Journal of Integrative Neuroscience

J. Integr. Neurosci. **2023**; 22(6): 137
https://doi.org/10.31083/j.jin2206137

Review

Mold and Mycotoxin Exposure and Brain Disorders

Mojtaba Ehsanifar[1,2,*], Reihane Rajati[1], Akram Gholami[1], Joseph P Reiss[3]

[1]Torbat Jam Faculty of Medical Sciences, 9571786917 Torbat Jam, Iran
[2]Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, 1419733141 Tehran, Iran
[3]Environmental Sciences at Certified Site Safety of New York, LLC, and International Institute of Environmental and Medical Studies, White Plains, NY 10603, USA
*Correspondence: Ehsanifar@gmail.com (Mojtaba Ehsanifar)
Academic Editor: Parisa Gazerani
Submitted: 9 May 2023 Revised: 7 June 2023 Accepted: 10 June 2023 Published: 17 October 2023

Abstract

Gene-environment interaction is an emerging hypothesis to explain the increased incidence of neurological disorders. In this context, the health and clinical effects of exposure to air pollutants have received increasing attention. One of these pollutants is the growth of fungi and molds in the form of multicellular filaments, known as hyphae. Fungi and molds not only grow in outdoor environments, but they also thrive indoors with excessive moisture, producing mycotoxins. Mold enters the body through the nose via the olfactory neurons, which directly communicate with the brain. Mycotoxins induce toxicological effects similar to those associated with brain disorders such as oxidative stress and inflammation. One mold species can produce several different mycotoxins, and one mycotoxin can be produced by several different molds. Even a small amount of mold growth in the air conditioners and their ducts or the panels inside the buildings and even the cars cause the occupants to be chronically exposed to and constantly inhaling spores and mycotoxins, which causes illness. In this review, we focused on mold and mycotoxin exposure and brain disorders.

Keywords: molds; outdoor/indoor environments; mycotoxins; brain disorders; cognitive impairment

1. Introduction

Mold contamination is widespread in buildings, while mold growth is generally considered a significant problem. Mold is a type of fungus that grows as multicellular filaments in food and other moist surfaces [1,2]. Any disease caused by fungi (molds) is called mycosis; fortunately, they are not contagious. Mycosis can be exacerbating, as in athlete's foot, or critical, as in invasive aspergillosis. Mycoses have increased over the past 4 decades as a result of the acquired immunodeficiency syndrome (AIDS) epidemic, the advent of chemotherapy, transplantation, immunosuppression with drugs such as corticosteroids, access to the vascular system, as well as climate change which has caused more floods, hurricanes, and storms in homes, schools, public buildings, and the workplaces [3]. The patients affected by molds and mycotoxins must no longer be exposed to them before starting the treatment [4]. As we have come to understand, biotoxins from bacteria by weight and by mass are far more important than mycotoxins possibly [5]. When actinomycetes are detected in the sample, they are tabulated as the abundance expressed per milligram of the sample. Presently there is no normal range of actinomycetes in the dust of USA homes and other countries that has been established. However, studies in the USA and other countries have shown that some actinomycetes species are frequently found in moisture-damaged buildings [6]. A normal index value is not the same as a safe indoor environment, which is a relevant term and different for everyone's toxic load burden within their bodies. Further, one should consult with an expert in the field, such as an indoor environmental professional (IEP) or a council-certified indoor environmental professional (CIEC), preferably with indoor safety or illness experience. Testing and remediation of molds are not standard. Testing for airborne mold spores in an indoor space only shows what is present at the time of the test, not 24 hours a day, 7 days a week so that test results can vary from hour to hour, depending on the activity in the room. Also, this test does not reveal any hidden mold like that found in attics, insulation, ventilation ducts, basements, damp spaces, wall cavities, etc. The Environmental Protection Agency (EPA) warns that 50% of fungal and mold growth can be hidden from the human view. Therefore, after testing and modification, some hidden mold may remain [3,7]. Many of these indicator molds have served in understanding the possible levels of water damage, the extent of potential ventilation problems, and the types of surfaces and substrates they are known to thrive on. It is imperative to understand further how fungal ecology plays an important part in many neurological disorders. As we unfold our hypothesis in this study, we detail the production of mycotoxins and the toxicological effects associated with brain disorders where mycotoxins are known first to attack the brain.

