IMPACT OF MYCOTOXINS ON HUMAN AND ANIMAL HEALTH

Assoc Prof E. Tzika, DVM, PhD, Dipl ECPHM

Lect. PD Tassis, DVM, PhD

Faculty of Veterinary Medicine
Farm Animals Clinic
Aristotle University of Thessaloniki, Greece

2nd FOODSEG Symposium
Bucharest, 14-15 June 2013
The incidence of mycotoxicoses may be more common than suspected!


➢ The main human and veterinary health burden of mycotoxin exposure is related to chronic exposure (e.g., cancer induction, kidney toxicity, immune suppression)

➢ However, the best-known mycotoxin episodes are manifestations of acute effects (e.g., turkey X syndrome, human ergotism, stachybotryotoxicosis).
More than 1000 mycotoxins have been described.

Kuiper-Goodman (1998) ranks mycotoxins as the most important chronic dietary risk factor, higher than synthetic contaminants, plant toxins, food additives, or pesticide residues.

Chemical structure and toxic properties of mycotoxins are conserved during both storage and processing/cooking of food or feed.
MAJOR MYCOTOXINS

- Aflatoxins B1,B2,G1 and G2
  - (Aspergillus flavus; A. parasiticus)

- Fumonisins (B1)
  - (F. moniliforme)

- Ochratoxin (A)
  - (A. ochraceus; Penicillium viridicatum; P. cyclopium)

- Trichothecenes
  - (DON: Fusarium culmorum; F. graminearum; F. sporotrichioides, T-2: F. sporotrichioides; F. poae, Diacetoxyscirpenol: F. sporotrichioides; F. graminearum; F. poae)

- Zearalenone
  - (F. culmorum; F. graminearum; F. sporotrichioides)

- Ergot alkaloids
  - (Claviceps purpurea)
Factors affecting mycotoxin occurrence in the food and feed chain (Pestka and Casale 1989)
Mycotoxins

Factors causing variation in effects

- Species, breed
- Age
- Sex
- Nutritional status
- Other diseases
- Other mycotoxins
- Extent of exposure
Over a dozen other aflatoxins (e.g., P1, Q1, B2a, and G2a) have been described - especially as biotransformation products of the major metabolites - are associated with both toxicity and carcinogenicity in human and animal populations.

Linked to increased mortality in farm animals

Lowers the value of grains as an animal feed and as an export commodity

Cases of aflatoxin-contaminated milk in Serbia, Croatia, Bosnia, Montenegro and Albania (2013)

Total conversion AFB1 to AFM1 in cow’s milk= approx. 1-6%

Carcinogenic potency of AFM1= 2-10% of AFB1

Williams et al. (2004) have estimated that 4.5 billion of the world’s population is exposed to aflatoxins.
AFLATOXINS

- Exposure to aflatoxins in the diet
- Aflatoxins’ carcinogenic potency is correlated with the extent of total DNA adducts formed in vivo
- Evidence associating aflatoxin with neoplasms in extrahepatic tissues
- International Agency for Research on Cancer classification aflatoxins

important risk factor for primary hepatocellular carcinoma, particularly after exposure to hepatitis B

Liver cancer relative risk

Aflatoxins alone relative risk = 2, Hepatitis B alone relative risk = 5, combination relative risk = 60 [Case – control study, China 1992]

lung neoplasms in Dutch peanut processing workers exposed to dust contaminated with aflatoxin B1 (1984)

Group of aflatoxins B and G in group 1 (carcinogenic to humans)

Especially aflatoxin M1 in group 2B (possible carcinogenic)
At 1974 Indian outbreak of hepatitis (100 deaths) possibly due to aflatoxin contaminated maize

*consumption of 2 to 6 mg of aflatoxin daily for a month (Outbreak report, 1975)*

Aflatoxins in humans have been reported also to cause:

