MYCOTOXINS: Health & Economic Effects, and Interventions




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Presentation Outline

- Mycotoxins*: What are they?*
  - Aflatoxins
  - Fumonisins
  - Deoxynivalenol (Vomitoxin, DON)
- Existing regulations on aflatoxin, & economic impacts
  - Case studies in maize and pistachios
- Health effects & interventions
  - Aflatoxin-related liver cancer worldwide
  - Aside from regulations, other interventions for all mycotoxins
  - Case study: liver cancer reduction in China

Mycotoxins: What are they?

- Toxic & carcinogenic chemicals produced by fungi
- Long history of mycotoxins affecting society
  - Leviticus 14:37
  - 11th c.: *Claviceps purpurea* produces ergot in rye → St. Anthony's Fire
  - Mysterious human & animal deaths in 1930s (Great Depression horses)
  - 1960 aflatoxin discovery: UK turkey deaths
  - Today: several dozen mycotoxins identified

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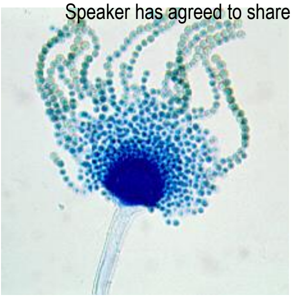
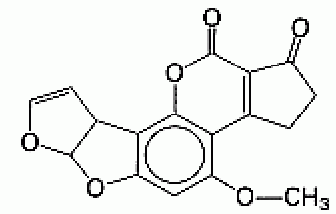


Aflatoxins: Background

- Produced by fungi *Aspergillus flavus, A. parasiticus* in warm climates
  - **Maize, peanuts, tree nuts**, cottonseed, spices
  - Africa, south/southeast Asia, Central America, US South

- Group 1 **human liver carcinogen**
  - **Synergistic with hepatitis B (HBV):** ~30-fold greater liver cancer risk
    - ½ billion people worldwide have chronic HBV; 4.5 billion chronically exposed to aflatoxin

- Other effects: immune dysfunction, child stunting, acute liver failure → death



Aflatoxin B_1
(Aspergillus flavus)

Fumonisins

- Produced by fungi *Fusarium verticillioides*, *F. proliferatum*
- Common in corn grown in temperate & subtropical climates
  - Few other crops affected: limited evidence for wheat, sorghum
- Discovered in 1988 in South Africa & US
  - Esophageal cancer in men drinking moldy beer
  - Horses dying of leukoencephalomalacia (ELEM, “staggers”), swine dying of pulmonary edema
- Animal effects well-characterized; human effects less so
  - Associated with neural tube defects, esophageal cancer (IARC 2B “possible carcinogen”), child growth impairment

Deoxynivalenol (DON, "vomitoxin"): Background and health effects

- Produced by fungi *Fusarium graminearum* and *F. culmorum* in wheat, barley, oats, and maize
- Inhibits protein & DNA synthesis in multiple species
  - Swine: diminished feed consumption, lower weight gain (swine regulate toxin ingestion by adjusting feed intake), vomiting
  - Poultry & cattle have higher DON tolerance

- Causes immunosuppression
- Human health effects? *No epidemiological evidence.*

Of these 3 most agriculturally important mycotoxins, FDA regulates differently:

- **Action level:**
  - "Total aflatoxins" (AFB1 + AFB2 + AFG1 + AFG2): 20 µg/kg in corn, peanuts, & tree nuts for human food & pet food
  - Aflatoxin M1 (metabolite of aflatoxin B1): 0.5 µg/kg in milk & other dairy products
- **Industry guidelines:**
  - Fumonisins: 4 mg/kg in whole corn products, 2 mg/kg degermed corn products (corn meal, corn flour, corn grits)
  - DON: 1 mg/kg in corn, wheat, barley, & oats

To protect populations from aflatoxin, >100 nations have regulatory standards in food

Nation	Allowable aflatoxin in food (µg/kg)
Canada	15
China	20
European Union (EU)	4/10
Ghana	No regulation
Guatemala	20
India	30
Kenya	20
United Arab Emirates	No regulation
USA	20

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?
  - Which nations are most at risk?

– **INTERVENTIONS**. How do global health & economics improve when we introduce interventions to reduce aflatoxin?

Strict aflatoxin standards can have severe economic impacts

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

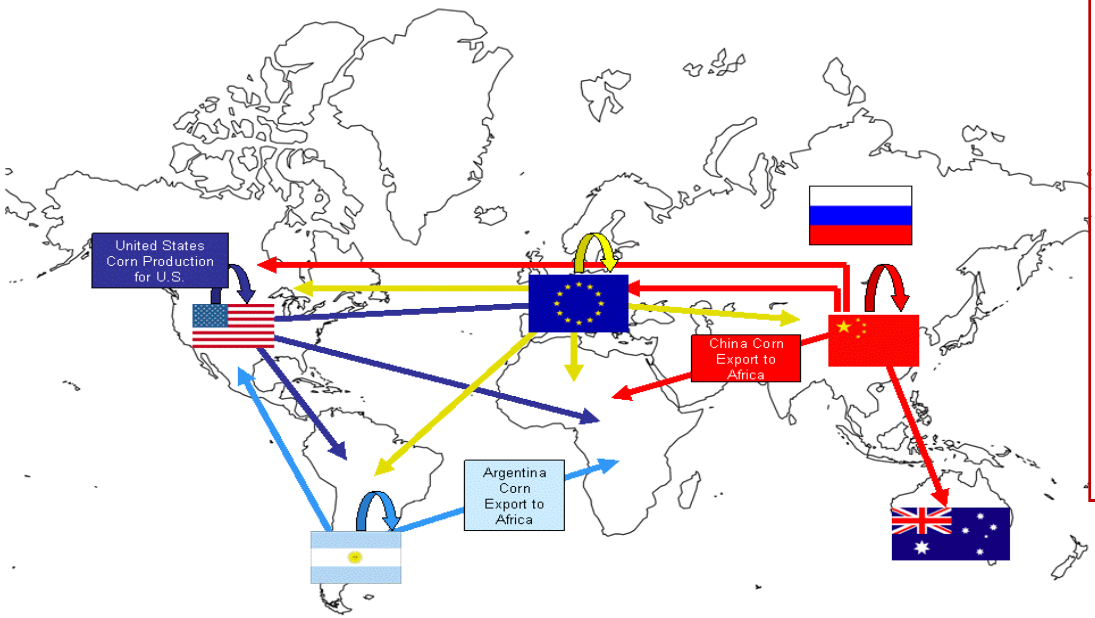
- "A World Bank study calculated that the European Union regulation on aflatoxins costs Africa $670 million each year in exports of cereals, dried fruit and nuts. *And what does it achieve? It may possibly save the life of one citizen of the EU every two years*… Surely a more reasonable balance can be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

But who experiences health benefits of strict aflatoxin standards?

- JECFA 1998: health effects of 20 to 10 μg/kg AF standard
  - If 25% population has HBV, tighter standard reduces liver cancer by **300 cases per year** per billion people
  - If 1% population has HBV, tighter standard reduces liver cancer by **2 cases per year** per billion people
- Which populations have hepatitis B?
  - High HBV populations: China (major food exporter), Africa
  - Low HBV populations: most of industrial world
- **Health policy dilemma:**
  - Nations that can't afford to set strict aflatoxin standards get more contaminated food, but have more HBV
  - Nations that import high-quality food (EU, Japan) have low health benefit
  - ***Is this in fact true? Can we quantify it?***

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?

