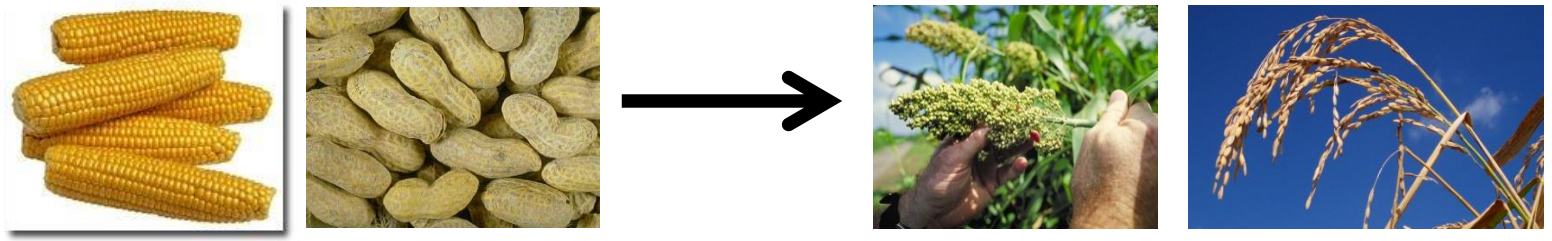
Aflatoxin as a Global Food Safety Problem:
Health Effects, Market Impacts, Interventions



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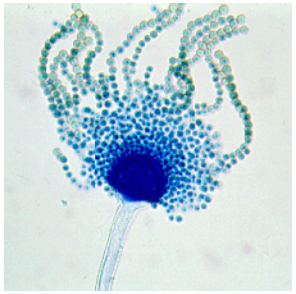
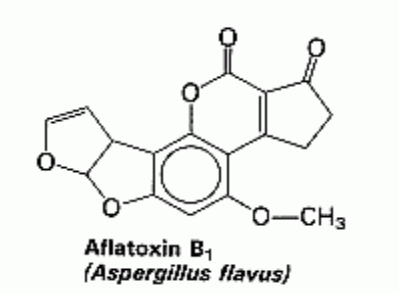
Outline

- 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



Aflatoxin B_1
(Aspergillus flavus)

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
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 (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

  - Wu F (2004). Mycotoxin Risk Assessment for the Purpose of Setting International Regulatory Standards. *ES&T* 38:4049-55.

Conversely: who experiences health benefits of stricter aflatoxin standards?

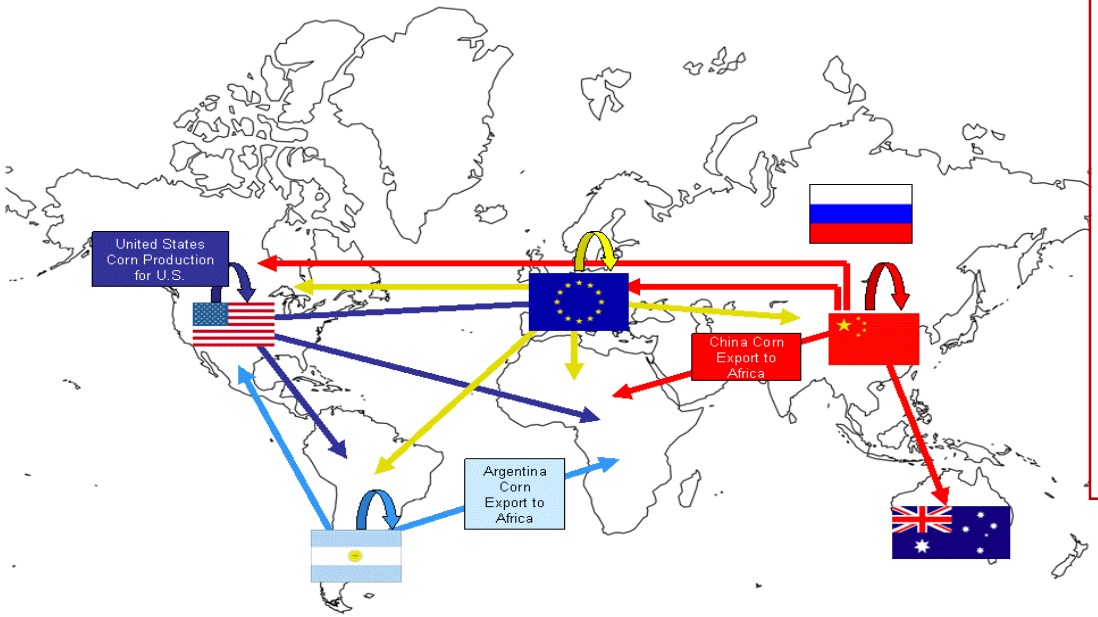
- JECFA (FAO/WHO) 1998: health effects of tightening global aflatoxin standard from 20 to 10 μg/kg
  - Where 25% population has HBV, tighter standard reduces liver cancer by 300 cases per year per billion persons
  - Where 1% population has HBV, tighter standard reduces liver cancer by 2 cases per year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

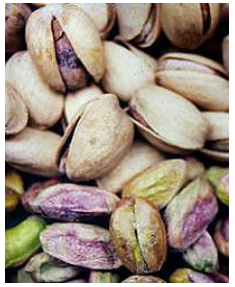
Impact of aflatoxin regulations on world food trade: Insights from network models

- **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

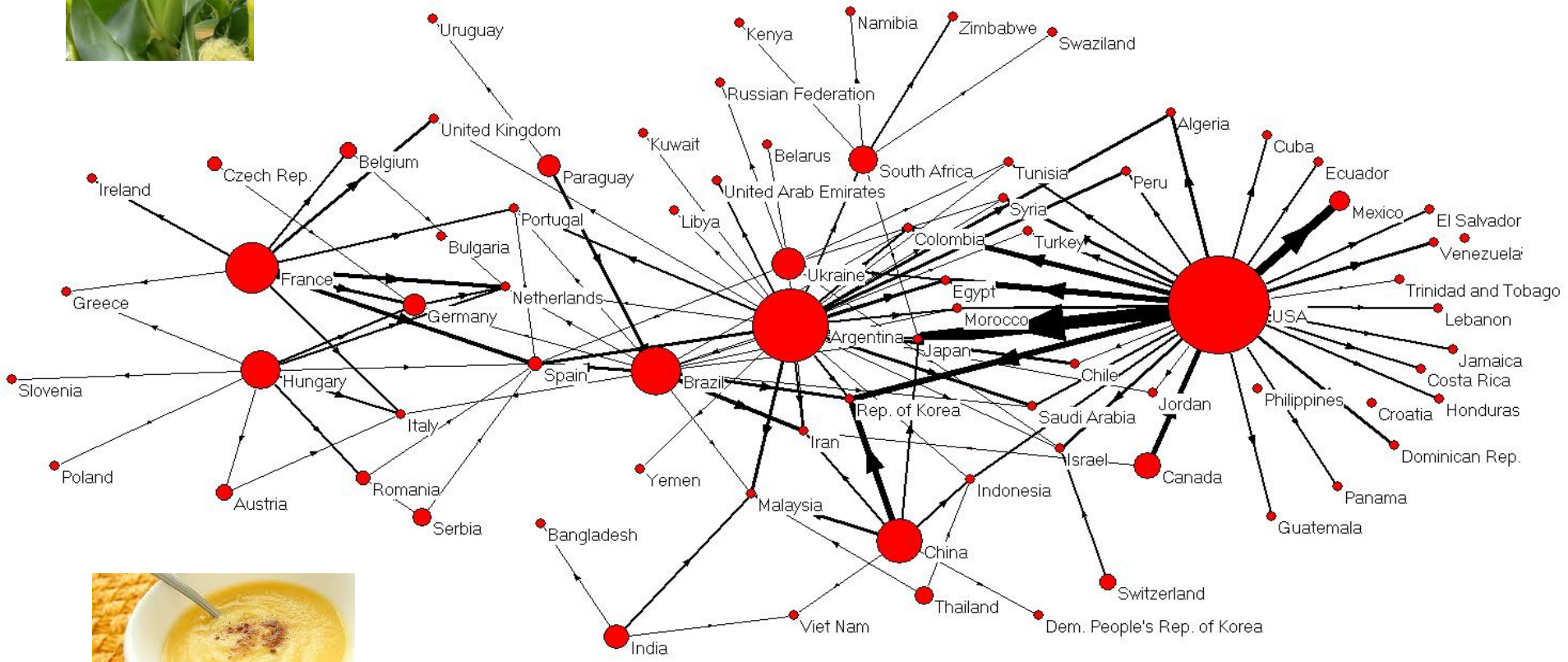


- Collected global maize & pistachio trade data
  - Maize: 2000-2009
  - Pistachios: 1996-2010
- Developed global network models for trade for each year
- Determined impact of aflatoxin regulations on trade patterns

