Aflatoxin: Economic & Health Impacts

How to assess public health interventions

Felicia Wu, PhD
Assistant Professor of Environmental & Occupational Health
Graduate School of Public Health
University of Pittsburgh, USA

Motivating question: *How can we best reduce aflatoxin-induced illness & market loss through a combination of appropriate standards and interventions?*

- What is aflatoxin?
- Aflatoxin’s health effects
- Impact of aflatoxin standards on trade & health
- Kenya: Case study
- Public health interventions & their global feasibility
Two approaches to reduce aflatoxin’s economic & health risks worldwide

Aflatoxin standards

Net Economic Impact

Amount of aflatoxin consumed

Aflatoxin-induced disease

HBV prevalence

Aflatoxin control methods

Dietary interventions

HBV vaccination

Top down…

vs. bottom up
Aflatoxin: Background

- Produced by fungi *Aspergillus flavus, A. parasiticus*
  - Corn, peanuts, tree nuts, cottonseed, spices
- Type 1 human liver carcinogen
  - Synergistic with hepatitis B (HBV): up to 60X greater liver cancer risk
    - ~400 million people worldwide have chronic HBV infection
- Other effects: immune system disorders, stunting in children, acute aflatoxicosis
Aflatoxin metabolism & DNA damage

Aflatoxin M₁ (urine) → Aflatoxin – mercapturic acid (urine)

Aflatoxin M₁ (urine) → CYP1A2 → Aflatoxin B₁ → Aflatoxin-8,9-epoxide

Aflatoxin-8,9-epoxide → GSTs → DNA

DNA → Aflatoxin – N⁷-guanine (urine)

Aflatoxin – mercapturic acid (urine) → AP site

Aflatoxin albumin adduct (serum) → other metabolites

Kensler T, 2006
We can’t eliminate aflatoxin in food, so we regulate it

<table>
<thead>
<tr>
<th>Nation</th>
<th>Total aflatoxin standard in human food (μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>5</td>
</tr>
<tr>
<td>China</td>
<td>20</td>
</tr>
<tr>
<td><strong>European Union (EU)</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td>Guatemala</td>
<td>20</td>
</tr>
<tr>
<td>India</td>
<td>30</td>
</tr>
<tr>
<td>Kenya</td>
<td>20</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

*applies to cereals & cereal products, nuts not subject to further processing, & dried fruit*
3 questions relevant to these regulations

- **FOOD TRADE.** What is the global food export market loss at different aflatoxin standards?
  - Which nations are most at risk?

- **HEALTH.** How many additional global liver cancer cases attributable to aflatoxin occur at different aflatoxin standards?
  - Which nations are most at risk?

- **INTERVENTIONS.** How do global health and trade improve when we introduce vaccines, dietary supplements, or aflatoxin control methods?
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 European Union 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 European Union every two years… Surely a more reasonable balance can be found.”
  
  -- *Kofi Annan, former UN Secretary General*

- “Milder” calculation: **$450 million** annual loss to ALL food exporters if ALL nations harmonized to EU aflatoxin standard (Wu 2004)
Liver cancer risk calculations

- Population cancer risk = Potency * Average aflatoxin intake
- Potency = 
  \[ \text{Potency factor for HBV+ persons} \times \% \text{ of HBV+ persons} \]
  + \[ \text{Potency factor for HBV- persons} \times \% \text{ of HBV- persons} \]

- \% of HBV+ persons: prevalence data from WHO
- Individual cancer risk: Calculate based on HBV status & aflatoxin intake
- Average aflatoxin intake: FAO corn & peanut consumption data worldwide, & estimates of aflatoxin contamination

Key differences from JECFA 1998:
1. True HBV+ prevalence per nation (not 1% vs. 25%)
2. Nations export best food; keep worst at home
“Average individual’s” lifetime liver cancer risk: THEORETICAL

<table>
<thead>
<tr>
<th>HCC RISK BY WORLD REGION</th>
<th>Individual’s lifetime risk, no HBV infection (in a million)</th>
<th>Individual’s lifetime risk, chronic HBV infection (in a million)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aflatoxin standard</strong></td>
<td>20 μg/kg</td>
<td>4 μg/kg</td>
</tr>
<tr>
<td>United States</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>EU</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>S. America</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>China</td>
<td>13</td>
<td>6.7</td>
</tr>
<tr>
<td>Africa</td>
<td>40</td>
<td>22</td>
</tr>
</tbody>
</table>
How does aflatoxin compare to other risks in rich nations?