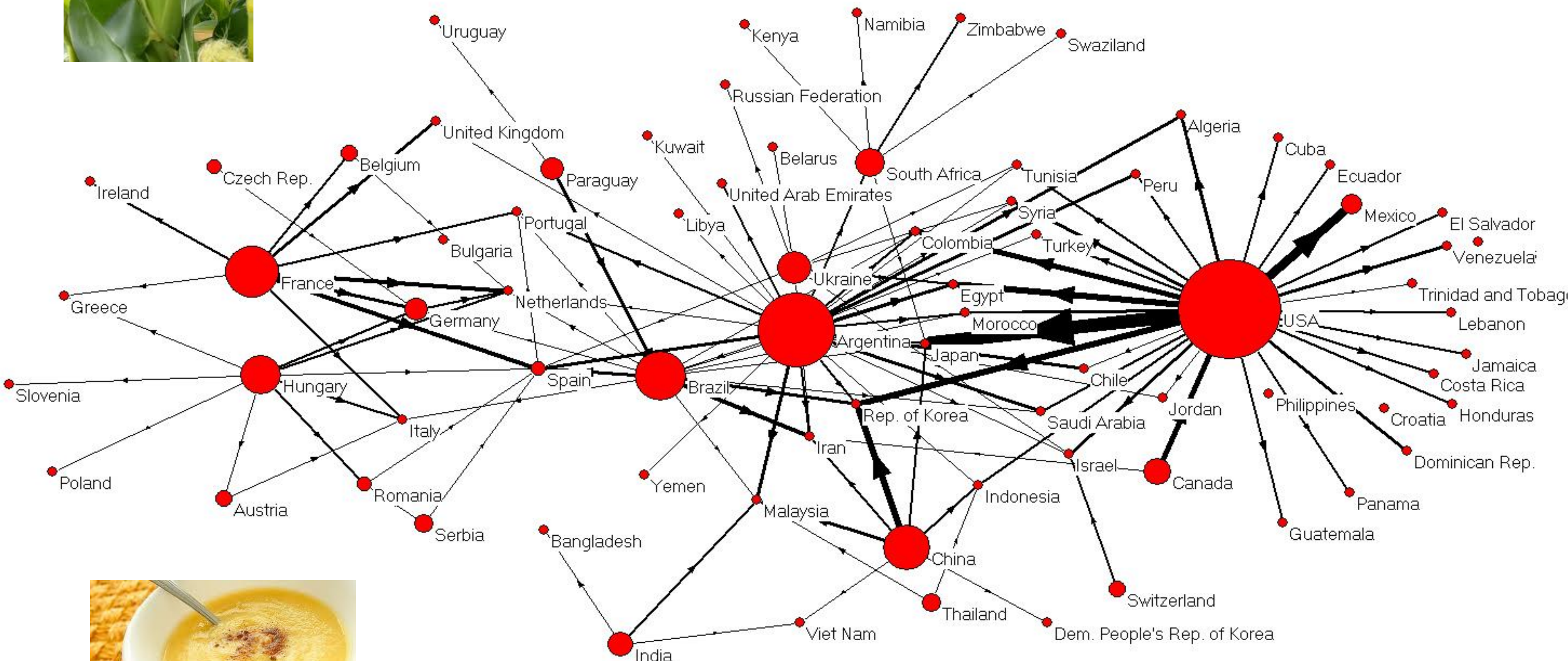
How we developed global trade networks for corn & pistachios

- Collected global maize & pistachio trade data
  - Corn: 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 report 2004
  - European Union (EU) Rapid Alert System for Food & Feed (RASFF)
- *Network model software*: Pajek™

Top exporters of corn worldwide:

Three trading clusters emerge

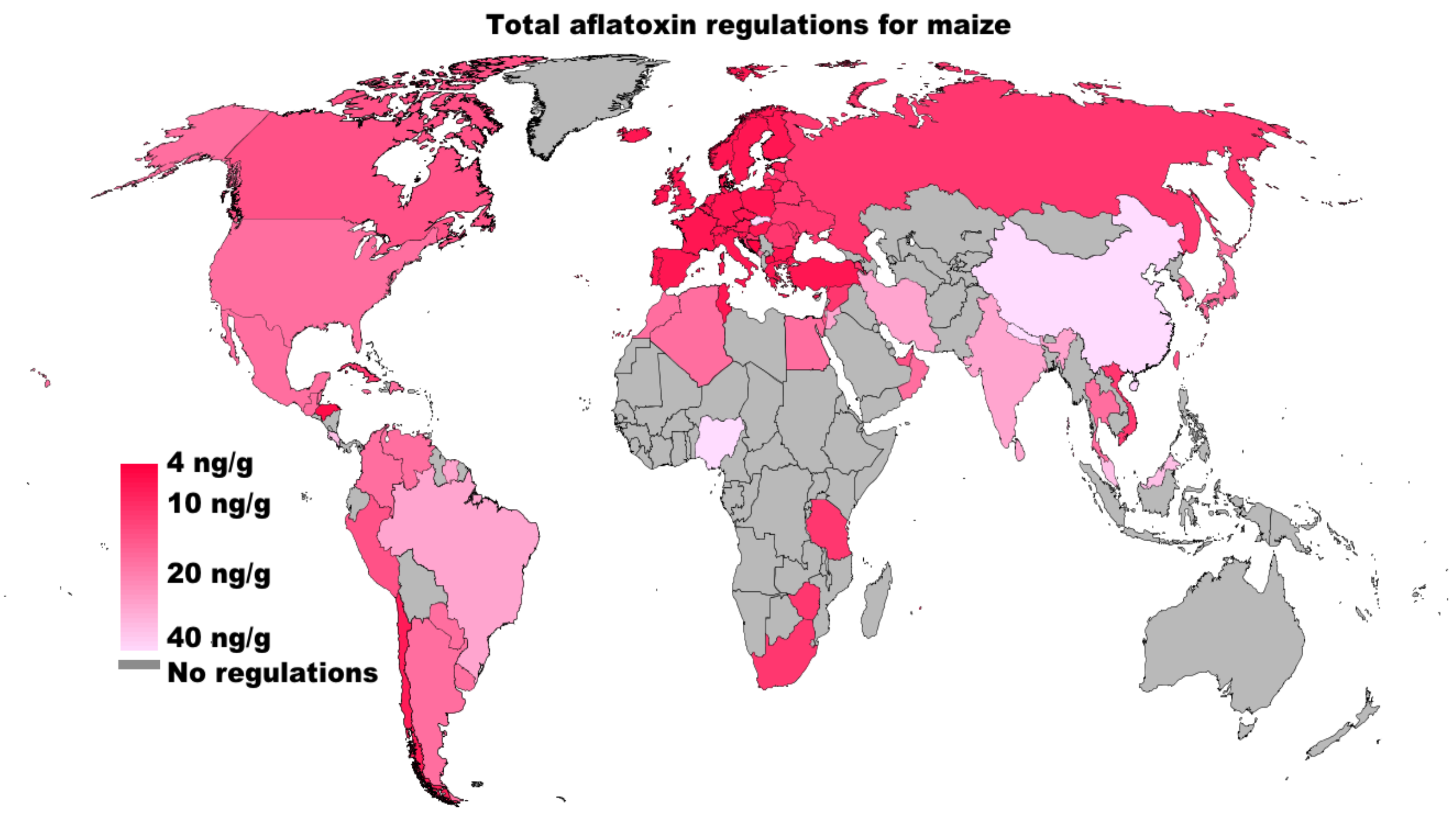


Wu F, Guclu H (2013). Global maize trade and food security: Implications from a social network model. *Risk Analysis* 33:2168-78.

