G-LO-C-AL ONE HEALTH DIMENSIONS OF AFLATOXIN-FUMONISINS IMPACTS

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Background

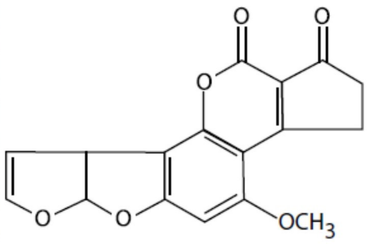
A group of surgeons (Partners for Surgery) working for more than 15 years in the Guatemalan highlands - mainly in the Department of Alta Verapaz - treating indigenous children with oral cleft, approached us – in efforts to identify measures for preventing the high incidence of such birth defects (Workshop, 2016). **We identified an overall high incidence of congenital anomalies; –potential causes included a largely monotonous diet, high in corn, a grain frequently contaminated with mycotoxins.** Aflatoxins and fumonisins are secondary fungal toxins (mycotoxins) in corn, and these may contaminate 25% of the world's food supply (Smith 2017). Aflatoxins and fumonisins are the related toxins. The National Cancer Institute is conducting research on hepato-carcinogenesis and aflatoxin exposure in these populations, but epidemiologic research has greatly ignored birth defects that demonstrated *in vivo* experiments (CODEX 2017). **Current standards do not fully consider the developing fetus, nor the vulnerable populations most exposed.** According to current estimates more than 2 billion people are highly exposed worldwide. We examine the complex plant / animal / human interrelations for the control of mycotoxin related risks, the influence of international trade regulations and the influence of global change.

Methods / Approach

A **systemic relational diagram** was developed.

- In collaboration with Universidad Rafael Landivar and Asocación Compañeros para Cirugía, we organized a workshop in Guatemala that included local and world experts on teratology, toxicology, environmental health, agronomy, and community health (Workshop 2016).
- We further embarked on a literature review complementing the discussions.
- We identified the human exposure paths related to the agro-processing conditions, local commercial practices and commercialization of imported products, as well as their geophysical-weather determinants.
- We identified the role of climate change patterns on the expansion of production of the toxins.
- We reviewed human and animal exposure patterns including the toxicological and epidemiologic risk assessments, mostly focusing on hepato-carcinogenesis and some data on neural tube defects, as well as the broad scope of mycotoxin related diseases.
- We considered the economic implications of the population effects.
- We examined the mechanisms for regulating trade of food products in the local and global markets.

Results



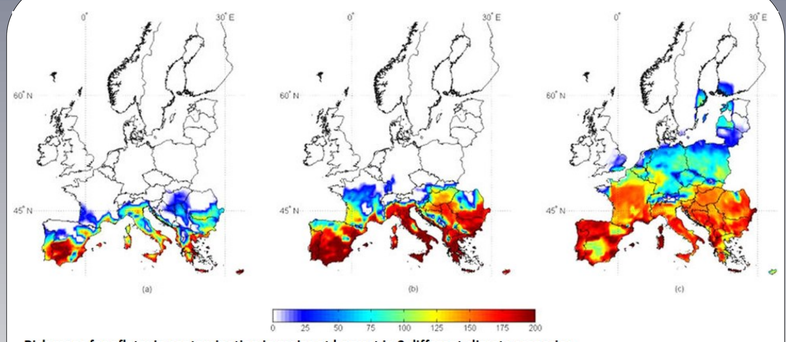
Aflatoxin B_1

Source: Mario Fuentes, in Workshop (2016) https://publichealth.gwu.edu/content/congenital-anomalies-guatemala-causes-and-actions

Agro-commercial and storage practices. The mycotoxin presence in corn, in other grains, and ground nuts is determined by farming, storage and processing practices.

- Corn is grown locally by traditional practices, manually managed and harvested.
- Complementary corn is bought in the market, frequently of low quality given the economic capacity of the population;
- Corn is imported from neighboring countries as part of a long chain of waste corn trade. Market surveys have shown that up to 37% are contaminated with mycotoxins.
- Corn is stored inside the homes, either under the roof, or in side storage areas, exposed to ambient heat and humidity (at 1300mts of altitude with average 22oC temperature and 80% relative humidity), all favorable to the growth in the plant and in storage of the *Aspergillus flavus*, the corn fungi, source of aflatoxins. Of the total samples of corn kernels, 67% have proven positive to aflatoxins in Alta Verapaz (Torres 2015)

Climate. Worldwide analyses reveal an expansion of the geographic areas where *Aspergillus flavus* is present in corn. European researchers have developed models examining water activity, temperature, pH, competition and nutrient availability to predict the expanded latitude of presence of the toxins due to climate change (Batillani 2016).



Risk maps for aflatoxin contamination in maize at harvest in 3 different climate scenarios, present, +2 °C, +5 °C. Mean daily data used as input result from 100-year run of the predictive model AFLAmaize in 2254 geo-referenced points throughout Europe, in the 3 scenarios. (Source, Batillani 2016)

Exposure. Human exposure is mainly through food, although a portion might be inhaled from dust inside homes. Humans can consume mycotoxin contaminated corn directly through corn prepared food, or through animals consumed mainly chickens (in the study region), or other animals such as pigs and cows. Aflatoxin is metabolized in the animals and may bioaccumulate and be present in animal food products such as meat, eggs, and milk and their products (Torres 2015).

