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Mold and Mycotoxin Exposure

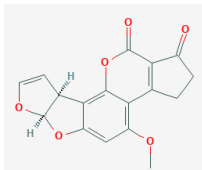
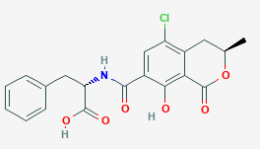
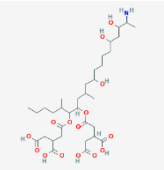
Evidence Summary

Exposure to mycotoxin producing mold can induce respiratory disease, and depending on the systemic immune response, could negatively impact other organ systems, including the brain.

Brain health risk: Case studies suggest that mold exposure may promote cognitive impairment in a vulnerable subset of people, likely mediated by pathogenic neuroinflammation.

Aging and related health risk: Mold exposure is associated with asthma and respiratory disease. Exposure to high levels of the carcinogenic mycotoxin aflatoxin B1 can lead to hepatocellular carcinoma.

Safety: Water damaged buildings and food are the main routes of mold/mycotoxin exposure. Since there are no effective treatments after exposure, prevention is paramount. Government regulations can help protect the food supply.

<p>Routes of exposure: Damp buildings and food</p>	<p>Dose: No clear dose-relationships between mold exposure and disease have been established</p>	<p><u>Aflatoxin B1</u> Chemical formula: C₁₇H₁₂O₆ MW: 312.27 g/mol</p>
<p>Half-life in serum: Aflatoxin B1 2 to 3 months Ochratoxin-A 35.5 days Fumonisin B1 1.03 to 3.15 hours (rats); estimated 128 minutes in humans</p>	<p>BBB: Aflatoxin B1 is penetrant Ochratoxin-A is penetrant Fumonisin B1 likely not penetrant</p>	 <p>Source: PubChem</p>
<p>Clinical trials: N/A</p>	<p><u>Ochratoxin-A</u> Chemical formula: C₂₀H₁₈ClNO₆ MW: 403.8 g/mol</p>	<p><u>Fumonisin B1</u> Chemical formula: C₃₄H₅₉NO₁₅ MW: 721.8 g/mol</p>
<p>Observational studies: Mold exposure is linked to asthma and rhinitis. Aflatoxin B1 exposure is associated with hepatocellular carcinoma.</p>	 <p>Source: PubChem</p>	 <p>Source: PubChem</p>

What is it?

Mold belongs to the organismal kingdom of fungi. Mold produces spores which can travel through the air and survive for long periods of time. Moisture is needed in order for mold to grow on surfaces, so it generally thrives in areas that are warm and damp, such that it can spread quickly in buildings following water damage [1]. Mold exposure can occur through skin contact, inhalation, or ingestion. Inhalation is the most prevalent route of exposure, consequently the clearest link between mold exposure and human disease relates to respiratory ailments, such as asthma. Some species of mold are also capable of producing toxins, known as mycotoxins, and while they have been implicated in a variety of conditions, there is very little direct evidence to support they act as causative agents in disease [2]. Part of the challenge in determining whether there is a relationship between mold and disease has been in accurately measuring levels of exposure [3]. The primary routes of exposure for mycotoxins are through molds in the home or workplace and through contaminated food. Hundreds of mycotoxins have been

identified, and six kinds are found in food with enough regularity to be subject to maximum limit regulations in some countries [4]. These mycotoxins include aflatoxins, trichothecenes, zearalenones, fumonisins, ochratoxins, and patulin.

Aflatoxin B1: Aflatoxins are the most toxic of the identified mycotoxins, and thus have been the subject of the greatest amount of study and regulation. Aflatoxins are primarily produced by *Aspergillus*, including *Aspergillus parasiticus*, *Aspergillus flavus*, *Aspergillus nomius*, as well as various species of *Penicillium*, *Rhizopus*, *Mucor*, and *Streptomyces* [2]. Aflatoxin B1 is the most potent of the aflatoxins, and has been associated with hepatocellular carcinoma. Aflatoxins are metabolized by cytochrome CYP450 enzymes in the liver, and are considered neurotoxic because, due to their lipophilic nature, they are able to cross the blood-brain barrier (BBB). Aflatoxin B1 levels in food are regulated, and must be less than 20 µg/kg in the USA. Due to these regulations, aflatoxin B1 exposure rates and levels in the USA are far lower than in developing countries. Aflatoxin B1 levels were measured in a subset of participants (n=2051) in the National Health and Nutrition Examination Survey (NHANES) study between 1999-2000, when exposure to aflatoxins through the food supply was potentially elevated due to higher levels of contaminated corn in the Midwest the prior year [5]. Exposure incidence was estimated to be 1.2% (95% Confidence Interval (CI): 0.68 to 1.92%) of the US population, which represented about 274,000 persons (95% CI: 168,000 to 447,000) with an average (geometric mean) level of 0.842 pg/mg albumin (95% CI: 0.530 to 1.34). In contrast, a similar study in Kenya found that aflatoxin B1 was present in 78% of samples, with a median level of 1.78 pg/mg albumin (95% CI: 1.46 to 2.12) [6].

