Syndromes associated with children exposure to mycotoxins and health risk assessment to multiple mycotoxins in infant foods

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National Institute of Health Doutor Ricardo Jorge, IP

ASPOMM meeting
"LOCAL MYCOLOGY MEETING", 10 october 2015, Lisbon
OUTLINE

1. Children health and mycotoxins
2. Routes of exposure
3. Syndromes associated with children exposure to mycotoxins: ingestion and inhalation
4. Health risk assessment to multiple mycotoxins in infant foods - MYCOMIX project (PTDC/DTP-FTO/0417/2012)
5. Critical role of health professionals
1. Children health and mycotoxins

Children are more vulnerable than adults to health risks because:

• Children are constantly growing. They breathe more air, consume more food, and drink more water than adults do, in proportion to their weight.

• Children's central nervous, immune, reproductive, and digestive systems are still developing. At certain early stages of development, exposure to environmental toxicants (as mycotoxins) can lead to irreversible damage.

(http://www.who.int/ceh/en/)
Mycotoxins are secondary metabolites of fungi that cause toxic and carcinogenic outcomes in humans and children are a population group particularly vulnerable to the biological effects of these compounds.

(Etzel, Curr Probl Pediatr Adolesc Health Care, 2006)
2. Routes of exposure

1. Eating food or drink containing mycotoxins
2. Breathing moldy air in damp indoor areas
3. Dermal absorption
1. Eating food or drink containing mycotoxins – major foods.

<table>
<thead>
<tr>
<th>Toxic and biological effects of mycotoxins in foods</th>
<th>Mycotoxins</th>
<th>Major foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoxicity Carcinogenicity</td>
<td>Aflatoxins</td>
<td>maize, groundnuts, figs, tree nuts, milk, milk products, meat</td>
</tr>
<tr>
<td>Nefrotoxicity</td>
<td>Ochratoxins</td>
<td>maize, cereals, coffee beans, wine</td>
</tr>
<tr>
<td>Vomiting, gastrointestinal disturbs</td>
<td>Deoxynivalenol</td>
<td>cereals and derivatives</td>
</tr>
<tr>
<td>Oestrogenecity Infertility</td>
<td>Zearalenone</td>
<td>maize, barley, wheat</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Fumonisins</td>
<td>maize</td>
</tr>
<tr>
<td>Edema, hemorrhage, possibly cancer</td>
<td>Patulin</td>
<td>apple and pear juice pear, damaged apples &amp; pears</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Ergot alcaloids</td>
<td>rye</td>
</tr>
</tbody>
</table>

(Alvito et al, 2014)
1. Eating food or drink containing mycotoxins – clinical presentation

### Table 2: Clinical features of vomiting illness from exposure to mycotoxins

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Latent period</th>
<th>Clinical features</th>
<th>Foods associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomitoxin</td>
<td>3-15 min</td>
<td>Vomiting, Nausea, Headache, Abdominal cramps, Prompt resolution, No sequelae</td>
<td>Food made from wheat and corn (e.g., burritos)</td>
</tr>
<tr>
<td>T-2</td>
<td>5 min-1 h</td>
<td>Nausea, Vomiting, Diarrhea (bloody), Abdominal pain, Dizziness, &quot;Burning&quot; in mouth, Symptoms improve in 3-9 days</td>
<td>Food made with wheat, rice, millet, or corn</td>
</tr>
<tr>
<td>Fumonisins</td>
<td>N/A</td>
<td>Nausea, Vomiting</td>
<td>Peanuts, maize, soybeans, cassava</td>
</tr>
<tr>
<td>Patulin</td>
<td>N/A</td>
<td>Nausea, Vomiting</td>
<td>Food made from corn</td>
</tr>
</tbody>
</table>

Exposure to mycotoxins must be considered in differential diagnosis

1997,98 – USA, 1700 school children

1942, 48 – Alimentar Toxic Aleukia, Russia (bone marrow failure), 100 000 died

2004 – Kenya, 317 people ill and 125 died

(1990 - neural tube defects, USA)
Questions to consider in the clinical history if **INGESTION** of mycotoxins is suspected:

- Have other persons who ate the same food become ill?
- Did the symptoms begin within minutes to 3 hours of eating?
- Did any pets or animals eat the same food and become sick?
- Was diarrhea absent or a minor part of the illness?
IARC classification for carcinogenicity

