# MycoToxin Panel Interpretation Guide

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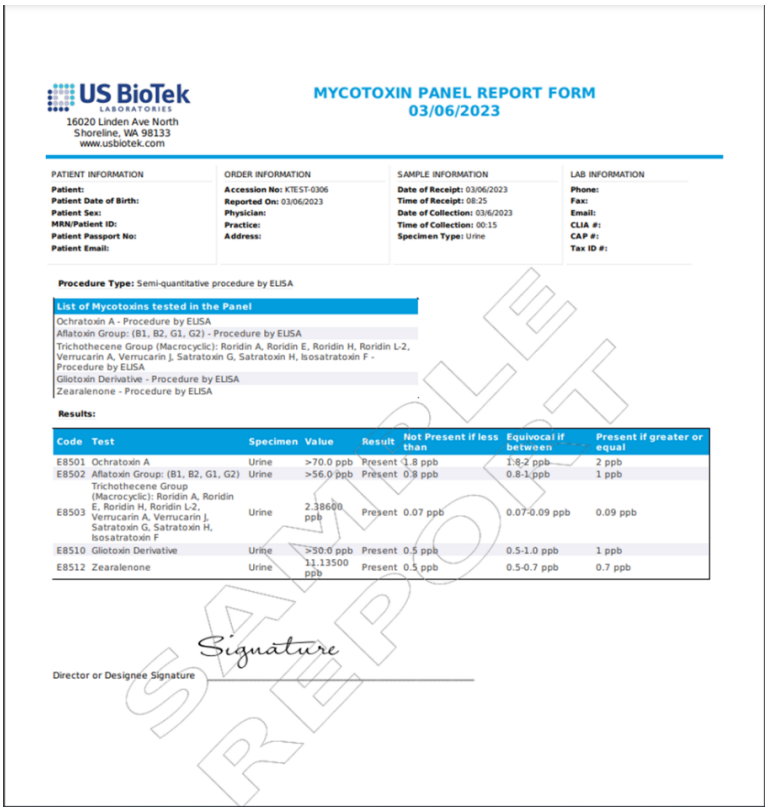
## Introduction

**The RealTime MycoToxin Panel** identifies16 common mold mycotoxins. *Mycotoxins* are secondary metabolites; compounds produced by many varieties of fungus (molds and mushrooms). There are over 99,000 species of fungi and while fungal exposure may occur as direct infection of human tissues, such as athlete's foot or *Aspergillus fumigatus* infection of the lungs, these direct infections do not significantly contribute to measured mycotoxin exposure. Environmental exposures are the most common source and mycotoxin exposures can occur through dermal absorption the ingestion or inhalation of mycotoxins. Most human mycotoxin exposures occur through dietary exposure to contaminated food or through environmental inhalation exposures in damp or moldy environments. Medically important mycotoxins include aflatoxins, citrinin, ergot alkaloids, fumonisins, ochratoxin A, patulin, trichothecenes, and zearalenone.



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**MYCOTOXIN PANEL REPORT FORM**
**03/06/2023**

| PATIENT INFORMATION | ORDER INFORMATION | SAMPLE INFORMATION | LAB INFORMATION |
|---|---|---|---|
| **Patient:** | **Accession No:** KTEST-0306 | **Date of Receipt:** 03/06/2023 | **Phone:** |
| **Patient Date of Birth:** | **Reported On:** 03/06/2023 | **Time of Receipt:** 08:25 | **Fax:** |
| **Patient Sex:** | **Physician:** | **Date of Collection:** 03/6/2023 | **Email:** |
| **MRN/Patient ID:** | **Practice:** | **Time of Collection:** 00:15 | **CLIA #:** |
| **Patient Passport No:** | **Address:** | **Specimen Type:** Urine | **CAP #:** |
| **Patient Email:** | | | **Tax ID #:** |

**Procedure Type:** Semi-quantitative procedure by ELISA

| List of Mycotoxins tested in the Panel |
|---|
| Ochratoxin A - Procedure by ELISA |
| Aflatoxin Group: (B1, B2, G1, G2) - Procedure by ELISA |
| Trichothecene Group (Macrocyclic): Roridin A, Roridin E, Roridin H, Roridin L-2, Verrucarin A, Verrucarin J, Satratoxin G, Satratoxin H, Isosatratoxin F - Procedure by ELISA |
| Gliotoxin Derivative - Procedure by ELISA |
| Zearalenone - Procedure by ELISA |

**Results:**

| Code | Test | Specimen | Value | Result | Not Present if less than | Equivocal if between | Present if greater or equal |
|---|---|---|---|---|---|---|---|
| E8501 | Ochratoxin A | Urine | >70.0 ppb | Present | 1.8 ppb | 1.8-2 ppb | 2 ppb |
| E8502 | Aflatoxin Group: (B1, B2, G1, G2) | Urine | >56.0 ppb | Present | 0.8 ppb | 0.8-1 ppb | 1 ppb |
| E8503 | Trichothecene Group (Macrocyclic): Roridin A, Roridin E, Roridin H, Roridin L-2, Verrucarin A, Verrucarin J, Satratoxin G, Satratoxin H, Isosatratoxin F | Urine | 2.38600 ppb | Present | 0.07 ppb | 0.07-0.09 ppb | 0.09 ppb |
| E8510 | Gliotoxin Derivative | Urine | >50.0 ppb | Present | 0.5 ppb | 0.5-1.0 ppb | 1 ppb |
| E8512 | Zearalenone | Urine | 11.13500 ppb | Present | 0.5 ppb | 0.5-0.7 ppb | 0.7 ppb |

Signature
Director or Designee Signature

SAMPLE REPORT

Molds, and their mycotoxins, have been with us, always. The earliest known mold fossil is about 900 million years old. As members of the kingdom Fungi mold species are ubiquitous and play a vital role in the decomposition of organic matter. Because humans and molds co-evolved on Earth, the human liver contains detoxification enzymes that can degrade small amounts of mycotoxins. Since humans have evolved with the capacity to detoxify mycotoxins, why are mycotoxin exposures now considered significant enough to worry the World Health Organization (WHO) and the Centers for Disease Control (CDC)?

Mycotoxins are currently considered a global *food safety* issue by the CDC and WHO because they are ubiquitous in the food supply. Mycotoxins, like other chemical or metal toxicants, may be found together in foods and may have cumulative or synergistic effects. In the food supply mycotoxin production is enhanced by warm, humid conditions. Mycotoxins in animal feeds can bioaccumulate in meat, eggs, and dairy products. Mycotoxins are typically found in grains, dried nuts, dried fruits or fruit juices, coffee beans, and spices. Mycotoxins found in foods include trichothecenes, fumonisins, ochratoxin A, aflatoxins, and zearalones. Large doses of mycotoxins can result in adverse health effects in both humans and livestock.

Increasing use of tropical and subtropical foodstuffs, food animal bioaccumulation, poor nutrition or decreased nutrient availability have combined to increase human mycotoxin esposure and burden. Most detoxification enzymes require nutrient co-factors. Environmental co-exposures to chemicals, toxic metals, pharmaceuticals, food additives and colorants combine with mycotoxins to increase the overall toxic burden while reducing overall energy production and detoxification capacity.