2. Mycotoxin Toxicity

Mycotoxins are secondary metabolites of fungi. Most of the mycotoxins that affect human health are from fungi of the genera *Penicillium*, *Aspergillus,* and *Fusarium*. Each

of these genera can produce several different mycotoxins [8]. Mycotoxins can exert their harmful impacts by affecting translation and transcription or via inflammatory cytokine responses. It is essential to note the mycotoxins are 0.1 µm, about the virus size (for reference: a hair is 100 µm thick, mold spores are 2–3 µm). Field studies of damp, moisture-damaged homes have shown that the number of nanoparticles indoors is at least 1000 times or more than the mold spores in indoor air. These nanoparticles are mycotoxins [7]. A mycotoxin sample must be collected within the affected environment of concern to validate further if an influence can be pinpointed to a health concern. Mycotoxin sampling is achieved by strategically collecting 5 mg of dust from various reservoirs where they have accumulated over a long period. Collecting dust in this manner provides a historical value within the dust reservoirs, potentially harboring these mycotoxins and other biotoxins as well [9].

Our previous studies have shown that airborne nanoparticles can cross the blood-brain barrier (BBB) [10–13] and cause behavioral changes and neurotoxicity by changing gene expression and causing oxidative stress and neuroinflammation [14–16]. So, when an indoor air quality report shows a spore count, the mycotoxin count can be 1000 times higher. Mycotoxins are odorless, invisible, and tasteless [17,18]. Mycotoxins are diverse and differ in molecular structure, which leads to differences in their toxicological and biological properties. Mycotoxins can have various adverse effects on human health and pose a serious threat to health, from acute toxicity to long-term impacts such as neurological disorders, cancer, and autoimmune diseases [19,20].

Various mechanisms are involved in mycotoxins toxicity, such as the inhibition of ribosomal protein synthesis and disruption of RNA and DNA biosynthesis and mitochondrial function. At the cellular level, the mycotoxins lead to apoptosis, oxidative stress, cell membrane dysfunction, and cell cycle arrest [20]. Altered immune responses due to chronic mycotoxin exposure may also negatively affect the ability of the immune system to respond to environmental challenges. The immunosuppressive effects of mycotoxins include microbiocidal activity, inhibition of superoxide release, T-lymphocyte-mediated cytotoxicity, and cytokine release by leukocytes [20,21]. Also, mycotoxins can affect nerve axons by activating a number of kinases, including MAPK (mitogen-activated protein kinase) [8,22,23]. Macrocyclic trichothecenes are MAPKs' potent activators [24]. Exposure to satratoxin H may cause induction of oxidative stress, activation of MAPKs, and depletion of reduced glutathione. Exposure to ochratoxin can reduce the function of mitochondria and may lead to apoptosis in neurons [25,26] and dysfunctional responses in cultured mouse astrocytes and microglia [27,28]. It would be valuable to mention that the effect of ochratoxin A on neuronal survivability is dose-dependent, as a 2023 study showed that a realistic dose does not induce survivability changes compared to a higher dose [29]. In a study on mice, satratoxin G induced apoptosis in sensory neurons in the olfactory bulb (OB) [30], such as encephalitis, related to persistently high levels of proinflammatory cytokines in the brain's frontal region. Molds and mycotoxins do not inhibit the immune system from forming antibodies in response to antigens. A common misconception is that mycotoxins are stored in fat cells. Since mycotoxins affect mitochondrial function and cause cell death, they destroy fat cells and are, therefore, not stored in them. Fat cells store persistent organic compounds that are toxic but not mycotoxins. Mast cells are immune cells, found perivascularly in all tissues, including brain tissue [31,32], and many inflammatory cytokines are secreted by them [33,34]. Mast cells exist in most tissues surrounding blood vessels and nerves and are found in the skin, lung mucosa, digestive system, oral cavity, nose, and conjunctiva. Recent findings indicate a strong correlation between mast cell prevalence and increased autism spectrum disorder (ASD) risk [35,36]. Exposure to mycotoxins is associated with mast cell activation. Immunoglobulin E (IgE) antibodies to mycotoxins stimulate mast cells to release heparin, histamine, proinflammatory cytokines, and prostaglandin GD2. This release induces neurological symptoms such as brain fog, headache, nausea, fatigue, and respiratory-tract irritation [20]. Recent studies suggest that this stimulation by IgE antibodies to mycotoxins in serum can lead to mast cell activation syndrome (MCAS), an often undiagnosed disorder. It has been reported that the ASD prevalence in children with mastocytosis is 10 times higher than in the general population [36]. In addition, based on studies, one-third of mastocytosis patients show neuropsychological symptoms such as fatigue [37], depression, and cognitive impairment [38]. Interestingly, mycotoxins can stimulate mast cells [39] and microglia [40] because mast cell-microglia interactions are involved in neuropsychiatric disorders, particularly "brain fog".

