Mold toxins: Hazard to animal and human health

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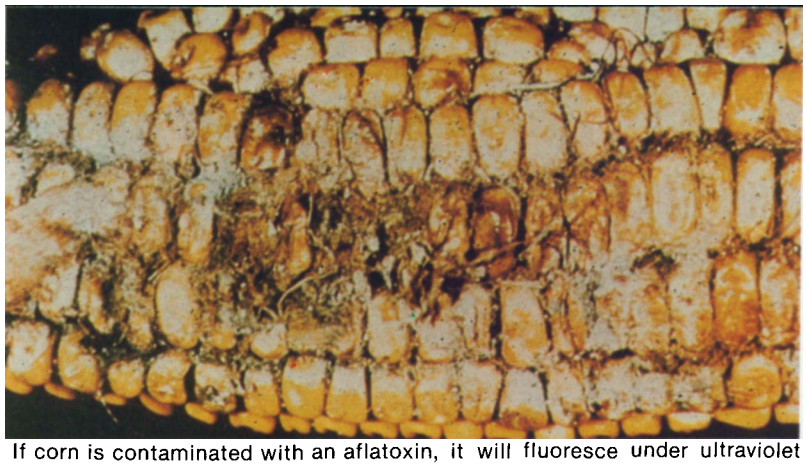
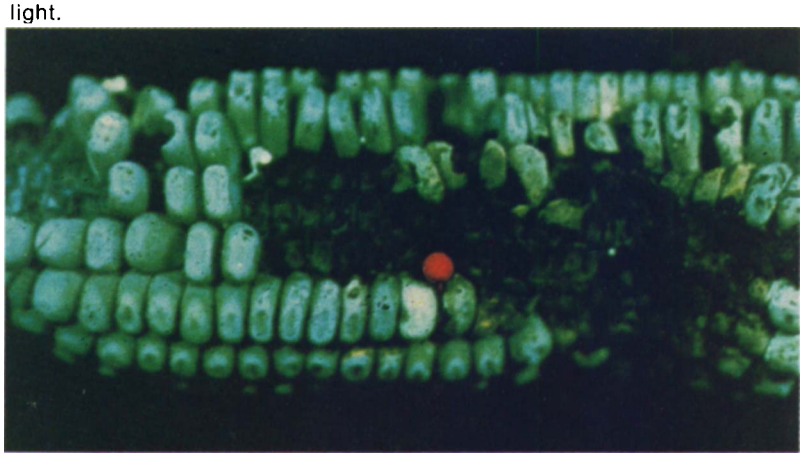


If corn is contaminated with an aflatoxin, it will fluoresce under ultraviolet light.



Mold toxins or mycotoxins are new "in" words among microbiologists and toxicologists and may soon also be familiar to the general public. At times we all have encountered colorful layers of mold growth on spoiled bread, fruit, or vegetables. Recent research has shown that these harmless looking invaders have to be taken seriously; some produce potent toxins and carcinogens.

Food spoilage by fungi is a familiar problem, although it was not always recognized as such. During the Middle Ages large-scale outbreaks of "St. Anthony's Fire" (ergotism) were attributed to witchcraft rather than to the consumption of mold-contaminated bread. (The toxin has been identified as a relative of lysergic acid—LSD.) Other human afflictions have sporadically been reported; in Russia, the "Alimentary Toxic Aleukia" claimed many victims, who had consumed overwintered grains; in postwar Japan, many people suffered from "Yellowed Rice Disease."

In general, however, mycotoxin diseases were mainly considered a veterinary problem. Many animal diseases were associated with mycotoxins, like facial eczema, stachybotryotoxicosis, or hyperestrogenic syndrome (table 1). This was still so until the early 1960s when a large number of poultry in England died of a mysterious illness originally called "turkey X" disease. As the causative agent, a new group of mycotoxins, named aflatoxins after its main producer, *Aspergillus flavus,* was isolated from the peanut meal used as feedstuff. When the new toxins turned out also to be potent carcinogens, and the *Aspergillus* fungus to be a common invader of foodstuffs, it became apparent suddenly that the molds could also pose a great hazard to human health.

