Risks and Myths about Animal Source Food Contamination with Chemicals:

Case Studies in Aflatoxin M1 and Antibiotics

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Presentation outline

Aflatoxin M_1 (AFM_1) in dairy products

- Mycotoxins: background
- Aflatoxin
- AFM_1 occurrence in dairy products worldwide
- Human health risk?

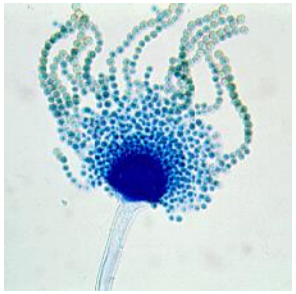
Antibiotics & antibiotic-resistant bacteria

- Antibiotics in US animal agriculture
- Antibiotic-resistant bacteria: background
- Human health risks of livestock-acquired MRSA

Summary: Which are risks, which are myths?

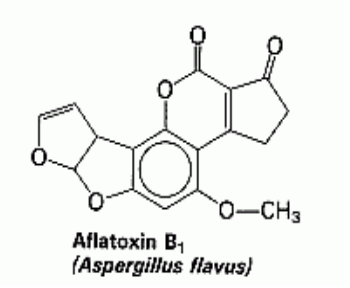
Mycotoxins: What are they?

- Toxic chemicals produced by fungi (mold) in our food
- Long history of mycotoxins affecting society
  - Leviticus 14:37
  - 11th c.: *Claviceps purpurea* produces ergot in rye → St. Anthony's Fire
  - 1960 aflatoxin discovery: UK turkey deaths
  - Today: several dozen mycotoxins identified



Background on AFLATOXIN B_1: When it is in dairy feed, its metabolite AFM_1 is in dairy products

- Produced by *Aspergillus flavus, A. parasiticus*
  - Maize, peanuts, tree nuts, cottonseed
  - Exposure highest in warm regions where maize & peanuts are dietary staples (Africa, Asia)

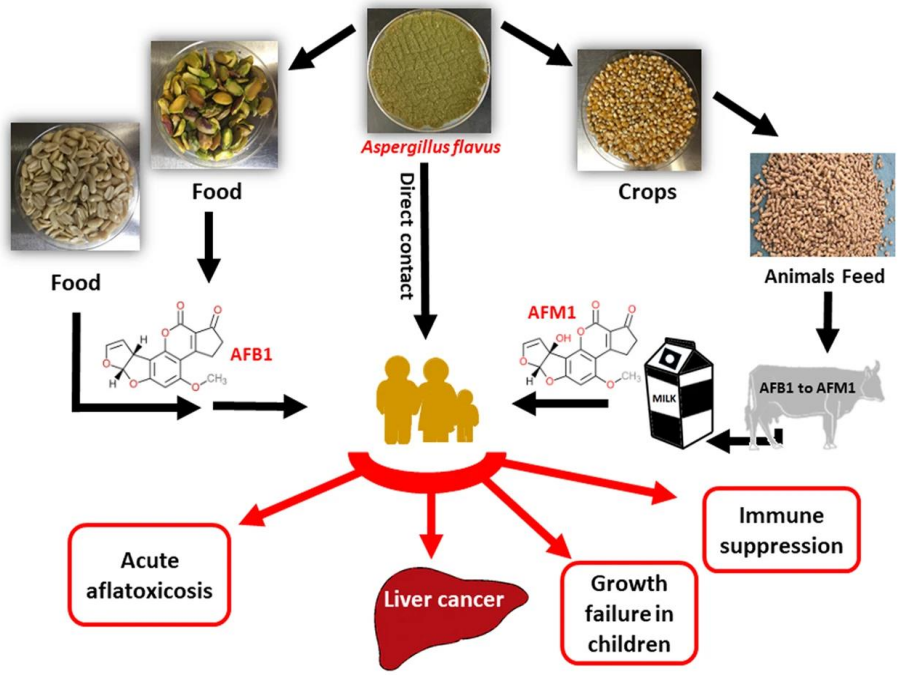


- Human health effects
  - Liver cancer
    - Synergizes with chronic hepatitis B virus (HBV) infection
    - **25,000-172,000 cases/yr** worldwide caused by aflatoxin (Liu & Wu 2010, Liu et al. 2012)
  - Childhood stunting
  - Acute aflatoxicosis: liver failure & death at high doses
  - Immune system dysfunction

