Children's Health and the Environment
WHO Training Package for the Health Sector
World Health Organization
www.who.int/ceh

October 2011

<<NOTE TO USER: Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation in the space indicated.>>

<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the problem. Present only those slides that apply most directly to the local situation in the region.>>

This presentation will deal with mycotoxins and other toxins and their links to diseases in children.
Most medical students learn very little about mycotoxins during their training. This is in contrast to veterinary medical students, who often learn quite a lot about mycotoxins because mycotoxins are well known to affect the health and development of horses, cows and other animals who eat moldy grains. Nonetheless, their effects on humans are increasingly being recognized.
Mycotoxins

OUTLINE

- Case study
- Routes of exposure
- Toxin-related diseases
- Diagnosis and treatment
- The role of climate change
- Prevention, remediation, education
- Role of the health care provider
CASE STUDY: SCHOOL OUTBREAK

155 of 452 elementary school children in USA became ill 15 minutes after eating school lunch

Predominant symptoms:
- abdominal cramps in 88%
- vomiting in 62%
- headache in 62%
- nausea in 39%

Here is the story of this school outbreak: On March 23, 1998, a health department in the USA received a report that students in an elementary school became ill after eating lunch. Health officials obtained food and illness histories from 452 (77%) of the 584 students. A case was defined as nausea, abdominal cramps, vomiting, or diarrhea within 24 hours in a person after eating the school lunch on March 23. Of the 452 students, 155 (34%) had illnesses meeting the case definition.

Symptoms most commonly reported were nausea, headache, abdominal cramps, vomiting, and diarrhea. The median incubation period was approximately 15 minutes (range: 5-25 minutes), and median duration of illness was 4.5 hours (range: 10 minutes-8 hours).

From October 1997 through October 1998, 16 outbreaks of gastrointestinal illness associated with eating burritos occurred in the USA (in Florida, Georgia, Illinois, Indiana, Kansas, North Dakota, and Pennsylvania). All but one outbreak occurred in schools, and most of the approximately 1700 persons affected were children.

Ref:

Image: WHO
During October 1997-March 1998, burritos from three outbreaks of gastrointestinal illness were traced to company A, and during May-October 1998, burritos from another 13 outbreaks were traced to company B. Three outbreaks were linked to chicken and bean burritos, pork-sausage and egg burritos, and beef burritos; the other 13 were linked to beef and pinto bean burritos. All burritos used tortillas made with wheat flour. The burritos were distributed frozen and prepackaged except in Florida, where the filling was prepared locally.

The major symptoms were nausea, headache, abdominal cramps, and vomiting, typically beginning within 60 minutes after eating a burrito and lasting less than 24 hours. No one was hospitalized.

Ref:
In a case-control study at one school, eight (57%) of 14 case-patients and five (13%) of 38 well children ate burritos (odds ratio (OR)=8.8; 95% Confidence Interval=1.8-47.6). In the other school, 11 (85%) of 13 case-patients and 11 (33%) of 33 well children ate burritos (OR=11.0; 95% Confidence Interval=1.8-87.6). The tortillas used to make the burritos were supplied by company B; the fillings, beef at one school and beef and pinto beans at the other, were made in the two school kitchens.

Ref:
Because of the short incubation period, each of the following should be considered:

- **Staphylococcus aureus** (preformed toxins)
- **Bacillus cereus** (emetic toxin)
- Heavy metals (copper, tin, cadmium, iron, zinc)
- Natural toxins (vomitoxin = deoxynivalenol (DON))

For the differential diagnosis of foodborne illness with such a short incubation period, each of the following should be considered:

1. **Staphylococcus aureus** (which makes preformed toxins)
2. **Bacillus cereus** (emetic toxin)
3. Heavy metals (copper, tin, cadmium, iron, zinc)
4. Natural toxins (such as vomitoxin)

The short incubation periods suggest that a preformed toxin or other short-acting agent was the cause of illness. Possible agents include bacterial toxins (e.g., **Staphylococcus aureus** enterotoxin and **Bacillus cereus** emetic toxin); mycotoxins (e.g., deoxynivalenol (DON), acetyl-deoxynivalenol, and other tricothecenes), trace metals, nonmetal ions (e.g., fluorine, bromine, and iodine), plant toxins (e.g., alkaloids such as solanines, opiates, ipecac, and ergot; lectins such as phytohemagglutinin; and glycosides), pesticides (e.g., pyrethrine, organophosphates, and chlorinated hydrocarbons), food additives (e.g., bromate, glutamate, nitrite, salicylate, sorbate, and sulfite), detergents (e.g., anionic detergents and quaternary amines), fat-soluble vitamins, spoilage factors (e.g., biogenic amines, putrefaction, and free fatty acids), or an unknown toxin. Mass sociogenic illness is an unlikely explanation based on the number of different sites where outbreaks have been reported over a short interval and the link to only two companies.