Meanwhile a few other carcinogenic mycotoxins have been discovered. For example, traces of patulin were extracted from apple juices; luteoskyrin has been identified as one of the "Yellowed Rice Toxins." However, the aflatoxins still remain the most widespread and most dangerous contaminants. Aflatoxin B_1 is the major member of the family, and the most potent liver carcinogen known to date. It is the most studied mycotoxin, serving, for example, as a model compound to investigate the molecular mechanisms of cancer induction. One laboratory concerned with this intricate problem is that of Professor Gerald N. Wogan at the Massachusetts Institute of Technology. The researchers have shown that aflatoxin B_1 binds to DNA, thereby apparently disturbing normal cell function. The exact mechanism—the steps from binding to uncontrolled growth of a cancerous cell—is still largely a mystery; its unravelling would mean a big step toward understanding and possibly preventing certain cancers.

Aside from this important basic research, the group's efforts also focus on practical medical aspects. Currently, a sensitive method for measuring minute amounts of aflatoxin in urine samples is being devised. Detection of aflatoxin or its metabolic products could provide valuable information about the metabolism of this toxin in the body, and it would be a warning about the exposure to aflatoxin and possible liver damage.

Another approach to assess human exposure has been the use of epidemiological studies, where scientists have looked for a possible correlation between the consumption of aflatoxin-contaminated foods and the incidence of liver cancer. Surveys were carried out in Africa and Asia where high temperature, humidity, and poor harvest and storage methods favor mold infestation. In one investigation, led by Professor Ronald C. Shank (then at M.I.T. and now at U.C. Irvine), food samples were collected from markets and households in Thailand and Hongkong. The research team found that about 80 percent of the peanut samples and 50 percent of the rice, corn, beans, and other cereals were infected with molds; about one-third of the contaminated samples were toxic or produced tumors in laboratory rats. Simultaneously conducted hospital studies, in which liver carcinoma cases were registered, revealed that in a district where the food contamination had been ten times higher than in another, the incidence of the liver disease was three times higher than in the district with low aflatoxin contamination. Epidemiological information like this does not necessarily establish a cause-effect relationship, but it strongly

suggests that the risk of liver cancer is greatly increased by the exposure to aflatoxin.

The prevention of mold contamination, therefore, has to be a high priority concern, especially since it is difficult to detoxify foodstuffs. Better harvesting techniques, sufficient drying, and adequate storage could greatly reduce toxin formation. Prevention measures might even have to be extended to preharvest time, since recent reports show that *Aspergillus flavus* can also invade insect-damaged or mechanically-damaged plants in the field. The Food and Agricultural Organization (FAO) of the United Nations has set a tolerance level of 30 ppb (parts per billion) for mycotoxins in foods. This level, it admits, is rather high, but in light of increasing food scarcity (40 percent of the world's annual harvest is lost through pests and rodents), the FAO takes the view that perhaps the danger of malnutrition is greater than the danger of contracting liver cancer from eating aflatoxin-contaminated foods. An understandable view, but it could lead to a two-standard world in terms of mycotoxins —one for the poor, one for the rich.

In the U.S., the Food and Drug Administration (FDA) has set an "action level" for aflatoxins in foods and feeds of 20 ppb (25 ppb for raw shelled peanuts), i.e., the FDA will prohibit the shipment in interstate commerce of commodities that exceed this level, and the agency encourages local authorities to take similar actions in intrastate commerce.

Staples particularly susceptible to mold infestation are peanuts, corn, cottonseed, and imported items like pistachio and Brazil nuts. Spoilage molds grow also well on fruits, red pepper, onions, or even dried fish, as the author found during a study in Nigeria.

Many U.S. manufacturers have now introduced careful sorting procedures of their raw material, which minimizes the possible contamination of products for human consumption. For example, screening of raw peanuts with subsequent roasting can reduce initial aflatoxin contamination to one-third. Inasmuch as rejected lots of peanuts or corn are used as animal feed, however, low levels of aflatoxin can still enter our diet as residues of animal products. Most reports claim that aflatoxin residues in meats or eggs are negligible, because animals metabolize and excrete most of the toxin.

One important animal product, milk, can be contaminated with an aflatoxin metabolite, and this has greatly concerned the dairy industry. When lactating cows feed on aflatoxin B_1-contaminated corn or cottonseed, a small fraction of the B_1 is converted to aflatoxin M_1, and about .6 percent is excreted into the milk. Although this seems a small amount, it can pose a health hazard, especially to infants and young children, the main consumers of milk. Many laboratory tests have shown that young animals are particularly sensitive to the adverse effects of aflatoxins. And preliminary studies suggest that the potency of aflatoxin M_1 is about the same as that of aflatoxin B_1.