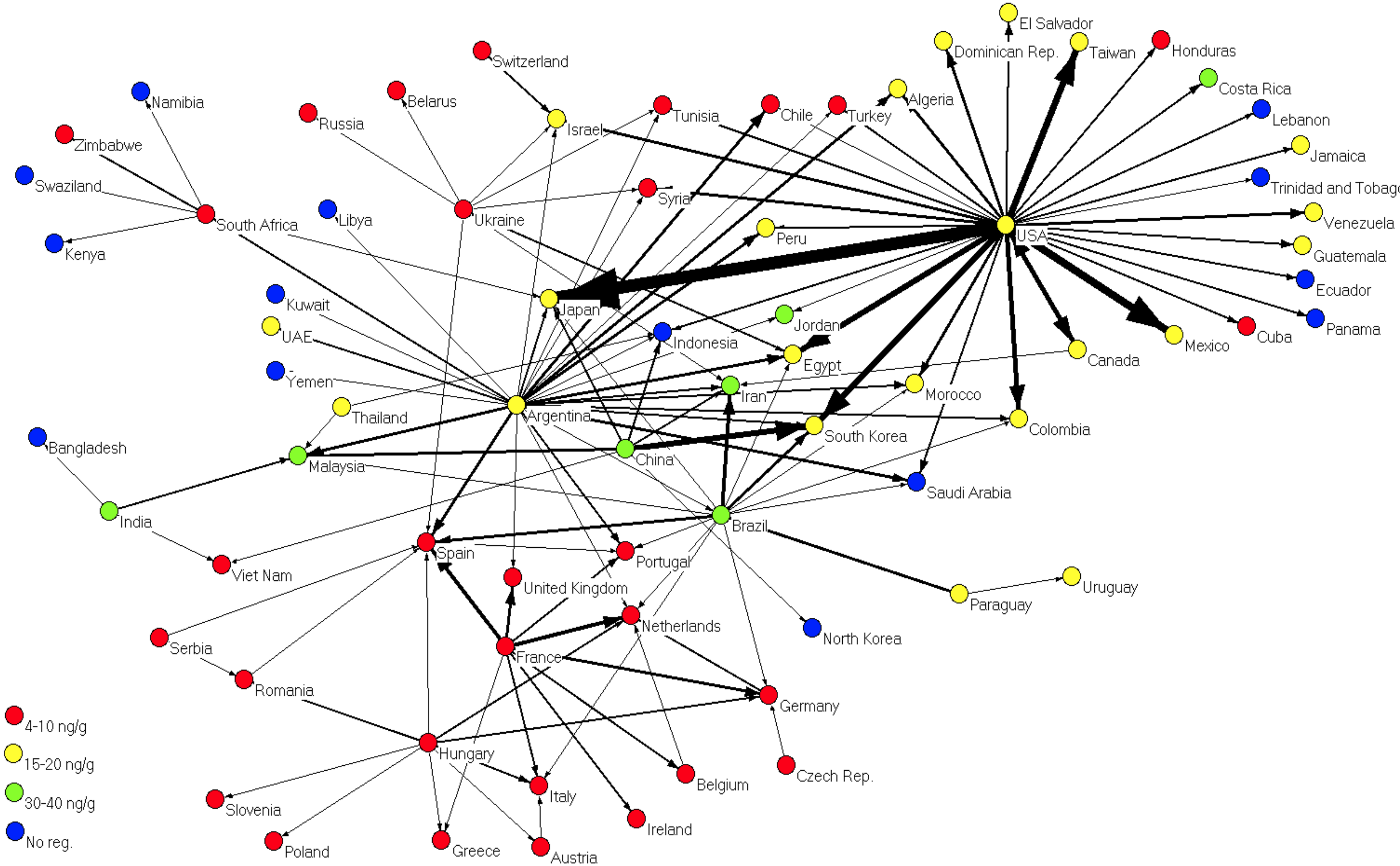
Vulnerabilities revealed in global corn trade

- 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 corn trade network

Aflatoxin standards vary widely across nations: Effects on food trade?



Nations trade corn with nations that have similar aflatoxin standards



Wu F, Guclu H (2012). *PLOS ONE* 7(9):e45141

Top corn-trading pairs have near-identical AF standards

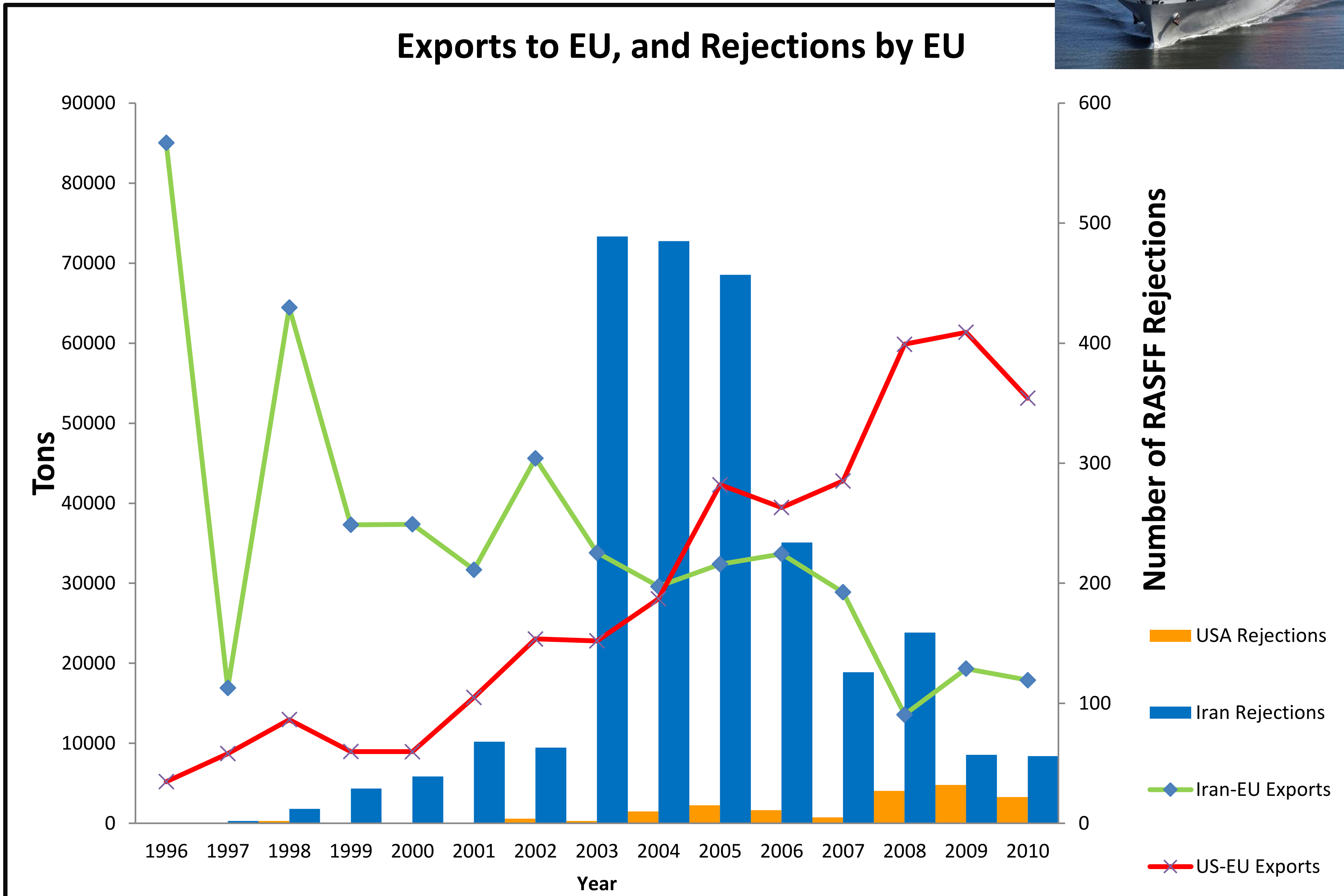
Rank	Top pairs & their total aflatoxin (AF) standards in μg/kg maize				Total amount (MT)
	Exporter	AF standard	Importer	AF standard	
1	USA	20	Japan	20	159,377,000
2	USA	20	Mexico	20	69,764,700
3	USA	20	Taiwan	15	44,212,000
4	USA	20	Korea	20	41,657,300
5	China	20	Korea	20	36,446,400
6	USA	20	Egypt	20	35,540,100
7	USA	20	Canada	15	25,933,000
8	USA	20	Colombia	20	21,726,900
9	Canada	15	USA	20	21,161,900
10	France	4	Spain	4	18,682,400
11	France	4	Netherlands	4	14,901,600
12	Brazil	30	Iran	30	12,588,000
13	Mexico	20	USA	20	10,947,000
14	Argentina	20	Chile	5	10,625,700
15	USA	20	Algeria	20	10,457,700
16	USA	20	Dominican Rep.	20	10,325,300
17	Argentina	20	Spain	4	10,311,600
18	China	20	Malaysia	35	10,119,800
19	France	4	UK	4	9,899,890
20	Argentina	20	Egypt	20	9,734,360

Do nations' aflatoxin regulations affect global pistachio trade?