- Digestive system effects: diarrhea, vomiting, intestinal hemorrhage, and liver necrosis and fibrosis
- Toxic encephalopathy: loss of balance, recent memory decline, headaches, insomnia, loss of coordination

Aflatoxins have been implicated as potential factors in the increased incidence of human gastrointestinal and hepatic neoplasms in Africa, Philippines and China
Humans

Exposed to chronic aflatoxin-contaminated foods

- Higher aflatoxins concentrations in the semen of infertile men.
- In Nigeria, about 37% of the infertile men had aflatoxin in their blood and semen.
- Immunosuppression and increase susceptibility of humans and animals to bacterial, viral and parasitic infections.

Aflatoxins have been reported to depress growth and alter many aspects of humoral and/or cellular immunity

As at the case of liver cancer, childhood stunting is prominent in regions such as Southeast Asia and Sub-Saharan Africa, where aflatoxin exposure through consuming contaminated food is common.
Cattle: decreased rumen motility and function - changes in the gastrointestinal tract physiology + blood coagulation defects (impairment of prothrombin, factors VII and X and possibly factor IX)

Poultry: decreased feed consumption, body weight, testes weight and semen volume (Sharlin et al., 1980) and decreased plasma testosterone values and reduction in egg output
Aflatoxin disease pathways in humans (Adopted from Wu, 2010; Wu, 2011)
Ergot = the common name of the sclerotia of fungal species (*Claviceps* spp.), which produce ergot alkaloids

Ergot alkaloids are derivatives of lysergic or isolysergic acid or dimethylergoline (+ metabolites of some strains of *Penicillium, Aspergillus* and *Rhizopus*)

- **ERGOT ALKALOIDS**
  - **Ergotism**
    - The disease occurring after ingestion of contaminated food (usually cereals) by ergot sclerotia.
    - **Gangrenous** = affects the blood supply to the extremities → leg oedema, paraesthesia and tendons gangrene (Ethiopia 1977-1978, 140 persons affected, 24% mortality)
    - **Convulsive** = affects the central nervous system (India 1975, 78 persons affected) → gastrointestinal and central nervous system symptoms (vomiting and nausea followed by blindness and paralysis)
  - **Two forms of ergotism**
  - **Animal species at risk**
    - Cattle, sheep, pigs, chickens.
    - Ergotism in animals: gangrene, abortion, convulsions, suppression of lactation, hypersensitivity, ataxia
FUMONISINS

The most abundantly produced member: **Fumonisin B1**

Fumonisins affect animals by interfering with sphingolipid metabolism (other mechanisms of action co-occur)

- Leukoencephalomalacia (staxia, paresis etc) in equines and rabbits
- Pulmonary edema and hydrothorax in swine
- Hepatotoxic/carcinogenic effects and apoptosis in the liver

EU Cooperation
| **Probable link with esophageal cancer.** | The occurrence of fumonisin B1 is correlated with the occurrence of a higher incidence of esophageal cancer in regions of South Africa, China, and northeast Italy (1994) |
| **Possible acute form** | Clinical symptoms of transient abdominal pain, borborygmus, and diarrhea in people of 27 villages in India, after consumption of unleavened bread made from moldy sorghum or corn. All affected fully recovered |
| **High Incidence of neural tube defects due to inhibition of folic acid uptake, after consumption of contaminated maize, (rural populations in South Africa and Northern China) (2004)** | |
Of the Aspergillus toxins, only ochratoxin is potentially as important as the aflatoxins.

Kidney = primary target organ

Ochratoxin A is a nephrotoxin to all animal species studied to date and is most likely toxic to humans, who have the longest half-life for its elimination of any of the species examined.

Animal studies indicate that ochratoxin A is also a liver toxin, an immune suppressant, a potent teratogen, and a carcinogen.

Ochratoxin has been detected in blood and other animal tissues and in milk, including human milk.

It is found in pork intended for human consumption.

