Aflatoxin as a Global Food Safety Problem: Health Effects, Market Impacts, Interventions

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Outline

• Aflatoxin: background
• Regulations on aflatoxin in food
  – Economic impacts of aflatoxin regulations
  – Social network models of world food trade
• Health impacts
  – Aflatoxin-related liver cancer worldwide
  – Do aflatoxin regulations really protect health?
  – Interventions that control aflatoxin & adverse effects
  – Liver cancer in China: success story
Aflatoxin: Background

- Produced by fungi *Aspergillus flavus*, *A. parasiticus* in warm climates
  - Maize, peanuts, tree nuts, cottonseed, spices
  - Africa, south & southeast Asia, southern USA

- Group 1 human liver carcinogen
  - Synergistic with hepatitis B (HBV): ~30-fold greater liver cancer risk
    - ~400 million people worldwide have chronic HBV; 4.5 billion chronically exposed to aflatoxin

- Other effects: immune dysfunction, child stunting, acute liver failure
To protect populations from aflatoxin, >100 nations have regulatory standards in food.

<table>
<thead>
<tr>
<th>Nation</th>
<th>Allowable aflatoxin in food (µg/kg)</th>
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</thead>
<tbody>
<tr>
<td>Canada</td>
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<td>China</td>
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</table>
3 questions relevant to these regulations

– **FOOD TRADE.** What are the impacts of these aflatoxin standards on global food trade?
  • Which nations are most at risk?

– **HEALTH.** Do these aflatoxin standards actually protect human health (and to what extent)?
  • Which nations are most at risk?

– **INTERVENTIONS.** How does global health improve when we introduce aflatoxin control methods & dietary diversity?
Strict aflatoxin standards can have severe economic impacts

- **$670 million** annual loss to African food exporters from attempting to meet EU aflatoxin standard (Otsuki et al. 2001)

- “A World Bank study has calculated that the EU regulation on aflatoxins costs Africa $670 million each year in exports of cereals, dried fruit and nuts. *And what does it achieve? It may possibly save the life of one citizen of the EU every two years. Surely a more reasonable balance can be found.*”
  
  — Kofi Annan, former UN Secretary General

- Vardon et al. (2003): nearly **$1 billion** annual loss in US from 3 mycotoxins

- “Milder” estimate: **$450 million** annual loss to ALL food exporters (**$40 million** loss to African exporters) if ALL nations adopted EU standard
  
Conversely: who experiences health benefits of stricter aflatoxin standards?

- **JECFA (FAO/WHO) 1998**: health effects of tightening global aflatoxin standard from 20 to 10 $\mu$g/kg
  - Where 25% population has HBV, tighter standard reduces liver cancer by 300 cases per year per billion persons
  - Where 1% population has HBV, tighter standard reduces liver cancer by 2 cases per year per billion persons
    - Undetectable by epidemiological methods

- Where are the populations with hepatitis B?
  - High HBV populations: China (major food exporter), Africa
  - Low HBV populations: most of industrial world (food importers!)
Countervailing risks

• Health policy dilemma:
  – Regions that can’t afford to set strict aflatoxin standards get more contaminated food, & often have more HBV
  – Regions that import this higher-quality food (EU, Japan, Canada, Taiwan) experience insignificant health benefit

• *Is this in fact true?*
  – We developed global network models of maize & pistachio trade to find out
Impact of aflatoxin regulations on world food trade: Insights from network models

- **Network model** = Collection of nodes, joined in pairs by edges
  - Friendships, co-authors, roads, trade
  - Why network models are useful

- Do trade clusters emerge?
- If drought or crop disease hits one nation, which other nations are affected?
- How do food safety regulations affect global trade patterns?
How we developed global trade networks for maize & pistachios

• Collected global maize & pistachio trade data
  – Maize: 2000-2009
  – Pistachios: 1996-2010

• Developed global network models for trade for each year

• Determined impact of aflatoxin regulations on trade patterns

• Data sources:
  – United Nations Commodities Trade Database (UN Comtrade)
  – Iranian Pistachio Association Trade Database
  – USDA Foreign Agricultural Service Global Agricultural Trade System (GATS)
  – Food and Agriculture Organization (FAO) mycotoxin regulation reports: 1995, 2003
  – European Union (EU) Rapid Alert System for Food & Feed (RASFF)