The FDA has established an action level of 0.5 ppb for aflatoxin M_1 in fluid milk. In the fall of 1978 30,000 gallons of milk and $125,000 worth of dairy products had to be dumped in Arizona, because the M_1-contamination had greatly exceeded this level. Testing of feedstuffs to be used for dairy cattle is now strongly recommended by FDA officials and dairy councils. The large-scale survey of milk is still hampered by inefficient and time-consuming test procedures. Professor Dennis Hsieh and his group at the Department of Environmental Toxicology at U.C., Davis, are currently developing a more accurate and simplified method for detecting aflatoxin M_1 in milk.

The toxicology group has been engaged in aflatoxin research for many years. One effort has been to compare the effects of aflatoxin in different animal species. This is an important aspect, since—to complicate matters—the response to aflatoxin varies greatly among species. For example, the rat is susceptible to the carcinogenic action of aflatoxin, whereas the rhesus monkey and the mouse are fairly resistant. By comparing the animals in their ability to "handle" aflatoxin, the researchers hope to be able to estimate human susceptibility.

The effects on humans are obviously difficult to test, since it is impossible to conduct *in vivo* studies on human subjects; some indications, however, have been obtained from *in vitro* studies. Human liver tissue from medical sources was incubated with aflatoxin to see how the liver enzymes metabolize the toxin. The liver is the major "processing factory" for incoming nutrients, drugs, etc.; certain enzymatic actions "detoxify," whereas others "activate" a compound; the aflatoxins, therefore, become partly detoxified and partly activated to a potent carcinogen. These competing processes vary among species and probably account largely for their different susceptibilities.

Results from the incubation studies suggest that the human liver detoxifies more aflatoxin than the rat liver, and hence man seems to be more resistant than the rat. Scientists, however, are careful to draw conclusions from the few *in vitro* studies; the "real life" situation could be very different. *In vivo* experiments with animals have demonstrated that susceptibility to aflatoxin is greatly influenced by the individual's strain, gender, health, and nutritional status.

The "mycotoxin story" shows that yet another group of compounds, this time not man-made pollutants but nature's own products, has to be added to the list of hazardous substances. But before totally condemning the molds, a word should be said in favor of them. Some produce important antibiotics: penicillin, streptomycin, or tetracyclines. In fact, the line between toxin and antibiotic is not well defined; many mycotoxins were discovered when new antibiotics were being sought. Patulin has some antibiotic activity and was actually tested to combat the common cold, but was abandoned because of adverse side effects. Sometimes a mycotoxin can, with a little chemical modification, be turned into a useful pharmacological agent; an example is zearalanol, which is produced commercially from the estrogenic mycotoxin, zearalenone, and is marketed as a growth-promoting agent for livestock.

There are also fungi used in the fermentation industry to produce "natural" food colors and preservatives, like carotenes and citric acid, and there are molds that ferment Camembert and Roquefort cheeses.

While the scientific struggle to sort out the good fungi from the bad ones continues, the practical distinction is clear: There is tasty cheese, and there is moldy bread.

TABLE 1. Major Mycotoxins, Their Origins and Biological Activity.

Mycotoxin	Fungus	Biological Activity
Aflatoxins	*Aspergillus flavus*	Liver toxin and carcinogen
Cytochalasins	*A. clavatus*	Inhibition of cell division
Ergot alkaloids	*Claviceps purpurea*	Ergotism
Luteoskyrin	*Penicillium islandicum*	Liver toxin and carcinogen
Ochratoxin	*A. ochraceus*	Kidney toxin
Patulin	*A. clavatus*	Carcinogen
Sporidesmin	*Pithomyces chartarum*	Facial eczema
Sterigmatocystin	*A. flavus*	Liver carcinogen
Tremorgens	*A. clavatus*	Tremors
Trichotecenes	*Fusarium spp.*	Alimentary toxic aleukia,
	Stachybotrys alternans	Stachybotryotoxicosis
Zearalenone	*Fusarium graminearum*	Hyperestrogenic syndrome

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