Ochratoxin is probably responsible for a porcine nephropathy that has been studied in the Scandinavian countries. Denmark: rates of porcine nephropathy and ochratoxin contamination in pig feed are highly correlated.

It is also associated with disease and death in poultry.
Speculation that ochratoxins are involved in a human disease called *endemic Balkan nephropathy*.

- Progressive chronic nephritis in populations who live in areas bordering the Danube River in parts of Romania, Bulgaria, and former Yugoslavia.
- The current consensus is that endemic Balkan nephropathy is of unknown etiology, but many mycotoxin reviews considered it as an ochratoxicosis.

Studies from Canada, Sweden, West Germany, and Yugoslavia detected ochratoxin in human blood and serum.

- Analyses of urine from children in Sierra Leone detected both ochratoxin and aflatoxin throughout the year.

The International Agency for Research on Cancer has rated ochratoxin as a possible human carcinogen (category 2B).
The Joint Expert Committee on Food Additives of the Food and Agriculture Organization of the United Nations and the World Health Organization (JECFA2001) presented data indicating that the **major sources of human ochratoxin exposure are:**

- **cereals** (58% of total intake - levels range 100-700 ng/kg in cereals),
- **wine** (21% of total intake, 30 to 9000 ng/L in European wines)
- **grape juice** (7% of total intake),
- **coffee** (5% of total intake, 170 to 1300 ng/kg in coffee)
- **pork** (3% of total intake, 150 to 2900 ng/kg)

**European red wines typically contain higher ochratoxin levels than rose or white wines.**
A family of > 60 sesquiterpenoid metabolites
(Type A: T-2 toxin etc, Type B: DON etc)

Consumption of these mycotoxins can result in alimentary hemorrhage and vomiting; direct contact causes dermatitis

Extremely potent inhibitors of eukaryotic protein synthesis

Deoxynivalenol (DON) is one of the most common mycotoxins found in grains.
- High doses in animals: nausea, vomiting, and diarrhea
- Lower doses: pigs and other farm animals exhibit weight loss and food refusal

T-2 and diacetoxyscirpenol (DAS) in animal studies: cytotoxic activity + immunosuppressive effect that results in decreased resistance to infectious microbes. They cause a wide range of gastrointestinal, dermatological, and neurologic symptoms

It has been hypothesized that T-2 and DAS are associated with a human disease called alimentary toxic aleukia (Inflammation of the skin, vomiting, and damage to hematopoetic tissues)
**ZEARALENONE (ZEN)**

*A nonsteroidal estrogen or mycoestrogen or a phytoestrogen*

ZEN resembles 17-β estradiol, (hormone produced by the human ovary), to allow it to bind to estrogen receptors in mammalian target cells

Dietary concentrations of zearalenone as low as 1.0 ppm → hyperestrogenic syndromes in pigs; higher concentrations → disrupted conception, abortion and other problems. Reproductive problems have also been observed in cattle and sheep

The reduced form of zearalenone, zearalenol, has increased estrogenic activity.

Canadian and Scandinavian epidemiological data → the risk to human populations is minimal.
hyperestrogenic syndrome
hyperestrogenic syndrome
- According to the International Agency for Research on Cancer:

Fusarium graminearum, F. culmorum, and F. crookwellense, and toxins derived from (ZEN, DON, nivalenol, and fusarenone X), as well as Fusarium sporotrichioides, and toxins derived from (T-2 toxin) have been classified in group 3 (Not classifiable as to its carcinogenicity to humans)
The most common genera of indoor molds are Alternaria, Aspergillus, Cladosporium, and Penicillium.

The most prevalent symptoms are irritation of the eyes and respiratory tract, + other vague complaints (headache and fatigue, skin irritation, nonspecific hypersensitive reaction, and peculiar odor and taste sensations) have also been reported.

Sick-building syndrome is often associated with the presence of toxic molds, especially *Stachybotrys*.