Mycotoxin-producing fungi may be found in the soil, and mycotoxin exposure is also possible for those exposed to contaminated building materials, although an organic substrate (such as wood cellulose) is necessary before moldy building materials can produce significant amounts of mycotoxins. About half (28/51) of naturally mold-infested building materials had detectable mycotoxins in a recent study. Typically, such exposures occur through inhalation. Most mycotoxins can be produced by multiple species of fungi, and typically, knowing the type of mycotoxin is more important than knowing the type of mold that produced it:

| | Aflatoxin | Gliotoxin | Ochratoxin A | Zearalenone | Roridin E | Verrucarin A |
|---|---|---|---|---|---|---|
| Alternaria | | ■ | | | | |
| Aspergillus Favus | ■ | | | | | |
| A. Fumigatus | | ■ | | | | |
| A. Niger | | | ■ | | | |
| A. ochraceeus | | | ■ | | | |
| A. parasiticus | ■ | | | | | |
| A. Veridictum | | | ■ | | | |
| Cylindrocarpon | | | | | ■ | |
| Dendrodochium | | | | | ■ | ■ |
| Fusarium avenaceum | | | | ■ | | |
| F. cerealis | | | | ■ | | |
| F. clumonrum | | | | ■ | | |
| F. equiseti | | | | ■ | | |
| F. graminearum | | | | ■ | | |
| F. incarnatum | | | | ■ | | |
| F. moniliforme | | | | ■ | | |
| F. verticilloides | | | | ■ | | |
| M. verrucaria | | | | | ■ | ■ |
| Penicilium carbonarius | | ■ | ■ | | | |
| P. nordicum | | ■ | ■ | | | |
| P. stoloniferum | | ■ | ■ | | | |
| P. verrucosum | | ■ | ■ | | | |
| Stachybotrys | | | | | ■ | ■ |
| S. chartarum | | | | | | |
| Trichoderma viride | | ■ | | | | |

Only fungi produce mycotoxins, but not all fungal mycotoxins are harmful to humans. Fungi may produce toxic compounds that affect only plants, invertebrates, or bacteria. The early antibiotic penicillin is a fungal toxin still used in modern medicine, and other mycotoxins are now being studied for their pharmaceutical effects. Human health effects typically arise from either an excessive mycotoxin exposure that overwhelms the individual's detoxification capacity or from an allergic reaction to the mycotoxins. Allergic complications can occur at much lower levels of mold exposure and can produce similar symptoms to a mycotoxin body burden.

## Mycotoxins and Human Health

This guide is focused on the identification and detoxification of molds that may be causing "occult" symptoms. Mold tissue infections, such as athlete's foot or aspergillosis, are beyond the scope of this guide and require medical assessment and treatment. There are two typical types of illness that result from environmental mycotoxin exposure: allergy or mycotoxicosis (accumulation of mycotoxins in the body). Mold allergy or sensitivity may induce or exacerbate asthma or other atopic disorders and either type of illness may result in local or systemic effects, including:

- Mitochondrial dysfunction
- Immunological dysregulation (inflammation)
- Metabolic dysregulation
- Gastrointestinal dysregulation

Each of these disorders requires different types of assessments, interventions and supports:

- Mycotoxicosis (mycotoxin accumulation)
  - "Urine mycotoxin assessment
  - Detoxification support for gut, liver, kidneys, metabolism, mitochondria
- Immunologic reactions (allergy or sensitivity)
  - Mast cell stabilization, anti-inflammatory support, restoration of immunotolerance

Excessive mycotoxin exposure is considered a toxic environmental exposure similar to chemical or metal exposures. Once inhaled or ingested, mycotoxins eventually enter the bloodstream and lymphatic system and cause inflammation and symptoms. Mycotoxins can affect many different biological systems including the liver, mitochondria, the gastrointestinal tract and the GI microbiome. The symptoms that occur with a mycotoxin exposure can vary due to a variety of factors, including:

- Increased age
  - Higher toxic burden, immune and mitochondrial dysfunction, chronic inflammatory disease, loss of GI function, altered gut microbiome, etc.
- Gender and genetics
  - Differential regulation of enzymes by sex hormones
  - Differential expression of detoxification enzymes in males and females
  - Genetic variation in detoxification capacity
- Comorbid disease and/or mitochondrial dysfunction
  - Obesity may exacerbate the liver-toxic effects of some Fusarium mycotoxins (animal study); other chronic inflammatory diseases may have similar effects but studies are needed to confirm effects
- Nutritional status and diet
  - Chemical additives, fiber content, nutrient availability, etc.
- Concomitant mycotoxin, chemical or metal exposures
  - Background chemical exposure, air pollutants, alcohol, pharmaceuticals, smoke, etc. can be cumulative and synergistic
- Allergic reactions to mold exposure and immune system dysregulation
  - Mycotoxins can disrupt the macrophage system and promote inflammatory immune responses from white blood cells
  - Mycotoxin-induced immune stimulation can intensify the inflammatory response to bacterial lipopolysaccharide or LPS (endotoxin) from the gastrointestinal microbiome

The effects of individual mycotoxins are well-documented and reviewed in this chart:

| EFFECTS OF INDIVIDUAL MYCOTOXINS | |
|---|---|
| **Mycotoxin** | **Health Effects (Human And Animal Studies)** |
| Ochratoxin A | Kidney and urinary tract damage, potential cancer induction, neurotoxic, decreased dopamine levels. Disruption of intestinal barrier functions and immune responses. Inhibition of normal fetal development. |
| Aflatoxin Group B1, B2, G1, G2 | Acute toxicity symptoms of jaundice, hepatitis, low-grade fever, malaise, anorexia, abdominal discomfort and tachycardia. Genetic mutation, liver cirrhosis, kidney damage, cancer induction. Disruption of intestinal barrier functions and immune suppression. Inhibition of normal fetal and child development. |
| **Macrocyclic Trichothecene Group** | Inhibition of protein synthesis, protein folding, and antioxidant enzymes. ↑ oxidative stress (ROS), mitochondrial and cellular damage. Symptoms include immune system dysregulation or suppression, nausea & vomiting, dermatitis, bleeding lesions. |
| Roridin A, E, H, L-2 | Inhibition of protein synthesis, protein folding, and antioxidant enzymes. ↑ oxidative stress (ROS), mitochondrial and cellular damage.Symptoms include immune system dysregulation or suppression, nausea & vomiting, dermatitis, bleeding lesions. |
| Verrucarin A, J | Inhibition of protein synthesis, protein folding, and antioxidant enzymes. ↑ oxidative stress (ROS), mitochondrial and cellular damage. Symptoms include immune system dysregulation or suppression, nausea & vomiting, dermatitis, bleeding lesions. |
| Satratoxin G, H | Inhibition of protein synthesis, protein folding, and antioxidant enzymes. ↑ oxidative stress (ROS), mitochondrial and cellular damage. Inhalation induces cellular damage and death of nasal tissues (high dose), acute nasal inflammation (low dose), and olfactory neuroinflammation and damage in animal studies. |
| Isosatratoxin F | Inhibition of protein synthesis, protein folding, and antioxidant enzymes. ↑ oxidative stress (ROS), mitochondrial and cellular damage. |
| Gliotoxin | Genotoxic DNA damage, immune suppression, inflammation, ↑ oxidative stress, cellular damage. Inhibition of angiogenesis. |
| Zearalenone | Genotoxic cancer induction ↑ esophageal, liver, pituitary cancer risk. Liver and kidney damage. May have estrogenic or other hormonal effects that increase risk of infertility. Increased lipid peroxidation and cell damage. Altered amino acid, lipid, and glucose metabolism (animal study). |

While the individual effects of mycotoxins are known and well documented, investigation into the cumulative and synergistic effects of mycotoxin co-exposure, either with other mycotoxins or in conjunction with toxic chemical or metal exposures is needed. What is known at present is that excessive toxic exposure can result in a type of fatty liver disease known as toxicant-associated fatty liver disease (TAFLD). Fatty liver disease is associated with the development of metabolic syndrome and type II diabetes. Both metabolic syndrome and type II diabetes are associated with dysregulation of mitochondrial function and primary biochemical pathways; such disruptions can be detected using **RealTime's** dried urine **Organic Acids Profile**. The **Mycotoxin Panel** can be ordered simultaneously with the **Organic Acids Profile** and the **Environmental Pollutants Profile** as the **RTL-Tox Profile** to provide a more complete overview of the patient's metabolic function and overall toxic burden.

## Mycotoxicosis

*Mycotoxicosis* refers to the symptoms caused by excess mycotoxin exposure. Symptoms typically include vague general symptoms and can affect immune, gastrological, neurological, liver, and kidney functions. Exposures may affect individuals differently, and may be mitigated or exacerbated by diet, genetics and environment as discussed; these same factors may also reduce or exacerbate cancer risks associated with mycotoxin exposures. The exposure symptoms experienced often depend on the specific mycotoxin exposures, the route of exposure (inhalant, ingested, or dermal), and the organs affected by the mycotoxins.