Aflatoxin contamination in dairy animals' feed → **AFM_1 in milk of animals**

- AFM_1 has 10% cancer potency of AFB_1 (JECFA 2001)
- FDA regulates AFM_1 at **0.5 µg/kg** allowable in dairy (EU: 0.05 µg/kg)
- Causes cytotoxicity, & suggestive risk of genotoxicity → IARC classifies as Group 2B carcinogen (possible carcinogen), 2002

- Additional results forthcoming by Wu et al; cannot be shared at this time



Major contamination/exposure routes of AF and health risks to humans (Alshannaq et al. 2018)

Health effects of AFM_1

- **Human studies**
  - *Carcinogenic effect* - Dose-response relationship between serum/urinary AFM_1 levels and risk of liver cancer in chronic hepatitis B virus patients in Asia & African (Lu et al. 2010; Mokhles et al. 2007; Yu et al. 1997).

- **Animal studies**
  - *Immune effects* in T cells from spleens in the mice exposed to AFM_1 (Shirani et al. 2019)
    - Reduced proliferation of splenocytes (lower spleen weight), decreased IFN-ɣ, increased IL-10
  - *Intestinal function disorders* - Increase DNA fragmentation & change gene expression in mice (Jebali et al. 2018)

Implications for human health from AFM_1 exposure

- AFM_1 in dairy products may cause human health risks, especially for children who consume large quantities of milk.
  - But risk is much lower than that of "parent" aflatoxin (AFB_1) in corn and nuts: not all aflatoxins are created equal!
- High occurrence of AFM_1 demonstrates need for monitoring in dairy products to reduce risk of toxicity to humans.
- Most effective way to prevent AFM_1 in dairy foods: reduce AFB_1 in animal feed.
  - Monitor AFB_1 in corn, nuts, & cottonseed fed to dairy animals, or switch to other feed crops with low aflatoxin.

Of interest: No AFM1 monitoring data publicly available in US dairy foods.

ANTIBIOTICS: Another chemical of concern in livestock feed

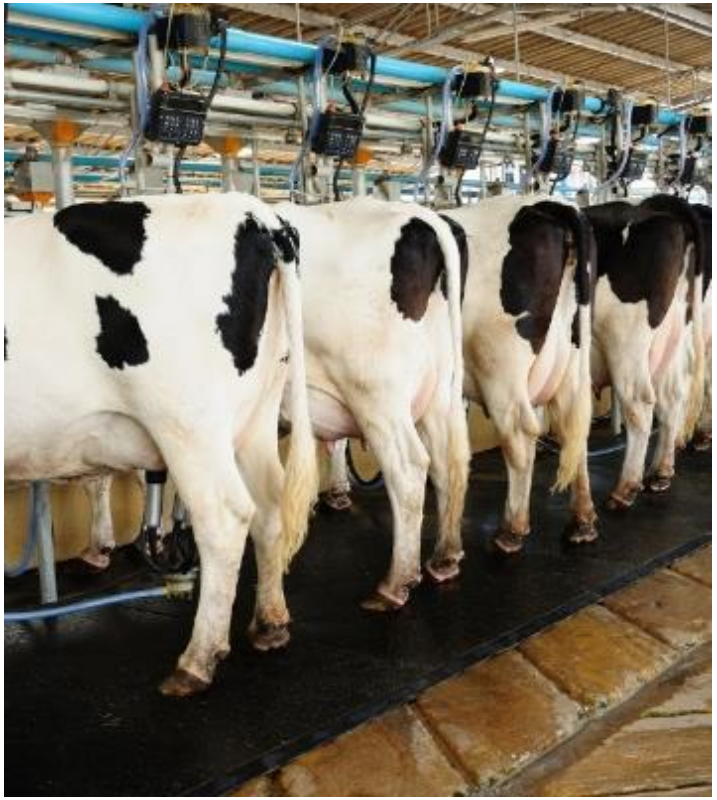
Main reasons for antibiotic use in livestock:

- ***Treatment*** – of animals with diagnosed illness
- ***Prophylactic control*** – to reduce risk of infectious disease among livestock & poultry, even in absence of diagnosed illness
- ***Growth promotion*** – for ~70 years, known that adding antibiotics to animal feed helps animals grow quickly (likely by killing certain bacteria in GI tract) → producers' profit