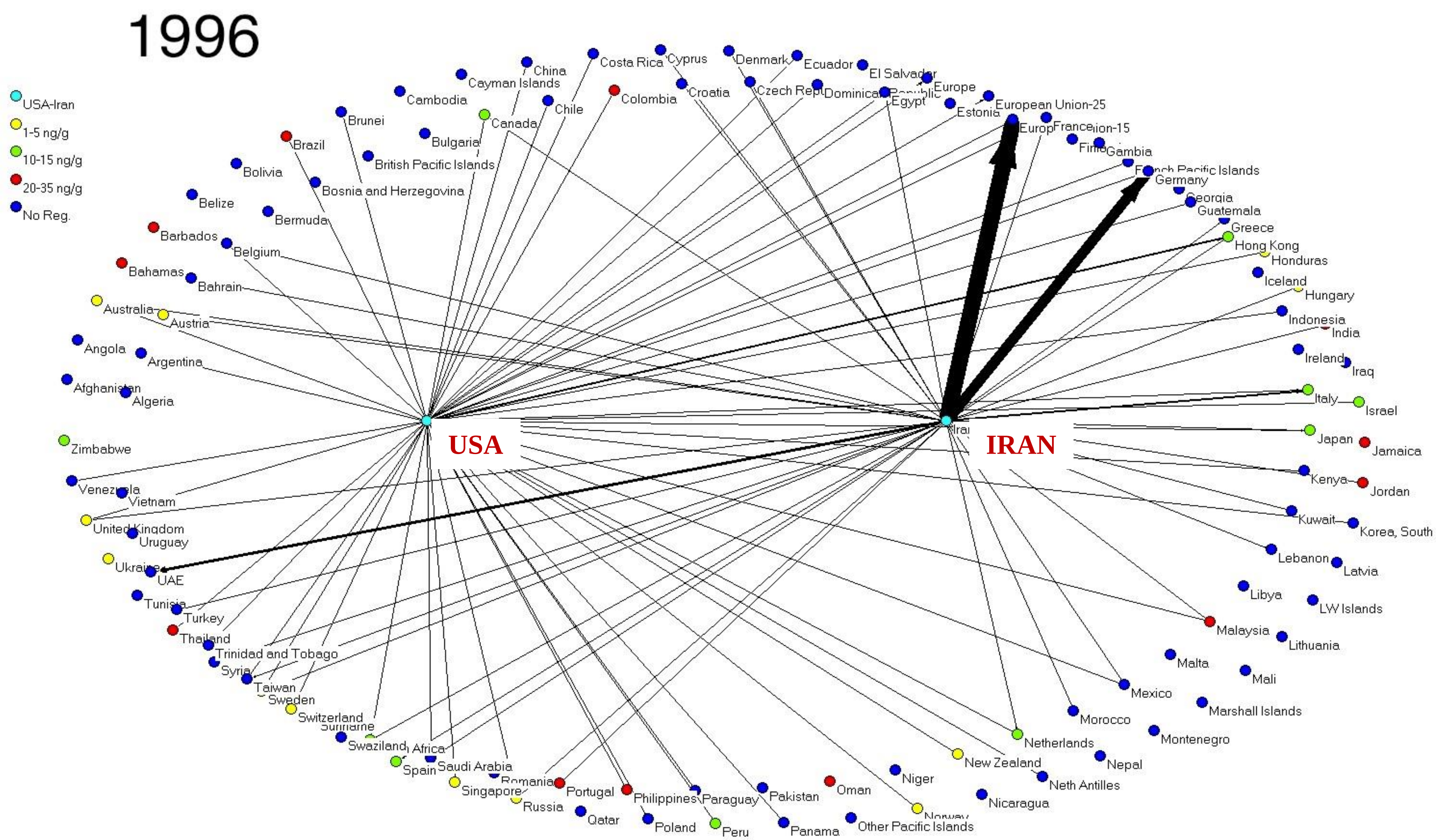
- Global pistachio market dominated by Iran and US
  - Iran (50%)
  - US (25%)
- Pistachios commonly contaminated with aflatoxin
  - Pistachios contribute **7-45% of aflatoxin** in human diets
  - Aflatoxin levels in Iranian pistachios: avg **54 ng/g** (JECFA 2007)
  - Aflatoxin levels in US pistachios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



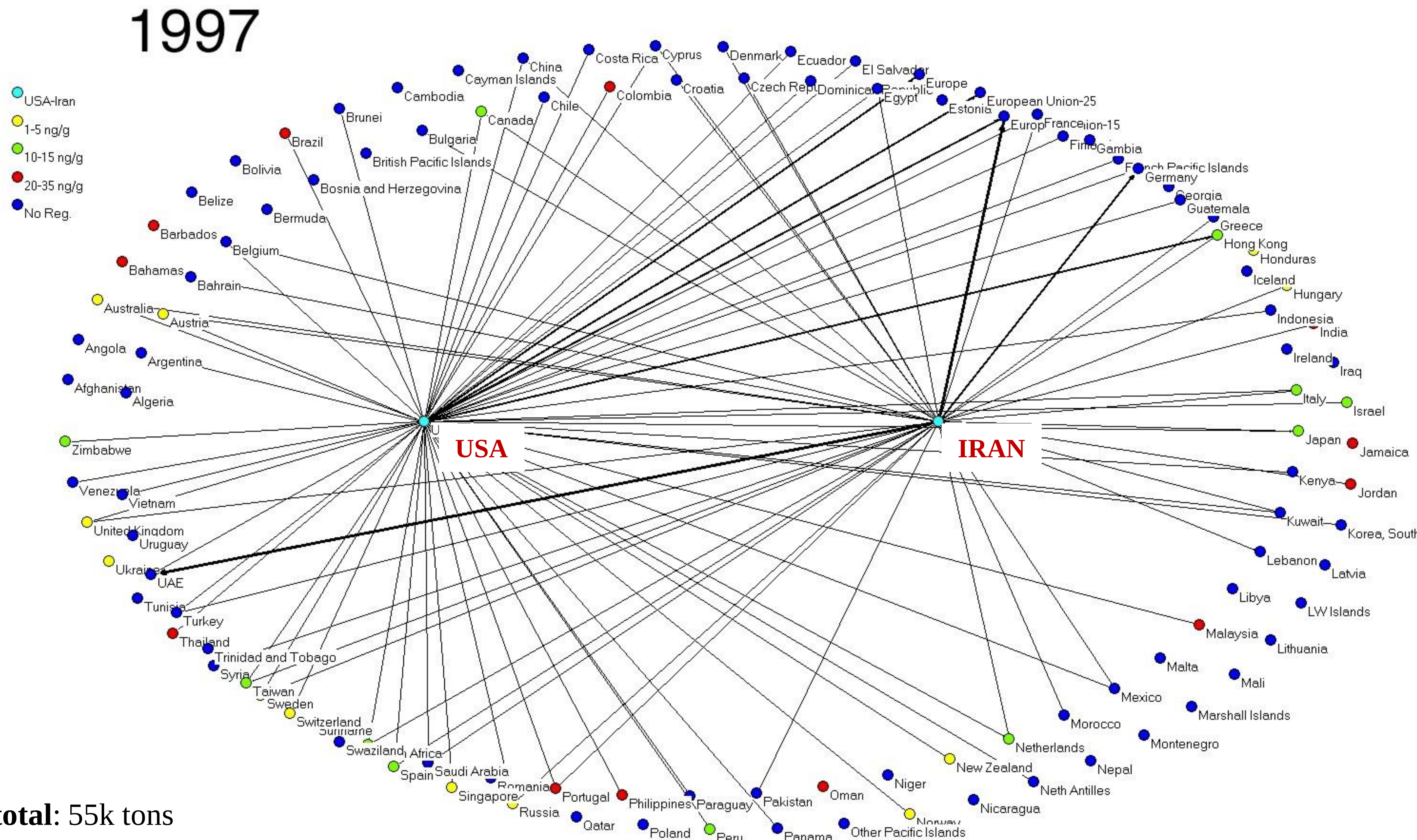
In 1996, Iran was major pistachio exporter to EU & worldwide