- *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



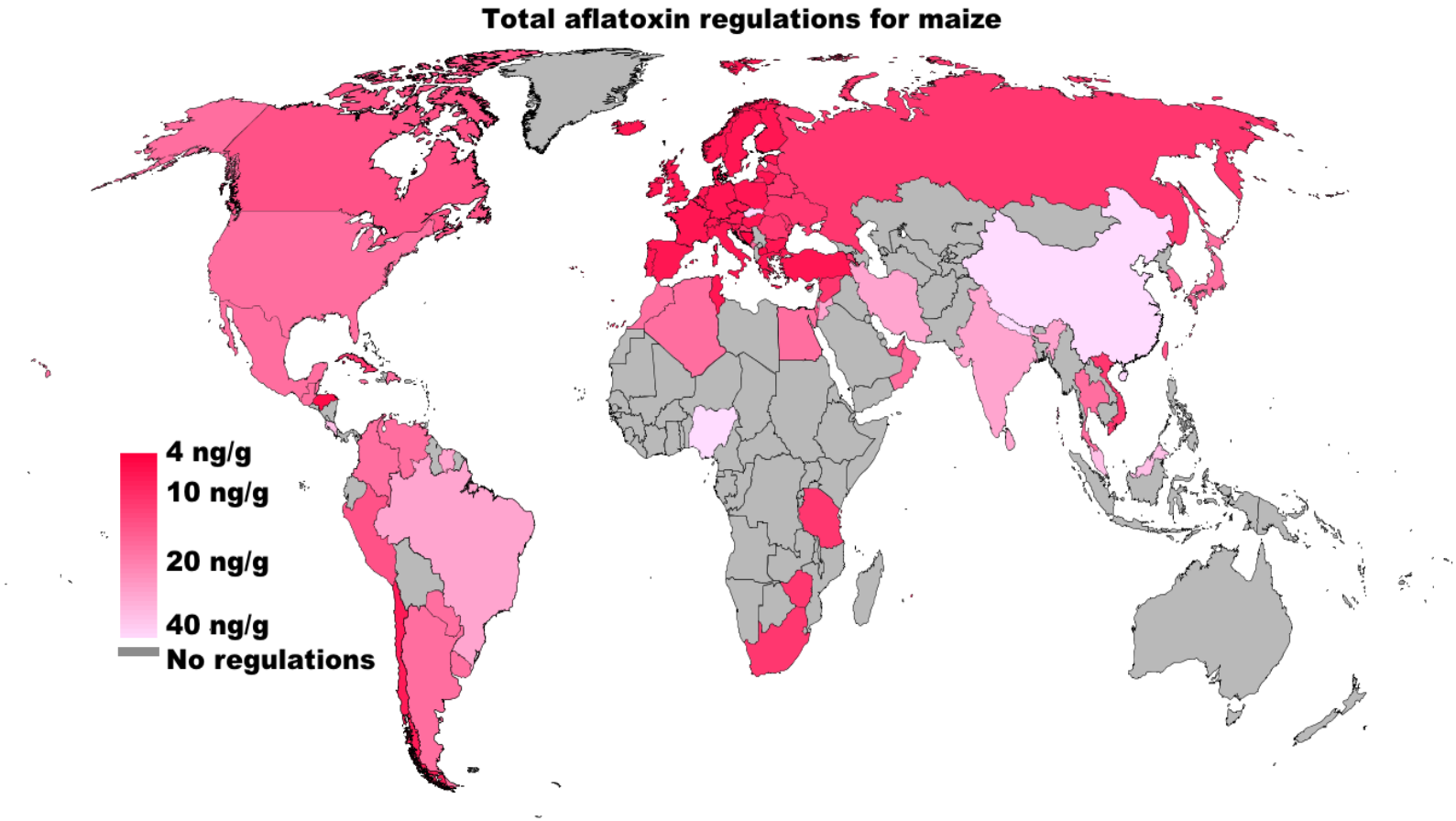
Wu F, Guclu H (2013). Global maize trade and food security: Implications from a social network model. *Risk Analysis* 33:2168-78.

Vulnerabilities revealed in global maize trade

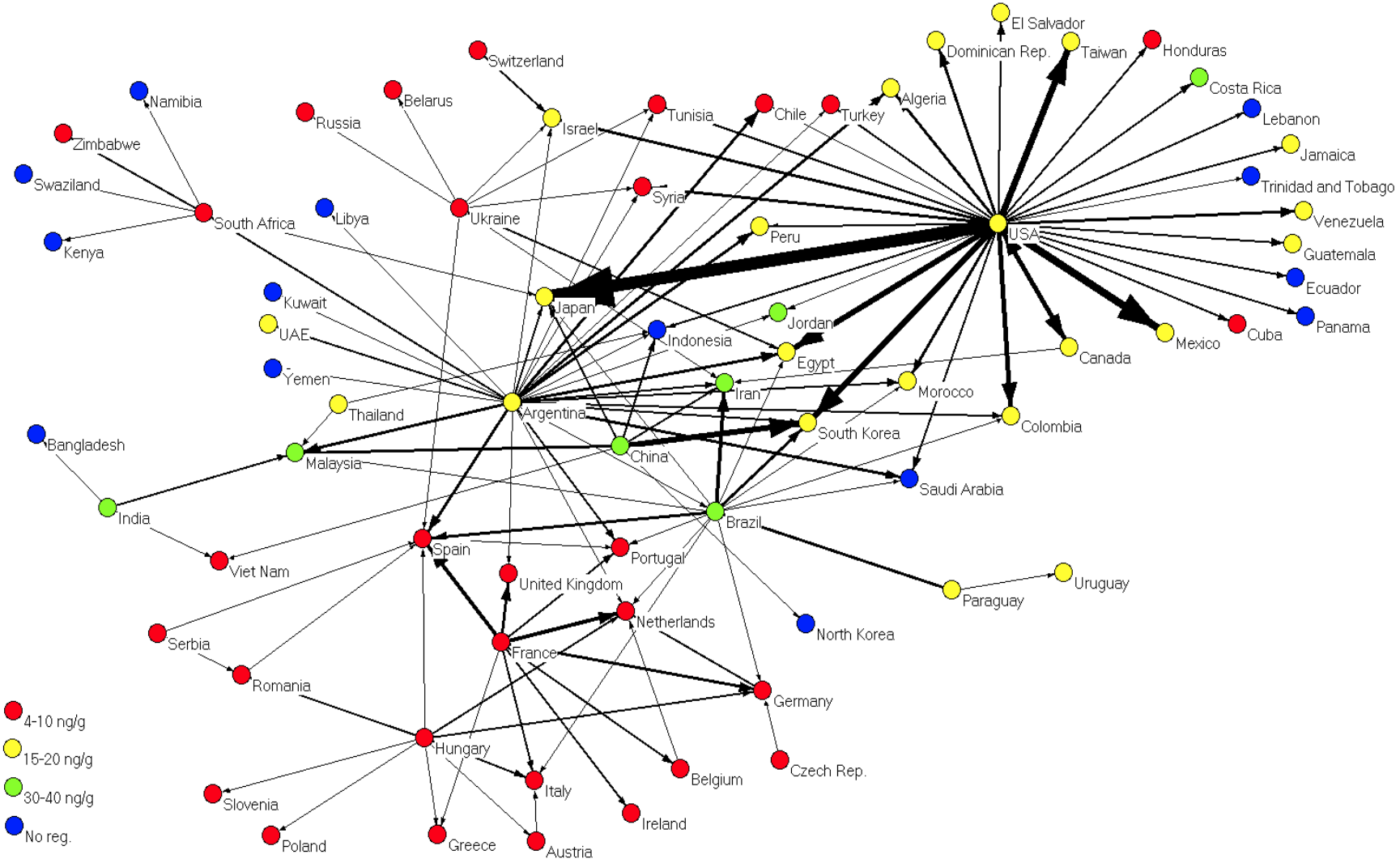
- US at center of star-shaped cluster
  - Nations with high maize consumption that import exclusively from US are vulnerable to US supply changes
  - Drought, plant disease may reduce supply
  - **US maize ethanol production**: in 2007, riots in 22 nations