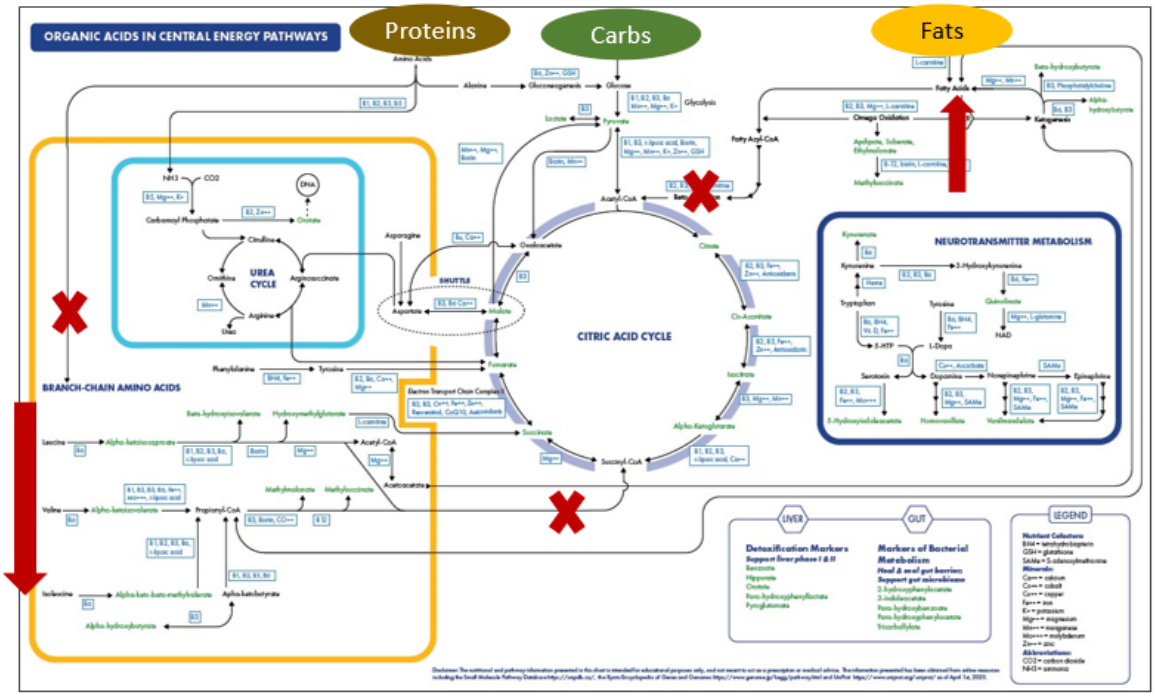
Respiratory symptoms typically occur when mycotoxins are inhaled. Disorders associated with respiratory mycotoxin exposure include asthma, chronic sinus and nasal inflammation, and hypersensitivity pneumonitis. These conditions are associated with IgE-allergic responses to mycotoxins; additional information and strategies for therapeutic intervention may be found in the "**Mold Allergy and Sensitivity**" section. Allergy and sensitivity are invariably associated with immune system dysregulation and can also affect gastrointestinal functions.

Mycotoxins alter immune functions. While many mycotoxin exposures increase inflammation some, such as gliotoxin, are known to suppress immune functions. Immune system tolerance and inflammation is programmed in large part via antigen exposures, however mitochondrial function also plays a large part in regulating immune responses. Mitochondria create the energy that all the cells in the body require for normal functions. Dysregulation of energy production activates pro-inflammatory signaling pathways. Both inflammatory immune signals and mitochondrial dysregulation will impair peripheral and central nervous system functions resulting in mycotoxin-associated neurotoxicity and neurological symptoms. Other mycotoxins may increase the permeability of the blood-brain barrier, allowing further inflammatory compounds, such as bacterial endotoxin from the GI tract into the central nervous system (CNS). Once in the CNS the immune system has difficulty breaking the endotoxin down, and the endotoxin becomes a source of chronic neuroinflammation.

Mycotoxins also directly irritate and inflame the gut mucosal lining and disrupt the balance of the gut microbiome. Inflammation of the GI tract, decreased nutrient assimilation, increased intestinal permeability, altered motility, and alterations in the gut microbiome may result from either allergic responses to ingested molds or directly due to the effects of mycotoxins on the intestinal mucosal cells or the underlying tissues of the GI tract. Depending upon the mycotoxin and dose, symptoms may resemble food poisoning (chills, nausea, vomiting, bloating, abdominal pain, diarrhea, and dizziness); many of these symptoms may occur with allergy reactions as well. Other mycotoxins such as trichothecenes may be associated with poor nutrient assimilation, low blood sugar, loss of gut white blood cells, weight loss and an overall drop in blood cell counts. The alteration of intestinal glucose and water absorption typically results in diarrhea. Much of the damage done to the gut is due to the mycotoxin's negative effects on cell mitochondrial function. Damaged mitochondria secrete inflammatory signals to encourage the deliberate destruction of damaged cells (apoptosis). While eliminating damaged cells can promote healing, too much apoptosis can result in significant tissue destruction. Dysregulation of apoptosis pathways can result in the survival of damaged cells, which become local sources of chronic inflammatory signals.

Mitochondrial dysregulation also contributes to metabolic dysregulation. Animal studies demonstrate dysfunction of lipid, glucose, and amino acid metabolism and may also affect the cardiovascular system and inhibit normal bone formation after mycotoxin exposure. Zearalenone and related mycotoxins may down-regulate the synthesis of branch chain amino acids (AA), glycine, serine, and threonine. Branch chain AAs and serine are important in glucose regulation and immune system signaling. Glycine, serine, and threonine are also important in liver function and detoxification. Threonine also modulates the synthesis of gut mucin proteins essential for normal gut barrier function and microbiome diversity. In addition, serine participates in glycogen storage processes in the liver and regulates genetic expression that may increase the risk of fatty liver disease. Branch-chain amino acid metabolism and glucose regulation can be evaluated using **RealTime's Organic Acids Profile**.

# Mycotoxins dysregulate protein/lipid metabolism



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## Mycotoxicosis: Detoxification and Therapeutic Interventions

Humans and fungi have co-evolved on the planet, and mycotoxin exposure is not a new phenomenon. What is new is the increased toxic burden of chemicals and metals, the nutritional deficiencies of the modern diet, and sedentary lifestyles. All of these factors can increase incidence of comorbid chronic inflammatory conditions that may inhibit detoxification capacity in many individuals. Impaired detoxification capacity then exacerbates the effects of mold exposure. Successful mycotoxin detoxification requires mold allergy management and:

- Elimination of mold exposure
- Reduction of oxidative stress and restoration of antioxidant status
- Support of liver and kidney detoxification pathways including
  - Adequate mitochondrial function
  - Phase I cytochrome P450 enzymes
  - Phase II conjugation enzymes
  - Phase III ATP-dependent cellular export enzymes
- Restoration of digestion, elimination, and gut microbiome diversity
- Reduction of mold-induced cancer risks

### Elimination of Mold Exposure

The first step for any toxic exposure is the elimination of the exposure; this is especially true for cases of mold allergy and mycotoxin exposure. The patient's internal and external environments must both be cleansed of mold. Exposure can be reduced by discarding any potentially mold-exposed clothing, textiles, wood products, or books. Hard surfaces in houses can be cleaned with bleach disinfectant (2.4% sodium hypochlorite) – a study of moldy household surfaces demonstrated that Aspergillus spore allergens were decreased up to 95% after a 30-second exposure, and all other molds were non-viable (could not be cultured) after a 10-minute bleach exposure. If mold re-contamination is likely, appropriate repairs to eliminate sources of excess moisture should also be pursued. Ideally the patient relocates to a mold-free habitation. If relocation is not possible, mold remediation, dehumidifiers and ion-releasing air purifiers may improve the indoor atmosphere. Air filters should be used with caution, and carefully maintained, as the filter pads may provide a substrate for mold growth.

### Restoration of Antioxidant Status

Mitochondria produce reactive oxygen species (ROS) during normal enzyme activity. Mycotoxins can induce mitochondrial dysfunction and increase ROS levels, as can several of the detoxification pathways needed to degrade the mycotoxins. When ROS levels increase and overwhelm the body's antioxidant reserves, oxidative stress occurs. Oxidative stress can further inhibit mitochondrial enzymes and disrupt mitochondrial function and phase I detoxification enzymes found in the liver, kidneys and mitochondria. Toxic exposures and chronic inflammation are both additional sources of oxidative stress which can be further exacerbated by a poor diet lacking in antioxidant vitamins, fruits and vegetables.