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

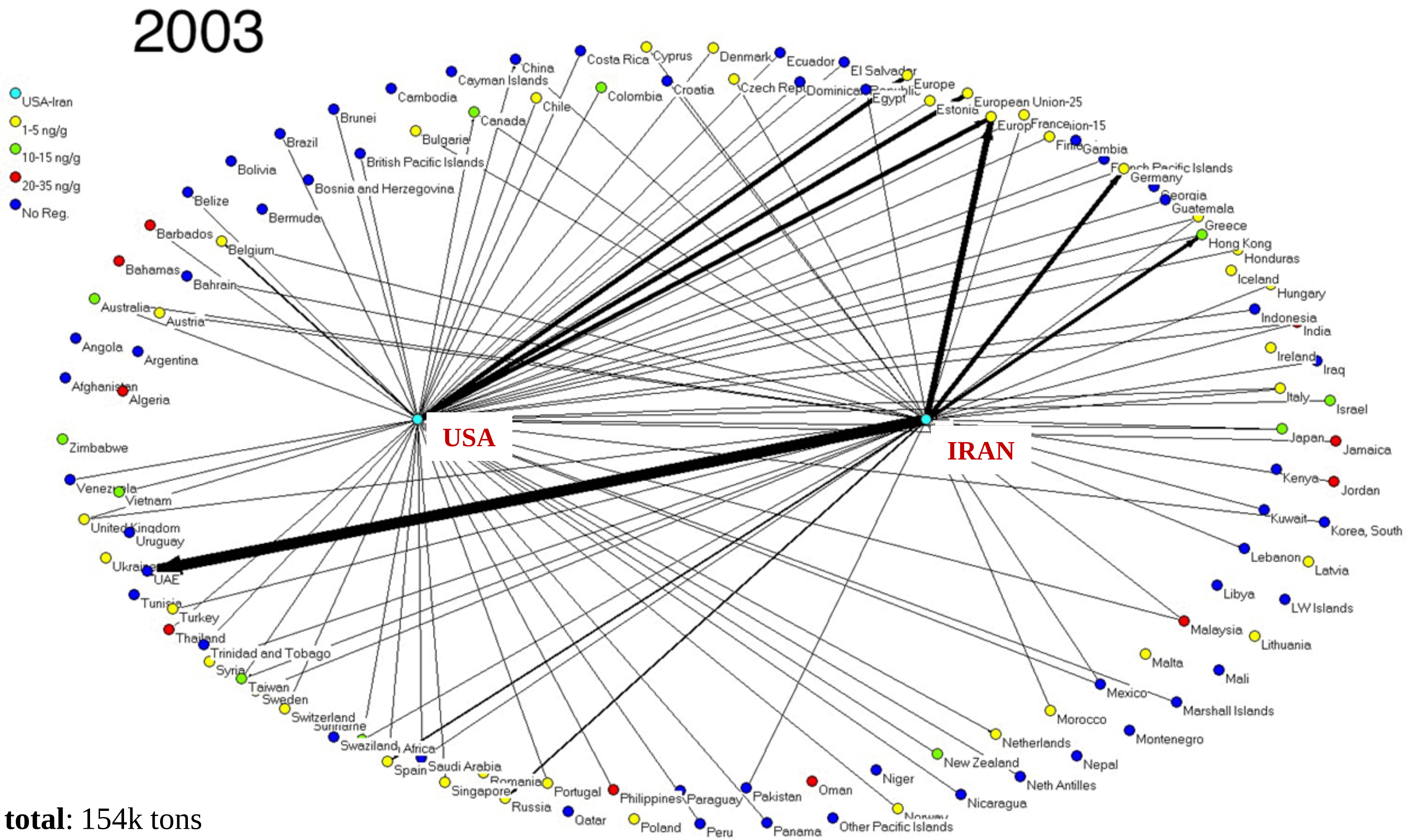
Iran: No reg. for pistachios
US: 15 ng/g

… Next year, high aflatoxin levels (up to **400 ng/g**) drove Iranian exports to EU down dramatically



Iran total: 55k tons
US total: 26k tons
Iran-EU: 17k tons
US-EU: 8700 tons

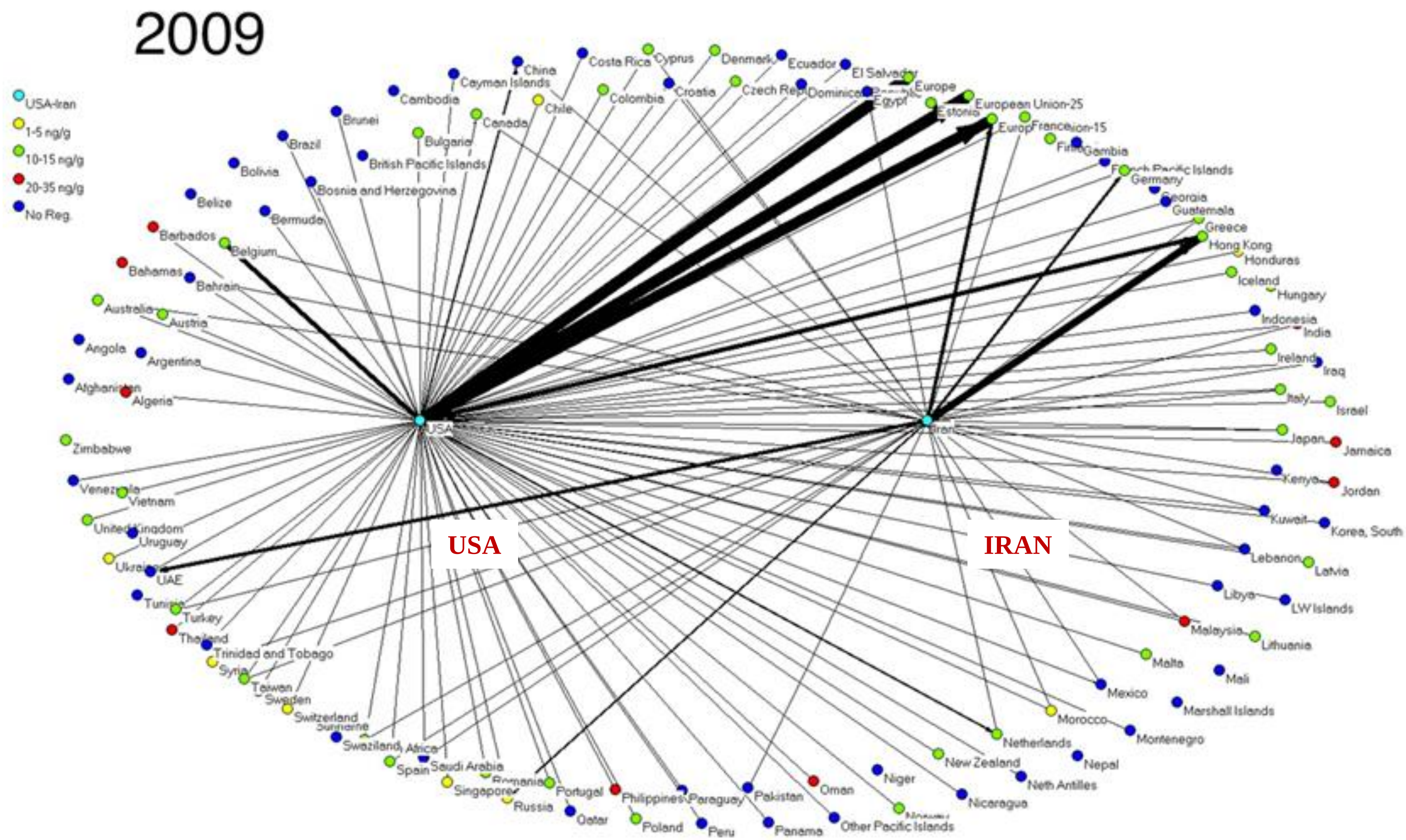
In 2003, US started exporting large amounts of pistachios to EU; Iran shifted markets