- 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

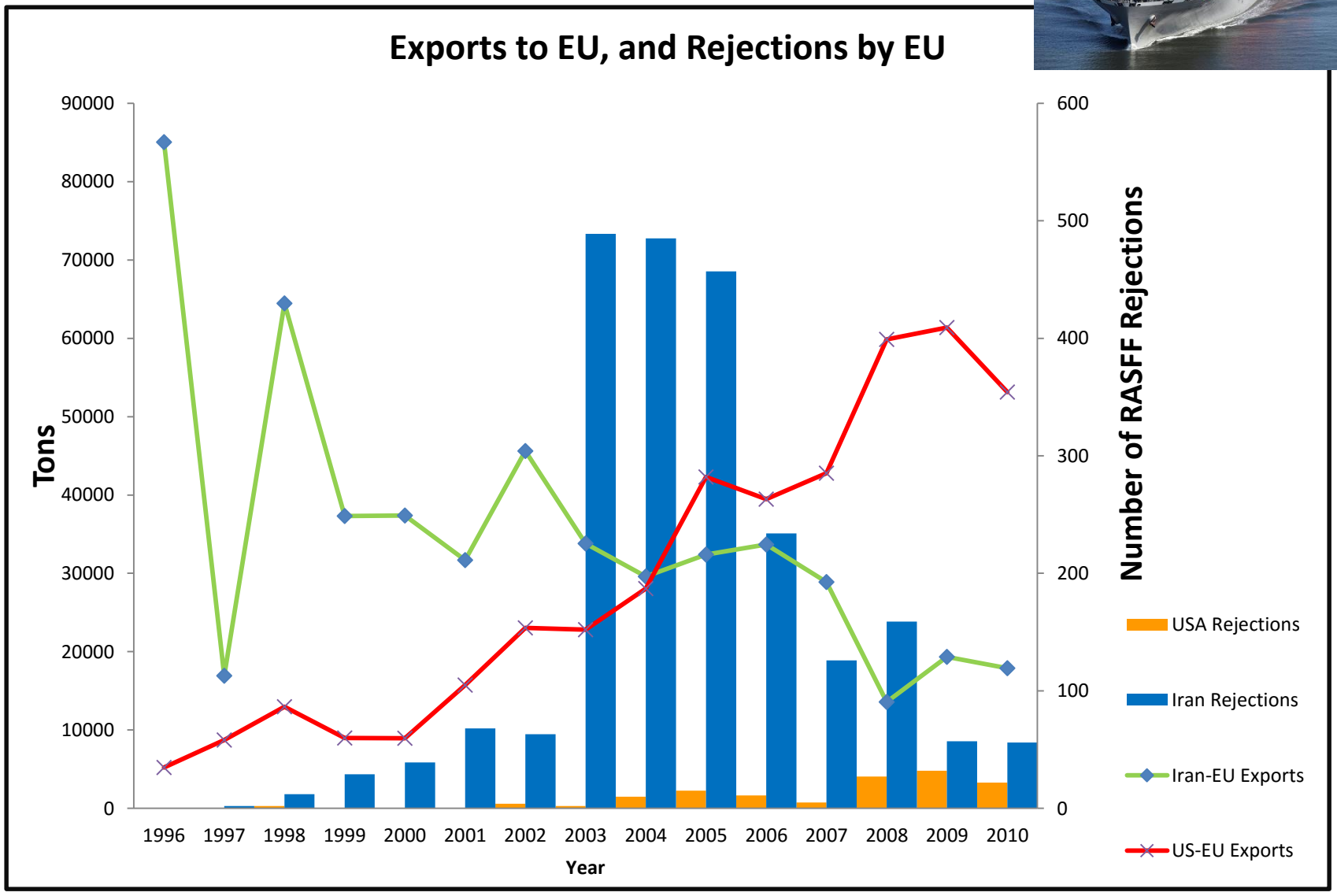
Rank	Top pairs & their total aflatoxin (AF) standards in µg/kg maize				Total amount (MT)
	Exporter	AF standard	Importer	AF standard	
1	USA	20	Japan	20	159,377,000
2	USA	20	Mexico	20	69,764,700
3	USA	20	Taiwan	15	44,212,000
4	USA	20	Korea	20	41,657,300
5	China	20	Korea	20	36,446,400
6	USA	20	Egypt	20	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?

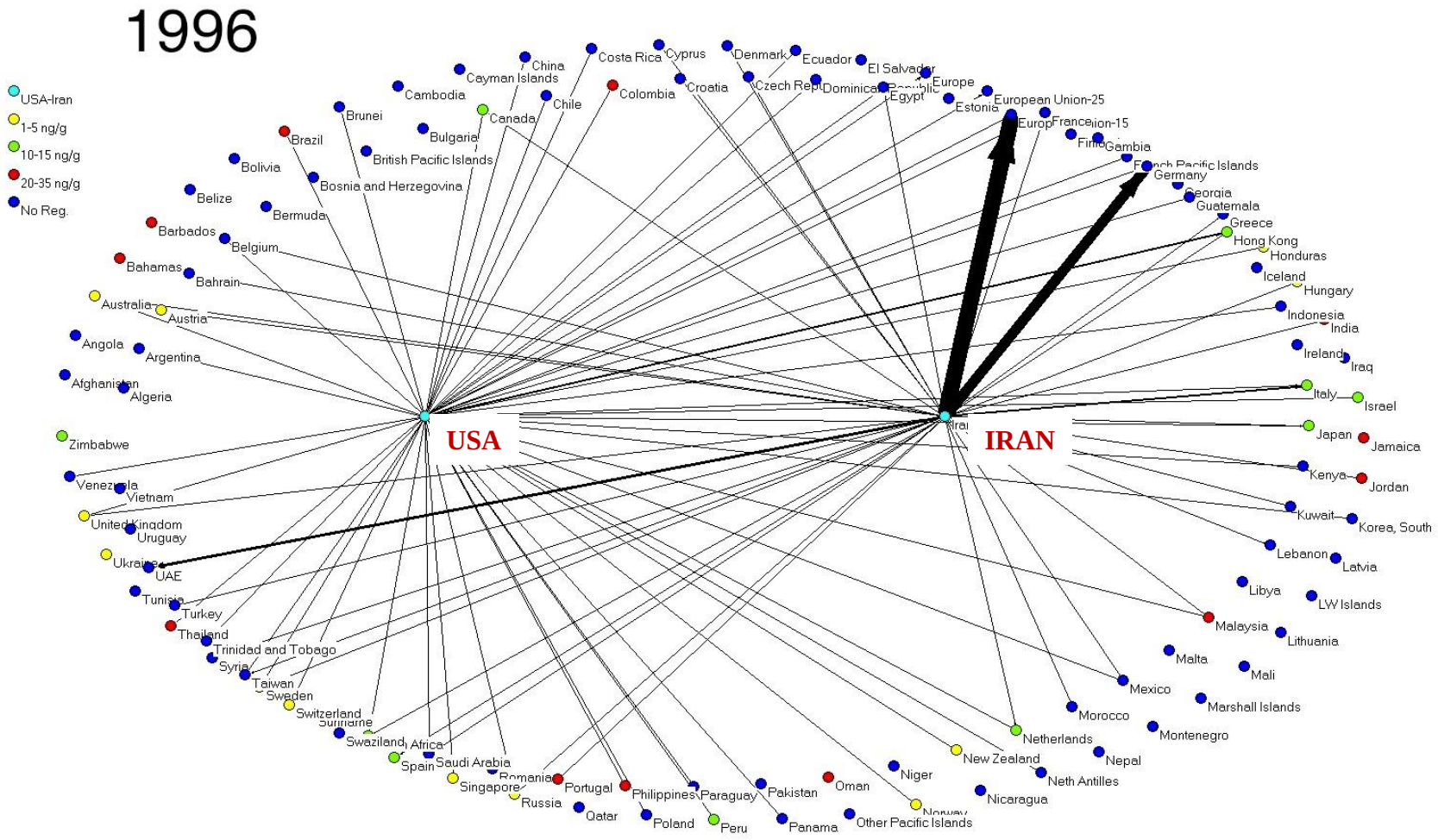
- Global pistachio market dominated by Iran and US
  - Iran (50%)
  - US (25%)
- Pistachios commonly contaminated with aflatoxin
  - Pistachios contribute **7-45% of aflatoxin** in human diets
  - Aflatoxin levels in Iranian pistachios: avg **54 ng/g** (JECFA 2007)
  - Aflatoxin levels in US pistachios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