**Bacillus cereus** emetic toxin and **Staphylococcus aureus** enterotoxins are common causes of food poisoning, but headache is not usually a prominent feature, and most outbreaks traced to these toxins have incubation periods of 2-4 hours, which is longer than observed in these outbreaks. Food samples from five outbreaks were negative for **B. cereus** and **S. aureus** by culture and toxin analysis; testing from these same outbreaks for alkaloids, biogenic amines, and pesticides also did not identify the causative agent.

Some metals, such as cadmium, copper, tin, and zinc, can irritate mucosal membranes and cause gastrointestinal illness after short incubation periods; however, only elemental aluminum was mildly elevated in the burrito samples, and there is no evidence that it causes these symptoms. Several plant toxins, such as phytohemagglutinin, may survive cooking and cause gastrointestinal symptoms; however, outbreaks associated with phytohemagglutinin have been linked to red kidney beans and not pinto beans.

Outbreaks with symptoms and incubation periods similar to those described in this report have occurred in China and India, where illness has been linked to consumption of products made with grains contaminated with fungi. These fungi produce heat-stable tricothecene mycotoxins called vomitoxin. In China, 35 outbreaks affecting 7818 persons during 1961-1985 were attributed to consumption of foods made with moldy grain. Corn and wheat samples collected during two outbreaks had higher levels of DON than those collected at other times. In India in 1987, 97 persons consumed wheat products following heavy rains. DON and other tricothecene mycotoxins were detected in the implicated wheat products, and extracted toxins caused vomiting in laboratory tests on puppies. High doses of DON are known to cause vomiting in pigs.

Refs:

CASE STUDY: SCHOOL OUTBREAK

- Burritos also implicated in 15 other outbreaks in 6 different states
- 2 million pounds of burritos recalled from two companies

The US Department of Agriculture requested that both companies A and B initiate timely national recalls, and approximately 2 million pounds of burritos were recalled or withheld from distribution. Company A and its tortilla supplier were unrelated to company B and its supplier.

Ref:
CASE STUDY: SCHOOL OUTBREAK

- 1700 primary schoolchildren in 6 states developed vomiting 15 minutes to 2 hours after eating lunch at the school cafeteria

- Lunch food (burritos) contained 0.3 ppm vomitoxin

Epidemiologic investigations in outbreaks implicated burritos, which consisted of meat or vegetable filling wrapped in a tortilla. Data from the Florida outbreak suggest that the etiologic agent was in the tortillas because the filling was made locally. Outbreaks associated with products made by two unrelated companies that used different tortilla suppliers suggest that the agent was an ingredient common to the products made by both companies. No common first-line suppliers were identified; however, whether the source of any ingredients was shared has not been determined.

Laboratory testing from burrito samples from some of the U.S. outbreaks in this report detected deoxynivalenol of 0.3 parts per million, which was within the acceptable Food and Drug Administration advisory level of 1 ppm for finished wheat products. However, the possibility remains that a mycotoxin is the cause, because children are more susceptible to vomitoxin than adults, and the advisory level was set for adults.

Ref:
There are over 200,000 species of fungi, including mold, yeast, and mushrooms. More than 100,000 mold species have been identified.

Paediatricians are familiar with poisonous mushrooms, such as Amanita, which can be eaten by mistake while hunting for mushrooms.

Exposure to molds can also occur by ingestion, but also occurs via inhalation of contaminated air and dermal contact with surfaces on which they are deposited.

Molds are ubiquitous in the outdoor environment and can enter the home through doorways, windows, air conditioning systems and heating and ventilation systems. Molds proliferate in environments that contain excessive moisture, such as from leaks in plumbing, roofs, walls, and pet urine and plant pots. The most common molds found indoors are Cladosporium, Penicillium, Aspergillus, and Alternaria. If a building is extremely wet for an extended period, other molds with higher water requirements, including Stachybotrys and Trichoderma species, can grow.

Refs:

Image: Courtesy of Halshka Graczyk.
There are many species of molds and hundreds of known mycotoxins. Species of mycotoxin-producing molds include *Fusarium*, *Trichoderma*, and *Stachybotrys*. A single mold species may produce several different toxins, and a given mycotoxin may be produced by more than one species of mold. Furthermore, toxin-producing molds do not necessarily produce mycotoxins under all growth conditions, with production being dependent on the substrate, temperature, water content and humidity.

*Refs:*

The mycotoxins probably evolved as a kind of "chemical defense system" to protect the mold from insects, microorganisms, nematodes, grazing animals and human. The photo on the slide depicts mold growing on wood. Molds come in many colors; both white and black molds are shown here.