- **As of January 2017, use of "medically important" antibiotics for livestock growth promotion no longer permitted in the US (FDA)** → reduces risk of antibiotic resistant bacteria

FDA Guidances #209, #213; Veterinary Feed Directive (VFD)

- Effective January 1, 2017
- Limits “medically important” antibiotics (i.e., those also used in human medicine) to therapeutic purposes, “to protect animal health and well-being.”
- Non-therapeutic uses of medically important antibiotics are no longer permitted.
- Veterinarians have oversight into all on-farm antibiotic decisions: farmers cannot purchase feed-grade antibiotics over-the-counter (OTC) anymore.
- All animal performance & production claims removed from feed-grade antibiotic labels.



Which antibiotics are included under VFD?

Antimicrobial Class	Specific Drugs Approved for use in Feed
Aminoglycosides	Apramycin, Hygromycin B, Neomycin, Streptomycin
Diaminopyrimidines	Ormetoprim
Lincosamides	Lincomycin
Macrolides	Erythromycin, Oleandomycin, Tylosin
Penicillins	Penicillin
Streptogramins	Virginiamycin
Sulfas	Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfaquinoxaline
Tetracycline	Chlortetracycline, Oxytetracycline

Risk from antibiotics in animal-source foods is low and expected to decrease

- Role of veterinarians in managing antibiotics given to livestock is larger
- Residues of antibiotics monitored by USDA
  - "Withdrawal" period required before animals are slaughtered (24h, 72h, or 5 days, depending on antibiotic)
  - If dairy animals require antibiotics for infections, isolated & milk disposed until clear antibiotics from milk
  - Rapid traceback & corrective actions to remove antibiotic-containing products from food supply: immediate feedback to producers
- Bacteria on meat and poultry, whether antibiotic resistant or not, are destroyed through cooking
- → **But problem of antibiotic-resistant bacteria remains!**

Burden of disease caused by antimicrobial resistance (AMR)

- Antibiotic-resistant bacteria pose serious threat to US & global public health: **2 million cases** of illness and ~**23,000 deaths** annually in US

How could antibiotics in animal agriculture affect human health?

- Directly: Antibiotics from animal agriculture may result in human exposures through food consumption and livestock contact (in farms, slaughterhouses, meat processing plants)
- Indirectly: Antibiotics in manure spread through environment (water, soil, air) increase selection pressure for bacteria to evolve resistance → AMR in pathogenic bacteria

- **Methicillin-resistant *Staphylococcus aureus* has become a major cause of antibiotic-resistant human infections**
  - Skin and soft tissue infections (SSTI), pneumonia, sepsis
  - MRSA infections killed over 11,000 hospitalized patients in 2011 in the US

- **Livestock animals: important reservoir for livestock-associated MRSA (LA-MRSA)**
  - Persons in close contact with livestock: higher risk of LA-MRSA
  - LA-MRSA has shown high transmission potential in animal population, and is able to persist within that population

Systematic review and meta-analysis of colonization with LA-MRSA among livestock workers/vets

Ongoing work – results cannot be shared at this time

Chen C, Wu F (2019). Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) colonization and infection among livestock workers and veterinarians: A systematic review and meta-analysis. *Bulletin of the World Health Organization*, submitted.

Summary: Risks and myths of aflatoxin M1 and antibiotics / AMR bacteria in animal source foods

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- Not all aflatoxins are equally harmful.
- AFM_1 found in dairy foods is a metabolite of most toxic aflatoxin AFB_1 in dairy animal feed.
  - AFM_1 much less toxic, but possible cancer risk and immune system dysfunction
  - AFM_1 in dairy products worldwide often exceed US and EU maximum levels
  - Reduce AFM_1 by decreasing aflatoxin in dairy feed
- Antibiotics themselves are rarely a concern in US animal source foods.
  - Recent FDA regulations increase vet. oversight of antibiotic use → no longer for growth promotion
  - Withdrawal period before slaughter clears antibiotics from livestock
- Antibiotic-resistant bacteria are a serious risk.
  - No documented direct risk to consumers, but high environmental load → more resistant bacteria
  - Livestock workers: significantly higher risk of LA-MRSA colonization and subsequent infection