Aflatoxin M1 is the primary hydroxylated metabolite of aflatoxin B1 and is primarily found in milk [4]. In the USA, maximum limits have been established at 0.5 µg/kg, while it is set even lower at 0.05 µg/kg in the EU. High levels of aflatoxin M1 in the breast milk of women in developing countries poses a potential health risk for children in these regions [7].

Ochratoxin-A is one of the most abundant mycotoxins found in food. It is produced by *Aspergillus ochraceus*, *Aspergillus niger*, as well as species of *Penicillium*, *Petromyces*, and *Neopetromyces* [2]. It can be difficult to eliminate from food under normal cooking conditions, and due to its lipophilicity, has a tendency to accumulate in the body [4]. Due to less stringent regulation, ochratoxin-A levels in the blood have not been found to vary considerably across the world [3]. Based on a review of global studies (n=7664 people), 74% of samples were found to be positive for ochratoxin-A, with an average level of 0.45 ng OTA/mL plasma [8].

Fumonisin B1 is the most abundant and toxic of the fumonisins found in food. It is produced by several *Fusarium* species, including *Fusarium verticillioides*, and is primarily found in corn [9]. Fumonisin B1 has

been found to disrupt sphingolipid metabolism by inhibiting ceramide synthesis, so exposure can be read-out through changes to sphingolipid concentrations. Unlike aflatoxins and ochratoxins, fumonisins are hydrophilic, so they have very low bioavailability within the body.

Brain health risk: Case studies suggest that mold exposure may promote cognitive impairment in a vulnerable subset of people, likely mediated by pathogenic neuroinflammation.

Types of evidence:

- 6 observational studies for mold exposure and cognitive/neurological impairment.
- Numerous laboratory studies

Human research to suggest risk for dementia, accelerated decline, or impaired cognitive function?

Several mold-derived mycotoxins have the capacity to act as neurotoxins, however, aside from cases of acute poisoning following exposure to high doses of mycotoxins, the evidence that exposure to mycotoxin producing molds through food or the environment contributes to cognitive decline is circumstantial. Several studies have identified cases of cognitive impairment in mold-exposed individuals, but the key outstanding question is whether this is due to a direct effect on the nervous system, or if it is solely via indirect mechanisms. The **predominant hypothesis is that there is a subpopulation of individuals who are particularly susceptible to mold exposure-related cognitive impairment**, as there is considerable inter-individual variability [10]. The difference in susceptibility may be related to genetic and physiological factors, especially the metabolic processing of mycotoxins, as well as the lifetime burden of exposure. Overall, no conclusive direct relationships have been found between cognitive impairment and exposure to certain species of mold, the duration of exposure, the route of exposure, the age of exposure - though children are thought to be the most vulnerable to all mold-related toxicities, or whether there is a threshold level of exposure/mycotoxin accumulation for neurological damage.

EVIDENCE SUPPORTING LINK BETWEEN MOLD AND COGNITIVE IMPAIRMENT

In the early 2000s, several case series emerged which revealed signs of neurological impairment in people who had been exposed to mold, primarily via water-damaged buildings.

One study found that 100 individuals with confirmed mold exposure, based on serum antibody and skin testing, had autonomic nervous system abnormalities, and 70% also showed signs of neurological



dysfunction [11]. Brain scan abnormalities were detected in 26/30 of those examined, and objective neurological testing revealed that deficits were primarily related to memory, executive function, attention, and coordination.

A study assessing neuropsychological and electrocortical effects in 182 mold-exposed individuals found evidence for decreased cognitive functioning, particularly with respect to attention [12]. Electrocortical measures using QEEG found evidence suggesting frontal lobe hypoactivity, with lower activity associated with greater cognitive impairment. However, similar to the previous study, this one is limited by the lack of a comparator control group.

Another group of clinicians initially reported on a group of 20 people with self-reported memory complaints following mold exposure [13]. Clinical neurological testing revealed that the majority scored in the low end of the normal range. A follow-up study by that group compared 31 people with mold-exposure related cognitive complaints with 47 controls and 91 people with traumatic brain injury [14]. The symptom reports of mold-exposed individuals were more similar to people with mild brain injury than to controls. Based on 25 neurological measures, 97% of mold-exposed individuals showed reduced functioning on at least one measure, while 70% showed impairment on at least one measure, which was defined as one standard deviation below the normative mean. Due to the high number of tests relative to the small sample size, the association with any particular measure is unlikely to be reliable, but some trends did emerge. Reduced functioning and/or impairments were most frequently found on measures of memory (90%), executive function (45%), attention (39%), and speed of processing (17%).

A study comparing people with mold (n=105) and chemical (n=100) exposure, relative to a control community reference group (n=202), found that the two groups had similar levels of neurobehavioral and pulmonary abnormalities (6.1 mold vs 7.1 chemical vs 1.2 control) [15]. Exposed groups showed decreased performance on tasks related to memory, executive function, balance and coordination, and visual acuity.