<table>
<thead>
<tr>
<th>IARC group</th>
<th>Definition</th>
<th>Mycotoxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>carcinogenic to humans</td>
<td>Aflatoxins (AFB1, AFB2, AFG1, AFG2)</td>
</tr>
<tr>
<td>2B</td>
<td>possibly carcinogenic to humans</td>
<td>AFM1, FB1, FB2, OTA</td>
</tr>
<tr>
<td>3</td>
<td>not classifiable as to its carcinogenicity to humans</td>
<td>DON, PAT, ZEA, T-2, NIV</td>
</tr>
</tbody>
</table>

(Lerda, 2011; Mycotoxins factsheets JCR)

- AFTs – hepatocellular carcinoma (hepatitis B infection)
- FB – esophageal cancer
- OTA – renal cancer (testicular cancer?)
2. Breathing moldy air in damp indoor areas – clinical presentation

INFANT ACUTE PULMONARY HEMORRHAGE

Emerging data show an association with indoor exposure to moldy home environments (trichothecene mycotoxins).

Mycotoxins on surface of spores may lead to capillary fragility.

Massive pulmonary hemorrhage associated with mycotoxins - 1994 (10 child, USA, New Zealand)
Living in moldy indoor environment could also be associated with:

Recurrent apnea and/or “pneumonia”

- Recurrent apnea
- Cyanosis
- Cough
- “Pneumonia”

Sick Building Syndrome:

- Fatigue
- Headache
- Difficulty in concentrating
Questions to consider in the clinical history if INHALATION of fungi and mycotoxins is suspected:

- Has the house or apartment been flooded?
- Is there any water-damaged wood or cardboard in the house?
- Has there been a roof or plumbing leak?
- Have occupants seen any mold?
- Have occupants noticed a musty smell?
Mycotoxins associated health effects could be increased by:

Climate change

- Extreme precipitation, storms and floods
- Drought
- Increased temperatures

(Myrto, WHO, Climate change and Health, 2011)

Mycotoxins mixtures

The natural co-occurrence of mycotoxins is an increasing concern due to the hazard of exposure of combined mycotoxins to humans and particularly to children, which could be expected to exert greater toxicity and carcinogenicity than exposure to single mycotoxins.

(Speijers & Speijers, Toxicology Letters, 2004)
Are children exposed to mycotoxins through diet?

**TASK 1** - MULTIMYC. ANALYSIS

Interactive effects in toxicity of mixtures of mycotoxins?

**TASK 2** – CYTO & GENOTOXICITY
**TASK 3** - BIOAVAILABILITY

Children are exposed to mycotoxin mixtures through their diet and this constitutes a health threat.

Could this exposure be a health threat to children?

**TASK 4** – RISK ASSESSMENT TO MULTIPLE MYCOTOXINS IN INFANT FOODS

PTDC/DTP-FTO/0417/2012
4. Health risk assessment to multiple mycotoxins in infant foods
MYCOMIX project

- 92% of the analyzed breakfast cereals revealed the presence of two to six mycotoxins, simultaneously, in the same sample (Tox Letters, 238, 2015).

- Interactive toxic effects between binary mixtures of AFM$_1$ & OTA, FB$_1$ & OTA, and PAT & OTA indicate that these effects should be taken into account for the hazard assessment of mycotoxins (World Mycotoxin Journal, 2013; Tox Letters, 238, 2015).

- Cumulative risk assessment suggests an urgent need to establish legal limits for multiple mycotoxins in breakfast cereals (submitted, 2015).

Best Poster Award, 5th MoniQA Conf, September Porto, 2015
5. CRITICAL ROLE OF HEALTH PROFESSIONALS

Do research and publish results
Detect sentinel cases
Inspire community-based interventions

Take history of childhood exposures

Diagnose and treat

Educate
Patients and families
Colleagues and students

Advocate

Provide good role model

TOGETHER, WE CAN DO BETTER!
For more informations, consult INSA publications available at: www.insa.pt

Journal of Toxicology and Environmental Health, Part A: Current Issues
Publication details, including Instructions for authors and subscription information:
http://www.tandfonline.com/loi/utnh20

Applicability of In Vitro Methods to Study Patulin Bioaccessibility and Its Effects on Intestinal Membrane Integrity
Ricardo Assunção, Mariana Ferreira, Carla Martins, Irene Díaz, Beatriz Padilla, Didier Dupont, Márcio Bragança & Paula Alvito