• Network model software: Pajek™
Top exporters of maize worldwide: Three trading clusters emerge

**Vulnerabilities** revealed in global maize trade

• US at center of star-shaped cluster
  – Nations with high maize consumption that import exclusively from US are vulnerable to US supply changes
  – Drought, plant disease may reduce supply
  – **US maize ethanol production**: in 2007, riots in 22 nations

• Conversely, who is **less vulnerable**?
  – Nations that are well-connected
  – Nations near center of maize trade network
Aflatoxin standards vary widely across nations: Effects on food trade?
Nations trade maize with nations that have similar aflatoxin standards

Wu F, Guclu H (2012). PLOS ONE 7(9):e45141
Top maize-trading pairs have near-identical AF standards

<table>
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<tr>
<th>Rank</th>
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Do nations’ aflatoxin regulations affect global pistachio trade?

- Global pistachio market dominated by Iran and US
  - Iran (50%)
  - US (25%)
- Pistachios commonly contaminated with aflatoxin
  - Pistachios contribute 7-45% of aflatoxin in human diets
  - Aflatoxin levels in Iranian pistachios: avg 54 ng/g (JECFA 2007)
  - Aflatoxin levels in US pistachios < 15 ng/g

- Which nations differentially import from Iran vs. US?
- Do aflatoxin regulations play a role?
EU used to import **Iranian** pistachios; now imports **US** pistachios.
In 1996, Iran was major pistachio exporter to EU & worldwide

1996

Iran total: >120k tons
US total: 22k tons
Iran-EU: 85k tons
US-EU: 4k tons

Iran: No reg. for pistachios
US: 15 ng/g
Next year, high aflatoxin levels (up to 400 ng/g) drove Iranian exports to EU down dramatically. 1997

Iran total: 55k tons
US total: 26k tons
Iran-EU: 17k tons
US-EU: 8700 tons
In 2003, US started exporting large amounts of pistachios to EU; Iran shifted markets

Iran total: 154k tons
US total: 35k tons
Iran-EU: 33k tons
US-EU: 23k tons

Iran Reg: 15 ng/g
EU: 4 ng/g
Recently, US became main pistachio exporter to EU

Iran total: 116k tons
US total: 129k tons
Iran-EU: 19k tons
US-EU: 63k tons
US vs. Iran Pistachio Export Share:
Clear evidence of market segregation
Iran vs. Greece Export Share – Grape Control Crop: No evidence of market segregation

Conclusions from network models of world food trade

• When nation sets food safety standard, ripple effects all over world (*disturbing one part of web*)

• Aflatoxin regulations associated with global food trade patterns

• Nations trade more food with other nations that have identical or similar AF standards

• Nations with more relaxed standards import food with higher AF contamination
  – These patterns exist irrespective of other political factors

• Who is vulnerable?
  – Low-income nations depending on food trade (exports or imports) with relaxed or nonexistent AF standards
  – Nations that import staple food only from one other nation
Meanwhile, what are the health impacts of aflatoxin exposure worldwide today? Focus on liver cancer

- **Dose-response assessment**
  - Slope of curve = cancer “potency”
    - Aflatoxin → HCC: 0.01 cases / 100,000 / yr / ng/kg bw/day
    - Aflatoxin+HBV → HCC: 0.30 cases / 100,000 / yr / ng/kg bw/day (JECFA 1998)

- **Exposure assessment**
  - Find, for each nation:
    - Daily consumption of maize / nuts
    - Aflatoxin levels in maize / nuts
    - HBV prevalence
    - Population size
    - *Captured 5.96 billion people*
Risk characterization: Simplified model

- Global population cancer risk =
  \[ \sum_{\text{all nations}} \left( \left( \frac{\text{Population}_{\text{HBV+}}}{100,000} \times \text{Potency}_{\text{HBV+}} \times \text{Average aflatoxin intake} \right) + \left( \frac{\text{Population}_{\text{HBV-}}}{100,000} \times \text{Potency}_{\text{HBV-}} \times \text{Average aflatoxin intake} \right) \right) \]