Antioxidant status is primarily determined by glutathione levels. Glutathione is the body's primary antioxidant. Whether due to the presence of inherited low activity enzymes, increased oxidative stress, or toxic exposures, not everyone can synthesize enough glutathione. Such individuals may benefit from a plant-rich diet and supplemental glutathione or supplemental nutrients (per manufacturer recommendations) to support glutathione synthesis and antioxidant status:

- Oral liposomal glutathione
- N-acetylcysteine
- Omega-3 fatty acids
- B-vitamins
- Vitamin C 500 mg QD

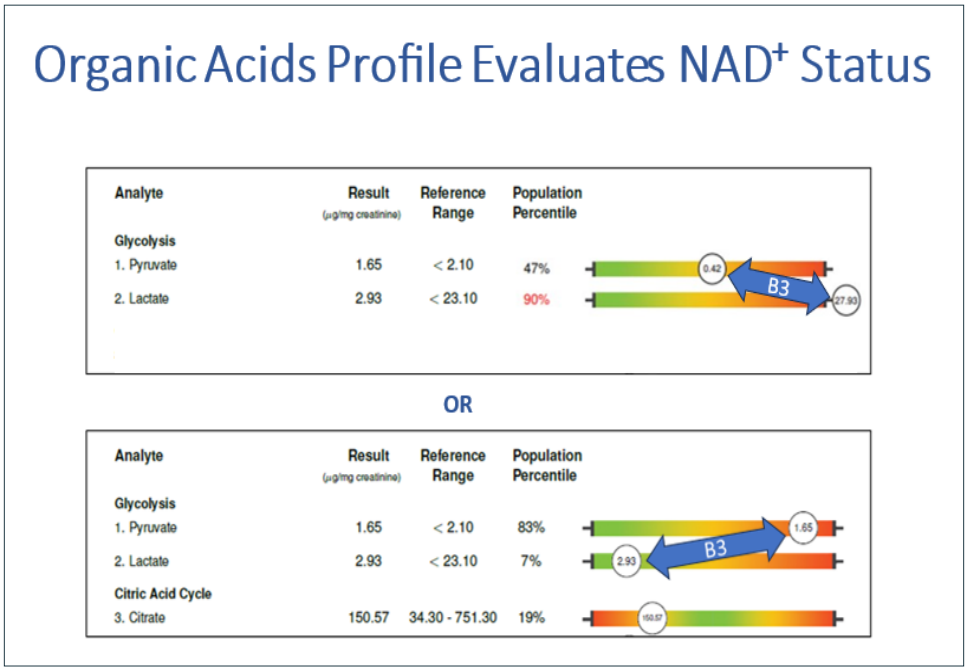
- Vitamin E
- Alpha-lipoic acid
- Selenium is a cofactor for antioxidant enzyme glutathione peroxidase
- Fruits (citrus) and vegetables
- Green tea

## Support Liver, Kidney and Mitochondrial Detoxification Enzymes

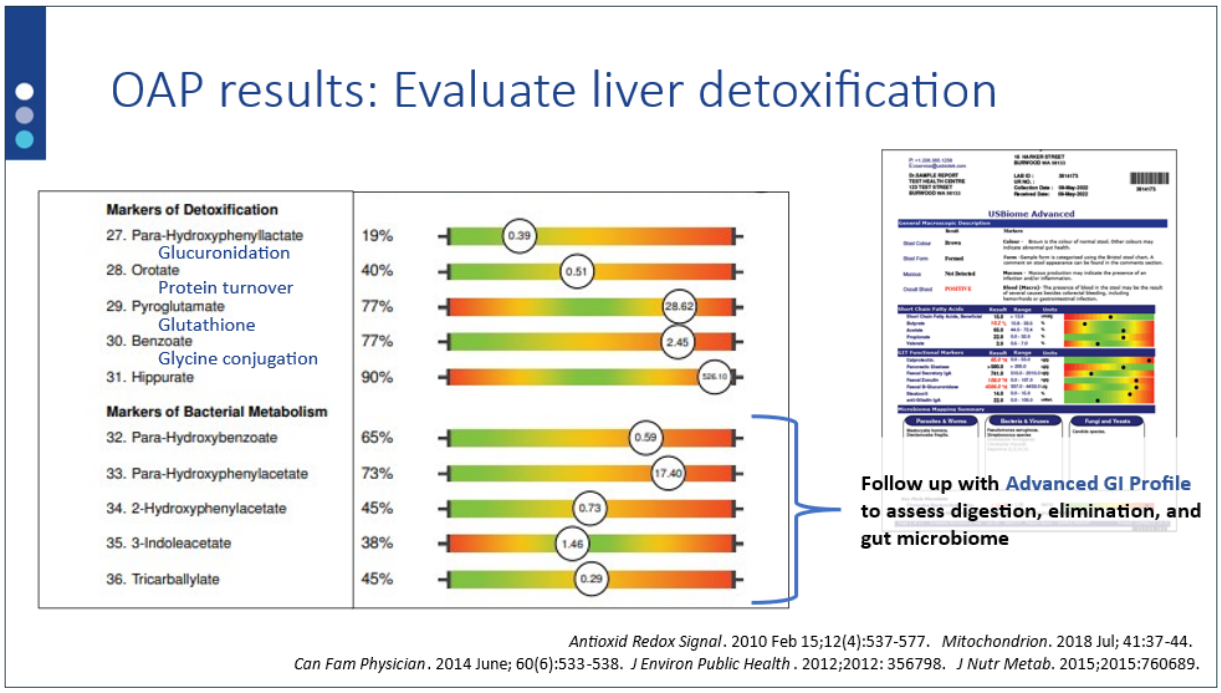
Mycotoxin decontamination requires a series of biochemical conversions and currently little is known about human detoxification of mycotoxins. The cytochrome P450 enzymes necessary for mycotoxin transformation are found in both the mitochondria and the endoplasmic reticulum of cells; liver cells contain 1-2,000 mitochondria per cell to support detoxification processes, and kidney cells are also rich in mitochondria. P450 enzymes found in the mitochondria include the CYP1, CYP2, CYP3, and CYP4 families. These four cytochrome P450 enzyme families participate in mycotoxin degradation and are also involved in drug metabolism, chemical degradation, vitamin D metabolism, steroid hormone synthesis, and lipid synthesis. In addition, both phase II conjugation and phase III cellular export of processed toxins are dependent upon mitochondrial ATP. Specific human enzymes already known for the detoxification of individual mycotoxins include:

- Aflatoxin oxidase [AKR7L; B3, selenium]
- Aldehyde reductase enzymes [ALDH1; B3], [ALDH2; B3]
- Aldo-keto reductase enzymes [AKR enzyme family; B3]
- CYP450 enzymes [B3; iron]

These enzymes and most of the detoxification enzymes and pathways used to degrade mycotoxins are heavily dependent upon nicotinamide adenine dinucleotide ($NAD^+$) or nicotinamide adenine dinucleotide phosphate ($NADP^+$) derived from vitamin B3. Aldehyde reductase and some of the CYP450 enzymes essential for mycotoxin degradation are found in the mitochondria. An assessment of mitochondrial function, liver detoxification and antioxidant status can be obtained from **RealTime's** dried urine **Organic Acids Profile** (OAP) and its interpretation guide. The OAP results provide guidance for necessary mitochondrial pathway nutritional supports and other corrective measures to support mycotoxin degradation and elimination. In addition, a patient's $NAD^+$ status can easily be determined using the **Organic Acids Profile** (below); a wide gap between lactate and pyruvate indicates a lack of interconversion, and probable need for B3 and resveratrol to restore $NAD^+$ and $NAD^+/NADH^+$ ratios.