Ref:

Mycotoxins are associated with human disease and cause acute and chronic effects

- Mycotoxins
  - Aflatoxins
  - Tricothecenes
  - Ochratoxins and citrinin
  - Hundreds of others
- Glucans
  (cell wall components)
- Volatile organic compounds
  (irritating)

Mycotoxins are associated with human disease. Tricothecenes inhibit protein synthesis and have many acute effects, including anemia and infant pulmonary haemorrhage. Ochratoxins and citrinin cause nephropathy and immunosuppression. Aflatoxins are hepatotoxins and are carcinogenic.

Refs:

Disease associated with exposure to mycotoxins is known as the "Great Masquerader" of the 21st century because of its complex natural history involving different tissues and resembling different diseases at each stage in its evolution. It can present with a variety of nonspecific clinical signs and symptoms such as rash, conjunctivitis, epistaxis, anemia, cough, wheezing, nausea, and vomiting. Some cases of vomiting illness, bone marrow failure, acute pulmonary hemorrhage, and recurrent apnea and/or "pneumonia" are associated with exposure to mycotoxins. Familiarity with the symptoms of exposure to the major classes of mycotoxins enables the clinician to ask pertinent questions about possible fungal exposures and to remove the infant or child from the source of exposure, which could be contaminated food(s), clothing and furniture, or the indoor air of the home. Failure to prevent recurrent exposure often results in recurrent illness. A variety of other conditions, including hepatocellular and esophageal cancer and neural tube defects, are associated with consumption of foods contaminated with mycotoxins. Awareness of the short- and long-term consequences of exposures to these natural toxins helps pediatricians to serve as better advocates for children and families. (Etzel RA).

A comprehensive up-to-date review of beta-glucans, their chemical and biological properties, and their role in immunological reactions. Beta-D-Glucans belong to a group of physiologically active compounds called biological response modifiers and represent highly conserved structural components of cell walls in yeast, fungi, or seaweed. Despite almost 150 years of research, the exact mechanisms of their action remain unclear. The present review starts with the history of glucans. Next, attention is focused on sources and structure, comparing the effects of physicochemical properties, and sources on biological effects.

Children can be exposed to mycotoxins through eating and drinking, breathing, and through their skin. Molds have been with us for hundreds, even thousands of years, and many of us used to consider them simply a nuisance in the house. They were rarely considered a health problem. But in the last decade, more scientific evidence is accumulating that the molds in water-damaged homes can be linked to health problems, at least in some children. Because of this emerging evidence, public health authorities are now cautioning people to keep homes dry and to fix any water problems within 24-48 hours. That will prevent the conditions that allow toxigenic molds (those that produce potent toxins) to grow. Special attention should be paid to fixing:

- roof leaks
- floods (broken pipes)
- toilet or sink leaks

To tell if you have a mold problem in your house, use your nose (musty smell is a good indicator)

Look for watermarks, discoloration, staining of ceilings, walls, woodwork.
Search behind and underneath carpets, wallpaper, furniture.

But be aware that cleaning up visible mold is not enough! mold requires water, and you should find out where the water is coming from. Unless you fix the source of water, it is likely that the conditions for mold growth will continue and the mold will recur.

Ref:

Children may be more vulnerable to the effects of mycotoxins than adults. This is because many mycotoxins (e.g. trichothecenes) target rapidly growing cells. Children are at risk for inhalation exposures to these mycotoxins because their lung development is not complete at birth. Lung development proceeds through proliferation of pulmonary alveoli and capillaries until the age of 2 years. Thereafter, the lungs grow through alveolar expansion until 5-8 years of age. Lungs do not complete their growth until full adult stature is achieved in adolescence. The fastest period of lung development is between birth and 1 year, this is a critical window for children. It may help to explain why infants are at risk of acute pulmonary hemorrhage.

Refs:

Mycotoxins have been linked to a variety of health effects in humans.

Refs:

  Reactive airways disease in children is increasing in many countries around the world. The clinical diagnosis of asthma or reactive airways disease includes a variable airflow and an increased sensitivity in the airways. This condition can develop after an augmented reaction to a specific agent (allergen) and may cause a life-threatening situation within a very short period of exposure. It can also develop after a long-term exposure to irritating agents that cause an inflammation in the airways in the absence of an allergen. (Paragraph) Several environmental agents have been shown to be associated with the increased incidence of childhood asthma. They include allergens, cat dander, outdoor as well as indoor air pollution, cooking fumes, and infections. There is, however, increasing evidence that mold growth indoors in damp buildings is an important risk factor. About 30 investigations from various countries around the world have demonstrated a close relationship between living in damp homes or homes with mold growth, and the extent of adverse respiratory symptoms in children. Some studies show a relation between dampness/mold and objective measures of lung function. Apart from airways symptoms, some studies demonstrate the presence of general symptoms that include fatigue and headache and symptoms from the central nervous system. At excessive exposures, an increased risk for haemorrhagic pneumonia and death among infants has been reported. The described effects may have important consequences for children in the early years of life. A child's immune system is developing from birth to adolescence and requires a natural, physiological stimulation with antigens as well as inflammatory agents. Any disturbances of this normal maturing process will increase the risk for abnormal reactions to inhaled antigens and inflammaginic agents in the environment. The knowledge about health risks due to mold exposure is not widespread and health authorities in some countries may not be aware of the serious reactions mold exposure can provoke in some children. Individual physicians may have difficulty handling the patients because of the lack of recognition of the relationship between the often complex symptoms and the indoor environment. (Etzel RA).