However, none of these studies has been able to directly relate exposure levels to cognitive impairment. One study (n=50) found that there were no correlations between serum IgG levels toward a variety of fungal antigens with neuropsychological measures, although there was a subgroup of mold-exposed individuals with objectively defined impairments [16]. Furthermore, there is no defined set of neurological symptoms associated with exposure which could potentially differentiate it from an alternative cause [10]. This suggests that individual variation in the response to exposure plays an outsized role, such that some people are more adversely affected than others. The factors associated

with increased vulnerability have not yet been clearly identified, so **it is not currently possible to predict who is most at risk for mold-exposure-related cognitive impairment.**

POTENTIAL CONFOUNDERS AND INDIRECT CONTRIBUTORS TO ASSOCIATION

Litigation: The majority of the clinical cases described for neurological impairments in mold-exposed individuals involves people who sought a clinical evaluation in conjunction with litigation. This poses the potential risk that some complaints may have been exaggerated and some people may have deliberately underperformed on tests [16]. Some of the clinicians have also served as expert witnesses in cases related to mold-exposure. Even if all of the testing was accurate, there is also a participant selection bias in these studies, because they generally do not include the large number of people who have been exposed to mold, but because they are asymptomatic, do not seek medical attention [15]. This impedes the ability to determine the prevalence of cognitive impairment in mold-exposed individuals, and the ability to identify the characteristics that most strongly associate with vulnerability.

Depression: A variety of studies have found a greater likelihood for depression in mold-exposed individuals, which could in turn lower motivation, and can sometimes translate to lower scores on neurophysiological tests [17]. It is not clear if the mycotoxins themselves can influence mood, but is generally thought to stem from the stress and loss of a sense of control that follow mold-exposure in the home or workplace, particularly when related to water-damaged buildings that require renovation.

Mold-related physical ailments: Mold and mycotoxin exposure has been associated with several physical ailments, especially respiratory disorders [18]. In some cases, cognitive impairments could be related to underlying, untreated peripheral diseases, such as by increasing levels of systemic inflammation.

Socioeconomic factors: People who are chronically exposed to high levels of mold in their home and/or workplace tend to be of lower socioeconomic status [2; 18]. There is established evidence of health disparities in this population, as they tend to be exposed to a higher burden of various toxins and pollutants, and have more chronic health conditions.

Assessment of exposure: The ability to reliably determine whether a given individual has been exposed to mold and mycotoxins in a biologically meaningful manner has been challenging (See Biomarkers of Exposure section under Safety). Environmental estimates of mold counts in a given environment or mycotoxin levels in the food supply can only provide approximations of potential exposure [3]. Methods of detecting a response to mold antigens through a skin reaction or the presence of serum IgE antibodies may indicate exposure to a mold capable of producing mycotoxins, but not necessarily exposure to the mycotoxins themselves [16]. Due to considerable cross-reactivity between the antigens,



it can be difficult to confirm exposure to a particular fungal species, and thus to determine if adverse cognitive effects are associated only with particular species. The levels of some mycotoxins can be measured in bodily fluids, such as blood and urine, though validated tests are lacking for most. Additionally, both interindividual and intraindividual variation in the processing and metabolism of mycotoxins is the major challenge in the use of these biomarkers to link exposure with disease at the individual level [3]. Biomarker levels of a given mycotoxin have been found to vary widely within a given individual depending on changes in dietary patterns or other physiological factors. As a result, associations between mycotoxin exposure and disease incidence are only useful at a population level, and cannot be identified as a causative agent in disease etiology at the individual level. The use of these peripheral markers to assess relationships to neurologic impairments is especially difficult, since there is currently not a clear method to use them to determine the level of mycotoxins within the CNS tissues.

Human research to suggest increased risk to patients with dementia:

There is currently no direct evidence indicating whether exposure to mold and mycotoxins worsens the cognitive decline trajectory in people with dementia. There is circumstantial evidence to suggest that it may worsen outcomes. Finland has the highest mortality rate from dementia in the world, and its cold, humid climate, which facilitates mold growth in heated buildings, has been suggested to contribute to the elevated mortality risk [19]. Mycotoxin exposure and a heightened immune response to mold has also been implicated in mortality from other illness in Finland, though definitive studies have not been conducted [20].

Mechanisms of action for neurological harm identified from laboratory and clinical research:

Alzheimer's disease:

There is no direct evidence that exposure to mycotoxins can induce the onset of Alzheimer's disease (AD), or that mold-exposed individuals have a higher probability of developing AD or other dementias. There is clinical evidence to indicate that some people exposed to mold can develop mental confusion or delirium, and that in some cases this can result in a permanent decline in cognitive function [10]. One clinician noted that the projected mold-related cognitive impairment does not respond to the drugs traditionally used for AD [10]. This is notable, because it has been found that certain mycotoxins can influence acetylcholine levels in some species by inhibiting acetylcholinesterase [21]. In this context then, it would not be surprising if treatment with acetylcholinesterase inhibitor drugs did not show benefit.