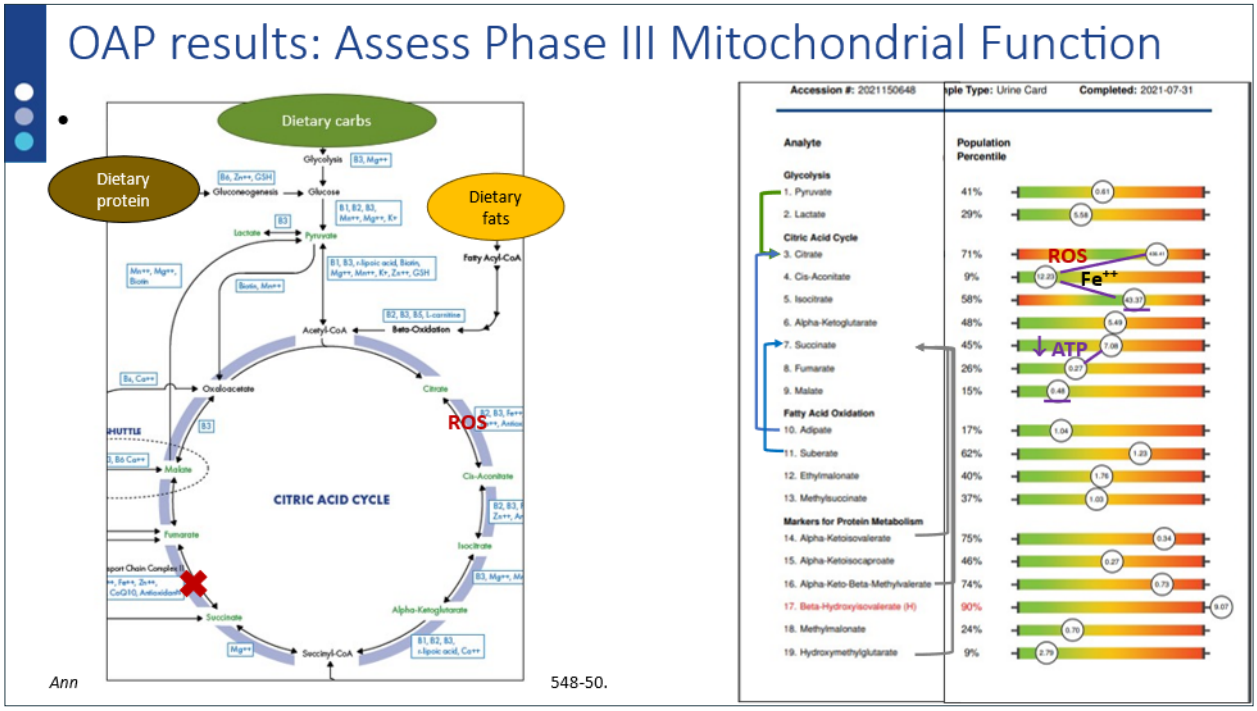
Specific needs for phase I or phase II support may be indicated by the Markers of Detoxification section on the **Organic Acids Profile** (below). If all the analytes in the section are low, it may indicate either a genetic or nutritional phase I inhibition. As seen below, individual analytes provide information regarding specific phase II processes and overall liver status.




*Antioxid Redox Signal*. 2010 Feb 15;12(4):537-577. *Mitochondrion*. 2018 Jul; 41:37-44.
*Can Fam Physician*. 2014 June; 60(6):533-538. *J Environ Public Health*. 2012;2012: 356798. *J Nutr Metab*. 2015;2015:760689.

In each phase of detoxification, in addition to $NAD^+$, the enzymes require specific nutrient supports:

- **Phase I** detoxification occurs as cytochrome P450, oxidase, reductase and dehydrogenase enzymes add a hydroxyl group (-OH) onto organic compounds. This step converts fat-soluble compounds into water-soluble compounds. Some phase I metabolites may be more toxic than the original compound. Supporting phase II and III can help decrease the time these toxic metabolites are in circulation.
  - Toxic metals such as arsenic, cadmium, mercury and lead may inhibit cytochrome P450 enzymes.
  - Nutrients that may support phase I include include vitamin B3, iron, selenium. Plant compounds, such as sulforaphanes found in broccoli and other *Brassica* family vegetables also support detoxification.
- **Phase II** detoxification occurs through a variety of different reactions including glucuronidation, sulfation, methylation, N-acetylation, and conjugation with amino acids or the attachment of glutathione. Phase II support minimizes the amount of time that toxic phase I metabolites are in circulation.
  - Phase II conjugation may be inhibited by arsenic, cadmium, lead, mercury and hexavalant chromium which inhibit the enzyme glutathione S-transferase.
  - Nutrients that may support phase II include reduced glutathione, N-acetyl cysteine (glutathione precursor), B vitamins and calcium-D-glucarate. The amino acids methionine, cysteine, glutamine, glycine, and taurine are also used in Phase II conjugation.
- **Phase III** detoxification occurs when the metabolized xenobiotic is transported out of the cell for excretion in urine or bile. Phase III efflux pumps require ATP produced by mitochondria.
  - Nutrients that may support phase III include B vitamins, magnesium, manganese, iron, alpha-lipoic acid and CoQ10. The need for these nutrients can be evaluated on the dried urine **Organic Acids Profile**.



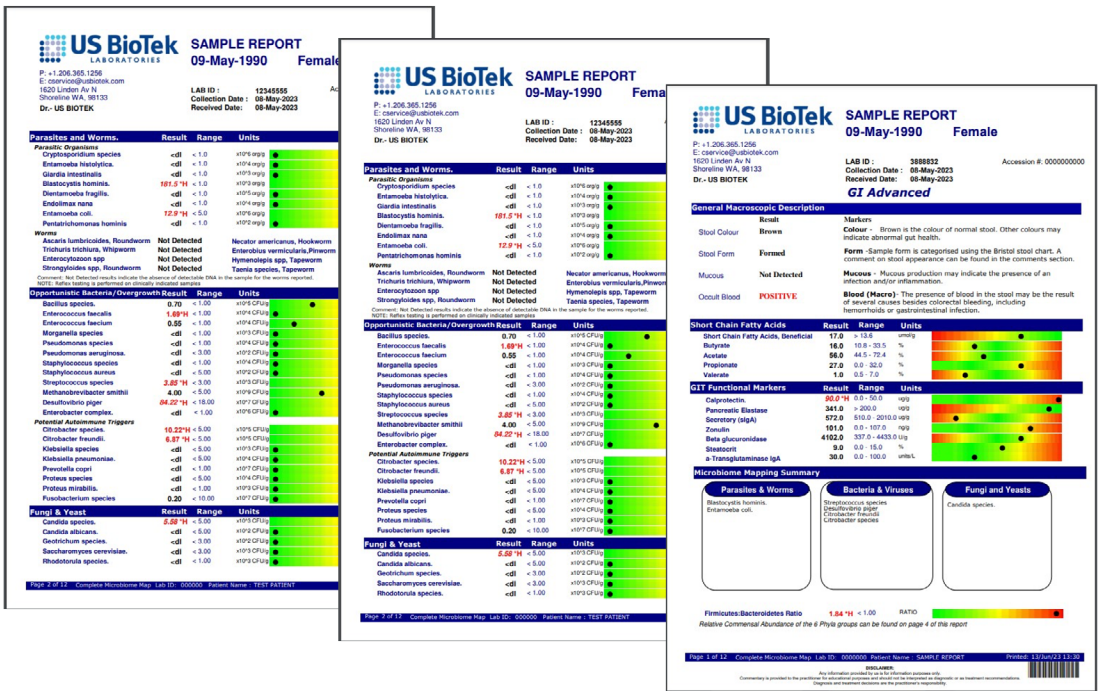

It is easy to see why the symptoms of mitochondrial dysfunction and the symptoms of chronic mycotoxin exposure may be similar. Both can produce vague general symptoms and affect immune, neurological, liver, and kidney functions and may, in some cases, exacerbate certain cancer risks. Allergic reactions to mold exposures may cause similar vague general symptoms; see the "**Mold Allergy or Sensitivity**" section for more information.

## Support Elimination From the Body

Elimination of mycotoxins from the body also requires a functional gastrointestinal system as the mycotoxins processed by the liver are released via bile excretion into the gut. The detoxified mycotoxins are then excreted in the stool. Sauna therapy (heat depuration) may or may not be beneficial for mycotoxins. While sweating has been proven effective for chemicals and some toxic metals, the only human study including sauna therapy used it as part of a much larger protocol that included IV antioxidants, oxygen therapy, and antigen desensitization. There is unfortunately no way to determine which of the treatments was most useful in the elimination of the mycotoxin burden in these patients, however human studies do support the use of sauna in the reduction of overall toxic burden, as toxic metals and chemicals are sweated out.

