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Ochratoxin-A: Its Cancer Risk and Potential for Exposure

Ochratoxin-A (OTA) is a naturally occurring toxin produced by two main types of fungi (mold), *Aspergillus* and *Penicillium*. Around the world, OTA is found most frequently in stored grain. OTA makes its way into a variety of food and beverages, particularly cereal and grain products, but also dried fruit, wine, coffee, beer, cocoa, juices, spices, pork, poultry and dairy products. There is increasing concern in many countries that OTA may be linked to kidney disease and possibly cancer. There is some evidence that OTA can cause damage to DNA. There is also evidence that OTA can cause kidney tumors in both male and female rats as well as mammary gland (breast) tumors in female rats. OTA has been found in human blood, tissue and breast milk in several countries. Scientists cannot yet conclude whether or not exposure to OTA causes cancer in humans—more research is needed. The United States (US) Food and Drug Administration (FDA) is currently conducting a multi-year monitoring program in order to determine if there is a need for regulatory limits for OTA in food in the US. Better farm management practices to prevent the occurrence of OTA are being implemented. Methods for decontaminating food supplies and preventing OTA toxicity are also being developed. This fact sheet focuses on the occurrence of OTA in food around the world, the extent to which humans are exposed, and how OTA may play a role in the development of human cancers.

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What is OTA and where does it come from?

OTA is a mycotoxin, which is a naturally occurring toxic chemical produced by fungi. Two main types of fungi produce OTA: *Aspergillus* and *Penicillium*. Scientists first discovered OTA in 1965 while studying mold in corn meal. In tropical regions, OTA is produced by *Aspergillus* species of fungi. In temperate regions, OTA is produced by *Penicillium* species. These two types of fungi, and the OTA they produce, are most commonly found as contaminants in stored supplies of grain but also occur in other raw and processed foods and beverages.

Why did BCERF select OTA for review?

The National Toxicology Program (NTP) has identified 42 chemicals (of the chemicals it has tested) that cause mammary gland tumors in laboratory animals. The Cornell Program on Breast Cancer and Environmental Risk Factors (BCERF) has made a priority to study some of these chemicals that have the greatest potential for human exposure. Ochratoxin-A is one of the 42 chemicals found to cause mammary tumors in laboratory animals.

In some countries, OTA is found in food and beverages often enough and at high enough levels to cause concern for human safety. OTA has been linked to kidney disease and may pose a cancer risk. This review was conducted to further assess the cancer risk of OTA and the risk of OTA exposure both worldwide and in the US.

What information is used by BCERF to evaluate OTA's cancer risk?

BCERF researchers use a variety of information in their evaluations of chemicals. Studies that look at cancer incidence in human populations provide valuable information. When human data are not available, information from studies of laboratory animals may provide clues about what effects might be expected in people. Although chemicals do not always cause the same effects in humans as they do in animals, laboratory animals can provide important information on the potential risks to human populations. Chemicals that are known carcinogens in humans have been found to also cause cancer in laboratory animals. Studies on chemical occurrence, exposure, cancer modes of action, non-cancer effects, regulatory policy and risk management practices are also used in BCERF risk evaluations.

Does OTA affect cancer risk in laboratory animals?

Studies using laboratory animals tested the effects of OTA fed to rats and mice compared to animals fed diets with no OTA (controls). These studies show that OTA exposure causes tumors of the kidney in male and female rats and male mice and also mammary gland (breast) tumors in female rats. There is some evidence that OTA may cause liver tumors in female mice, but more data are needed to confirm this finding.

The International Agency for Research on Cancer (IARC) has classified OTA as a "possible human carcinogen" based on these and other studies.

MAMMARY GLAND TUMORS

Two studies have demonstrated higher levels of mammary gland tumors in female rats exposed to OTA than in unexposed female controls. No mammary gland tumor data were reported for male rats in these studies.