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

Conclusions from network models of world food trade

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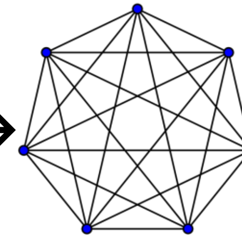


- When nation sets food safety standard, ripple effects all over world (*disturbing one part of web*)
- Aflatoxin regulations associated with global food trade patterns
- Nations trade more food with other nations that have identical or similar AF standards
- Nations with relaxed standards import more aflatoxin-laden food
- 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

In US, mycotoxin losses are primarily ECONOMIC, to growers:

Estimated economic losses due to aflatoxin in corn, millions USD

($52 million to $1.06 billion per year)

US Region	Aflatoxin					
	2011		2012		2013	
	low range	high range	low range	high range	low range	high range
Upper Midwest	--	--	40.4	445.4	--	--
Ohio Valley	30.3	423.9	170.1	454.1	18.1	484.1
South/Southeast/Southwest	258.4	377.9	47.2	162.8	34.0	202.8
Total US losses	**288.7**	**801.8**	**257.7**	**1062.3**	**52.1**	**686.9**

OC curve based losses:

$$\mathbf{L_i=[(B_i \times R_k) * (1-P_k) * D_k]}$$

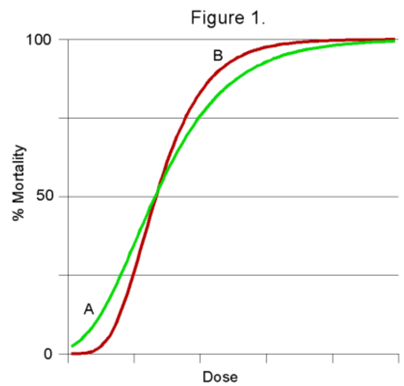
Where:

- L is the total loss in USD;
- B is the # of bushels of corn harvested;
- R is the ratio of corn within a specified FDA regulatory range;
- P is the probability of acceptance based on the OC curve;
- D is the discounted amount in USD;
- i is the state of interest;
- k is the FDA regulatory range of interest.

Mitchell NJ, Bowers E, Hurburgh C, Wu F (2016). *Food Addit. Contam*. 33: 540-50.

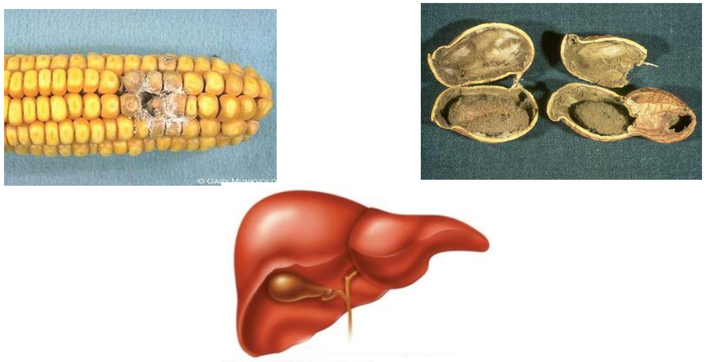
Meanwhile, what are the health impacts of aflatoxin exposure worldwide today?

- **<u>Dose-response assessment</u>**

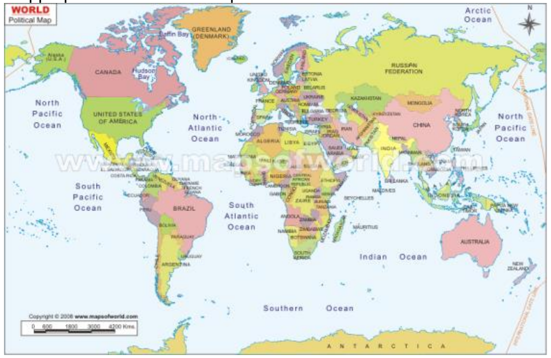


  – Slope of curve = cancer "potency"
    - Aflatoxin → HCC: **0.01** cases / 100,000 / yr / ng/kg bw/day
    - Aflatoxin+HBV → HCC: **0.30** cases / 100,000 / yr / ng/kg bw/day (JECFA 1998)

- **<u>Exposure assessment</u>**



- 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

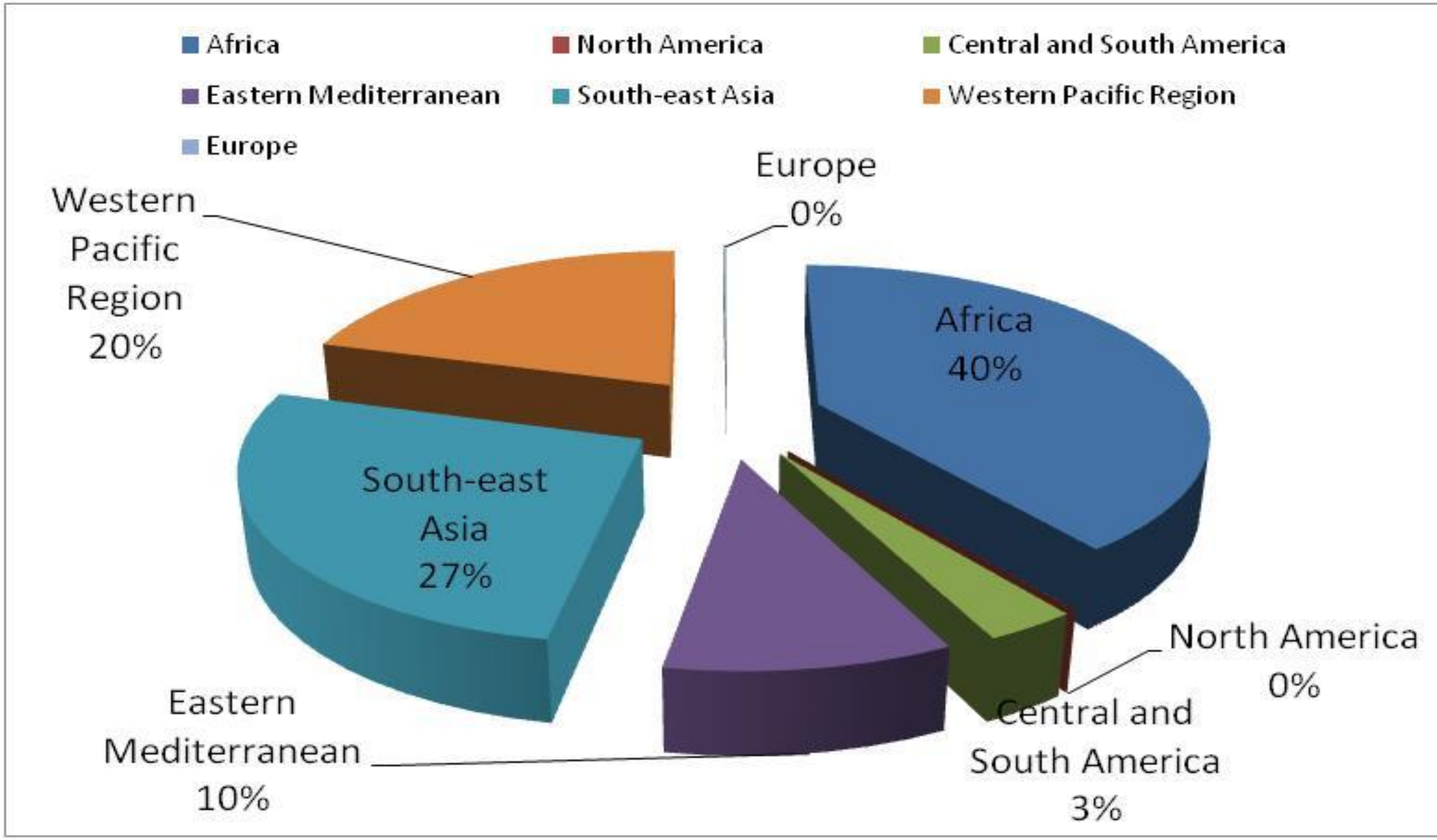
- Global population cancer risk = $\Sigma_{\text{(all nations)}}$ ([Population$_{HBV+}$ /100,000 * Potency$_{HBV+}$ * Average aflatoxin intake] + [Population$_{HBV-}$ /100,000 * Potency$_{HBV-}$ * Average aflatoxin intake])
  - Potency$_{HBV+}$ = 0.30 cases per 100,000/yr per ng/kg bw/day
  - Potency$_{HBV-}$ = 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

