that the renal carcinogenicity in rats constituted the highest health concern and was therefore considered as the pivotal effect (WHO 2001).

It is widely acknowledged that the risk assessment of dietary OTA based on available animal carcinogenicity data would significantly benefit from the elucidation of the mechanisms of actions involved. Direct acting genotoxins (which bind directly to DNA) are usually assumed to act through a non-threshold mechanism triggering the application of highly conservative low-dose modelling to quantitatively assess the risk. Other mechanisms may act through a threshold effect indicating that, for safety assessment, an approach that applies uncertainty factors to the pivotal animal No Observed Adverse Effect Level (NOAEL) should be used. It is important to note that the choice of the approach to be applied for risk assessment is likely to have a profound impact on tolerable levels of OTA in food

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and therefore on the management options to be developed in order to keep exposure to this toxin under control. The application of a science-based risk assessment procedure integrating relevant mechanistic information should help prioritizing the limited resources to ensure an adequate protection of human health.

## Scope of the presentation

Direct acting genotoxicity (DNA binding of any OTA moiety) versus epigenetic effects appears to be a key mechanistic question for OTA risk assessment. The possibility of a direct binding of OTA to DNA is highly debated and is thoroughly addressed by other contributors of the present workshop (see contribution of Dr Pfohl-Leskowicz and Dr Mally). Importantly, the observed OTA-mediated DNA damage such as lesions measured by $^{32}$P-postlabelling and clastogenicity may not necessarily require direct OTA-DNA binding, but may also be related to other, indirect modes of action such as oxidative stress and cytotoxicity.

In the present short review, the main modes of action of OTA toxicity previously reported will be briefly discussed and their relevance as potential epigenetic mechanisms of OTA carcinogenicity addressed. It is well recognized that toxicity may induce cell regeneration and proliferation, which may then lead to cell transformation and tumour development. In addition, new biochemical and toxicogenomic results obtained in the frame of a recent European project (Ochratoxin A risk assessment EU-Grant # QLK1-CT-2001-011614), will be described.

## OTA-toxicity: Putative modes of action

Over the last 30 years, numerous studies aimed at elucidating the mechanisms implicated in OTA toxicity have been published. Because of the diversity of experimental protocols employed, various, sometimes highly inconsistent, data have been obtained. The high dependency of the identified mechanisms and effects upon cell types, dose levels and treatment duration has constituted one of the major difficulties of the field. In addition, many mechanistic studies have applied cell line models, which may not always accurately reflect the situation *in vivo*.

### *Protein synthesis inhibition*

OTA has been shown to inhibit protein synthesis in all experimental systems tested including bacteria, yeast cells, mammalian cells *in vitro* and animals *in vivo* (Dirheimer and Creppy 1991). It is currently thought that the mechanism of OTA-mediated inhibition of protein synthesis may involve constraint of peptide elongation through competition with phenylalanine in the reaction catalyzed by phenylalanyl-tRNA synthetase (Dirheimer and Creppy IARC 1991). This hypothesis was supported by *in vivo* and *in vitro* data showing that co-administration of phenylalanine with OTA prevented the OTA-mediated protein synthesis inhibition (Dirheimer and Creppy 1991).

Many studies have indicated that inhibition of protein synthesis is likely to be involved in most of the acute toxic effects of OTA. When injected simultaneously, phenylalanine prevented OTA lethality (Creppy et al. 1979), immunotoxicity (Haubeck et al. 1981) and teratogenicity (Mayura et al. 1984). The role of protein synthesis inhibition in effects observed at lower doses is less obvious. *In vitro,* cell-signalling disturbances were observed at concentrations in the nanomolar range which did not affect protein synthesis (Gekle et al. 2005). There is currently no *in vivo* study available which directly addresses protein synthesis inhibition at chronic doses producing kidney tumours. Indirect data, exploiting the preventive activity of aspartame, a structural analogue of phenylalanine, and thus of OTA, suggested such a possibility. Aspartame was found to exhibit protective effects against the nephrotoxicity of OTA administered to rats at a level of 289 μg/kg bw/48 h over 6 weeks (Creppy et al. 1995). The mechanism of protection was assumed to involve a prevention of protein synthesis inhibition. However, the possibility that aspartame affected the distribution of OTA cannot be excluded.