- Average U.S. citizen’s lifetime death risk from:
  - Bathtub drowning: 83 in a million
  - **High school football:** 1.2 in a million
  - Motor vehicle accident: 10,500 in a million
  - Homicide: 3,900 in a million
  - Suicide: 7,600 in a million
  - Bee, hornet, or wasp sting: 11 in a million
  - **Lightning:** 23 in a million
  - Shark attack: 0.25 in a million

Source: Harvard Center for Risk Analysis
But a low relative risk doesn’t mean that we should not control aflatoxin

- … if there is a cost-effective and feasible way to do so

- Though aflatoxin is a minor public health problem in rich, temperate-zone nations with low hepatitis rates, it is still a HUGE issue in Africa & Asia
The Republic of Kenya

- 582,000 km²
- Population 32 M
  - 41% <15 yrs
- Maize is primary food staple
- Maize production is by small scale farmers
- Only ~ 20% suitable for rain-fed agriculture

Source: David Wilson, UGA/Tifton
Outbreaks of Aflatoxicosis in Kenya are Seasonal (Peak in May)  

Source: David Wilson, UGA/Tifton

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Eastern and Central Province Aflatoxin Outbreak - Kenya 2004 (Updated 6/25/04)

- 317 Cases
- 127 Dead
- Case fatality rate = 39%

E Azziz-Baumgartner, W Chege, A Bowen, K Gieseker, 2005
How the Outbreaks Unfolded

Symptoms of Aflatoxicosis

- High fever
- Gastrointestinal infections
  - Stomach pain
  - Vomiting
- Edema of the limbs
- Rapid progressive jaundice
- Swollen livers

Jaundiced sclera

Tested negative for: Yellow fever, Rift Valley fever, dengue, hepatitis A, B, and C; West Nile virus; Chikungunya, and Bunyamwera

Source: David Wilson, UGA/Tifton
Regions with Severe Outbreaks of Aflatoxicosis in Kenya

Source: David Wilson, UGA/Tifton

Azziz-Baumgartner et al., 2005
**2004 Levels of Aflatoxin in Maize Samples Were Highly Variable**

<table>
<thead>
<tr>
<th>District</th>
<th>Maize Aflatoxin (ppb) Geometric Mean</th>
<th>Maize Aflatoxin (ppb) Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makueni</td>
<td>52.9</td>
<td>1 – 5,400</td>
</tr>
<tr>
<td>Kitui</td>
<td>35.2</td>
<td>1 – 25,000</td>
</tr>
<tr>
<td>Machakos</td>
<td>17.8</td>
<td>1 – 3,800</td>
</tr>
<tr>
<td>Thika</td>
<td>7.5</td>
<td>1 – 46,400</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20.5</strong></td>
<td><strong>1 – 46,400</strong></td>
</tr>
</tbody>
</table>

Azziz-Baumgartner et al., 2005
Hypothesis for 2004 & 2005 Outbreaks

Source: David Wilson, UGA/Tifton

- Drought
- Food Scarcity
  - Plant stress
  - Poor storage
- Contaminated food
- Aflatoxicosis
Public health interventions also affect health & economics of aflatoxin

Top down…

Net Economic Impact
Aflatoxin-induced disease
Amount of aflatoxin consumed
HBV prevalence
Aflatoxin standards
Aflatoxin control methods
Dietary interventions
HBV vaccination

vs. bottom up
How feasible are public health interventions to combat aflatoxin?

Cost-effectiveness  Public compliance  Feasibility
3 categories of interventions to reduce aflatoxin’s health risks

- Agricultural interventions
- Dietary interventions
- Clinical interventions

These reduce aflatoxin risk in different ways

- **Agricultural**: Farmers can reduce aflatoxin → reduce trade & health losses
- **Dietary or clinical**: We can consume more aflatoxin & not significantly increase our liver cancer risk
How to analyze cost-effectiveness, compliance, feasibility of interventions

- **Cost-effectiveness:** very quantitative
  - $C_s = $Societal cost of aflatoxin
  - $E_i = $% efficacy of intervention’s risk reduction
  - $A_i = $Cost of applying intervention
  - $\rightarrow$ Net benefit: $B = E_i \times C_s - A_i$
  - Compare $B$ across interventions

- **Public compliance:** semi-quantitative
  - How likely will people adopt or comply with intervention?
  - Is it culturally appropriate?

- **Feasibility:** not very quantitative
  - How supportive are policies, infrastructure, funding sources?
Agricultural interventions to reduce aflatoxin

- **Preharvest**
  - Genetically enhance resistance
    - Transgenics
    - Conventional methods
  - Good agronomic practices
  - Biocontrol methods
  - Chemical methods
    - Fungicides
    - Antioxidants

- **Postharvest**
  - Physical methods
    - Sorting
    - Improved storage & transportation conditions
  - Chemical methods
    - Ammoniation
Dietary / clinical interventions

- Binding agents
  - Novasil clay, chlorophyll, chlorophyllin

- Phase II enzyme inducers
  - E.g., sulforaphane found in cruciferous & other vegetables, triterpenoids, Oltipraz

- Inflammation reducers
  - E.g., NSAIDs, green tea polyphenols

- Hepatitis B vaccine
Items to consider in evaluating interventions

- How many people need to implement the intervention? (Just growers, or all consumers?)
- How many times a day, week, year, lifetime?
- What are global attitudes toward GMOs and vaccines (even those that can reduce health risk)?
- Can farmers afford upfront costs?
- Can we deliver vaccines / medicines / technologies where needed?
- Will people comply with prevention regimes?
Summary & final points

- We can control aflatoxin via top-down (policy) or bottom-up (intervention) methods
- Top-down methods work best for developed nations, where aflatoxin standards are enforced
  - Standards can be very costly to food exporting nations
- Bottom-up methods work best for developing nations, where much food doesn’t enter regulatory oversight
  - Interventions can create a win-win situation