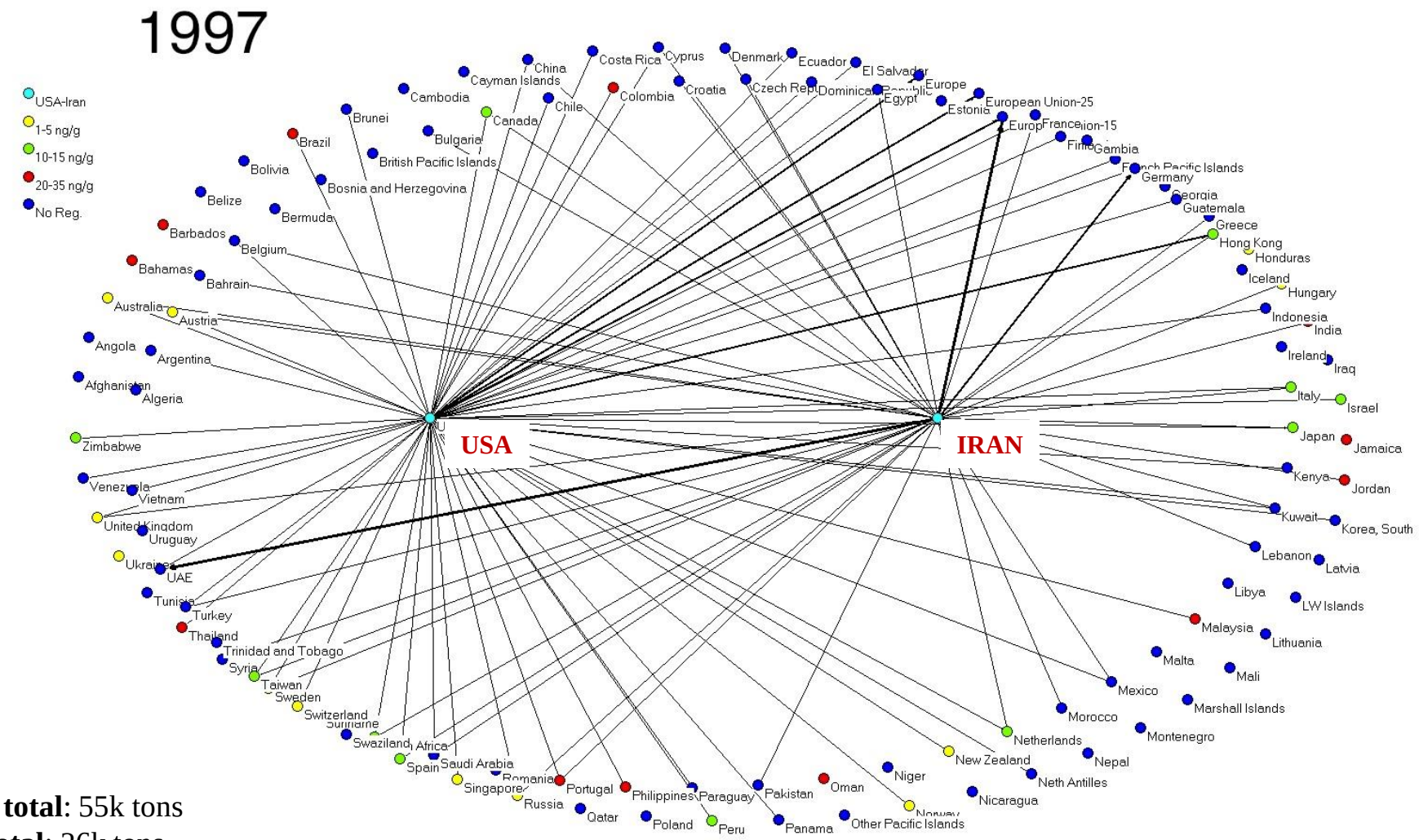
In 1996, Iran was major pistachio exporter to EU & worldwide



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

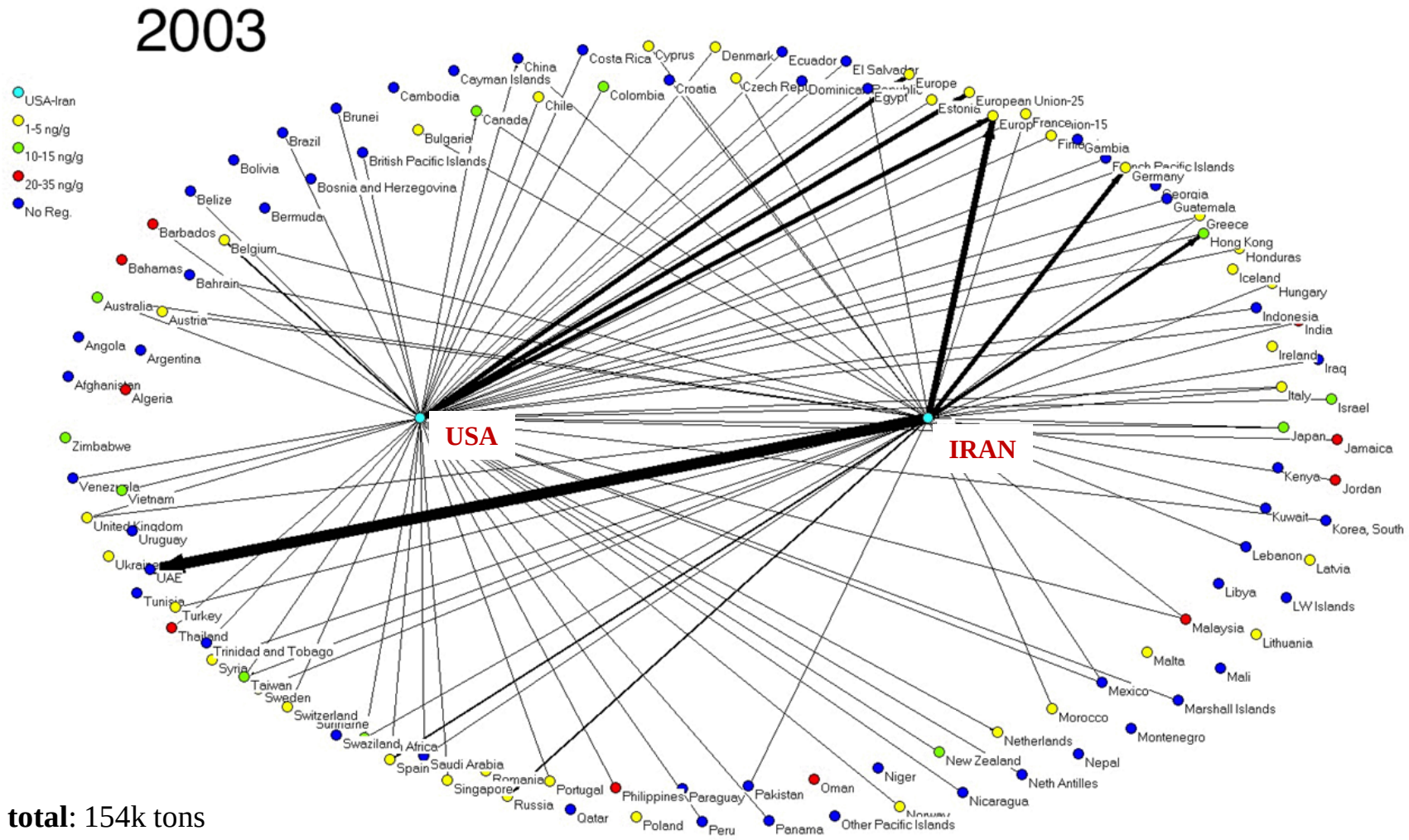
Iran: No reg. for pistachios
US: 15 ng/g