Mycotoxins

AFLATOXICOSIS

- Acute high exposures (Africa, Asia):
  - Vomiting
  - Abdominal pain
  - Hepatitis
  - Death

- Lethal dose for adults: 10-20 mg

- Chronic low-dose exposures:
  - Impaired growth

Aflatoxicosis causes abdominal pain, vomiting, hepatitis and (sometimes) death after acute exposure to high concentrations in food. Several high-profile epidemics have occurred in Eastern Africa in the past decade.

Chronic low-dose exposure to aflatoxin can result in impaired growth in children.

Refs:
  During January-June 2004, an aflatoxicosis outbreak in eastern Kenya resulted in 317 cases and 125 deaths. We conducted a case-control study to identify risk factors for contamination of implicated maize and, for the first time, quantitated biomarkers associated with acute aflatoxicosis. DESIGN: We administered questionnaires regarding maize storage and consumption and obtained maize and blood samples from participants. We recruited 40 case-patients with aflatoxicosis and 80 randomly selected controls to participate in this study. EVALUATIONS: We analyzed maize for total aflatoxins and serum for aflatoxin B1-lysine adducts and hepatitis B surface antigen. We used regression and survival analyses to explore the relationship between aflatoxins, maize consumption, hepatitis B surface antigen, and case status. RESULTS: Homegrown (not commercial) maize kernels from case households had higher concentrations of aflatoxins than did kernels from control households [geometric mean (GM) = 354.53 ppb vs. 44.14 ppb; p = 0.04]. Serum adduct concentrations were associated with time from jaundice to death [adjusted hazard ratio = 1.3; 95% confidence interval (CI), 1.04-1.6]. Case patients had positive hepatitis B titers [odds ratio (OR) = 9.8; 95% CI, 1.5-63.1] more often than controls. Case patients stored wet maize (OR = 3.5; 95% CI, 1.2-10.3) inside their homes (OR = 12.0; 95% CI, 1.5-95.7) rather than in granaries more often than did controls. CONCLUSION: Aflatoxin concentrations in maize, serum aflatoxin B1-lysine adduct concentrations, and positive hepatitis B surface antigen titers were all associated with case status. RELEVANCE: The novel methods and risk factors described may help health officials prevent future outbreaks of aflatoxicosis.

  Maize contaminated with aflatoxins has been implicated in deadly epidemics in Kenya three times since 1981, but the fungi contaminating the maize with aflatoxins have not been characterized. Here we associate the S strain of Aspergillus flavus with lethal aflatoxicoses that took more than 125 lives in 2004.

This slide shows that there are a variety of ways that natural toxins can affect children's health. The adverse health effects can be pictured as a pyramid, like the one shown here. At the top is death, the most severe consequence of exposure, such as the deaths that occurred during the aflatoxin epidemic in Kenya in 2005 when 125 persons died. Shown slightly lower on the pyramid are hospitalizations that occur as a result of exposure. Somewhat less severe health effects include visits to the clinic. At the low end of the pyramid are the adverse effects that children suffer for which they do not go to the clinic.

Ref:

Mycotoxins

ANIMAL EXAMPLE: BLEEDING FROM TRICHOTHECENES

- Mycotoxicosis in horses first reported in 1931 (Ukraine)
- Massive numbers of horses died with gastrointestinal bleeding
- Horses ate hay heavily contaminated with *Stachybotrys* mold

Refs:
**Alimentary Toxic Aleukia (ATA)**

- First appeared in 1913 in far eastern Siberia
- Responsible for the death of at least 100,000 Russian people between 1942 and 1948
- Necrotic ulcers in the mouth, throat, nose, stomach and intestines
- Bleeding from the nose, mouth, GI tract, and kidneys
- Associated with eating grains (wheat and corn) which had been under snow the previous winter
- Grains contaminated with *Fusarium* and *Stachybotrys*

Refs:
Acute pulmonary hemorrhage is quite unusual in infants. When it happens it is potentially fatal. Infant acute pulmonary hemorrhage has been linked by epidemiologic studies to indoor exposure to moldy home environments. Mycotoxins on the surface of the spores may lead to capillary fragility. Cigarette smoking in the household increases the risk significantly. Additional research is ongoing to more fully document the scope of this potential risk.