Mycotoxins can be used as chemical warfare agents (Bioterrorism)!!
*Stachybotrys chartarum* was implicated in the outbreak of eight cases of idiopathic pulmonary hemorrhage among infants in Cleveland, Ohio. Although toxic mold was found in the homes of the children with pulmonary bleeding, a cause-and-effect relationship has been difficult to prove.

The Committee on Public Health of the American Academy of Pediatrics issued a statement on the toxic effects of indoor molds, alerting pediatricians to the possibility that idiopathic pulmonary hemorrhage may be associated with molds.

- **Stachybotryotoxicosis** = First described as an equine disease of high mortality associated with moldy straw and hay
- **Human stachybotryotoxicosis** = Rare occupational disease limited largely to farm workers who handle moldy hay
- **Stachybotrys** grows well on all sorts of wet building materials with high cellulose content. It has been associated with pulmonary bleeding in infants
Research has demonstrated mycotoxins as possible causes of human disease (Chronic fatigue syndrome) in water-damaged buildings (87% positive urine samples for OTA - patients in Kansas city 2012)

Secondary metabolites of molds and bacteria have been identified in the dust, carpeting, wallpaper, heating, ventilation and air-conditioning systems and respirable airborne particulates

Mycotoxins have been identified in clinical isolates from corneal keratitis, body fluids, tissues of individuals exposed to moldy environments + blood serum of workers in Portuguese poultry and swine production facilities (Vegas et al. 2013)

More data are needed before any definite conclusions can be made about the health effects resulting from Inhalation of toxigenic mold spores
Future challenges

- Complete elimination of any natural toxicant from foods is an unattainable objective
- Chemical diversity of mycotoxins
- Trace concentrations
- Mycotoxin analytical techniques
- Regulatory limits
- Masked mycotoxins
- Sampling and analytical errors
- Concurrence of mycotoxins – synergy and additive effects
- A better evidence-base on mycotoxins and human health, supported by better biomarkers of exposure and effect in epidemiological studies
- One health initiative – collaboration and decrease of undetected cases – false diagnosis in humans and animals – a Universal issue
Future challenges II

Problems to reduce contamination in regions where occurrence is high (Asia, Africa, South America) (IARC 2010):

1) Knowledge of mycotoxins and the full range of their adverse health effects is incomplete + risks are poorly communicated to policy markers

2) Perceived "value" of interventions to reduce mycotoxin contamination may be relatively low (comparing to issues like a vaccination programme for the population)

3) Approaches to control mycotoxin contamination require consideration at numerous points pre- and post-harvest

4) The highest exposures occur in communities that produce and consume their own food → regulatory measures to control exposure are largely ineffective.

5) Need for an inter-sectoral approach at government level, that is often absent.
Other sources of information

- The Council for Agricultural Science and Technology (www.cast-science.org),
- The Mycotoxicology Newsletter (www.mycotoxicology.org),
- The Society for Mycotoxin Research (www.mycotoxin.de),
- The American Oil Chemists Society Technical Committee on Mycotoxins (www.aocs.org),
- The Food and Agriculture Organization of the United Nations (www.fao.org),
- The International Union for Pure and Applied Chemistry Section on Mycotoxins and Phycotoxins (www.iupac.org),
- The Japanese Association of Mycotoxicology (www.chujo-u.ac.jp/myco/index.html),
- The U.S. Food and Drug Administration Committee on Additives and Contaminants (www.fda.gov).
- The European Food Safety Authority (EFSA)
- And many many more...
References

• Isabelle P. Oswald. Animal Health, Nutrition and Mycotoxins. Mycotoxin Symposium :From seed to Feed, December 11, Quebec, Canada
• Joseph H. Brewer , Jack D. Thrasher , David C. Straus , Roberta A. Madison , Dennis Hooper. Detection of Mycotoxins in Patients with Chronic Fatigue Syndrome. Toxins 2013, 5, 605-617
References

Thank you for your attention!

One picture is worth a thousand words!