3. Mold Exposure and Brain

Based on the findings and results of various studies, the first area of effect of mycotoxins in humans is the central nervous system. Mycotoxins can cross BBB. A study has shown that T-2 toxin can cross BBB and accumulate in the brain, leading to neurotoxicity [41]. Other studies have shown that mycotoxin deoxynivalenol (DON) reduces BBB integrity and causes cytotoxic effects at very low concentrations [41–43]. *In vitro* and *in vivo* studies indicate that cellular and molecular oxidative stress is a direct mechanism of mycotoxin-induced cytotoxicity. Brain cells are vulnerable to oxidative stress damage caused by DON, ochratoxin A, and T-2 toxins from the environment [44]. Mycotoxins have significant toxic effects on the brain as well as the peripheral nervous system. Studies have shown that mycotoxins can cause myelin loss, leading to symptoms similar

to multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, and other demyelinating disorders. In the peripheral nervous system, loss of myelin can be to sensory nerves, motor nerves, or both. One survey of 119 patients exposed to mold and mycotoxins in whom the mycotoxin antibody test was positive in blood serum observed demyelination of nerves. One study showed that all participants developed blood serum antibodies to nerve tissue, including myelin basic protein antibodies, myelin-associated glycoprotein antibodies, and others, which had significant neurological effects [45]. Another study found that patients can develop demyelinating optic neuritis due to mycotoxin exposure, which leads to blurred vision, reduced visual fields, and reduced pupillary response. Patients with this disorder were successfully treated with oral itraconazole and intravenous gamma globulin [46]. Researchers at Rutgers School of Medicine suggested in 2010 that mycotoxins are the primary cause of multiple sclerosis and thus may offer a path toward an effective treatment [47]. A study in the Journal of Neuroscience found both *in vivo* and *in vitro* that mycotoxin gliotoxin causes demyelination, which leads to multiple sclerosis [47,48]. Brasel *et al*. [49] showed that antibodies to trichothecene mycotoxin from *Stachybotrys chartarum* could be measured in the blood serum of patients exposed to mold-contaminated indoor environments. A study on 500 patients with mold and 500 controls showed that Immunoglobulin G (IgG) serum antibodies to mycotoxin satratoxin were significantly higher in patients than in the control group ($p < 0.001$) [50]. Mycotoxins may be effective in ASD. A study on 172 children with ASD with 61 controls showed significant differences comparing antibodies to mycotoxins between the 2 groups, and the ASD group indicated higher serum antibodies to mycotoxins [51]. Research findings from the Tufts University School of Medicine suggested that mycotoxins cause ASD. According to the survey results, exposure to mycotoxins and molds can directly affect the nervous system or through the activation of immune cells and contribute to ASD and other neurodevelopmental disorders. A follow-up study from the same institution the following year confirmed these findings [52,53].

In the medical textbook Environmental Contaminants and Neurological Disorders, published in 2021, Chaudhary and colleagues discuss the mechanisms by which mycotoxins affect the brain. Trichothecenes and T-2 toxins cause neuronal apoptosis and neuroinflammation. Ochratoxin A causes loss of dopaminergic neurons and apoptosis in the substantia nigra, striatum, and hippocampus, which can also be found in Parkinson disease patients. Satratoxin, DON, and T-2 toxins inhibit ceramide synthesis and cause neurodegeneration in the cerebral cortex. Satratoxin causes olfactory nerve apoptosis and olfactory nerve layer bilateral atrophy of OB in the brain and can lead to anosmia [54]. Inflammation stimulated by mycotoxins causes inflammatory markers such as NF-kappa B and TNF-alpha to access the OB and frontal cortex, leading to the deposition of amyloid-beta plaques (an Alzheimer disease pathological hallmark) and other neurological disorders. Neuroinflammation is commonly seen with amyotrophic lateral sclerosis (ALS). Motor neuron diseases such as ALS are fatal neurodegenerative conditions that affect motor neurons in the brain, and the spinal cord may cause muscle weakness. Increasing weakness of muscles used for breathing may lead to death. Familial ALS affects 5% to 10% of cases, and the remainder, 90% to 95%, is sporadic [55]. One of the hallmarks of ALS is the excessive release of glutamate from nerve cells. The mycotoxins verruculogen and penitrem increase glutamate release by 1300% [56,57]. This important evidence implicates the effects of mycotoxins on glutamate overactivation in ALS development [58].