Because they are lipid-soluble, mycotoxins are readily absorbed by the airways. Exposure to *Stachybotrys chartarum* (atra) and other molds has been associated with acute pulmonary hemorrhage among young infants in the U.S. (Cleveland, Ohio, Kansas City, Missouri, Delaware) and New Zealand. Exposure to *Trichoderma* and other molds has been associated with acute pulmonary hemorrhage in a North Carolina infant.

Studies of acute intratracheal exposure to the metabolites of *Stachybotrys* in male rats demonstrate lung tissue injury. The studies concluded that lung cell damage was more likely due to toxins than fungal cell wall components.

Refs:

A geographic cluster of 10 cases of pulmonary hemorrhage and hemosiderosis in infants occurred in Cleveland, Ohio, between January 1993 and December 1994. STUDY DESIGN: This community-based case-control study tested the hypothesis that the 10 infants with pulmonary hemorrhage and hemosiderosis were more likely to live in homes where *Stachybotrys atra* was present than were 30 age- and ZIP code-matched control infants. We investigated the infants’ home environments using bioaerosol sampling methods, with specific attention to *S atra*. Air and surface samples were collected from the room where the infant was reported to have spent the most time. RESULTS: Mean colony counts for all fungi averaged 29 227 colony-forming units (CFU)/m³ in homes of patients and 707 CFU/m³ in homes of controls. The mean concentration of *S atra* in the air was 43 CFU/m³ in homes of patients and 4 CFU/m³ in homes of controls. Viable *S atra* was detected in filter cassette samples of the air in the homes of 5 of 9 patients and 4 of 27 controls. The matched odds ratio for a change of 10 units in the mean concentration of *S atra* in the air was 9.83 (95% confidence interval, 1.08-3 X 10⁶). The mean concentration of *S atra* on surfaces was 20 X 10⁶ CFU/g and 0.007 x 10⁶ CFU/g in homes of patients and controls, respectively. CONCLUSION: Infants with pulmonary hemorrhage and hemosiderosis were more likely than controls to live in homes with toxigenic *S atra* and other fungi in the indoor air.

Aflatoxin causes cancer, based on studies conducted in areas with a high incidence of hepatocellular carcinoma, such as Asia, where the incidence of chronic hepatitis B viral infections is also high.

Refs:
Fumonisins linked to neural tube defects

- Finding emerged from studies of women who consumed tortillas in Mexico

Exposure to fumonisins (from eating contaminated corn and corn-based products) has been linked to neural tube defects.

Refs:

*Image: WHO*
### TOXICITY & BIOLOGICAL EFFECTS OF MYCOTOXINS IN FOODS

<table>
<thead>
<tr>
<th>Mycotoxin</th>
<th>Major Foods</th>
<th>Species</th>
<th>Health effects</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxins</td>
<td>Maize, groundnuts, figs, tree nuts (Aflatoxin M&lt;sub&gt;1&lt;/sub&gt; (secreted by cow after metabolism of aflatoxin B&lt;sub&gt;1&lt;/sub&gt;), milk, milk products</td>
<td>Aspergillus flavus</td>
<td>Hepatotoxic, carcinogenic</td>
<td>0.5 (dog) 9.0 (mouse)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspergillus parasiticus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclopiazonic acid</td>
<td>Cheese, maize, groundnuts, Rodo millet</td>
<td>Aspergillus flavus</td>
<td>Convulsions</td>
<td>36 (rat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillium aurantiogriseum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deoxynivalenol</td>
<td>Cereals</td>
<td>Fusarium graminearum</td>
<td>Vomiting, food refusal</td>
<td>70 (mouse)</td>
</tr>
<tr>
<td>T-2 toxin</td>
<td>Cereals</td>
<td>Fusarium sporotrichioides</td>
<td>Alimentary toxic aleukia</td>
<td>4 (rat)</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Rye</td>
<td>Claviceps purpurea</td>
<td>Neurotoxin</td>
<td>-</td>
</tr>
</tbody>
</table>

This chart shows the relative toxicity of some of the mycotoxins in foods. Note that the LD<sub>50</sub> of T-2 toxin is lower than that of aflatoxins, cyclopiazonic acid, or deoxynivalenol.