… 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

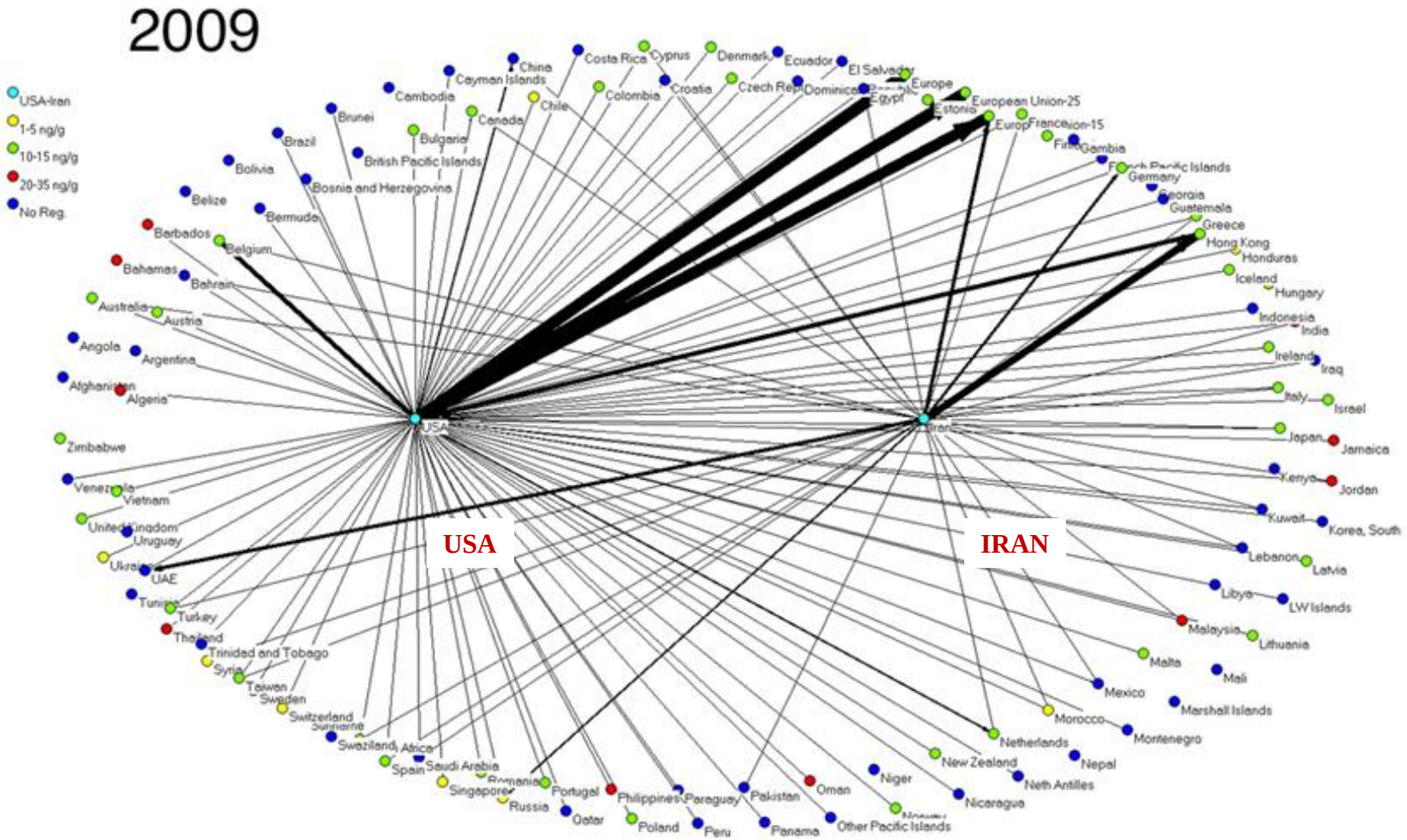
In 2003, US started exporting large amounts of pistachios to EU; Iran shifted markets