The potential link between mold and AD comes from the microbial hypothesis, such that amyloid is an anti-microbial agent, so a fungal infection in the brain could trigger the production of amyloid. Mold and mycotoxin exposure are also associated with an inflammatory response, and there is a hypothesis, that in a subset of people this could trigger AD. Dale Bredesen has suggested that mycotoxin exposure could represent a 'type 3 AD', though this more likely refers to a mycotoxin-triggered form of dementia [22], rather than pathologically defined AD, per se. Based on small sample of cases, Bredesen hypothesizes that there may be a particular set of HLA-DR/DQ haplotypes which are especially vulnerable to mycotoxin-induced dementia, possibly due to an altered or excessive neuroimmune response to the mycotoxin antigens [22]. Further studies are needed to validate this proposed susceptibility phenotype.

The increased susceptibility to mycotoxin-induced disease, may relate to differences in the capacity of the body to clear the toxins. Aldo-keto reductases (AKRs) act to detoxify reactive aldehydes generated from lipid peroxidation. Increased levels of reactive aldehydes have been found in regions of the brain associated with neurodegenerative disease, and it is hypothesized that a decrease in aldehyde detoxification capacity may contribute to the onset or progression of disease [23]. Genetic differences in the function or expression of AKRs may play a role. Genetic associations between AKRs and dementia have not yet been examined, but mutations in AKRs have been identified in cases of aflatoxin B1 related cancer [24]. AKR7A2 is an aldehyde reductase responsible for the detoxification of aflatoxin B1. In postmortem brain tissue, immunoreactivity for AKR7A2 was found to be elevated in reactive astrocytes and microglia in patients with AD and Dementia with Lewy Bodies in disease affected areas [25]. Levels of AKR7A2 were found to be 25% higher in AD patients relative to controls. Although, AKR7A2 has other biological functions, this data could indicate higher levels of mycotoxins in these individuals, or that the immune response is exacerbated.

Parkinson's disease:

There is no direct evidence that mycotoxin exposure can lead to the development of Parkinson's disease (PD) in humans, however, there is some evidence that animals exposed to high levels of certain mycotoxins can develop Parkinsonian-like symptoms.

Ochratoxin-A is one of the most common toxins found in contaminated food and water-damaged buildings. The prevalence of PD is higher in men, and males have been found to be more sensitive to ochratoxin-A mediated toxicity [26]. Ochratoxin-A induces oxidative stress and has been shown to induce mitochondrial-dependent apoptosis in neuronal cell culture [27]. In mice, ochratoxin-A exposure led to a dose-dependent decrease in striatal dopamine content and turnover [28]. Treatment with L-DOPA was found to improve behavioral deficits and oxidative stress markers following ochratoxin-A

exposure in mice, suggesting that the dopaminergic system is a major site for ochratoxin-A related neurotoxicity [26].

Mold-derived volatile organic compounds may also contribute to dopamine depletion. The compound 1-octen-3-ol, which produces the odor typically associated with mustiness or mold, was shown to induce dopaminergic neurodegeneration in flies by disrupting dopamine handling and homeostasis [29]. 1-octen-3-ol exposed flies had decreased dopamine levels and uptake by the dopamine transporter, along with an increase in levels of the dopamine metabolite DOPAC and markers of oxidative stress.

A major caveat of these studies is that they tend to involve exposure to high doses of a specific mycotoxin for a short period of time, and it is not clear whether long-term exposure to more clinically relevant low doses would have the same effects [28]. Additionally, mold exposure involves being exposed to a cocktail of at least hundreds of different compounds which may interact with one another, so the effects may vary from those seen with a single compound/toxin.

MECHANISMS

Inflammation: Mold and mycotoxin exposure can activate an immune response, and in some cases, this can lead to excessive inflammation and/or the dysregulation of the immune system [18]. **Differences in the inflammatory response are thought to underlie differences in the susceptibility to mold-related ailments** [22]. One study assessing 100 mold-exposed individuals found that over 80% had lymphocyte abnormalities, though there was no consistency in which subsets were most affected or whether levels were increased or decreased [11]. Another study examining 209 mold-exposed adults also found abnormalities in lymphocyte subsets, particularly in B and T cells, and increased levels of autoimmune disease-associated autoantibodies [30].

A biomarker study assessing the *ex vivo* chemokine and cytokine signature of peripheral blood mononuclear cells (PBMCs) in mold-exposed individuals (n=33 cases vs n=17 controls) found that this immune signature could be used to classify mold exposure with an area under the curve (AUC) greater than 0.97 [31]. The chemokine/cytokine signature varied depending on which strain of mold PBMCs were exposed to *ex vivo*, but there was considerable overlap between strains. Notably, the cytokines IL-17, IL-10, TGF- α , and MIP-1 β were elevated in mold-exposed asthmatics compared to mold-exposed non-asthmatics and unexposed controls, suggesting that there may be distinct immune signatures involved in different mold-related diseases.