**Refs:**
### TOXICITY & BIOLOGICAL EFFECTS OF MYCOTOXINS IN FOODS

<table>
<thead>
<tr>
<th>Mycotoxin</th>
<th>Major Foods</th>
<th>Species</th>
<th>Health effects</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumonisin</td>
<td>Maize</td>
<td><em>Fusarium moniliforme</em></td>
<td>Esophageal cancer</td>
<td>?</td>
</tr>
<tr>
<td>Ochratoxin</td>
<td>Maize, cereals, coffee beans</td>
<td><em>Penicillium verrucosum</em></td>
<td>Nephrotic</td>
<td>20-30 (rat)</td>
</tr>
<tr>
<td>Patulin</td>
<td>Apple juice, damaged apples</td>
<td><em>Penicillium expansum</em></td>
<td>Edema, hemorrhage, possibly cancer</td>
<td>35 (mouse)</td>
</tr>
<tr>
<td>Penitrem</td>
<td>Walnuts</td>
<td><em>Penicillium aurantiogriseum</em></td>
<td>Tremors</td>
<td>1.05 (mouse)</td>
</tr>
<tr>
<td>Sterigmatocystin</td>
<td>Cereals, coffee beans, cheese</td>
<td><em>Aspergillus versicolor</em></td>
<td>Hepatotoxic, cancer</td>
<td>166 (rat)</td>
</tr>
</tbody>
</table>

This chart shows the relative toxicity of some of the mycotoxins in foods.

**Refs:**
Mycotoxins

TOXICITY & BIOLOGICAL EFFECTS OF MYCOTOXINS IN FOODS

<table>
<thead>
<tr>
<th>Mycotoxin</th>
<th>Major Foods</th>
<th>Species</th>
<th>Health Effects</th>
<th>LD₅₀ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenuazonic acid</td>
<td>Tomato paste</td>
<td>Alternaria tenuis</td>
<td>Convulsions, hemorrhage</td>
<td>81 (female mouse)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>186 (male mouse)</td>
</tr>
<tr>
<td>Zearolenone</td>
<td>Maize, barley, wheat</td>
<td>Fusarium graminearum</td>
<td>Oestrogenic</td>
<td>Not acutely toxic</td>
</tr>
</tbody>
</table>

This chart shows the relative toxicity of some of the mycotoxins in foods. Some mycotoxins, such as zearolenone, are not acutely toxic but have long-term effects on the child (in this case, estrogenic effects).

Refs:
OTHER CONDITIONS UNDER STUDY

- **Sick Building Syndrome**: Living in moldy indoor environments. Symptoms include:
  - Fatigue
  - Headache
  - Difficulty in concentrating

- Many pure microbial toxins have been shown to be neurotoxic in vitro and in vivo such as the products of:
  - *Fusarium* (fumonisin B1, deoxynivalenol)
  - *Stachybotrys* (satratoxin G)
  - *Aspergillus* (ochratoxin A)
  - *Penicillium* (ochratoxin A, verrucosidin)

There have been a variety of neurologic symptoms associated with living in moldy environments, including fatigue, difficulty concentrating and headaches. Although few studies of children have been done, it is biologically plausible that these symptoms could be associated with mycotoxin exposures.

Many mycotoxins that have been isolated from spores, mold fragments and dust from moldy areas are significantly toxic. In vitro and in vivo studies have demonstrated adverse effects – including immunotoxic, neurological, respiratory, and dermal responses – after exposure to specific toxins, bacteria, molds, or their products. Many pure microbial toxins, such as the products of *Fusarium* (fumonisin B1, deoxynivalenol), *Stachybotrys* (satratoxin G), *Aspergillus* (ochratoxin A) and *Penicillium* (ochratoxin A, verrucosidin), have been shown to be neurotoxic in vitro and in vivo. In the indoor environment, various microbiological agents with diverse, fluctuating inflammatory and toxic potential are present simultaneously with other airborne compounds, inevitably resulting in interactions. Such interactions may lead to unexpected responses, even at low concentrations.

**Refs:**
Aflatoxins are expected to become more prevalent as climate continues to change

Young children among most vulnerable

Warmer temperatures and extreme weather events encourage the growth of mycotoxin-producing fungi, including Aspergillus, Claviceps, Stachybotrys, and Fusarium spp. Mycotoxins are implicated in the pathogenesis of cancers, ergotism, and birth defects. Aspergillus can produce aflatoxin, a potent mycotoxin that has cause much death and disease in Africa and Asia.

Several such environmental changes have now been confirmed, in particular stratospheric ozone depletion and climate change. These large-scale environmental changes do not necessarily pose qualitatively new risks to health. Rather, they amplify and extend the health risks posed by many existing environmental hazards. Global warming (climate change) is well studied and provides a good example of a global change with health consequences that affect everyone, but children more than most.

Refs:

Image: WHO
Mycotoxins

CLIMATE CHANGE MANY INCREASE EXPOSURE TO MYCOTOXINS

- **Extreme precipitation, storms and floods**
  cause moist conditions that promote fungal growth

- **Drought**
  weakens seed kernels of plants, allowing greater fungal contamination

- **Increased temperatures**
  promote fungal growth

Climate change may alter human exposure to mycotoxins. The physical changes in temperature, wind, and rainfall caused by climate change will affect the distribution of mycotoxins in complex ways. The effect on human exposure will vary widely according to the properties of specific mycotoxins, soil and water conditions, wind patterns, topography, land use, level of development, and human population characteristics. Climate change-related chemical exposures may pose disproportionate threats to populations in high risk groups. Malnutrition, particularly in the very young, may compound and worsen effects from mycotoxin exposure.