Since mycotoxins are known to be eliminated in the stool, correction and support of gastrointestinal elimination is necessary and must be accomplished prior to detoxification attempts. Many mycotoxins can undergo biotransformation and degradation in the gastrointestinal lumen or during intestinal assimilation. Evidence is accumulating that certain gut microbiome bacteria have enzymes that can break down mycotoxins into less harmful forms. Other gut bacteria may bind mycotoxins to their cell wall glycans and inactivate them. It is essential that normal digestion, assimilation, motility, and gut barrier functions be restored to facilitate mycotoxin detoxification and elimination. All mycotoxins are small molecules. It is easier for small molecules to pass through a biological mucosal membrane barrier (such as the gut wall or the blood-brain barrier) if the mucosal barrier is already "leaky". Mycotoxin exposures may contribute to mucosal barrier disruption via the inflammation and mucosal damage caused by the mycotoxins. In addition to the contributing factors listed above, the presence of digestive disorders, microbiome disruption (dysbiosis) and psychological stress can further compromise gastrointestinal and gut barrier functions. Gastrointestinal function and gut microbiome status can be best evaluated using **US BioTeks's Advanced GI profile**.

The status of the digestion, elimination and the gastrointestinal microbiome can be evaluated with **RealTime's GI profiles** and their interpretation guide:




Sequestering agents may be used to further bind the mycotoxins in the gut and may not only ensure elimination but minimize the absorption of dietary mycotoxins as well. Effective sequestering agents have been shown to bind mycotoxins, however, they may also bind necessary nutrients and medications. Ideally these agents are taken on an empty stomach away from food, supplements, and medications.

| Sequestering Agent | Benefits | Concerns |
|---|---|---|
| Cholestyramine | *In vitro* efficacy binding ochratoxin A, fumonisins and zearalenone. Animal studies confirm the efficacy for zearalenone. May also bind endotoxin from gut bacteria or environment. | Also binds bile acids, cholesterol. Decreases GI tract macronutrient digestibility and impairs absorption of fats, fatty vitamins A, K (animal studies). |
| Activated carbon (charcoal) | Potential for use during acute exposure. | Variable efficacy in studies. |
| Clays | Calcium montmorillonite effective for aflatoxin B1 and M1 in human and animal studies. Small human studies of Novosil™ support short-term use < 3 gm daily.<br><br>Bentonite efficacy for aflatoxin B1 variable; does not significantly adsorb other mycotoxins. | Variable efficacy dependent upon the type of clay and associated geologic features. |
| Red grape pomace | Animal studies indicate pomace (grape pulp and skins) effective for aflatoxin B1, zearalenone, ochratoxin A and fumonisin B1. | Unknown. Has not been adequately assessed in animal models or human studies. |
| Fiber | Animal studies confirm efficacy for aflatoxin B1, zearalenone, ochratoxin A. | Some fibers may be contaminated by Fusarium molds. |
| Humic or fulvic acids | Non-toxic in early cell culture and animal studies. No mycotoxin efficacy studies in animals or humans. | Have not been adequately assessed in animal models or human studies. |

| | | |
|---|---|---|
| **Probiotics** | *Saccharomyces cerevisiae*<br>*Saccharomyces boulardii*<br><br>*Lactobacillus rhamnosus, Lactobacillus amylovorus, Lactobacillus plantarum, Lactobacillus pentosus,*<br><br>and some Bifidobacteria species can sequester mycotoxins in their cell walls. (Animal studies). | Efficacy strain-dependent.<br><br>High levels of live *S. cerevisiae* in the GI tract may result in yeast overgrowth symptoms. |
| **Algae** | Spirulina and edible seaweeds Ascophyllum, Porphyra, and Palmaria contain polysaccharides and β-glucans that can bind mycotoxins (animal studies). | Animal studies. Have not been adequately assessed in human studies for mold detoxification. |
| **Chlorophyll and Chlorophyllins** | Reduce aflatoxin-induced DNA damage and antioxidant properties (human and animal studies). | Considered safe at oral doses of 100 to 300 mg/day in three divided doses. NOTE: chlorophyllins are semi-synthetic and contain copper. |
| **Flavonoids** | Green tea polyphenols 500-1000 mg daily significantly reduced aflatoxin B1 in human studies.<br><br>Flavonoids have been shown to inhibit environmental fungal growth in laboratory studies.<br><br>Flavones (luteolin, apigenin, tangeritin) inhibited Aspergillus species aflatoxin production in laboratory study. | Not all flavonoids have been adequately assessed for mold/mycotoxin inhibition in animal models or human studies.<br><br>Dried herbs, green tea and other teas may also be sources of mold contamination. |

A recent study in mycotoxin-exposed pigs vs controls demonstrated that a combination supplement containing bentonite, calcarium algae powder (seaweed), and *S. cerevisiae* reduced mycotoxin organ damage and increased mycotoxin excretion. It is unknown which agents in the combination were the most effective, and equally possible that multiple agents are required to fully detoxify, bind, and remove mycotoxins from the body. Additional human studies are required on many of the agents promoted for mold detoxification.

## Decrease Cancer Risks

While some mycotoxins have been definitively associated with cancer risk in human studies, other mycotoxins still require further human studies to firmly establish cancer risks. Since an in-depth review of cancer risk management is beyond the scope of this guide, only a brief overview is provided. As persistent mycotoxin exposures do result in chronic inflammation, which is an established cancer risk, any mold exposures may indeed contribute to overall risk. Therefore, any action that reduces such toxic exposures, promotes healthy antioxidant status, or supports detoxification pathways is likely to reduce overall cancer risks. Almost 20% of human cancers and infections have been associated with chronic inflammation. Cancer risks increase further increase if comorbid infections are present, such as *Helicobacter pylori* (stomach cancer), hepatitis B or C (hepatocellular carcinoma), and human papilloma virus (cervical cancer). *H. pylori* status can be determined using **RealTime's GI profiles**.

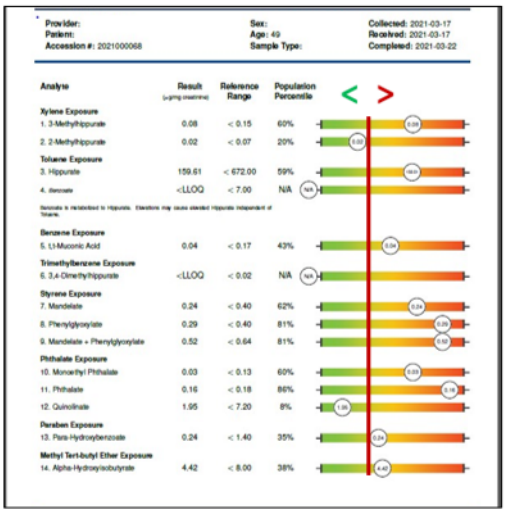
Mycotoxins contribute to cancer induction by damaging cellular DNA. Mitochondrial DNA or proteins may also be damaged and affect cellular energy status. If the DNA is not properly repaired, then cellular proteins and signaling may change from homeostasis to inflammation. If these damaged, inflammatory cells are not detected or destroyed by the immune system, they will continue to promote local and systemic inflammation. **RealTime's** dried urine **Organic Acids Profile** evaluates two analytes associated with DNA repair:

- Methylmalonate is a precursor for DNA building blocks. Low levels of methylmalonate may prevent or delay DNA synthesis or repair.
- Orotate is metabolized into uridine, another DNA building block. A high orotate level, with low levels of other protein status markers (alpha-ketoglutarate, fumarate, branch-chain amino acids, etc.) may indicate a blockage in the DNA repair pathway.

Toxic exposures are now known to be cumulative and synergistic in their impact on human health. The impact of chemical exposures on human health are finally being acknowledged in the medical community, and the associated cost to society has been recently estimated as about $250 billion in 2018. Adult disorders associated with plastics exposure include obesity, heart disease and cancers. **RealTime** offers a convenient assessment of everyday background chemical exposures. The **Environmental Pollutants Profile (EPP)** evaluates chemical exposures from combustion, vehicle exhaust and household exposures. The same dried urine collection needed for the **Mycotoxin Panel** can be used for the simultaneous collection of the **EPP** and the **Organic Acids Profile**.