KIDNEY TUMORS

Several studies have shown that male mice develop kidney tumors after exposure to OTA in their diet. Most studies have not included female mice. In one study of both male and female mice, OTA caused kidney tumors in male but not female mice. OTA caused more kidney tumors in male and female rats fed OTA for two years compared to controls.

LIVER TUMORS

There is some evidence that OTA may cause liver tumors in mice. In one study, tumors of the liver were observed in female mice fed OTA in their diet, but not in male mice. No tumors of the liver were found in male or female rats fed OTA for two years. It is not uncommon for such species differences to be observed.

Does OTA affect cancer risk in humans?

Currently there is not enough scientific information to determine whether or not OTA causes cancer in humans. Cancer risk to human populations exposed to OTA has not been adequately studied.

Studies examining the set of kidney diseases collectively known as Balkan Endemic Nephropathy (BEN) provide some clues about the possible health effects of OTA. Some studies have shown a relationship between the occurrence of BEN among populations in Eastern Europe and OTA exposure via contaminated food.

Other studies have also shown a high incidence of kidney cancer and cancer of the urinary tract in some BEN-afflicted populations. Together, these data suggest that OTA may play a role in human kidney cancer.

One study has investigated a possible relationship between OTA exposure and testicular cancer. Positive associations were found between the incidence of testicular cancer and the consumption of foods typically associated with OTA contamination, such as coffee and pork. However, no causal relationship can be made from this type of study.

No human populations have been studied to assess whether OTA affects the risk of developing breast cancer. Studies in which OTA-exposed individuals are compared to unexposed individuals are needed before a conclusion can be made about a causal relationship between OTA exposure and human cancer.

To adequately assess the human cancer risk of OTA, a variety of factors must be considered. Specific exposure information is needed along with ample follow-up time. Large sample sizes improve the ability to detect actual effects. It is also important to control for confounding factors that may also affect cancer risk. Studies should also include adequate numbers of both males and females. Without thorough studies that take these factors into account, it is not possible to conclude whether or not exposure to OTA increases cancer risk in humans.

Do we know how OTA may affect cancer risk?

Scientists do not yet know exactly how OTA may cause cancer. Some data show that OTA may be able to damage DNA, but other data do not show any DNA damage from OTA. DNA damage can play a role in cancer

formation. OTA may act indirectly by affecting certain processes in the body, such as cell damage, that lead to the formation of other substances that may cause damage to DNA. Studies continue to be done to further understand how OTA may cause cancer.

In what kinds of foods has OTA been found?

OTA is found in a variety of foods and beverages, including both plant-based products, such as grains, beans, coffee and wine, and animal products such as milk, cheese and meat. OTA can be found in raw commodities such as stored grain and also processed foods like baked goods. Table 1 provides examples of the many types of foods and beverages where OTA contamination has been found. Not all OTA-contaminated foods are included here.

In what countries has OTA been found in food?

The occurrence of OTA is widespread across both temperate and tropical regions of the world. Table 2 lists many of the countries in which OTA occurs (but data on OTA occurrence are not available from all countries). Most data come from European countries and

Canada. Very little data is currently available from certain regions of the world, such as Asia and Africa. More complete data on the occurrence of OTA is needed from many countries, including the US.

At what levels has OTA been found in food?

OTA has been found in food and beverages at both low and high levels in many countries. While the molds that produce OTA may be visible on contaminated commodities, no studies were found citing cases where OTA was detectable by taste or smell in food or beverages.

Table 1. Examples of Ochratoxin-A in Food and Beverages*

Food	Beverages
Cereal grains, including corn, wheat, barley, flour, oats, rye, rice, bran and semolina	Wine: red, white and rose
Beans: coffee, cocoa, soy and others	Coffee
Malt	Beer and other malt beverages
Cheese and other dairy products	Milk
Dried fruit	Fruit juices
Pork and pork products	
Poultry and poultry products, including eggs	
Spices	
Nuts	
Peas and other legumes	

**Includes representative examples. This list is not comprehensive and does not include all raw or processed food products in which OTA may be found.*

Most often, OTA occurs in food and beverages at levels detectable only by laboratory analysis.