**Refs:**

**Image:** WHO
This list does not include all poisonous plants and animals; only the most widespread. Ciguatera is found mainly in tropical reef fish. Since it accumulates in the food chain, large predatory fish are the most toxic. Poisoning causes gastrointestinal, cardiovascular and neurological symptoms, such as a reversal of hot/cold sensations. Other dinoflagellates produce shellfish poisonings. While dinoflagellates have specific geographical ranges, "blooms" have occurred outside traditional areas because of climate changes. Pyrrolizidine alkaloids, which can cause liver damage, are found in plants that may be consumed unintentionally with edible plants. Histamine is usually associated with decomposing scombroid fish, produced by the decarboxylation of histidine by bacteria. Usually, tingling, rash or drop in blood pressure occurs within 30 minutes of ingestion, and symptoms disappear after 3 hours.
EXAMPLE OF OTHER TOXINS: INCREASE IN SHELLFISH POISONINGS

- Heat-resistant toxins produced by algae
- Sudden increase ("bloom") in an area
- Four distinct syndromes:
  - Paralytic (saxitoxin, gonyautoxin)
  - Diarrhetic (okadaic acid, inophysistoxin)
  - Neurotoxic (brevetoxins)
  - Amnesic (domoic acid)
- Paralytic poisoning has high mortality rate

Algal blooms can result from a combination of climatic conditions, light, salinity, and nutrient supply. Increased agricultural discharges into an area of the ocean can be associated with algal blooms. The only known preventive measure is to ban the harvesting and consumption of shellfish from the affected area.

Ref:
### ALGAL INTOXICATIONS ASSOCIATED WITH SHELLFISH

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptoms</th>
<th>Toxin</th>
<th>Algal Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnesic shellfish poisoning</td>
<td>Choking, vomiting, diarrhoea, incapacitating headaches, seizures, short-term memory loss</td>
<td>Domoic acid</td>
<td>Pseudonitzschia pungens</td>
</tr>
</tbody>
</table>
| Diarrheic shellfish poisoning | Diarrhoea, vomiting, abdominal pain, nausea (may persist for several days) | Okadaic acid  | Dynophysis acuta  
                        |                                                        |                | Dynophysis acuminata | Dynophysis fortii |
| Neurotoxic shellfish poisoning | Paresthesia, reversal of hot and cold temperature sensitivity, myalgia and vertigo (generally mild) | brevetoxins    | Ptychodiscus brevis                    |
| Paralytic shellfish poisoning | Tingling, numbness in fingertips and lips, giddiness, staggering, incoherent speech, respiratory paralysis | Saxitoxin gonyautoxin | Alexandrium (Gonyaulux) catenella  
                        |                                                        |                | Alexandrium tamarensis |

Ref:
Mycotoxins

INTERVENTIONS

- To reduce airborne exposures to molds:
  - Keep indoor areas dry
  - Fix all leaks and clean up flooding within 24 hours
  - Do not smoke indoors

- To reduce foodborne exposure to aflatoxin:
  - Protect agricultural crops from moisture during both growth and post-harvest storage
  - Do not eat grains with visible mold
  - Computer models to predict mycotoxin levels

Refs:

The public health impact of aflatoxin exposure is pervasive in economically developing countries; consequently, we need to design intervention strategies for prevention that are practicable for these high-risk populations. The adverse health consequences of aflatoxins in populations are quite varied, eliciting acute effects, such as rapid death, and chronic outcomes, such as hepatocellular carcinoma. Furthermore, a number of epidemiological studies describe a variety of general adverse health effects associated with aflatoxin, such as impaired growth in children. Thus, the magnitude of the problem is disseminated across the entire spectrum of age, gender, and health status in the population. The aflatoxins multiplicatively increase the risk of liver cancer in people chronically infected with hepatitis B virus (HBV), which illustrates the deleterious impact that even low toxin levels in the diet can pose for human health. Thus other aflatoxin interactions, which likely contribute to the disease burden, still remain to be identified. Therefore, many diverse and appropriate strategies for disease prevention are needed to decrease the incidence of aflatoxin carcinogenesis in developing countries.


<<READ SLIDE>>
Guidance about molds and mycotoxins should be included in prevention messages regarding health harms related to flooding both during an acute event and in the aftermath. As shown on this slide, prevention messages should include interventions on various aspects of human health and safety.

Ref:

Education is vitally important to ensure that parents and communities understand that mycotoxins and other toxins can cause diseases in children. Health promotion activities are needed to demonstrate the importance of protecting agricultural crops, particularly cereals and oilseeds, during both growth and post-harvest storage.