4. Mold Exposure and Neuropsychiatric Effects on Children

Neurophysiological studies in children showed that brainstem, somatosensory, and visual evoked potentials were abnormal after prolonged exposure to mycotoxins [59,60]. One study indicated a correlation between respiratory problems, including infections, frequent wheezing and prolonged coughing, and exposure to mold or excessive humidity in the home or school environment [61–64]. Some researchers have investigated cognitive developmental deficits caused by air pollutant exposure during childhood and pregnancy [65,66]. Abnormalities have been observed in a series of neurophysiological tests, including somatosensory evoked potentials, electroencephalography, brainstem evoked potentials [67], and visual evoked potentials, in children with long-term mold exposure [60]. Exposure to mold's potent toxins has been related to hemosiderosis and acute pulmonary hemorrhage among infants [68]. Recent epidemiologic findings have shown a significant association between ASD and mycotoxin exposure; it reads as 1 in 59 children are affected by ASD that is caused/linked by mycotoxin exposure [69], and despite progress in identifying multiple mutations, it remains without clear pathogenesis [70,71]. In one study, the comparison of urine and serum ochratoxin A levels in 52 children with ASD with healthy children (27 unrelated individuals and 31 siblings) was significant [51]. Also, in a cross-sectional study, the different mycotoxins levels (fumonisin B1, ochratoxin A, and aflatoxin M1) were notably higher in the urine and serum of 172 children with ASD compared to 61 healthy individuals [72]. A comparison of neurobehavioral and pulmonary function between boys with ASD exposed to mold, mold-unexposed ASD boys, terbutaline-exposed children, and unaffected children from a non-chemically exposed community was conducted in another study. The results showed that mold-exposed ASD boys had significantly higher mean abnormalities in balance, vision, and blink reflex latency than other groups [73]. Furthermore, based on the results of other studies, children exposed to mold experienced cog-

nitive impairment compared to the control group [74,75]. However, in individuals exposed to mycotoxins, IgE or IgG serum levels may be a more reliable indicator of prolonged exposure.

5. Mold Exposure and Neuropsychiatric Effects in Adults

A wide variety of symptoms, including fatigue, malaise, and cognitive disorders, have been reported by people exposed to mold, which appear to be associated with the exposure duration [76–79]. In a study, patients exposed to mold had various cognitive impairments, including disturbances in visuospatial memory and learning, verbal learning, emotional functioning, and psychomotor speed [78]. In other research, mold-exposed patients also showed symptoms of neurological dysfunction compared to controls, including the inability to walk with eyes closed in a straight line, failure to stand on one's toes, verbal recall impairments, altered blink-reflex latency, short-term memory loss, as well as reaction time issues and problems with color discrimination [80,81]. In another study, researchers evaluated the neuropsychological, electrocortical, and psychological effects of toxigenic molds of mixed colonies in 182 patients with a history of confirmed mold exposure. Neuropsychological tests showed impairment similar to mild traumatic brain injury with signs of impaired cognitive functions in these patients [79]. These findings are consistent with another study, which examined neuropsychological data in 31 individuals exposed to toxic mold and found that cognitive function, including impaired memory and executive functions, was reduced in most participants in various domains. These findings were similar to the symptoms of the matched group of 26 people with moderate traumatic brain injury and the group of 65 people with mild traumatic brain injury [75]. The results of a study on individuals in water-damaged buildings exposed to mixed mold contamination showed that mycotoxin exposure was associated with the development of multisystem issues related to the immune and nervous systems [81]. Researchers in other studies using subjective and objective measures have shown that dampness and mold are associated with emotional distress and depression prevalence [82,83]. In addition to the confirmation of these results in various studies, there are also conflicting reports that do not confirm it. The results of one study did not show a considerable reduction in academic performance, unlike the cognitive disorders suggested in other research. Also, they did not show the effect of duration and the dose of mold exposure on the development of cognitive impairments [84]. Another study found no association between mold exposure and neuropsychiatric symptoms [85]. When researchers examined neurobehavioral and pulmonary impairments in 105 adults exposed to indoor molds, compared to a control group and 100 adults exposed to chemicals, they found an increase in neurobehavioral impairments related to exposure to mold is comparable to damage from exposure to chemicals. Therefore, cognitive impairment symptoms may not be unique to mycotoxin exposure [86]. Also, it is unclear whether neuropsychiatric problems and mental disorders are caused by the adverse effects of molds and mycotoxins or the financial and emotional stress of keeping the house clean in frequent mold exposure [82]. Researchers have also suggested that housing is closely related to an individual's conception of control; therefore, those who experience living in a moldy home with a low sense of control may be at increased risk for depression and anxiety [87,88]. In addition, since living in a moist and moldy home is related to poor physical health outcomes, such as gastrointestinal and respiratory problems, illness and physical weakness can also be possible factors in depressive tendencies [62,82,83,89]. Also, there is concern that some neuropsychiatric symptoms and psychiatric disorders may be related to socioeconomic factors in people living in moldy homes [90]. Findings show that exposure to mold due to contaminated onions in the workplace increased fumonisins B1 and B2 [91]. In a study in Portugal, increased aflatoxin B1 levels were reported in workers of a waste management company [92]. The aflatoxin B1 presence in breast milk in Lebanon was associated with low socioeconomic status [93]. Also, a cross-sectional study in Kenya reported a strong association between poverty and aflatoxin exposure [94].