A study in mice found that memory impairment following chronic inhalation of mold spores was associated with increased levels of pro-inflammatory IL-1 β + immune cells in the hippocampus,



suggesting that the impairment was mediated by neuroinflammation [32]. Animal models exposed to mycotoxins also show evidence of neuroinflammation. For example, exposure of rats to chronic low-dose aflatoxin B1 (1/600th LD50) for up to 90 days resulted in evidence of reactive gliosis, particularly in astrocytes [33]. Aflatoxin B1 has high lipid solubility and can cross the BBB. Some mycotoxins not expected to cross the BBB in appreciable quantities due to their hydrophilic nature, such as fumonisins, may still impact the brain by affecting the microbiome and promoting 'leaky gut syndrome' [34]. In this way, they can promote the release of neurotoxins as well as neuro- and immune-modulatory agents into the bloodstream. The digestive system is the major target of deoxynivalenol, also known as vomitoxin, thus it may also exert neurotoxic effects in this manner [35].

Oxidative stress: The production of oxidative stress appears to be a predominant mechanism of mycotoxin-induced neurotoxicity based on cell and animal models [2]. Ochratoxin-A exposure increased oxidative DNA damage across six brain major regions vulnerable to neurodegenerative disease in mice [28]. Chronic low-dose aflatoxin B1 exposure (1/600th LDF50) in rats led to a decrease in brain antioxidants coupled with an increase in lipid peroxidation and protein carbonylation in the brain [33]. Studies in neuronal cell culture suggest that fumonisin B1 inhibits mitochondrial complex I and leads to a dysregulation of calcium homeostasis and signaling [36].

Vitamin B12 deficiency: Exposure to mold and mycotoxins may contribute to cognitive impairment by interfering with vitamin B12 [37]. People exposed to mycotoxin-producing molds commonly also present with a vitamin B12 deficiency that is unrelated to diet. There is some evidence to suggest that mycotoxins may interfere with the metabolic pathways that regulate B12, which in turn negatively affect B12 dependent cellular metabolic processes.

Hypercholesterolemia: Lipophilic mycotoxins can bind lipoproteins and interfere with cholesterol metabolism in the liver [38]. The abnormal clearance and metabolism of mycotoxins in lipoproteins may contribute to both hypercholesterolemia and neurodegeneration. In addition to lipoprotein membranes, mycotoxins may corrupt BBB membranes, and disrupt barrier function. Diet may influence this process, such that diets rich in alcohol, fat, and carbohydrates may promote the absorption of mycoproteins and their incorporation into lipoproteins. It is not known whether ApoE4 status influences the incorporation of mycotoxins into lipoproteins.

APOE4 interactions: Unknown

Aging and related health risk: Mold exposure is associated with asthma and respiratory disease. Exposure to high levels of the carcinogenic mycotoxin aflatoxin B1 can lead to hepatocellular carcinoma.

Types of evidence:

- 7 meta-analyses or systematic reviews (2 for hepatocellular carcinoma, 4 for respiratory disease, 1 for renal disease- based on observational studies assessing relationship between disease and mold or mycotoxin exposure)
- 3 observational studies (2 for hepatocellular carcinoma, 1 for chronic fatigue syndrome in relation to mycotoxin exposure).
- Numerous laboratory studies

Respiratory diseases Asthma, allergy, rhinitis: ASSOCIATED WITH MOLD EXPOSURE

Airborne exposure, involving inhalation of mold spores and fragments, is the most common route of mold exposure. Consequently, **respiratory ailments have the most well-established relationship with mold exposure** [2]. Several meta-analyses of observational studies have concluded that there is sufficient evidence to support an association between mold exposure and respiratory diseases.

The fungi, Cladosporium, Alternaria, Aspergillus, and Penicillium, were found in higher concentrations in the homes of those with asthma and the presence of these species increased the exacerbation of current asthma symptoms by 36% to 48% [39]. An analysis of 31,742 children from eight European birth cohorts (ENRIECO Initiative) found that exposure to visible mold and/or dampness during first two years of life was **associated with an increased risk of developing asthma** (adjusted odds ratio aOR: 1.39; 95%CI 1.05 to 1.84) [40]. There was also a significant association for the development of sinus rhinitis in children at least through age 10 (aOR: 1.12; 95% CI 1.02 to 1.23). A meta-analysis of 31 studies assessing the relationship between mold and rhinitis found increased risk with respect to the presence of mold odor with an effect estimate (EE) of 2.18 (95% CI: 1.76 to 2.71) and visible mold EE of 1.82 (95% CI: 1.56 to 2.12) [41]. A working group commissioned by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) concluded that there was sufficient evidence for a causal relationship between mold exposure and the development of asthma in children [42]. Additionally, that there was sufficient evidence for an association between workplace mold and occupational asthma, as well as for an **association between mold exposure and allergic rhinitis**, with an odds-ratio generally greater than 1.35.