Refs:

Image: WHO. Health Education.
Here are selected mycotoxins and major categories of disease. Notice the plus signs where health effects of mycotoxin reduction are supported by the scientific literature. It is important to note that this table does include all of the health benefits from mycotoxin reduction.

**Refs:**
In this summary slide, we see the complexity of the issues related to children’s environmental health. Hazards are introduced into environmental media with variable efficiency in different settings. A child’s activities bring him or her into contact with these hazards. Depending upon the individual susceptibility of the child, based upon age, general health and social supports, the exposure may cause harm varying in severity from subtle changes in function to death.

Children’s environmental health is the field that synthesizes these complex issues and attempts to make fundamental changes to improve children’s environments and prevent environment-related illnesses.

Ref:

Health professionals have a critical role to play in maintaining and stimulating changes that will protect children from diseases associated with natural toxins.

So, as we look to our political and personal lives to support sustainable development, we can look to our medical practices for ways of enhancing the health of our patients. All of us can do something.

At the one-to-one patient level we can include environmental etiologies in our differential diagnoses and in our preventive advice: is the child's disease linked to consuming contaminated food or to breathing air in a home this is water damaged and moldy? It is important to limit the number of diagnoses given as “idiopathic” and to look hard for environmental causes of children's diseases.

Health care providers should be alert and detect the "sentinel" cases. Their detection and study will be essential for developing, proposing and supporting community-based interventions. Publication of cases and research studies enables the communication of knowledge and experience that will benefit other communities and countries.

It is important to inform and educate patients, families, colleagues and students didactically, on the importance of preventing diseases by reducing exposure to natural toxins in foods and in the air.

Finally, we must become vigorous advocates for the protection of food from contamination with mycotoxins and other toxins. These and other measures are crucial for protecting the health of our children and future generations. It is not enough to be an informed citizen, we need to write letters, testify at hearings, convince decision-makers, approach our elected officials with information, education and clear messages based upon the evidence.

And, we must all recognize that as professionals with an understanding of both health and the environment, we are powerful role models.

Refs:
Example of the detailed questions on behaviours and habits that may be asked while taking the environmental history for a child with a disease that may be associated with exposure to mycotoxins or other toxins.

<< NOTE TO USER: State examples of questions that are applicable to the country or local community.>>

<< NOTE TO USER: See module on Paediatric Environmental History.>>

**Refs:**

POINTS FOR DISCUSSION

<<NOTE TO USER: Add points for discussion according to the needs of your audience.>>
ACKNOWLEDGEMENTS

WHO is grateful to the US EPA Office of Children’s Health Protection for financial support that made this project possible and for some of the data, graphics and text used in preparing these materials for a broad audience.

Further support was kindly provided by the UK Department of Health.

First draft prepared by Ruth A. Etzel, MD PhD (WHO)

With the advice of the Working Group Members on the Training Package for the Health Sector: Cristina Alonzo MD (Uruguay); Yona Amitai MD MPH (Israel); Stephan Boese-O’Reilly MD MPH (Germany); Stephania Borgo MD (ISDE, Italy); Irena Buka MD (Canada); Ernesto Burgio (ISDE, Italy); Lilian Corra MD (Argentina); Ligia Fruchtengarten MD (Brazil); Amalia Laborde MD (Uruguay); Jenny Pronczuk MD (WHO) Christian Schweizer TO (WHO/EURO); Kathy Shea MD (USA).

Reviewers: Dr Huw Brunt (UK), Prof Gary Coleman (UK), Dr Raquel Duarte-Davidson (UK), Dr Elaine Lynch Farmery (UK), Alison M Good BSc Dip Med Tox MSc (UK), Dr Mark Griffiths (UK), Dr John Thompson (UK), Dr Laura Yates (UK)

WHO Project coordination: Ruth A. Etzel, MD PhD
Marie-Noël Bruné, MSc

Latest update: October 2011 (H. Graczyk, L. Tempesta)
**Mycotoxins**

**DISCLAIMER**

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
- The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.
- The opinions and conclusions expressed do not necessarily represent the official position of the World Health Organization.
- This publication is being distributed without warranty of any kind, either express or implied. In no event shall the World Health Organization be liable for damages, including any general, special, incidental, or consequential damages, arising out of the use of this publication.
- The contents of this training module are based upon references available in the published literature as of its last update. Users are encouraged to search standard medical databases for updates in the science for issues of particular interest or sensitivity in their regions and areas of specific concern.
- If users of this training module should find it necessary to make any modifications (abridgement, addition or deletion) to the presentation, the adaptor shall be responsible for all modifications made. The World Health Organization disclaims all responsibility for adaptations made by others. All modifications shall be clearly distinguished from the original WHO material.