### *Mitochondrial dysfunctions*

The nephrotoxic potential of OTA may be related to mitochondrial dysfunction leading to energy shortage and to the production of reactive oxygen species. The treatment of isolated renal proximal tubules with large concentrations of OTA resulted in an inhibition of mitochondrial respiration (Aleo et al. 1991). Other *in vitro* studies applying direct treatments of mitochondrial preparations showed that OTA affected respiration and oxidative phosphorylation through an impairment of the mitochondrial membrane and an inhibition of the succinate-supported electron transfer activities of the respiratory chain (Wei et al. 1985). In addition, ATP synthesis in mitochondria isolated from renal cortex was significantly inhibited by micromolar concentrations of OTA (Jung and Endou 1989). In contrast to the data outlined above, nanomolar concentrations of OTA produced a stimulation of mitochondrial activity in cell cultures (Gekle et al. 2005). Based on the data available, a role for mitochondrial dysfunctions in OTA toxicity and

carcinogenicity is possible although more research will be necessary to clarify its relevance at chronic, low dose exposure *in vivo*.

*Oxidative stress*

Several reports have suggested a potential role for oxidative stress in OTA toxicity and carcinogenicity. For example, an increased formation of the lipid peroxidation product malondialdehyde (MDA) was observed in rats treated orally with 120 μg/kg bw/day of OTA over 60 days (Petrik et al. 2003). In cell culture, an OTA-dependent increase in DNA damage (such as formation of 8-oxoguanine) was correlated with a production of reactive oxygen species (Schaaf et al. 2002, Kamp et al. 2005). Antioxidants were shown to prevent OTA-mediated increases in MDA production *in vitro* (Baudrimont et al. 1997) and *in vivo* (Meki and Hussein 2001). In rats, the injection of superoxide dismutase and catalase provided protection against OTA-induced nephrotoxicity *in vivo* (Baudrimont et al. 1994), and in mice, antioxidant vitamins reduced an OTA-mediated increase in chromosomal aberrations (Manolova et al. 1990) and the formation of $^{32}$P-postlabelling spots (Grosse et al. 1997).

Several potential relevant oxido-reduction mechanisms have been identified and proposed. In a reconstituted system consisting of phospholipid vesicles, the flavoprotein NADPH-cytochrome P450 reductase and $Fe^{3+}$, OTA was found to chelate ferric ions ($Fe^{3+}$), facilitating their reduction to ferrous ions ($Fe^{2+}$), which in the presence of oxygen, provided the active species initiating lipid peroxidation (Omar et al. 1990). A role for cytochrome P450 in this reaction was also suggested (Omar et al. 1991). Other authors have reported that the OTA hydroquinone/quinone couple was generated from the oxidation of OTA (phenol oxidation) by electrochemical, photochemical and chemical processes (Gillman et al. 1999, Dai et al. 2002). The quinone is thought to be a likely candidate for covalent binding to DNA. It can also undergo reductions to form semiquinone and hydroquinone. Such events are likely to result in redox cycling and in the generation of reactive oxygen species (Gillman et al. 1999, Dai et al. 2002). The actual relevance of these reactions for the physiological *in vivo* situation has still to be elucidated.