## Evaluate toxic exposures and detox

- Identify and eliminate exposures
- Support detoxification
  - Ensure elimination
    - Correct gut functions as indicated onOAP, stool test
  - General supports
    - Phase I
      - Iron, selenium, zinc and vitamins A, C, D, E, K
    - Phase II
      - Glutathione, N-acetyl cysteine (glutathione precursor), B vitamins, calcium -D-glucarate, glycine, taurine
    - Phase III (mitochondria) per OA results
  - Specific supports for each toxin per OA
    - $Ca^{++}$D-glucarate, glycine
    - Glutathione, antioxidants, glycyrrhizin
    - K+, magnesium, manganese, molybdenum, rubidium
  - Sweating




*Can Fam Physician*. 2014 June; 60(6):533-538. *J Environ Public Health*. 2012;2012: 356798. *J Nutr Metab*. 2015;2015:760689.

Some nutritional compounds have been shown to modify cancer risk. Based upon the evidence, it is currently believed that these compounds either induce apoptosis (cell death) or act via anti-inflammatory or antioxidant effects on cell signaling pathways. Many of the nutritional supports recommended by this guide to support mycotoxin detoxification are also considered anti-inflammatory, antioxidant or cancer-protective agents, including:

- Carotenoids
  - Lycopene, a-carotene, β-carotene, zeaxanthin, etc.
  - Dosing per manufacturer
- Chlorophyll or chlorophyllin (semi-synthetic chlorophyll-sodium-copper compound)
  - Chlorophyllin oral doses of 100 to 300 mg/day in three divided doses
  - Monitor zinc and vitamin K status
- Glutathione (oral liposomal)
  - Dosing per manufacturer
  - Maintain glutathione levels via simultaneous supplementation with N-acetylcysteine, selenium, and vitamins A, B6, C, and E
- Lipids (dose per manufacturer)
  - a-linolenic acid
  - Docosahexaenoic acid (DHA)
  - Eicosapentaenoic acid (EPA)
- Plant polyphenols
  - Curcumin (dose per manufacturer)
  - Green tea polyphenols 500-1000 mg daily

- Resveratrol (dose per manufacturer)

- Vitamins
  - B12
    - Evaluate need for B12 using **RealTime's Organic Acids Profile**
  - D
    - Evaluate status with **US BioTek's Vitamin D (TOTAL, 25-HYDROXY D2 AND D3) Profile**

In addition to nutrition, multiple studies support lifestyle modifications as another way to decrease overall cancer risks. Lifestyle modifications may include:

- Correction of comorbid chronic inflammatory disorders such as type II diabetes
- Calorie restriction
- Diet modification
  - Increase fruit, vegetable and fiber consumption
  - Decrease red meat, saturated fats, chemical additives
- Appropriate exercise
- Stress reduction and management
- Reduction of toxic exposures
  - Smoking cessation
  - Toxic metals
  - Background chemical exposures

While there are no guarantees, the general expectation is the more health-promoting steps taken, the greater the expected cancer risk reduction. The measures discussed may also be protective against the development of cardiovascular disease, type II diabetes, and other chronic inflammatory disorders.

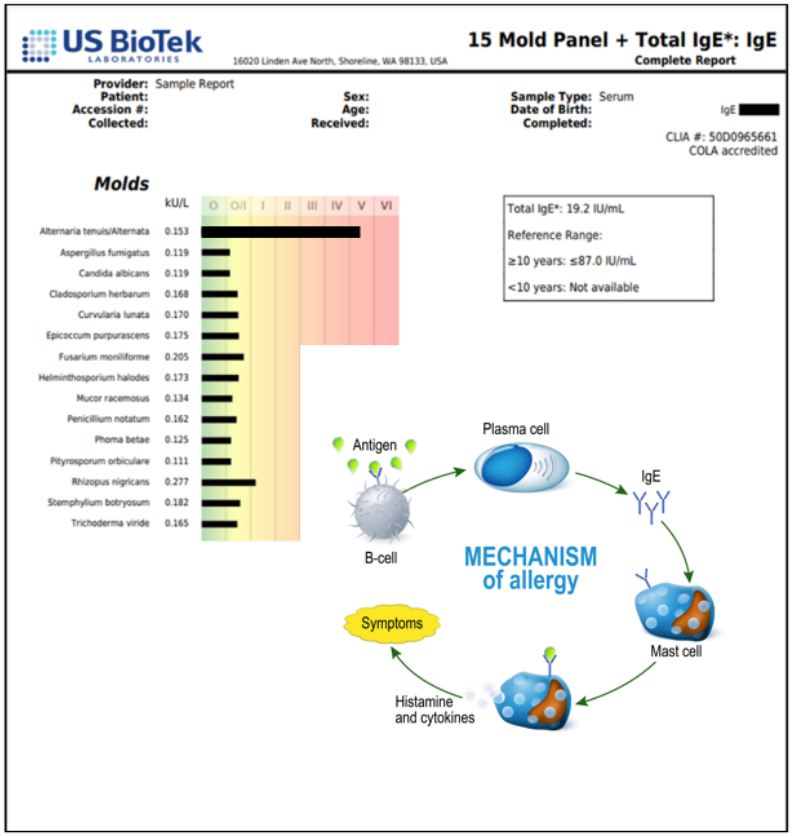
## Mold Allergy or Sensitivity

Respiratory symptoms typically occur when mycotoxins are inhaled. Epidemiology studies have consistently associated exposure to mold or indoor dampness with an increased incidence of atopic disorders and symptoms including:

- Asthma and asthma exacerbation
- Respiratory infections and symptoms such as wheeze, cough, bronchitis, difficulty breathing (dyspnea) in non-asthmatics
- Allergic rhinitis and sinusitis
- Hypersensitivity pneumonitis
- Eczema

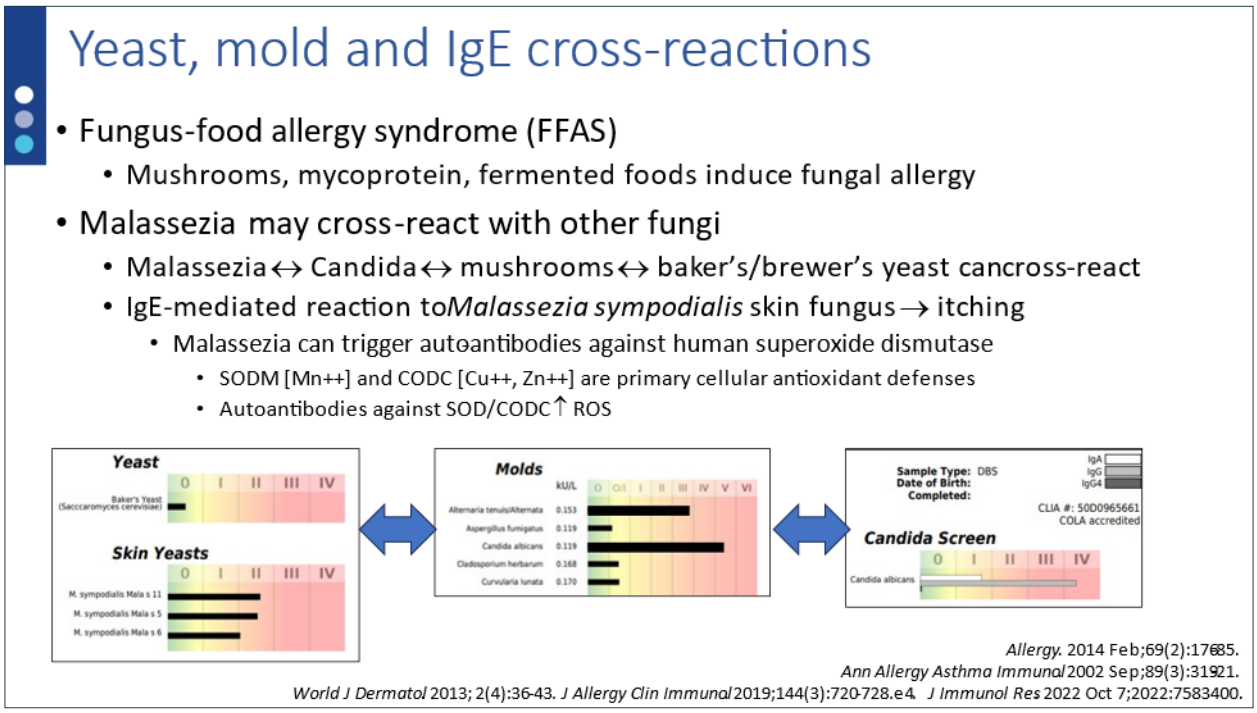
Across the study population, the increased symptoms were found in both subjects with no prior allergic history and those with prior atopic disorders. The symptoms and atopic disorders are associated with Th2 (IgE-allergy) immune system activation. Currently, there are too few human studies to support an association with IgG/IgA non-allergic sensitivity, although evidence is accumulating that recent mold/spore exposures may induce IgG antibodies as well.