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

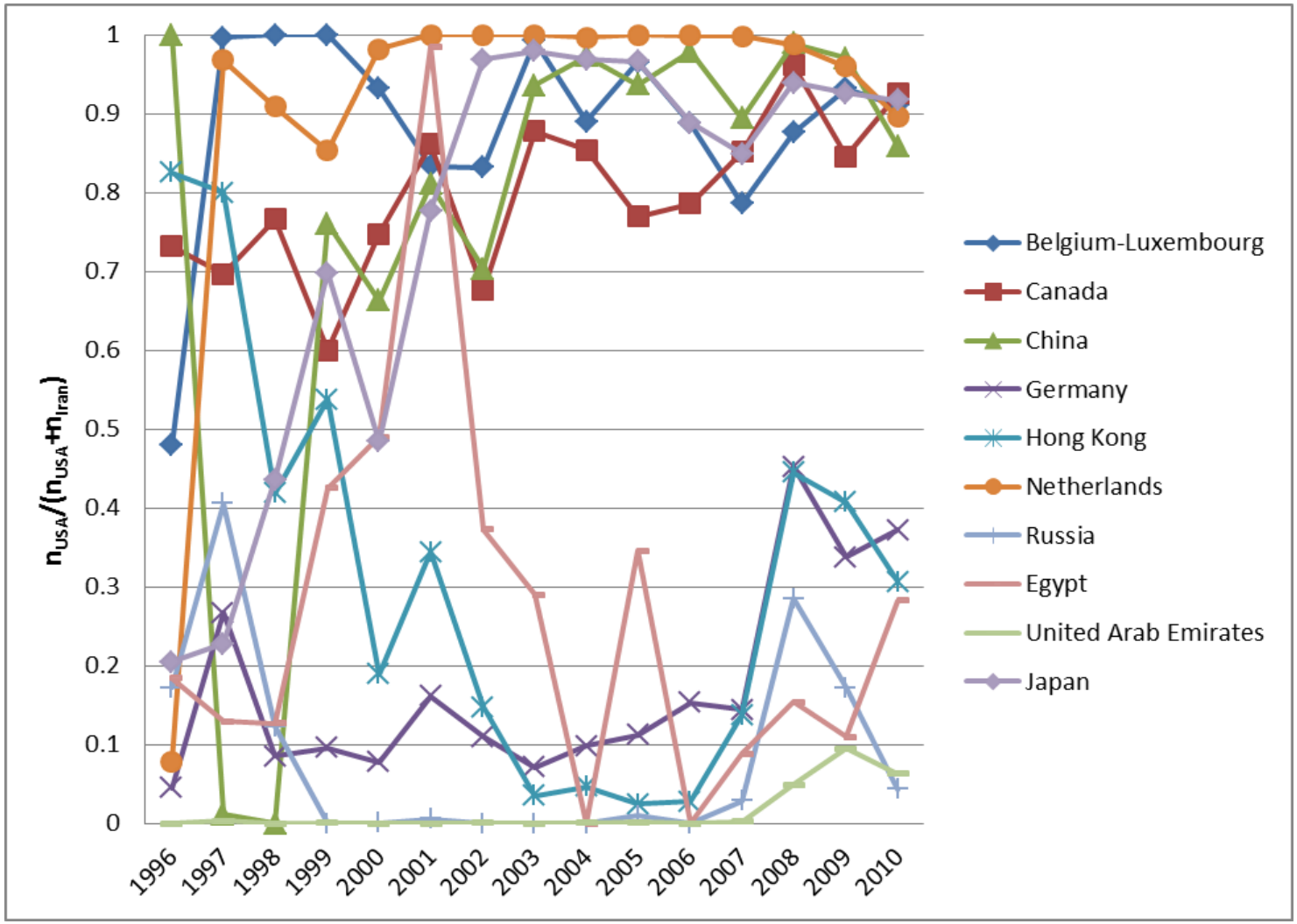
Iran Reg: 15 ng/g
EU: 4 ng/g

Recently, US became main pistachio exporter to EU

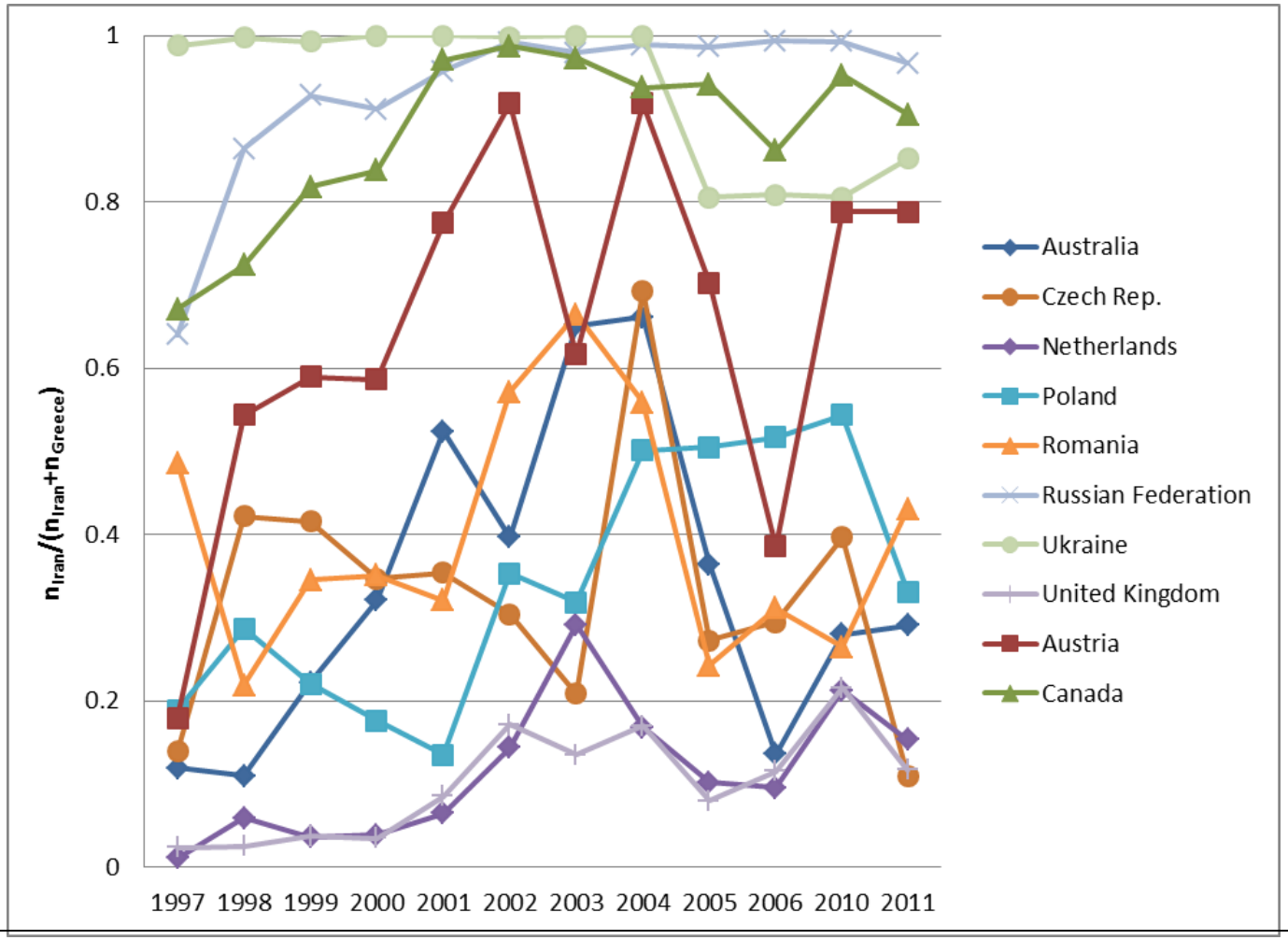


Iran total: 116k tons
US total: 129k tons
Iran-EU: 19k tons
US-EU: 63k tons

US vs. Iran Pistachio Export Share: Clear evidence of market segregation

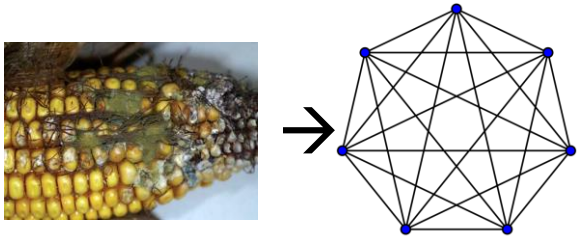


Iran vs. Greece Export Share – Grape Control Crop: No evidence of market segregation



Bui-Klimke TR, Guclu H, Kensler TW, Yuan J-M, Wu F (2014). Aflatoxin Regulations and Global Pistachio Trade: Insights from a Social Network Analysis. *PLOS ONE* 9(3):e92149

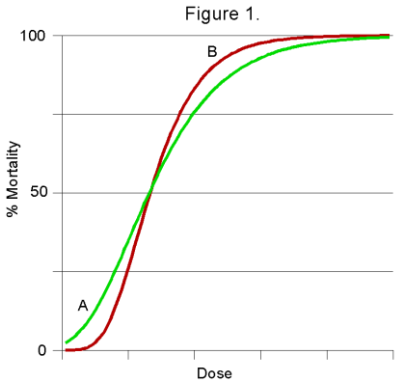
Conclusions from network models of world food trade



- 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

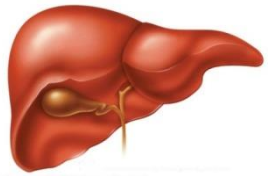
Meanwhile, what are the health impacts of aflatoxin exposure worldwide today? Focus on liver cancer