- The mean consumption of corn from products other than tortillas was 145 g/d.
- Daily per-capita corn consumption in Guatemala was 318 g/d. Urban corn consumption was 102 g/d and rural corn consumption was 454 g/d.
- Riley (2015) showed an average 358 g/d (about 14 tortillas per day) in all Departments.
- Torres (2015) showed an average of 36% of samples of corn for food were contaminated with aflatoxins, and in Alta Verapaz 56%, at a mean concentration of 151 (ng/g)[2].
- In Guatemala the national food standard for corn is 2 ng/g.
- 100% of samples were positive to fumonisins in Alta Verapaz (mean 1.6 (µg/g)[3]).
- In comparison National Surveys in the USA where about 1% of the U.S. population had detectable levels (≥0.02 µg/l) of aflatoxin B1-lysine (Schleicher 2013). Surveys in Alta Verapaz, revealed 15% of subjects had positive urinary AFM1, a biomarker of exposure (Torres 2015).

Toxicology.

- Aflatoxin B1 is a known hepatocarcinogen (IARC 2016), mutagenic and genotoxic (JECFA, 2017).
- Experimental animal studies link aflatoxin and congenital anomalies (Smith 2017).
- A 1991 outbreak study in Texas (Missmer 2006) suggested an association of fumonisin exposure and Neural Tube Defects (NTDs).
- Lacking: epidemiologic studies examining the teratogenicity of aflatoxins, of fumonisins, or their interaction (JECFA, 2017).
- Aflatoxins and fumonisins co-occur, and have been related mainly to long-term carcinogenic effects, stunting, immune impairment and endocrine disruption

Epidemiology.

- Hepatocellular carcinoma increases in USA with highest rates in Hispanics and blacks.
- Between 2004 to 2013 the rate of hepatocellular carcinoma has increased 400% in Guatemala affecting both males and females (Guarzozi in Workshop, 2016).
- Aflatoxins interact with hepatitis B and C virus (Smith 2017).
- Globally, birth defects are the fifth cause of under 5 yr of age mortality (GBD 2015).
- Overall burden from congenital birth defects in Guatemala is estimated at 8,817.23 DALYS in <5 children, more than 4 times higher than the USA burden of 2,113.17 DALYS (IHME, GBD 2015).
- Oro-facial cleft among Guatemalans in California is 1.7/1,000 (Workshop, 2016).
- Guatemala City, with limited surveillance and under registration, some hospitals report rates of 2/1,000 per registered live births for neural tube defects (NTDs).
- A Department of Chimaltenango community registry of pregnancies and live births reported a rate of 2.6/1000; 36% of the anomalies are leporo-palatine clefts.
- In Alta Verapaz, a predominantly rural, indigenous Department in northeastern Guatemala, leporo-palatine cleft incidence was 4/1000, 92% of the anomalies were diagnosed at birth (Cabrera J. in Workshop 2016).

Economic implications. The treatment of hepatocellular cancer is economically catastrophic for already impoverished families.

- Birth defects can be catastrophic for the life of the fetus. Survival means a large cost burden for treatment and rehabilitation, as well as social and psychological burdens.
- Guatemalan practitioners estimate orofacial cleft treatment costs $20,000 USD (Workshop 2016).
- Depending on severity, the cost for Neural Tube Defects might be much higher, a high burden for families and health systems.

Regulatory capacity.

- Current standards for aflatoxins and fumonisins, including those in CODEX ALIMENTARIUS (2017) only consider their acute or carcinogenic effect.
- The most recent review in April of 2017, did not consider any of the teratogenic effects in vivo, nor any precaution for human teratogenesis; this must change.
- Considering teratogenesis might require a more stringent exposure limit for both human food and animal feed.
- Production of these mycotoxins and population exposure are happening in countries with the weakest institutional regulatory capacity (Magan 2011), essential, for enacting measures from regulating local production and markets in order to handle the impact from global markets.
- None of these factors were considered in the workgroup report on public health strategies for reducing aflatoxin exposure in developing countries (2006).

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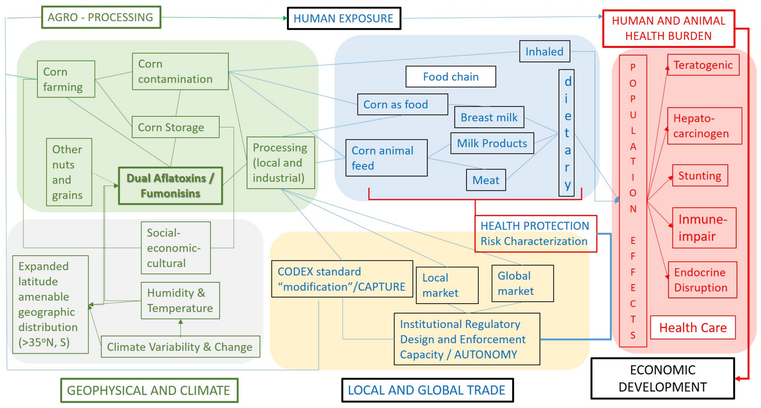

Discussion and Conclusions

Considering the generalized exposure patterns worldwide, the models showing future expanded latitudes favorable to the *Aspergillus flavus*, and the potential to review the current standards to consider its human teratogenic effects, all reveal a future scenario where aflatoxin and fumonisin exposure is not only a developing country problem but a global one. **For us, a local situation has clearly emphasized the need to integrate agricultural and farming practices with human health, in a self-evident One-Health approach.** We are working with local Guatemalan authorities on a project focused on improving food security and potential technologies to reduce exposure and increase diet diversify. **This experience in a local community has highlighted the effects of international trade, lack of regulatory control and potentially tolerant exposure levels that now may have to be reviewed, as the potential for exposure expands globally.** A GLOCAL ONE HEALTH integrated perspective (animal-human, local-global) of this complex panorama is pertinent. A **systemic approach** is helpful to identify the leverage points in the design of local and global interventions in the control of exposure to these toxins, and reduce their under-estimated burden of disease. Within this framework we need to provide evidence of human teratogenesis, and review and revise the risk assessment for these mycotoxins

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