Since mold exposure may be intermittent and the symptoms similar, it may be especially important to evaluate not only current exposure via the **MycoToxin Panel**, but prior allergic sensitization with **US BioTek's 15 Mold IgE Panel**.




Sensitization to molds has been linked to asthma incidence, severity, and persistence. Atopic patients often have mold allergies once they become polysensitized and often present with persistent rhinitis and/or asthma. Testing for specific IgE components, in addition to molds, may be required to identify all antigens contributing to their symptoms. Specific IgE (sIgE) components are proteins from the whole extract that have been identified as significant allergens. The inclusion of specific IgE components helps predict the likelihood of anaphylaxis and minimizes the risk of IgE reactions from cross-reacting foods or pollens. sIgE testing can also help identify potential cross-reactions between molds and other fungi, such as yeast.

Specific IgE components may facilitate fungus-mold cross reactivity in fungus-food allergy syndrome (FFAS). FFAS may affect multiple target organs, including the skin, GI tract, cardiovascular system, and respiratory system. Many fungal antigens are found in the cell walls of fungal spores; exposure can sensitize an individual to IgE allergic reactions upon re-exposure. Suspect environmental mold allergy in patients whose symptoms worsen in wet, humid weather, or when they are in indoor environments known for higher mold spore counts, such as laundry rooms, bathrooms, storage rooms or basements.




- Fungus-food allergy syndrome (FFAS)
  - Mushrooms, mycoprotein, fermented foods induce fungal allergy
- Malassezia may cross-react with other fungi
  - Malassezia ↔ Candida ↔ mushrooms ↔ baker's/brewer's yeast cancross-react
  - IgE-mediated reaction to *Malassezia sympodialis* skin fungus → itching
    - Malassezia can trigger autoantibodies against human superoxide dismutase
      - SODM [Mn++] and CODC [Cu++, Zn++] are primary cellular antioxidant defenses
      - Autoantibodies against SOD/CODC ↑ ROS

*Allergy.* 2014 Feb;69(2):176-85.
*Ann Allergy Asthma Immunol* 2002 Sep;89(3):319-21.
*World J Dermatol* 2013; 2(4):36-43. *J Allergy Clin Immunol* 2019;144(3):720-728.e4. *J Immunol Res* 2022 Oct 7;2022:7583400.

Ingestion of cross-reactive mushroom proteins may result in episodes of oral allergy syndrome or other allergic symptoms. Other cross-reactive fermented foods such as natto, tempeh, or shoyu may cross-react with mold antigens and induce symptoms. Cheeses that are specifically inoculated with molds, such as Roquefort or Camembert may also cross-react with mold antigens. *Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus,* and *Penicillium notatum* can cross-react with brewer's/baker's yeast (*Saccharomyces cerevisiae*) used to produce alcoholic beverages and may also cross-react. A list of potential "hidden" food sources of yeast may be found on the **RealTime** website https://www.usbiotek.com/hubfs/Hidden%20Food%20Ingredients%20List.pdf.

## Therapeutic Interventions for Mold Allergy

Once an allergy has been identified, avoidance of the allergic trigger is the primary treatment. Since mold exposures may be difficult or impossible to avoid completely, other strategies may also be employed to minimize reactions, including anti-inflammatory strategies, mast cell stabilization and/or allergen immunotherapy.

- Monitor, manage, or eliminate mold and other aeroallergen exposures:
  - Identify and eliminate environmental mold exposures that may contribute to antigen sensitization and inflammation as discussed in the detoxification section. Epidemiologic studies in the United States and Europe have associated mold sensitivity, particularly to *Alternaria alternata* and *Cladosporium herbarum*, with the development, persistence, and severity of asthma.
  - Monitor pollen counts and air pollution levels if there are seasonal exacerbations or comorbid seasonal inhalant allergies or air pollution exposures.
    - Keep doors and windows closed when counts are high, stay indoors and use air-conditioning, air purifiers, etc.
    - There is limited data regarding air filters; they should not be relied upon to remedy inhalant mold exposures. Ion-generating air purifiers may be preferred.
    - Per the CDC, NIOSH-approved N-95 respirators may be used for protection against inhalant exposures during mold clean-up: https://www.cdc.gov/disasters/disease/respiratory.html
- Evaluate food or inhalant aeroallergen IgG/IgA-mediated chronic inflammation
  - Dried blood-spot testing for $IgG_{1\text{-}3}$ and food-sensitivity testing to evaluate non-IgE-mediated reactivity and food-inhalant cross-reactions.
- Improve diet:
  - Eliminate processed foods, trans-fats and known IgE allergens.
  - Eliminate and rotate sensitivity foods per $IgG_{1\text{-}3}$ and IgA results to reduce the likelihood of additional food sensitization.
  - Increase fruit and vegetable consumption to support microbiome diversity and provide anti-inflammatory vitamins, flavones, and flavonoids.
  - Evaluate digestion, gastric pH and the gastrointestinal microbiome with **US BioTek's GI Advanced Profile** and treat per results, culture and sensitivities.
  - Reduce dust mite exposures:
    - Use pillow and mattress covers designed to prevent dust mites.
    - Wash bedding weekly in hot water.
    - Vacuum frequently.
  - Do not sleep with pets if dander is a problem and keep pets out of bedrooms.
- Use anti-inflammatory therapies to modulate the immune system. Dose per manufacturer's recommendations.
  - Consider nutritional supports to stabilize mast cells:
    - Vitamins A, C, D, E, B6
    - Flavonoids (quercetin, luteolin)
    - Herbs
      - *Ammi visnaga* (khella)
      - *Andrographis paniculata* (green chiretta)
      - *Astragalus membranaceus, Astragalus mongholicus*
      - Cordyceps (*Ophiocordyceps sinensis*)
      - *Petasites hybridus* L. (butterbur)
        - Use preparations free of pyrrolizidine alkaloids
      - *Urtica dioca* (stinging nettles)
      - Spirulina

- Support histamine breakdown
  - The histamine breakdown pathway requires copper and a functional methylation pathway.
- Balance Th2 T-cell expression
  - Consider:
    - Digestive enzymes to ensure the absorption of proteins, fatty vitamins A, D, E, K and minimize the potential for additional food allergy or sensitivity induction.
    - Consider amino acid supplementation if the patient has poor protein assimilation.
    - Fiber and probiotics to promote microbiome diversity and environmental immunotolerance:
      - Oligo-fucoidan (brown seaweeds)
      - Oligosaccharides (prebiotic fiber)
      - Larch arabinogalactan (*Larix laricina, Larix occidentalis*)
    - Branch chain amino acids (leucine, isoleucine, valine) to support normal immune functions.

If allergy reactions are extreme, or if exposure cannot be avoided, allergen immunotherapy may be considered. Allergen immunotherapy (AIT) involves the controlled delivery of small doses of a known allergen or an IgE specific component identified via serum IgE testing. The allergen is delivered over time to decrease hypersensitivity and induce tolerance and may be delivered subcutaneously or sub-lingually. AIT is only performed in a clinical setting capable of adequately responding to life-threatening anaphylaxis, which is always a risk during allergen exposure.

## In Conclusion

While the human capacity to detoxify mycotoxins has remained the same, environmental mold exposures and other toxic exposures continue to increase, overloading the body's ability to detoxify and eliminate all toxins effectively. With an improved awareness of the frequency and sources of mold and the ability to evaluate mycotoxin exposures clinicians are better able to fully evaluate each patient's environmental exposure. **RealTime** offers testing to assist clinicians in their evaluation of each patient's metabolic status, chemical exposures, gastrointestinal and microbiome status and immune response to food and inhalant allergens, including molds, mycotoxins. Reliable, reproducible test results not only detect the problem, but can be used to follow up the effects of therapeutic interventions as patients regain their health and well-being.

Molds, and their mycotoxins, have been with us, always. How high is your patient's burden? Find out today with **RealTime's Mycotoxin Panel** or **RTL-Tox Complete Profile**.

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