These studies suggest that children are the most vulnerable to the development of mold-related respiratory disease, but that high levels of mold exposure can potentially trigger respiratory problems at any point during the lifespan.

Hepatocellular carcinoma: ASSOCIATED WITH AFLATOXIN B1 EXPOSURE

Aflatoxin B1 is metabolized by the liver, which also serves as its primary organ of toxicity [43]. It forms covalent adducts on DNA (guanine) and on proteins (lysine), induces hepatic oxidative stress, and has been classified by the World Health Organization as a class A carcinogen. Observational studies have shown a relationship between areas with high levels of aflatoxin A1 exposure, primarily through food contamination, and elevated rates of hepatic carcinoma in developing countries [44]. A meta-analysis of 17 studies, primarily in Southeast Asia and sub-Saharan Africa, estimated that the population attributable risk (PAR) of aflatoxin-related hepatocellular carcinoma was 17% (95% CI: 14 to 19%) overall, and was higher in hepatitis B (HBV+) (21%) than HBV- (8.8%) populations [45]. The combination of aflatoxin B1 and HBV had an OR of 73.0 (95% CI: 36.0 to 148.3) for hepatocellular carcinoma, while the OR for aflatoxin exposure alone was 6.37 (95% CI: 3.74 to 10.86). The carcinogenic action of aflatoxin may be related to the mutation of the tumor suppressor p53. A meta-analysis of 48 studies found that a G to T transversion at codon 249 of the p53 gene (249ser) was positively correlated with aflatoxin exposure in patients with hepatocellular carcinoma [46].

Although several other mycotoxins have been classified as possible carcinogens, none have been definitely linked to cancer [44]. One study attempted to determine if there was an association between hepatocellular carcinoma and fumonisin B1 exposure in two Chinese cohorts with a total of 343 cases and 427 controls, but failed to find a significant association [47]. However, the study measured fumonisin exposure via levels in toenails, which is not a validated biomarker for this mycotoxin.

Nephropathy/Nephritis: POSSIBLE ASSOCIATION AT VERY HIGH OCHRATOXIN-A EXPOSURE

The kidney is the major target for ochratoxin-A toxicity, primarily by disrupting the mobilization of intracellular calcium [48]. It has been implicated in the pathogenesis of renal disease, particularly Balkan endemic nephropathy (BEN), which is a progressive renal disease associated with urinary tract tumors. However, despite the suggestive link, there is still insufficient evidence for a true association. A systematic review found that there was no statistically significant evidence to indicate a direct relationship between ochratoxin-A and kidney disease, with the exception of nephritic syndrome risk, but that was only found in areas with extremely high levels of ochratoxin-A exposure, and may have been confounded by small sample sizes [49]. The small Egyptian population (n=15) in the study that



showed a significantly elevated odds ratio for ochratoxin-A related nephritic syndrome (OR: 10.79; 95% CI 2.28 to 50.91) had urinary ochratoxin-A levels (3.09 ± 3.4 ng/ml) that were orders of magnitude higher than those found in studies in the rest of the world (Range: 0.001 ng/ml for control to 1.85 ng/ml for end stage renal disease). Some studies have found higher serum levels of ochratoxin-A in patients with kidney and urinary tract disorders, but the directionality is unclear, since people with decreased kidney function may have reduced capacity to clear mycotoxins from the blood [50].

Chronic fatigue syndrome: POSSIBLE LINK WITH MYCOTOXIN EXPOSURE

The etiology for chronic fatigue syndrome is not known. One study examining mycotoxin load in people diagnosed with chronic fatigue syndrome in the USA, found that 104/112 (93%) of tested individuals were positive for at least one mycotoxin, whereas levels were below the limit of detection or threshold for positivity in a corresponding group of controls (n=55) [51]. Urinary levels were significantly higher for aflatoxins (0.43 ± 1.36 ppb vs. 0 ± 0), ochratoxin-A (5.26 ± 3.65 ppb vs. 0.355 ± 0.457), and macrocyclic trichothecenes (0.422 ± 0.714 ppb vs. 0.0169 ± 0.0265). The authors suggest that due to mechanistic studies which reveal that many mycotoxins can alter mitochondrial function and induce oxidative stress, mycotoxin-induced mitochondrial dysfunction may be a possible mechanism linking mycotoxin exposure and chronic fatigue syndrome.

Safety concerns: Water damaged buildings and food are the main routes of mold/mycotoxin exposure. Since there are no effective treatments after exposure, prevention is paramount. Government regulations can help protect the food supply.