**Alteration of signal transduction**

*Calcium homeostasis*

Cytosolic calcium is maintained at low concentrations through active sequestration in extracellular medium, mitochondria and endoplasmic reticulum. Disruption of calcium homeostasis, leading to sustained increase in cytosolic level, has been associated with toxic cell injury. In addition, calcium is known to be one of the major players in cell signalling, for example through the activation of regulatory pathways involving calmodulin and protein kinase C. In immortalized human kidney epithelial cells-1 (IHKE-1), nanomolar concentrations of OTA induced rapid and reversible oscillations in intracellular calcium (Benesic et al. 2000). This effect was dependent upon extracellular calcium, phospholipase C and cAMP-dependent protein kinase. Interestingly, in the same system, OTA potentiated the calcium-dependent stimulation of cell proliferation induced by epidermal growth factor and angiotensin II (Benesic et al. 2000). These effects were observed in the absence of cytotoxicity, suggesting that OTA may interfere with calcium-dependent cell signalling to lead to increased cell proliferation. There are only limited and inconsistent data regarding OTA and calcium homeostasis *in vivo*. In rat, a single high dose (intraperitoneal administration, 10 mg/kg bw) or repeated lower doses (0.5–2 mg/kg bw) were found to stimulate calcium uptake by the endoplasmic reticulum, while moderate doses seemed to inhibit calcium sequestration (Rahimtula and Chong 1991). Because *in vivo* data was only derived from experiments using high doses of OTA, it is currently difficult to link *in vitro* and *in vivo* data. The elucidation of the actual role of calcium in OTA toxicity and carcinogenicity requires further investigation.

*Mitogen-activated protein kinases (MAPKs)*

MAPKs are key components of signalling cascades involving phosphorylation-activation reactions aimed at transducing signals from the cellular membrane to the nucleus. Extracellular regulated kinases isoforms 1 and 2 (ERK1/2) are part of the most studied MAPKs. ERK1/2 is generally thought to regulate cell proliferation. It has been implicated in cancer development including renal carcinoma (Oka et al. 1995). In Madin-Darby canine kidney-C7 cells (MDCK-C7, from collecting duct) and in renal proximal tubule cell lines (OK cells, NRK-52E), OTA was found to increase the phosphorylation and activity of ERK1/2 (Gekle et al. 2005, Sauvant et al. 2005). In MDCK-C7 cells, this effect was correlated with cell dedifferentiation (Gekle et al. 2005). In the same cellular systems, other MAPKs, c-jun amino terminal kinase (JNK) and the extracellular regulated protein kinase 38 (p38), were also activated by OTA treatments (Gekle et al. 2005, Sauvant et al. 2005). Unlike ERK1/2, JNK and

p38 do not seem to act as promitotic signals, but are predominantly implicated in stress response and apoptosis. Altogether, these data indicate that in renal cells OTA is able to stimulate MAPK activities promoting opposite effects, either proliferation or apoptosis. It is believed that the balance between the different MAPKs will determine the fate of the exposed cells. To date, no study has addressed the effects of OTA on MAPKs *in vivo,* and therefore the exact role of these pathways on the carcinogenicity of OTA needs to be clarified.

### *Apoptosis*

The literature on OTA and apoptosis is complex and inconsistent (O'Brien and Dietrich 2005, Gekle et al. 2005). Apoptosis refers to programmed cell death, an active process to be differentiated from necrosis. As suggested above, in MDCK-C7 and OK cell cultures, OTA activated JNK and p38 pathways leading to apoptosis (Gekle et al. 2005, Sauvant et al. 2005). In contrast, in other *in vitro* systems, OTA did not induce apoptosis or only at a very low rate (O'Brien and Dietrich 2005). Studies addressing the presence of apoptosis in OTA-treated animals provided some controversial data. Some authors did not find any apoptotic cells in the kidney of OTA-treated animals (Mantle et al. 1998) while others obtained results compatible with the presence of apoptosis (WHO 2001, O'Brien and Dietrich 2005). For example, using the TUNEL assay, apoptotic cells were observed in rats given OTA (120 μg/kg bw/day) for 60 days (Petrik et al. 2003). However, in this study, DNA electrophoresis did not show any characteristic fragmentation (DNA-laddering). In another study, some apoptotic bodies were found in proximal convoluted tubules of rats given 1 mg OTA/day for 5 days by gavage, while no apoptosis was observed when the same dose of toxin was administered in feed (Miljkovic et al. 2003). With respect to tumour development, the contribution of apoptosis is difficult to define. It is generally thought that apoptosis prevents tumour development while failure of apoptosis may be a causative factor for cancer. However, some authors have advocated that OTA-mediated apoptosis could lead to the selection of apoptosis-resistant cells characterized by a higher probability of transformation into tumour cells (O'Brien and Dietrich 2005).