6. Conclusions

Symptoms in mold- and mycotoxin-exposed patients may be due to the effects of mycotoxins on the peripheral and central nervous system rather than the gut and/or liver. As described, the amount of mycotoxins in foods and beverages is below the tolerable daily intake, too small to impact human health, and is usually excreted in the urine. Therefore, it is better to treat the peripheral and central nervous system first. Testing mycotoxins by serum antibodies is the most advanced and accurate method, well-established by numerous published studies. Antibodies to mycotoxins also add to the body's burden on these toxins. It is important to understand that antibodies to mycotoxins can form adducts and stick to human tissue, causing autoimmunity. Considering that most of the mycotoxins detected in urine originate from food, the detection of mycotoxins in urine does not indicate the body's mycotoxin load. It should not be used as a biomarker of exposure to mycotoxins in humid buildings and damaged with water. Before deciding to use urine levels of mycotoxins as an indication of mold exposure in damp, water-damaged buildings, it is important to consider the source of the mycotoxins detected in the urine. And why the detection of mycotoxins in urine is a sign of neo-antigen formation between mycotoxins and human tissue antigens that play a role in the pathophysiology of autoimmune and neurological diseases? Treating mycotoxicosis is just as important as treating autoimmunity. The autoimmune response may fade, rather than vice versa. Be-

cause these are toxins and not living organisms with cell membranes, an IgG antibody to mycotoxins indicates current exposure and/or colonization to the 4 pathogens in microbiology viruses, bacteria, parasites, and fungi. IgE antibodies to mycotoxins show mast cell stimulation and can lead to MCAS [20,95,96]. Understanding a condition I fungal ecology is simple; it is known to be where some fungal biomass (settled spores, hyphal fragments, traces of mold growth) on various building materials and reflects a "normal" fungal ecology in a similar indoor environment compared to the outdoor ecology. When we have condition II, settled spores or condition III, where there is visible microbial colonization or contamination, we may see or smell slight signs of mold. However, condition II is an "assumption" based on circumstantial evidence that cannot be verified without a laboratory test. An IEP must be able to produce the data and optics that are necessary to provide the scientific evidence that a potential correlatable condition exists where a mycotoxin, actinomycetes, or an endotoxin can be measured in the environment.

As we perform the deep dive assessment in capturing historical dust reservoirs and seek out through the questionable environment, we begin to understand various sources within many moist enriched areas that hold the key that can lead us to the root cause of the problem. Therefore, to obtain a complete picture of the effects of mycotoxins on the patient, including body burden and autoimmunity, and crossing the BBB, serum antibodies to mycotoxins are the most accurate method, confirmed by numerous studies published in reputable medicine.