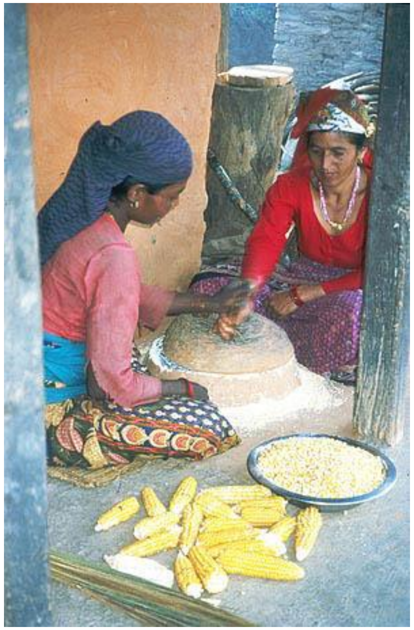
~5-28% of all liver cancer cases



Liu Y, Wu F. (2010). "Global Burden of Aflatoxin-Induced Hepatocellular Carcinoma: A Risk Assessment." *Environmental Health Perspectives* 118:818-824.

Agricultural interventions to reduce aflatoxin and other mycotoxins

- Preharvest
  - Genetically enhancing plants' resistance to drought, heat, or insects (conventional, transgenic, RNAi, CRISPR)
  - Good agricultural practices
  - Biocontrol
  - Chemicals (fungicides, plant volatiles, antioxidants)



- Postharvest
  - Sorting
  - Improved drying
  - Improved food storage
  - Storing foods for shorter period of time before use

Dietary & clinical interventions
("Eat your greens, garlic, or ground")

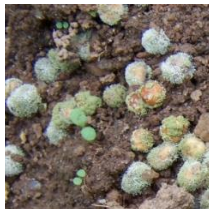
- Agents that bind aflatoxin in gut
  - Clays, chlorophyllin in leafy greens
- Competitive inhibitors: curcumin
- Phase 2 enzyme inducers
  - E.g., sulforaphane from cruciferous vegs, allicin from *Allium* vegs, triterpenoids
- Inflammation reducers
  - E.g., green tea polyphenols
- Increasing dietary diversity (switch to foods with lower aflatoxin levels)
- Hepatitis B vaccine





Khlangwiset P, Wu F (2010). "Costs and efficacy of public health interventions to reduce aflatoxin-induced human disease." *Food Addit Contam* 27:998-1014.

Feasibility: Is this intervention possible & sustainable where it is needed?



Government regulations & capacity

Characteristics of intervention (standardizability, safety, etc.)

How technically feasible is intervention?

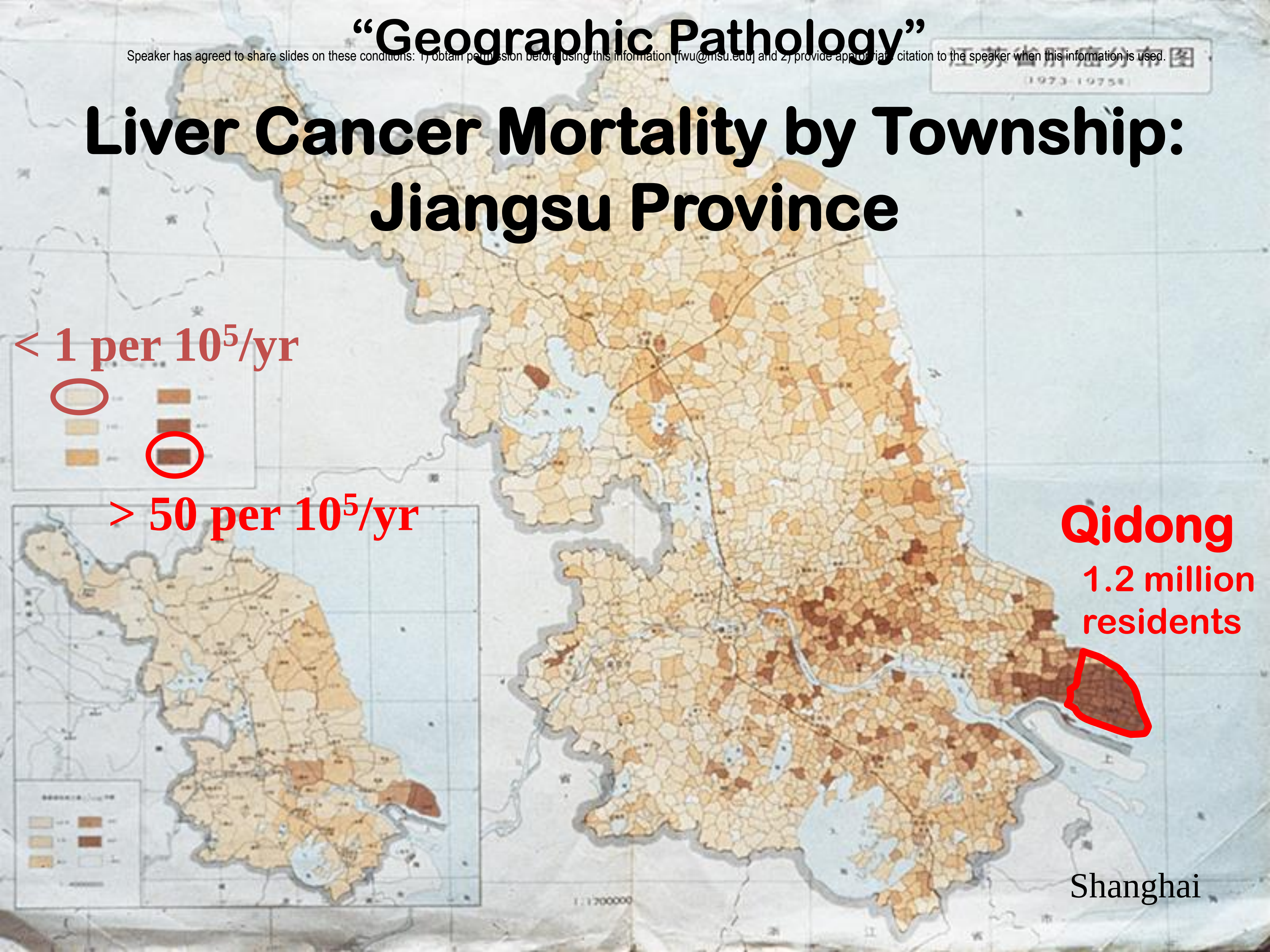
Usage Characteristics (ease, safety, # people)

Infrastructure & delivery characteristics

Wu F, Khlangwiset P (2010). "Evaluating the technical feasibility of aflatoxin risk reduction strategies in Africa." *Food Addit Contam* 27:658-676.

