National Institute of Environmental Health Sciences

Unraveling How a Natural Toxin Contributes to Liver Cancer

NIEHS-funded research has found ways to protect people from a disease caused by a fungus.

The National Institute of Environmental Health Sciences (NIEHS) has supported decades of research on aflatoxin, a harmful compound produced by certain fungi. People can accidentally consume aflatoxin by eating tainted corn, peanuts, and some grains. Risk of exposure is greater in regions where food safety is not or cannot be enforced.[38]

Extreme temperatures and weather conditions could lead to more toxic fungal outbreaks in food.[37]

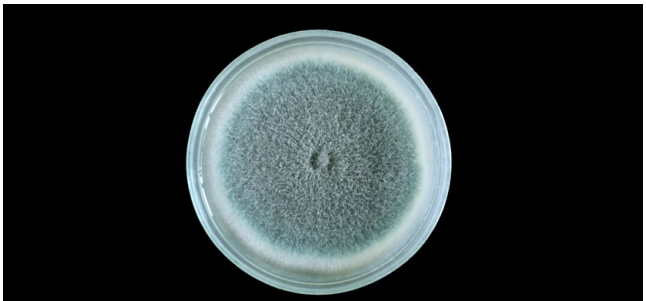
The health effects of aflatoxin exposure depend on how much is consumed and for how long. Eating highly contaminated food over the short term can cause sudden, severe reactions, like vomiting, liver failure, and even death.[38] Lower aflatoxin exposure over years can eventually lead to liver cancer.[19,20]

Research also shows that infection with the hepatitis B virus increases the risk of liver cancer among people exposed to aflatoxin.[8,9]

"It's like a conspiratorial relationship," said NIEHS grant recipient John Groopman, Ph.D., an aflatoxin expert at Johns Hopkins University. "The hepatitis B virus drives inflammation and cell growth in the liver that worsen the damage from aflatoxin."

"This is an interesting example of how different exposures can interact to compound health effects," added Kimberly McAllister, Ph.D., program administrator for the NIEHS Genes, Environment, and Health Branch.

To study whether someone has been exposed to aflatoxin or if a treatment will work, researchers look for clues called biomarkers. Biomarkers are molecules found in the body that represent a biological process of interest.[39]



The fungus Aspergillus flavus produces aflatoxin.

Marking Milestones

Pinpointing the Problem: Researchers found that a toxic form of aflatoxin, activated during metabolism, kickstarts the cancer process by attaching to DNA.[6]

Identifying Signs of Exposure: Scientists identified biomarkers of aflatoxin exposure in urine and blood.[7,10,11]

Validating Biomarkers: Research teams validated the use of blood and urinary biomarkers of aflatoxin exposure.[15,16,17,18]

Uncovering Health Effects: Investigators suggested that aflatoxin exposure may escalate the cancer-causing potential of the hepatitis B virus.[21,22]

Testing Interventions: Studies with animals and humans indicated that the drug oltipraz protected against aflatoxin exposure.[13,14,26,27] A less expensive intervention — hot water infused with broccoli sprouts — also conferred protection among people at risk of exposure.[33]

Collaborating Internationally: Collaborative dedication has enabled scientists to design aflatoxin studies, interpret data, and share findings over the course of decades.[36,38]

Making Health Decisions: The International Agency for Research on Cancer classified aflatoxin as cancer-causing to humans in 1993.[23]

Then and Now

- **Then:** Researchers described a toxic structure that aflatoxin forms with DNA.[6]
  Now: The toxic structure can be used as a urinary biomarker of aflatoxin exposure.[7]
- **Then:** Investigators observed that aflatoxin exposure may exacerbate the cancer-causing effects of the hepatitis B virus.[21,22]
  Now: Hepatitis B vaccination can prevent additional aflatoxin-related health effects.
- **Then:** Because of strict regulatory guidelines for aflatoxin levels in food and animal feed, exposure was not considered a major public health concern in the U.S.
  Now: Researchers observed increased aflatoxin exposure in Texas that may indicate shifting weather conditions favorable to fungal growth in the Southern and Southwest regions of the U.S.[37]

Milestones

This page shows a timeline with important dates and corresponding details about aflatoxin research. *Note: Some of these milestones may not appear in the text-accessible files used by TYY and TDD devices. For the full text, please see the separate PDF called "Unraveling How a Natural Toxin Contributes to Liver Cancer: Milestones."*

Fundamental Questions | Application and Synthesis | Implementation and Adjustment | Policy and Practice | Impact

1961

Described "turkey X disease" as the cause of numerous deaths on British farms among young turkeys and ducklings that ate peanut meal imported from Brazil; observed liver tumors in rats fed toxic Brazilian peanut meal; found chemical similarities between toxic extracts from Brazilian peanuts and extracts from a fungus called Aspergillus flavus, and that ducklings fed either substance developed liver lesions and died.[1*,2*,3*]

1963

Synthesized and described two major aflatoxins produced by Aspergillus flavus.[4*]

1974

Found that low aflatoxin doses could lead to liver cancer in rats.[5*]

1977

Described a toxic structure, called an adduct, that aflatoxin forms with DNA.[6]