- **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***

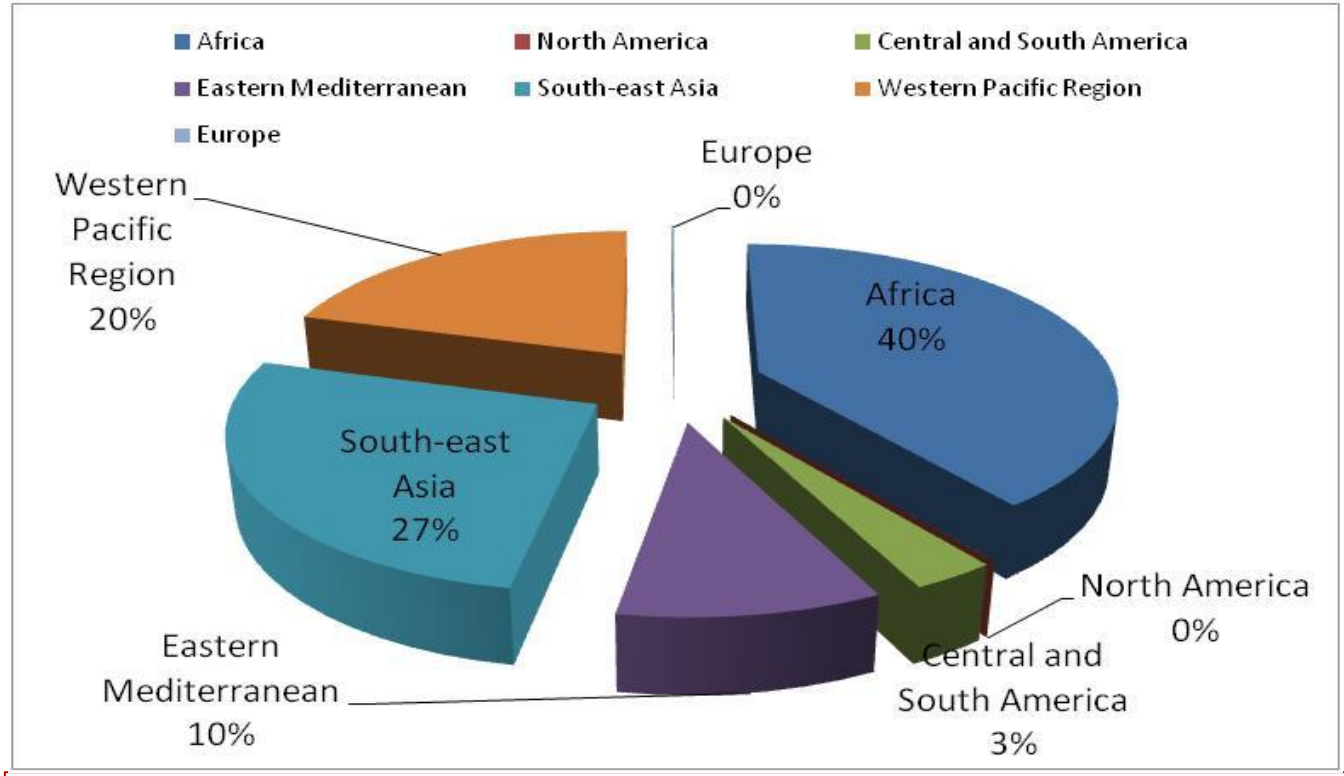
Risk characterization: Simplified model

- Global population cancer risk =
  $\Sigma_{(\text{all nations})}$
  ([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.

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

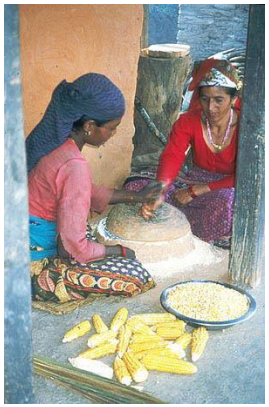
Don't increase cancer risk by >1/10,000 cases in population

- 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

Wu F, Stacy SL, Kensler TW. (2013). Global risk assessment of aflatoxins in maize and peanuts: Are regulatory standards adequately protective? *Tox Sci* 135:251-9.

Interventions to reduce aflatoxin risk

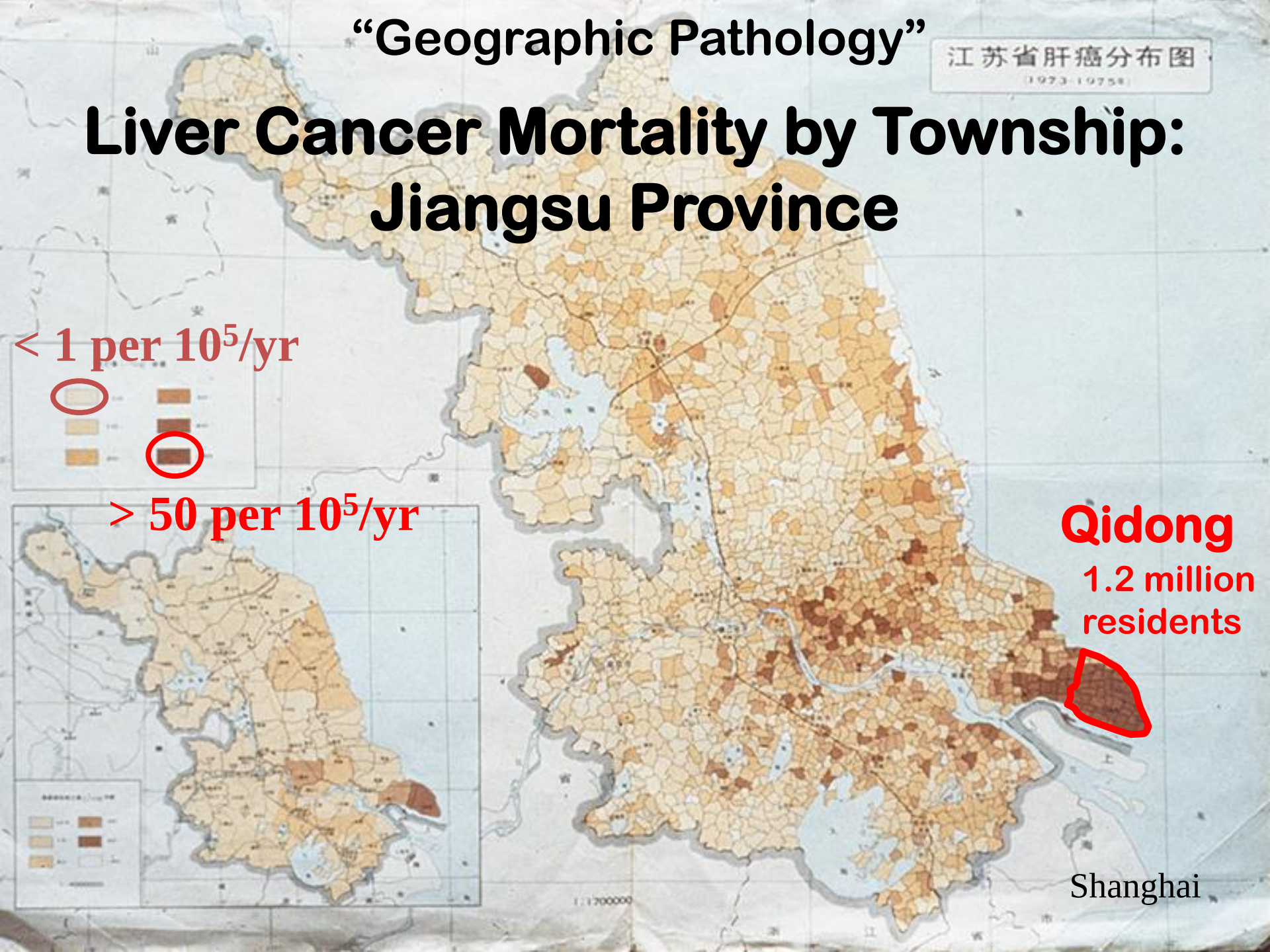
- Preharvest
  - Good agricultural practices
  - Genetically enhancing plants' resistance
  - Biocontrol
- Postharvest
  - Improved sorting, drying, food storage



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

"Geographic Pathology"