Furthermore, we need to continue to understand how the indoor environment can trigger or affect these conditions. It is imperative to understand further how a condition in fungal ecology plays an important part in many neurological disorders. As we have stated, this hypothesis goes into great detail about the production of mycotoxins and the toxicological effects associated with brain disorders, where mycotoxins first invade the brain. The goal is to understand the microbial and bacterial effects that develop in the environment from severe weather patterns that cause these constant and excessive water intrusion events with ongoing damage to our homes and buildings over a long period worldwide. This abnormal condition still goes unmeasurable today, with so much uncertainty yet to be identified, with the hopes of finding a correlation between environment and illness to help improve the lives of many suffering from these environmental triggers.

Author Contributions

ME designed the study and wrote the first manuscript and supervised the work. RR and AG contributed significantly to the initial concept and design and the final version and corrected some typographical errors. JPR contributed significantly to the initial concept and design, selected relevant references, and contributed to the English editing of the final version. All authors contributed to the editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have contributed sufficiently to the work and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank Dr. Ehsanifar Research Lab. Tehran, Iran.

Funding

This review received no external funding and was initiated and funded by Dr. Ehsanifar Research Lab, Tehran, Iran.

Conflict of Interest

Joseph P Reiss is from Environmental Sciences at Certified Site Safety of New York, LLC, and the International Institute of Environmental and Medical Studies. There is no conflict of interest for the authors of this article.

References

[1] Ismaiel AA, Papenbrock J. Mycotoxins: producing fungi and mechanisms of phytotoxicity. Agriculture. 2015; 5: 492–537.

[2] da Rocha MEB, Freire FCO, Maia FEF, Guedes MIF, Rondina D. Mycotoxins and their effects on human and animal health. Food Control. 2014; 36: 159–165.

[3] Campbell AW, Watson P. Mold, Mycotoxins, and their Effects in Children. Alternative Therapies in Health and Medicine. 2021; 27: 8–10.

[4] Bannister B, Gillespie SH, Jones J. Infection: microbiology and management. 3rd edn. John Wiley & Sons: Hoboken, NJ, USA. 2009.

[5] Suihko ML, Priha O, Alakomi HL, Thompson P, Mälarstig B, Stott R, *et al*. Detection and molecular characterization of filamentous actinobacteria and thermoactinomycetes present in water-damaged building materials. Indoor Air. 2009; 19: 268–277.

[6] Jayaprakash B, Adams RI, Kirjavainen P, Karvonen A, Vepsäläinen A, Valkonen M, *et al*. Indoor microbiota in severely moisture damaged homes and the impact of interventions. Microbiome. 2017; 5: 138.

[7] Thrasher JD. Fungi, bacteria, nano-particulates, mycotoxins and human health in water-damaged indoor environments. Journal of Community & Public Health Nursing. 2016; 2: 2.

[8] Lionakis MS, Iliev ID, Hohl TM. Immunity against fungi. JCI Insight. 2017; 2: e93156.

[9] Viegas S, Viegas C, Martins C, Assunção R. Occupational Exposure to Mycotoxins-Different Sampling Strategies Telling a Common Story Regarding Occupational Studies Performed in Portugal (2012–2020). Toxins. 2020; 12: 513.

[10] Ehsanifar M. Airborne aerosols particles and COVID-19 transition. Environmental Research. 2021; 200: 111752.

[11] Ehsanifar M, Tameh AA, Farzadkia M, Kalantari RR, Zavareh MS, Nikzaad H, *et al*. Exposure to nanoscale diesel exhaust particles: Oxidative stress, neuroinflammation, anxiety and depression on adult male mice. Ecotoxicology and Environmental Safety. 2019; 168: 338–347.