1981

Showed that the adduct can be used as a urinary biomarker of aflatoxin exposure.[7]

1983-1992

Indicated that the hepatitis B virus was a major risk factor for liver cancer.[8,9*]

1987-1988

Identified a biomarker in the blood that is associated with aflatoxin intake.[10,11]

1991-1996

Found that a drug called oltipraz protects aflatoxin-exposed rats from liver cancer.[12,*13,14]

1992

Validated use of blood and urinary biomarkers of aflatoxin exposure.[15,16,*17,18*]

1992-1997

Provided evidence from a large cohort in Shanghai that aflatoxin exposure contributes to liver cancer; suggested that aflatoxin exposure may enhance the cancer-causing potential of the hepatitis B virus.[19,20,*21,22]

1993

The International Agency for Research on Cancer classified aflatoxin as cancer-causing in humans.[23*]

1994

Identified liver proteins that activate aflatoxin into a toxic form.[24]

1997

Suggested that blood biomarkers can be useful for monitoring efficacy of aflatoxin exposure interventions in populations, but may be limited in identifying individuals destined to develop liver cancer.[25]

1998-1999

Used biomarkers to show that the drug oltipraz could reduce cancer risk in aflatoxin-exposed volunteers.[26,27]

2001

Indicated that ingesting a derivative of the plant compound chlorophyll could be a practical way to protect aflatoxin-exposed individuals from liver cancer.[28]

2002

Noted that aflatoxin exposure begins in the uterus and may affect child growth.[29,30,31*]

2005

Showed that a post-harvest technique to limit aflatoxin contamination in groundnuts reduced exposure among subsistence farmers in West Africa; observed that drinking hot water infused with broccoli sprouts may interrupt the toxic effects of aflatoxin exposure.[32,33]

2013

Documented that a food policy reform that incentivized farming rice instead of corn led to a decrease in aflatoxin exposure and reduced the death rate from liver cancer.[34]

2015

NIEHS-funded research helped inform a report published by the International Agency for Research on Cancer to guide decision-makers in reducing aflatoxin exposures in low- and middle-income countries.[35*]

2018

Synthesized results of a 25-year study investigating relationships between hepatitis B infection, aflatoxin exposure, and liver cancer.[36]

2021

Observed an increase in aflatoxin exposure in blood samples collected from Texas residents from 2004 through 2014 that may reflect increasing drought and higher temperatures favorable to fungal growth.[37]

NIH National Institute of Environmental Health Sciences

Research for the milestones highlighted above, except in cases marked with an asterisk, was supported through the following NIEHS grants: P01ES006052, P30ES003819, R01ES003755

Seeking Interventions, Tracking Trends

For decades, liver cancer was the leading cause of cancer deaths.[36] To investigate causes and potential solutions, a team partly funded by NIEHS followed more than 1,600 residents over 25 years. About half had hepatitis B, a known risk factor for liver cancer.[8,9]

Of 201 identified cases of liver cancer, around 50% were associated with signs of aflatoxin exposure. The finding highlighted the chemical's ability to cause cancer, the researchers noted.[36]

"Residents were being exposed through their diet, which for a time relied heavily on corn," said Groopman, a study co-author.

In search of health interventions for aflatoxin-exposed individuals, Groopman, longtime collaborator Thomas Kensler, Ph.D., and colleagues investigated the effects of a drug called oltipraz among volunteers. The team found that oltipraz conferred protection in different ways depending on the prescribed drug regimen. A high dose of oltipraz taken weekly for a month inhibited activation of aflatoxin into a toxic form. Daily intake of a lower dose improved elimination of aflatoxin from the body.[26,27]

Because oltipraz is expensive and can have side effects, the researchers also explored safer, more affordable interventions. In 2005, they reported on the effects of drinking hot water infused with broccoli sprouts.[33] The sprouts contain a chemical that has anti-cancer properties after being digested. Although study results varied widely, overall, the broccoli sprout drink appeared to interrupt the toxic effects of aflatoxin exposure, according to Groopman.

Broccoli sprouts contain a chemical that appears to interrupt the toxic effects of aflatoxin exposure.

Reporting in 2013, Groopman and team uncovered another important finding: Agricultural reforms that shifted the focus from corn to rice consumption led to a steep decline in aflatoxin exposure and, consequently, reduced liver cancer risk.[34]

"We are still seeing a decline in liver cancer that is very likely due to the reduction of aflatoxin exposure," Groopman noted.

Corn can harbor a fungus that produces aflatoxin. (Photo courtesy of John Groopman)

Challenges and Solutions

Challenge: Researchers needed a way to determine whether people were exposed to aflatoxin.

Solution: They identified biomarkers in urine and blood associated with aflatoxin metabolism.[15,16,17,18]

Challenge: Investigators were unsure about which liver proteins activate the toxic form of aflatoxin.

Solution: They identified metabolic proteins that cause aflatoxin to form a toxic structure with DNA.[24]

Challenge: Studies evaluating trends in human aflatoxin exposure in the U.S. did not exist.

Solution: Researchers tested blood samples from two Texas populations and observed an increase in aflatoxin exposure from 2004 through 2014.[37]