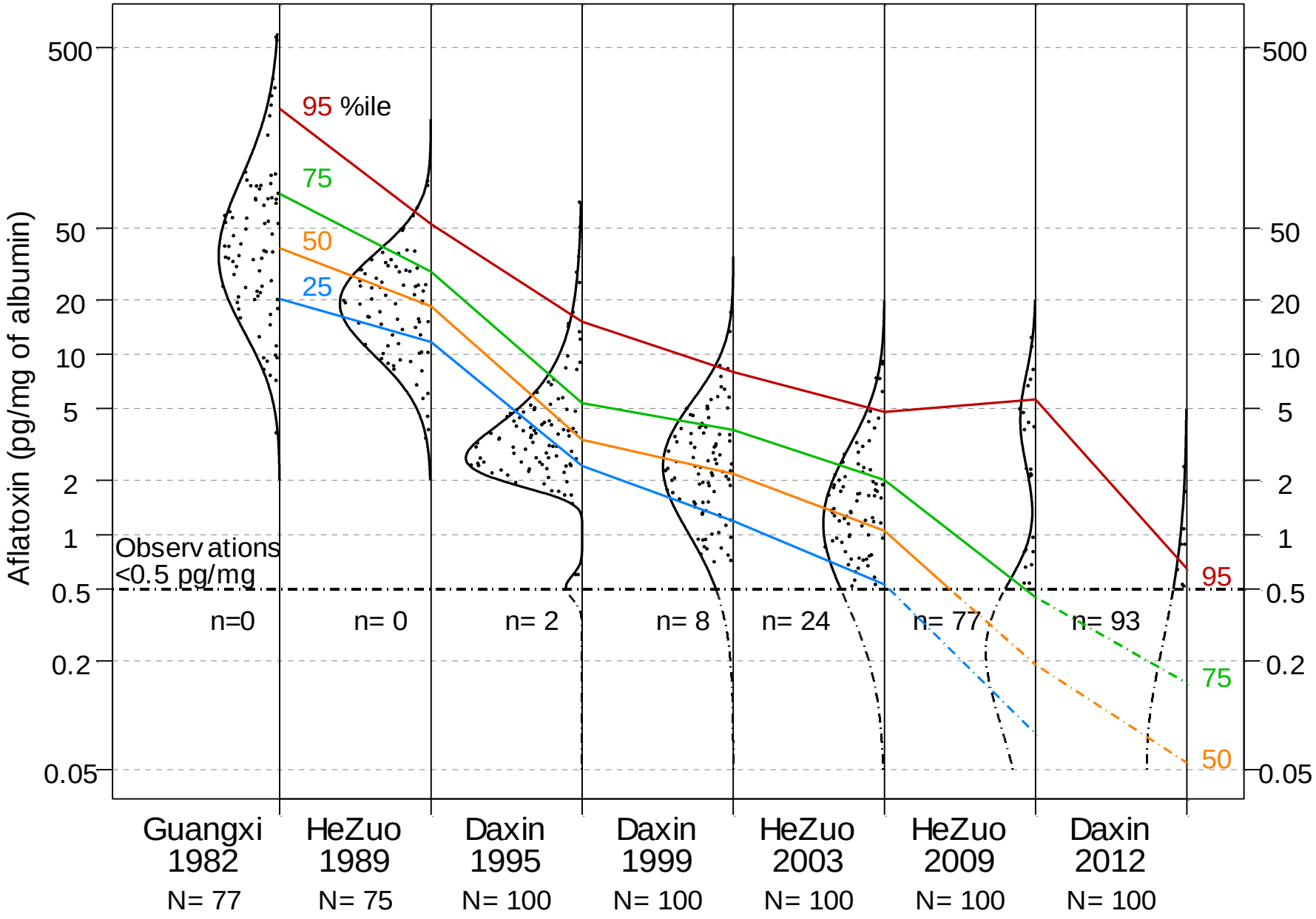
Liver Cancer Mortality by Township: Jiangsu Province



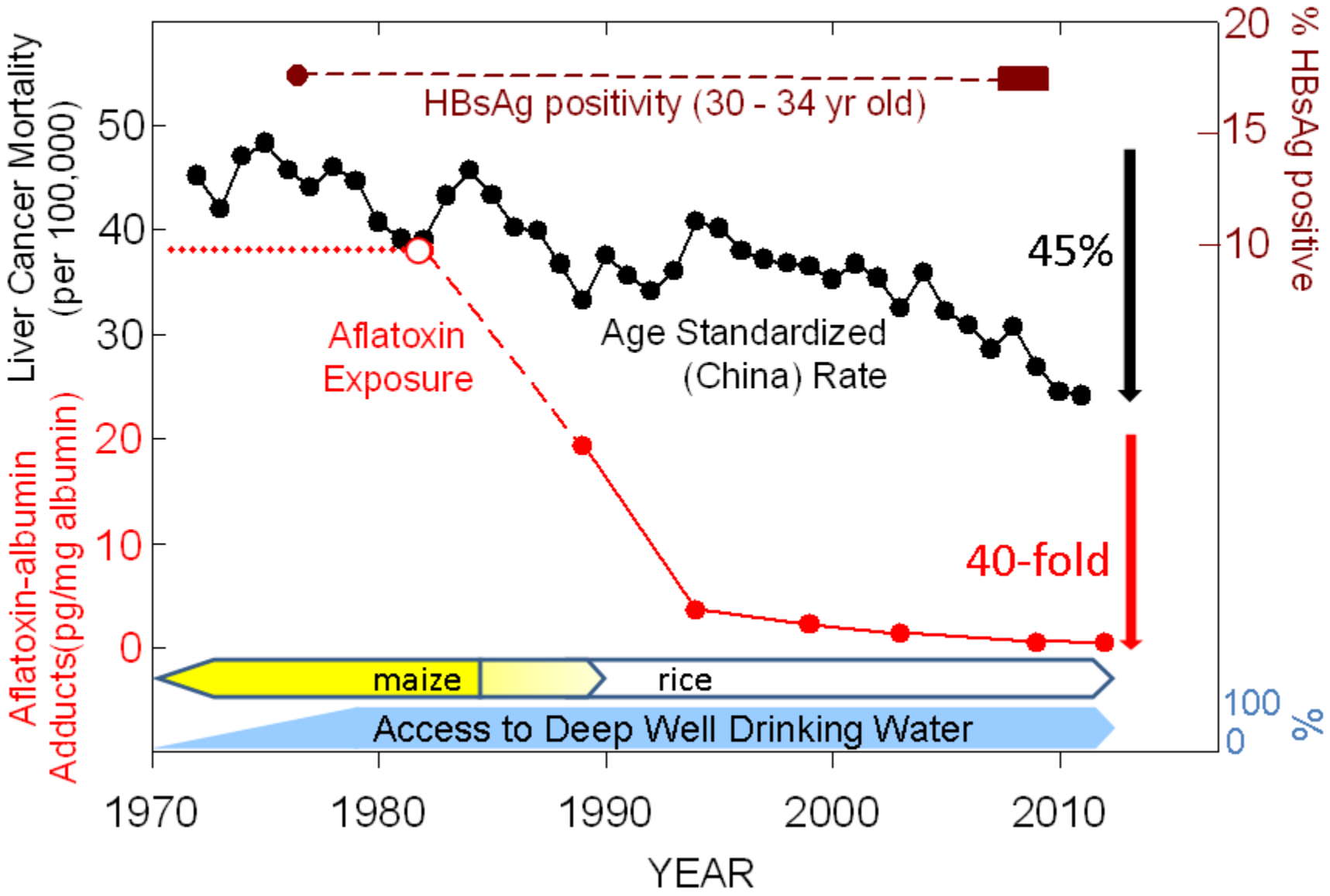
Why was liver cancer so high, and what happened in Qidong since 1980?

- 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 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

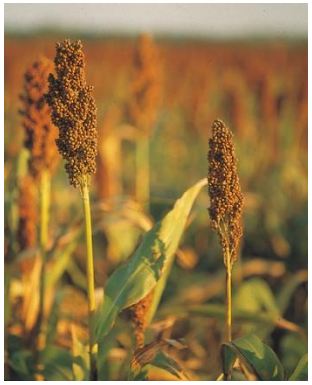


Reduced aflatoxin exposures, not HBV status, are associated with declining liver cancer mortality in Qidong (Chen et al. *CaPR* 2013).



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*

Wu F, Mitchell NJ, Male D, Kensler TW (2014). Reduced foodborne toxin exposure is a secondary benefit of dietary diversity. *Toxicological Sciences* 141:329-34.

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