[12] Ehsanifar M, Yavari Z, Rafati M. Exposure to urban air pollution particulate matter: neurobehavioral alteration and hippocampal inflammation. Environmental Science and Pollution Research International. 2022; 29: 50856–50866.
[13] Ehsanifar M, Montazeri Z, Zavareh MS, Rafati M, Wang J. Cognitive impairment, depressive-like behaviors and hippocampal microglia activation following exposure to air pollution nanoparticles. Environmental Science and Pollution Research International. 2023; 30: 23527–23537.
[14] Ehsanifar M, Jafari AJ, Montazeri Z, Kalantari RR, Gholami M, Ashtarinezhad A. Learning and memory disorders related to hippocampal inflammation following exposure to air pollution. Journal of Environmental Health Science & Engineering. 2021; 19: 261–272.
[15] Ehsanifar M, Jafari AJ, Nikzad H, Zavareh MS, Atlasi MA, Mohammadi H, *et al*. Prenatal exposure to diesel exhaust particles causes anxiety, spatial memory disorders with alters expression of hippocampal pro-inflammatory cytokines and NMDA receptor subunits in adult male mice offspring. Ecotoxicology and Environmental Safety. 2019; 176: 34–41.
[16] Ehsanifar M, Montazeri Z, Taheri MA, Rafati M, Behjati M, Karimian M. Hippocampal inflammation and oxidative stress following exposure to diesel exhaust nanoparticles in male and female mice. Neurochemistry International. 2021; 145: 104989.
[17] Dantzer R. Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. Physiological Reviews. 2018; 98: 477–504.
[18] Ehsanifar M, Rafati M, Wang J. Neurological complications related to COVID-19 infections following exposure to airborne aerosol particles. Journal of Clinical Trials & Research. 2022; 5.
[19] Janik E, Niemcewicz M, Ceremuga M, Stela M, Saluk-Bijak J, Siadkowski A, *et al*. Molecular Aspects of Mycotoxins-A Serious Problem for Human Health. International Journal of Molecular Sciences. 2020; 21: 8187.
[20] Campbell AW, Weinstock LB. Molds, Mycotoxins, the Brain, the Gut and Misconceptions. Alternative Therapies in Health and Medicine. 2022; 28: 8–12.
[21] Surai PF, Dvorska JE. Effects of mycotoxins on antioxidant status and immunity. The Mycotoxin Blue Book. 2005; 1.
[22] Pestka JJ, Amuzie CJ. Tissue distribution and proinflammatory cytokine gene expression following acute oral exposure to deoxynivalenol: comparison of weanling and adult mice. Food and Chemical Toxicology: an International Journal Published for the British Industrial Biological Research Association. 2008; 46: 2826–2831.
[23] Zhou HR, Jia Q, Pestka JJ. Ribotoxic stress response to the trichothecene deoxynivalenol in the macrophage involves the SRC family kinase Hck. Toxicological Sciences: an Official Journal of the Society of Toxicology. 2005; 85: 916–926.
[24] Bouslimi A, Ouannes Z, Golli EE, Bouaziz C, Hassen W, Bacha H. Cytotoxicity and oxidative damage in kidney cells exposed to the mycotoxins ochratoxin a and citrinin: individual and combined effects. Toxicology Mechanisms and Methods. 2008; 18: 341–349.
[25] Gautier JC, Holzhaeuser D, Markovic J, Gremaud E, Schilter B, Turesky RJ. Oxidative damage and stress response from ochratoxin a exposure in rats. Free Radical Biology & Medicine. 2001; 30: 1089–1098.
[26] Zhang X, Boesch-Saadatmandi C, Lou Y, Wolffram S, Huebbe P, Rimbach G. Ochratoxin A induces apoptosis in neuronal cells. Genes & Nutrition. 2009; 4: 41–48.
[27] Zurich MG, Lengacher S, Braissant O, Monnet-Tschudi F, Pellerin L, Honegger P. Unusual astrocyte reactivity caused by the food mycotoxin ochratoxin A in aggregating rat brain cell cultures. Neuroscience. 2005; 134: 771–782.
[28] Hong JT, Lee MK, Park KS, Jung KM, Lee RD, Jung HK, *et al*. Inhibitory effect of peroxisome proliferator-activated receptor gamma agonist on ochratoxin A-induced cytotoxicity and activation of transcription factors in cultured rat embryonic midbrain cells. Journal of Toxicology and Environmental Health. Part a. 2002; 65: 407–418.
[29] Sharma R, Gettings SM, Hazell G, Bourbia N. In vitro study of ochratoxin A in the expression of genes associated with neuron survival and viability. Toxicology. 2023; 483: 153376.
[30] Islam Z, Harkema JR, Pestka JJ. Satratoxin G from the black mold Stachybotrys chartarum evokes olfactory sensory neuron loss and inflammation in the murine nose and brain. Environmental Health Perspectives. 2006; 114: 1099–1107.
[31] Matsumoto I, Inoue Y, Shimada T, Aikawa T. Brain mast cells act as an immune gate to the hypothalamic-pituitary-adrenal axis in dogs. The Journal of Experimental Medicine. 2001; 194: 71–78.
[32] Taiwo OB, Kovács KJ, Sun Y, Larson AA. Unilateral spinal nerve ligation leads to an asymmetrical distribution of mast cells in the thalamus of female but not male mice. