RISK EVALUATION OF OCHRATOXIN A

J. FINK-GREMMEIS, J.R. v. GERNLER, M. JAHN and L. LEISTNER

Federal Centre for Meat Research, 8650 Kulmbach (Federal Republic of Germany)

Mycotoxins are classified as unavoidable contaminants and reach the consumer directly via infected cereals, beans and coffee and indirectly via food of animal origin. For only a few selected mycotoxins sufficient toxicologic data are available in the literature for a rational basis of risk assessment. Attempts for the evaluation of the mycotoxin ochratoxin A have to be based on hazard identification, exposure assessment and dose response assessment.

1. Hazard identification:

Adverse effects in animals and humans: Ochratoxicosis has been reported in a variety of animal species, especially in laboratory animals and monogastric farm animals. Ochratoxin A was considered to be causative agent for an endemic nephropathy in Yugoslavia, the Balkan nephropathy.

2. Exposure assessment:

Direct exposure: Ochratoxin A (OA) is a world-wide contaminant of cereals and is produced by various species of both Penicillium and Aspergillus. Ochratoxin A has been detected in coffee beans, green beans and ground nuts.

Indirect exposure: After consumption of contaminated feedstuffs by food producing monogastric animals OA is rapidly absorbed and distributed forming residues in various edible tissues.

Influence of food processing and storage: OA residues in cookies and bread as well as meat products (sausages) indicate the high chemical stability of this mycotoxin. However, OA contamination might be degraded by a natural bacterial flora on food and feed.

Incidence of exposure: OA has been detected in the blood of healthy people in W-Germany in small quantities (0.1 - 1.0 µg/l serum), but with high incidence (50 - 68 % of all samples).

Specific hazards: There is strong evidence that OA is secreted with the milk of monogastric animals including man resulting in an unexpected exposure of the neonatus.

3. Dose response assessment:

Mode of action: OA inhibits aminoacylation of the phenylalanine-t-RNA and thereby protein synthesis. Excessive phenylalanine supplementation reduces toxicity. However, it cannot be excluded that OA also acts on other enzymes using phenylalanine as substrate as well. No binding to DNA or RNA is detectable for OA, and in vitro tests in procaryotic cells remained negative. Thus in oncogenicity metabolites of OA may play an

unexpected role.

Kinetics: OA is rapidly absorbed in monogastric animals (the rate of absorption in pigs is 65 %), plasma bound and distributed. The highest tissue levels were detected in bloodserum, kidneys, liver and muscle. The elimination half life of OA varies considerably in different species, the pig having a serum half life of 88 hrs.. OA is excreted via feces (OA and OA-alpha), urine (OA-alpha and OA-beta) and milk of monogastric animals. There is evidence of excretion in eggs of laying hens. Persistent tissue levels were found in kidneys (< 30 days), liver, muscle, fat and serum. Residues were persistent in processed meat (sausages).

Toxicology: Dose dependent organ specific effects: Degeneration of proximal tubuli and reduced renal function, degranulated platelets and endothelial cells on glomerular capillaries. Affected liver glycogen storage, reduced protein synthesis. Myocardial changes, swollen sarcolemma, vascular thrombosis and endothelial damage. Necrotic enteritis and atrophia of villi. Reduced steroidogenesis. Primary hypofibrinogenemia. Necrosis and cytopenia in lymphoid tissues.

Dose dependent systemic effects: Dose dependent embryotoxicity and teratogenicity, behavioral retardation in postnatal development. There is evidence of various in vivo and in vitro assays for a systemic immunosuppression. Selective immunosuppression of natural killer cell-activity is correlated with an increased growth of transplantable tumor cells.

Non-linear dose dependent effects: Animal experiments revealed a carcinogenic potential of OA. Oncogenicity in vivo was characterized by sex differences in the incidence of hepatoma and neoplastic lesions in kidneys. Unscheduled DNA-synthesis in isolated hepatocytes supports the findings of these animal experiments.

Risk evaluation

Toxicity Data	Dosage /kg b.w.	Factor	VSD /kg b.w./day	ADI
NOAEL (rats/chron.tox.)	0.02 mg	100	0.2 µg	14.0 µg
NTEL (rats/teratogen.)	0.2 mg	1000	0.2 µg	14.0 µg
Carcinogenicity (mice)	> 1 ppm	1000000	0.1 ng	0.007 µg
Immune response (SRBC in mice)	0.005 µg	10x10x?	0.05 ng	0.0035 µg

NOAEL: no-adverse-effect-level; NTEL: no-teratogenic-effect-level; ADI: acceptable daily intake; VSD: virtual safe dose

The estimate demonstrates that values for immunosuppressive effects and carcinogenic risk compare closely evidencing again the hypothesis of an association between immune mechanisms and oncogenic potential. However, considering the measured serum concentrations in the population of W-Germany OA intake is presently at the border line of being an evident risk factor for consumers. Therefore, risk management is strictly recommended for OA in foods of plant and animal origin.