Data on the occurrence of OTA in food and beverages are not available for many commodities in many countries. The data that are available are often out of date and/or incomplete. It is also difficult to compare OTA levels between countries or between types of food.

Some of the highest levels of OTA have been found in cereal grains in Eastern Europe. For example, in Poland OTA levels were found in rye flour at levels up to 5,410 micrograms OTA per kilogram food (5,410 $\mu\text{g}/\text{kg}$) (2.2 kg = 1 lb). OTA levels in barley in Czechoslovakia have been found to be as high as 3,800 $\mu\text{g}/\text{kg}$. The highest OTA levels elsewhere tend to be much lower. For example, studies have reported such high OTA levels as: 120 $\mu\text{g}/\text{kg}$ in rye (Denmark), 442 $\mu\text{g}/\text{kg}$ in peas and beans (Sweden), 360 $\mu\text{g}/\text{kg}$ in coffee beans (US), and 200 $\mu\text{g}/\text{kg}$ in corn (France).

In many countries studies continue to find much lower levels of OTA across a variety of commodities. The OTA levels described above are given only as examples of some of the highest levels that have been found. OTA is often not detected in food at all. Research continues in many places to better understand how much OTA is in food.

Does OTA survive cooking, baking and other food processing?

The effects of heating and cooking processes on OTA contamination have been found to vary greatly. In some studies, OTA has broken down from heating and cooking, but in other studies OTA remained in the final baked or cooked products. The most variable results come from studies of coffee roasting in which remaining OTA levels range from 0-100%, depending on roasting conditions, contamination levels and measurement methods used. Scientists are working to better understand the conditions under which OTA degrades or

remains intact throughout food processing.

Who is exposed to OTA and how is exposure measured?

Many people around the world are exposed to OTA and many more have the potential to be exposed. The wide dispersal of food made possible by modern transportation and trade makes exposure more likely. It is not possible to know with certainty whether a population or an individual has been exposed without confirming exposure using one or more methods.

It is possible to verify exposure to OTA by directly measuring OTA levels in human blood, breast milk and some tissues. This is the most direct type of exposure measurement. OTA is metabolized slowly in the human body so it tends to remain present for several months or more allowing for measurement for a length of time after exposure. OTA has been found in human blood and breast milk in several European countries at levels sufficient to cause concern.

Exposure can also be estimated by measuring OTA levels in contaminated food that may have been consumed. Studies on some foods show that OTA levels often vary greatly from one batch of raw or processed food to the next. No comprehensive estimates currently exist on OTA levels in foods that comprise a typical American diet.

In some cases, exposure to OTA has also been estimated by sampling air and dust in households or workplaces, such as farms or food processing facilities, where OTA contamination is a suspected problem.

How much OTA is considered tolerable for people to ingest?

Several organizations in Europe have estimated tolerable levels of OTA exposure. These are levels of OTA that experts believe a person may ingest on a daily or weekly basis without harm over a lifetime. The Joint Expert

Table 2. Some Countries in which Ochratoxin-A Occurs in Food and/or Beverages*

Australia	El Salvador	Russia
Austria	France	Saudi Arabia
Belgium	Germany	Senegal
Brazil	Greece	Sierra Leon
Britain	Hungary	Slovakia
Bulgaria	India	Sweden
Canada	Italy	Switzerland
Chile	Japan	Thailand
Czech Republic	Netherlands	Turkey
Denmark	Norway	United States
Egypt	Poland	Yugoslavia

**This list is not comprehensive and does not necessarily include all countries in which OTA may occur in food.*

Committee on Food Additives (JECFA) established the Provisional Tolerable Weekly Intake (PTWI) of 100 nanograms OTA per kilogram body weight per week (100 ng/kg bw/week) (1 billion ng=1 kg). This estimate is nearly equal to 14 nanograms per kilogram body weight per day (14 ng/kg bw/day), the upper limit of the range proposed by the European Commission Scientific Committee on Food (1.2-14 ng/kg bw/day). Although these estimates are similar, there is still no worldwide consensus on what levels of OTA are considered tolerable for people to ingest. These guidelines are primarily meant to be used by scientists and regulatory agencies in their efforts in food safety protection. Intake guidelines are not intended to be used by consumers for calculating their personal intake levels.