Types of evidence:

- 2 meta-analyses of global studies of mycotoxin contamination of the food supply
- 1 systematic review of global observational studies of ochratoxin-A exposure
- 1 review of mycotoxin regulation limits in food
- 2 observational studies (Aflatoxin exposure in US population)
- Numerous laboratory studies

Sources and limits:

ROUTES OF EXPOSURE

The environment: water damaged buildings

It has been estimated that indoor air pollution contributes to up to 50% of illnesses [2]. The prevalence of residences with dampness and mold varies geographically, but has been estimated to be greater than 20% in many Western countries [52], with an estimated prevalence of 24% in the USA [53]. Differences are driven primarily by climate and socioeconomic factors, such that there can be considerable variation in the level of residential mold across neighborhoods in a given geographic region [54]. Older unrenovated homes with poor ventilation and carpeting tend to have the highest levels of mold. Obtaining accurate estimates of indoor mold exposure is challenging. Air spore counts only provide a snapshot of the molds present within a given time, can easily result in false negatives, and may not be reflective of the exposure history of someone dwelling in a contaminated building for a period of time [2]. Collections of floor dust samples or analysis of mold-related marker compounds in the air may provide for more accurate estimates.

Another challenge is that none of the methods commonly used to kill and remove mold, such as bleach or UV light can completely remove mold and mycotoxins, as leftover nonviable mycotoxin-containing mold and spore fragments can still be inhaled or ingested [2]. Boron and ammonium chloride-based chemicals are considered the most effective at reducing mold burden.

Food contamination

Approximately one-quarter of crops harvested globally each year are contaminated by mycotoxins [4]. Regulatory agencies in the USA, Europe, and various other developed countries have established guidelines for the amount of several key mycotoxins that are allowed in food products designated for human consumption. European limits tend to be lower than those in the USA (See Table) [4]. Of the six major types of regulated mycotoxins commonly found in food, only aflatoxin levels are mandated, the others are advisory levels. Ochratoxin-A, which similar to aflatoxin, is lipophilic and can accumulate in tissues does not yet have an FDA regulated limit. Since another possible route of exposure is through eating animals or animal products which have consumed mycotoxin-contaminated feed, some agencies also provide regulations for the level of mycotoxins allowed in food products designated for animal consumption. The limits are generally much lower for foods designated for direct human consumption. The risk for significant mycotoxin exposure through food, particularly aflatoxins, is highest in developing countries.

Mycotoxin	USA	EU	Major source
Aflatoxin B, G	20 ug/kg (20 ppb)	4-15 ug/kg	corn, nuts, wheat
Ochratoxin-A	Not set	2-10 ug/kg	cereals, coffee, grapes, cocoa
Fumonisin B	2000-4000 ug/kg (2-4 ppm)	200-1000 ug/kg	corn
Zearalenone	Not set	20-100 ug/kg	cereals
Deoxynivalenol	1000 ug/kg (1 ppm)	200-500 ug/kg	cereals
Patulin	50 ug/kg (50 ppb)	10-50 ug/kg	apples

(Table adapted and modified from Table 1 in Alshannaq et al., 2017 [4])

Systematic reviews of studies assessing mycotoxin levels in food products in various countries around the world have found that the presence of mycotoxins in the food supply is widespread, but there is regional variability in the levels, relative abundance of particular mycotoxins, and the type of food product that is most likely to be contaminated [55]. Certain types of crops are preferentially infected by certain species of fungal molds, which in turn, affects the composition of mycotoxins in a given food product. It should be noted, however, that the presence of a mold capable of producing mycotoxins does not necessarily indicate that mycotoxins are present at appreciable levels.

Similar to indoor mold exposure, the variability is primarily driven by climate and socioeconomics. The prevalence increases with rates of poverty and annual rain fall [56]. The presence of enforceable regulatory limits has a major influence on disparities in regional exposure. For example, a meta-analysis of studies assessing ochratoxin-A levels in coffee products (n=94) found that the global pooled concentration of ochratoxin-A was 3.21 µg/kg (95% CI: 3.08 to 3.34 µg/kg), which is below the maximum level set by the EU (5 µg/kg for roasted coffee) [56]. The lowest average levels were recorded in Taiwan (0.35 µg/kg), while the highest were in Turkey (79 µg/kg), with the USA falling near the middle (15.14 µg/kg). The global pooled prevalence of ochratoxin-A in coffee products was 53% (95% CI: 43 to 62%), with the USA falling near the lower end at 42%.

BIOMARKERS OF EXPOSURE

There are two major approaches to measuring human exposure to mycotoxins.

1). The first method only captures **potential mycotoxin exposure through food**, and can only be used to **provide a population estimate**. This involves an assessment of mycotoxins present in the food supply at a given time through sampling combined with dietary consumption patterns in a given population [3]. These are typically used to discern whether levels of mycotoxin exposure from food sources exceed guidance limits. The major caveat with this approach is that it can both over or underestimate exposure



levels in different subpopulations due to differences in dietary habits. Rural areas tend to have higher mycotoxin exposure than urban areas, which is thought to be driven by locally produced food [8]. Immigrant communities may also have different exposure levels due to differences in food preferences [5]. For example, one study found that a particular Hispanic community in Texas (n=184) had considerably higher prevalence of biomarker confirmed aflatoxin exposure (20.6% vs 1.2% nationally) and levels of aflatoxin byproducts in their blood (see second method below) at 3.84 ± 3.11 pg/mg albumin, compared to the national level of 0.842 pg/mg albumin (0.530 to 1.34) based on the NHANES study (n=2051) [5; 57]. This may be related to higher than average consumption of corn-based foods in this population.

Another potential source of misestimation of exposure relates to the way in which mycotoxins are measured. This approach quantifies the free or parent form of the mycotoxin, but does not capture modified forms, which could lead to an underestimation [3]. On the other hand, the bioavailability of the mycotoxin is also a key determinant of exposure, and this can vary considerably from person to person. Several of the caveats of this approach are addressed by the second method of analysis.

2). A more comprehensive method which accounts for mycotoxin exposure from all sources at the individual level involves the **monitoring of bodily fluids and tissues** [3]. Measures of mycotoxin levels in urine assess short term exposure, while serum/plasma measures tend to reflect longer term exposure, though these measures are affected by the elimination half-lives of the various mycotoxins. The serum half-life of ochratoxin-A is 35.5 days, which lasts longer in blood than in tissues due to a high binding affinity toward plasma proteins [58]. Fumonisin B1 has a short plasma half-life of 3.15 hours in rats [59] and is estimated to be only 128 minutes in humans [47], meanwhile, the serum half-life for aflatoxin B1 is approximately 2 to 3 months. A major hindrance toward interpreting the levels of mycotoxin biomarkers in bodily fluids is that there is **very limited toxicokinetic data for most mycotoxins** [3]. It is challenging to perform the studies necessary to collect this data since clearance rates and mechanisms tend to be species specific. Without a clear understanding of how long it takes for the body to clear individual mycotoxins, many studies present their findings using a range of possible exposures based on clearance estimates [60]. It has also become evident that there are **sex dependent differences in the tissue distribution** and concentration of various mycotoxins, and that on average, males tend to accumulate more toxins in their tissues and are disproportionately affected in terms of negative health effects [61].

There are some efforts to develop multiplex methods which can detect multiple mycotoxins from a single individual, but the most reliable methods at this time assess a single mycotoxin [3]. Urinary biomarkers for ochratoxin-A appear to be more reflective of dietary exposure and less variable than

serum measures [49]. Aflatoxin B1 is typically measured based on serum levels of aflatoxin B1-lysine adducts, due to their high stability [5]. In some cases, the biomarker can be a functional readout of toxin exposure. Fumonisin disrupt sphingolipid metabolism, and because of their short half-life, rather than be read-out directly, their presence is often assessed indirectly through the detection of elevated sphingolipid levels [9]. Measures that only detect a single form of the toxin may underestimate exposure, as modified forms may not be detected [62]. Due to the lack of toxicokinetic data, it is unclear how the modification and processing of most mycotoxins within the body influences their toxicity. Aflatoxin B1 is the best studied mycotoxin, and it appears that its metabolism into the ROS AFB1-8,9 epoxide accounts for the majority of its genotoxic effects [33]. Additionally, there is also a poor understanding of how various mycotoxins might interact with each other within the body and whether they may have synergistic or counteracting effects [61]. New technologies are needed to allow for a more comprehensive assessment of overall mycotoxin load in the body.

Research underway:

There are currently no effective methods to clear mycotoxins from the body, thus primary prevention is the best strategy to reduce mold and mycotoxin-related illness. Most efforts investigating methods to mitigate mycotoxin exposure focus on developing countries. One of the primary methods to try to prevent absorption of the mycotoxins is through sequestering agents such as activated charcoal or clay [2]. A clay substance called ACCS100 was tested in clinical trials to mitigate aflatoxin exposure from dietary sources. In a small clinical trial in Kenya (NCT02188953) (n=50), ACCS100 decreased urinary levels of aflatoxin-M1, but efficacy towards aflatoxin-B1 was inconclusive [63]. No consistent effect toward aflatoxin-B1 was seen in a larger clinical trial (NCT01677195) (n=234) in Bexar, Texas, which is a community found to have higher rates of exposure to aflatoxins related to the general US population [57].

Search terms:

Pubmed, Google: Mold, Mycotoxins

- Aflatoxin, Ochratoxin, Fumonisin, Alzheimer's, Parkinson's dementia, cognitive impairment, mortality, asthma, allergy, cancer, kidney disease, inflammation, oxidative stress, biomarker, contamination, exposure, clinical trial, meta-analysis, systematic review, regulation limits

Websites visited for Mold and Mycotoxins:

- Clinicaltrials.gov ([Mycotoxin](#), [Aflatoxin](#), [Ochratoxin](#), [Fumonisin](#))

- [Drugs.com](https://www.drugs.com)
- [WebMD.com](https://www.webmd.com)
- PubChem ([Aflatoxin B1](https://pubchem.ncbi.nlm.nih.gov/compound/Aflatoxin-B1), [Orchatoxin-A](https://pubchem.ncbi.nlm.nih.gov/compound/Orchatoxin-A), [Fumonisin B1](https://pubchem.ncbi.nlm.nih.gov/compound/Fumonisin-B1))

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