“Geographic Pathology”

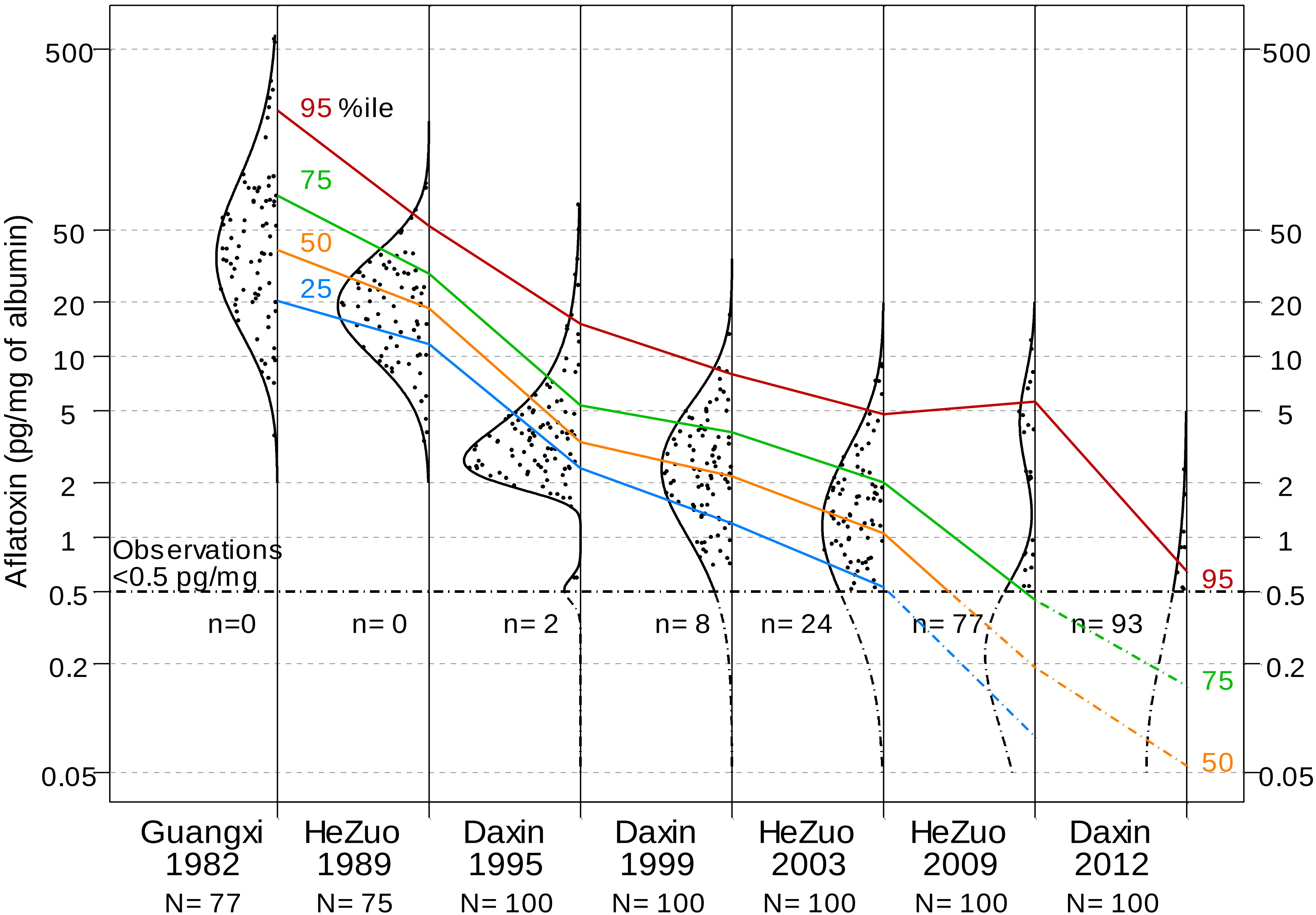
Liver Cancer Mortality by Township: Jiangsu Province



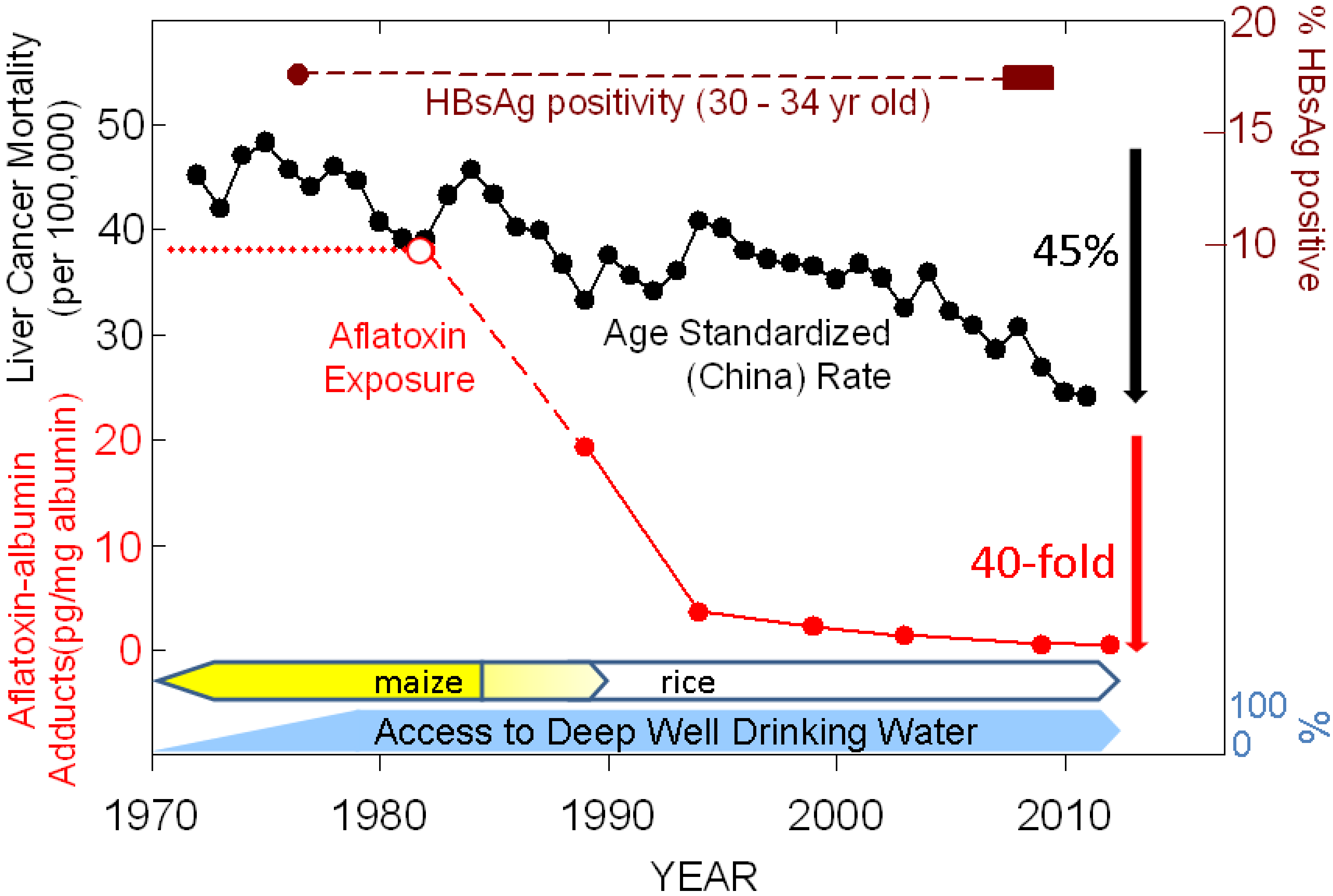
Why was liver cancer so high, and what happened in Qidong since 1980?

- 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 corn/yr infected with *Aspergillus flavus*
  - **HIGH AFLATOXIN EXPOSURE**: some years, 99% corn > 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 corn
  - 2012: hardly any corn 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 elsewhere?

- Instead of only focusing on how to reduce aflatoxin in corn & peanuts, consider increasing dietary variety or switching staple crops altogether
- E.g., 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*

Wu et al. (2014). Reduced foodborne toxin exposure is a secondary benefit of dietary diversity. *Toxicological Sciences* 141:329-34.

Summary

- Mycotoxins from fungi in crops pose serious human health & economic risks
- Aflatoxin & its standards worldwide have caused unintended trade-related risks
- Agricultural, dietary, & clinical interventions can reduce mycotoxin risks
- Switching dietary staples or increasing dietary diversity can also curb harmful effects of mycotoxins

Thank you!
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