How can the occurrence of OTA be minimized?

It is not possible to entirely prevent the formation of OTA in all places. However, formation can be minimized. Fungi that produce OTA grow best under certain environmental conditions. Factors that influence production of *Aspergillus* and *Penicillium* include temperature, pH and moisture. Eliminating the conditions necessary for fungal growth helps prevent formation of OTA.

In Canada, for example, grain stored in high moisture conditions quickly spoils, often leading to the production of OTA and other fungal toxins. Hot air dryers and ventilation systems are now being used in some countries to quickly dry and cool the grain. Other common agricultural practices can also help keep contamination to a minimum including insect management, proper irrigation and plant nutrition, crop rotation and use of mold-resistant crop varieties.

Cleaning and disinfecting storage and transportation equipment to prevent the cross-contamination of mold can also help minimize OTA formation. The use of other microorganisms that can compete with OTA-producing organisms is another possible method of preventing OTA formation. However, this option carries its own, possibly negative implications, including concerns about human allergies and food adulteration.

Have regulatory limits been established for OTA in food?

No regulations have been established yet for OTA levels in the US food supply. The US Food and Drug Administration (FDA) is currently monitoring levels of OTA in domestic and imported food supplies.

Regulatory limits for domestic and imported foods will be established if the FDA determines there is a great enough risk.

The World Health Organization (WHO) has proposed a maximum limit for OTA in cereals of 5 µg/kg (1 million µg=1 kg). In European Union (EU) countries, the maximum limits for OTA in plant-based food for human consumption are 5 µg/kg for raw cereal grains and 3 µg/kg for processed cereal products. Standards for OTA in other foods and beverages, such as baby foods and coffee, have been established in some countries in Europe and elsewhere, but more standards in many countries are needed.

Current Research and Research Needs

Research continues on many aspects on OTA in order to better understand:

- Where and to what extent OTA occurs
- How to prevent the formation of OTA
- How to minimize OTA contamination in food
- How OTA may cause cancer and other diseases
- How to best regulate OTA in food and beverages to protect public health

More research on OTA and its potential to cause human cancer is needed in the following areas:

- More research is needed to accurately assess the extent of OTA contamination in foods and beverages in many areas of the world, particularly Africa and Asia
- Studies are needed which examine the ways in which OTA may play a role in the development of cancer and other diseases
- Human studies on OTA's cancer risk are needed that include adequate numbers of both women and men and which control for a variety of confounding factors

Conclusions on OTA and Cancer Risk

OTA is a "possible carcinogen" in humans. This is based on data from whole animal studies and laboratory studies of DNA damage:

- OTA causes kidney tumors in male and female rats
- OTA causes mammary gland tumors in female rats but not in mice
- OTA may cause damage to DNA which may increase the risk of cancer

Current human exposure to OTA exists via consumption of OTA-contaminated foods and beverages in many countries around the world. Farm management practices, food decontamination and processing methods are being improved to minimize OTA-contamination.

Many countries have already set standards for OTA in food and beverages. Other countries, including the US, that do not yet have standards for OTA are beginning to look more closely at the potential risks posed by this naturally occurring toxin. ■

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A complete bibliography of references used in the preparation of this fact sheet on “Ochratoxin-A: Its Cancer Risk and Potential for Exposure” is available on the BCERF web site at <http://envirocancer.cornell.edu>

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