- Potency_{\text{HBV+}} = 0.30 cases per 100,000/yr per ng/kg bw/day
- Potency_{\text{HBV-}} = 0.01 cases per 100,000/yr per ng/kg bw/day

Data Sources:
- **HBV prevalence**: WHO, multiple peer-reviewed papers
- **Aflatoxin exposure & food consumption**: FAOSTAT, multiple peer-reviewed papers
Results: **25,200-155,000** global aflatoxin-induced liver cancer cases/yr

~5-28% of all liver cancer cases


Is this “bad”?
Whether nations’ aflatoxin standards are adequate depends on what is “acceptable risk.”

Don’t increase cancer risk by >1/100,000 cases in population

- Almost no nations have adequately protective aflatoxin standards
- Exceptions: European nations
  - Scandinavian nations could have AF standard as high as 82 ppb and still meet this low risk level!
  - ... Ironically, EU has strictest AF standards in world

Don’t increase cancer risk by >1/10,000 cases in population

- Almost all nations have adequately protective aflatoxin standards
- Exceptions: Kenya (20 ppb) & Peru (15 ppb)
  - Both nations have high maize consumption and high HBV
  - Cannot afford to have much aflatoxin in their maize

Interventions to reduce aflatoxin risk

• **Preharvest**
  - Good agricultural practices
  - Genetically enhancing plants’ resistance
  - Biocontrol

• **Postharvest**
  - Improved sorting, drying, food storage

• **Dietary**
  - Improved dietary variety
  - Dietary enterosorbents
  - Dietary chemoprevention
    - Curcumin
    - Compounds in cruciferous & *Allium* vegetables
    - Green tea polyphenols

• **Hepatitis B vaccine**
Liver Cancer Mortality by Township: Jiangsu Province

"Geographic Pathology"

< 1 per 10^5/yr

> 50 per 10^5/yr

Qidong
1.2 million residents

Shanghai
Why was liver cancer so high, and what happened in Qidong since 1980?

• 1920-1980: Maoist agrarian socialism in China
  – Each county must be self-sufficient
  – No imports/exports allowed between counties

• Qidong: soil unsuitable for planting rice
  – Consumed 82-124 kg maize/yr infected with Aspergillus flavus
  – **HIGH AFLATOXIN EXPOSURE**: some years, 99% maize > 20 µg/kg AF
  – Not allowed to purchase rice

• 1980: China relaxes agrarian socialism
  – 1987: >97% Qidongese consume some rice
  – 1998: <9% Qidongese ate any maize
  – 2012: hardly any maize consumed
Since 1980, aflatoxin biomarkers decreased dramatically in Qidong.
Reduced aflatoxin exposures, not HBV status, are associated with declining liver cancer mortality in Qidong (Chen et al. CaPR 2013).
What relatively aflatoxin-free crops could become dietary staples in Africa?

• Instead of only focusing on how to reduce aflatoxin in maize & nuts, consider increasing dietary variety or switching staple crops altogether

• Africa’s indigenous crops
  – Sorghum
  – Millet
  – Cowpea
  – Pigeonpea
  – Fonio (West Africa)
  – Teff (northeastern Africa)
  – Rice (some varieties native to Africa)

• These come with potential problems, but rarely *Aspergillus*

Conclusions

• >100 nations have aflatoxin standards to protect human health
  – But regulations may not have the direct protective effects intended
    (*indirect effects are important, though*)
  – And they may affect other countries’ economies and health

• Aflatoxin-related liver cancer highest in sub-Saharan Africa, Southeast Asia, & China
  – Recent agricultural policy changes improved liver health in China by indirectly lowering aflatoxin exposure

• While many interventions exist, long-term solutions should include switching to staple crops that are less infected with *Aspergilli*
  – In China, switch was made in <7 years, but other parts of world not same
  – Meanwhile, we must continue foci of reducing aflatoxin in maize & nuts