## New toxicogenomic data

In a recent project sponsored by the European Union, OTA was administered to male rats for 2 years (at 300 μg/kg bw up to a weight of 333 g, and then 100 μg/rat). Renal tumours, mainly carcinomas, were discovered during the last six months (see contribution of Dr P. Mantle this issue). Gene expression profile was studied in groups of animals from this study, taken at intervals from 7 days to 12 months. Publications of the results are in preparation. Most of the data cited below were presented in the last meeting of the project (Marin-Kuan et al. 2004). The OTA-mediated responses in kidney and liver were totally different. In kidney, several genes known as markers of kidney injury and cell regeneration were significantly modulated by OTA, suggesting that the dose regimen chosen may have been associated with some cytoxicity. The expression of genes known to be involved in DNA synthesis and repair, or genes induced as a result of DNA damage, was only marginally modulated. Very little or no effect was found amongst genes associated with apoptosis. However, alterations of gene expression indicating effects on calcium homeostasis and a disruption of pathways regulated by the transcription factors hepatocyte nuclear factor 4 alpha (HNF4$\alpha$) and Nuclear factor-erythroid 2-related factor 2 (Nrf2), were observed in the kidney, but not in the liver. Previous data have suggested that a reduction of HNF4$\alpha$ pathway may be associated with kidney carcinogenicity. The disruption of the Nrf2 pathway was characterized by an inhibition of Nrf2 binding to the Antioxidant Responsive Element (ARE) promoter, resulting in a reduction in the expression of downstream genes, at both mRNA and protein levels. Many Nrf2-regulated genes are involved in chemical detoxication and antioxidant defence. The depletion of Nrf2-regulated enzymes is likely to impair the defence potential of the cells resulting in a chronic low level of increased oxidative stress in the target kidney cells. This hypothesis was confirmed by *in vitro* and *in vivo* data showing that the depletion of the Nrf2-regulated enzymes by OTA was associated with increased levels of DNA abasic sites, a known marker for DNA-damage. Importantly, in cell cultures, the application of Nrf2-activators prevented the OTA-dependent reduction of Nrf2-regulated proteins as well as the increased formation of abasic sites.

## Summary and conclusion

Several potential epigenetic modes of action relevant for the expression of OTA toxicity and carcinogenicity have been identified *in vivo* and *in vitro*. Oxidative stress appears of particular interest because it has been observed in an OTA dose regimen that had already at 12 months elicited a renal tumourigenic response. In addition, oxidative stress may constitute a mechanism for many of the effects associated with OTA treatment.

Oxygen radicals may either originate from reactions directly involving OTA (with $Fe^{3+}$) or may be the consequence of the OTA-mediated reduction of antioxidant cellular defences, which could no longer cope with radicals generated over the normal oxidative metabolism. The production of oxygen radicals is likely to produce macromolecular damage including lipid peroxidation and DNA-damage. This latter effect may result in mutation and cancer initiation. In addition, it is well documented that reactive oxygen species modify gene expression through various mechanisms involving mobilization of MAP kinase cascades and activation of transcription factors such as NF$\kappa$B and AP1. According to cell type and doses involved, such biological effects may either lead to apoptosis or to cancer development (Klauning and Kamendulis 2004). In conclusion, the question of the possible direct DNA-binding as a mechanism of OTA carcinogenicity is still open. Available data indicate that epigenetic mechanisms resulting from oxidative stress may provide highly plausible alternative possibilities.

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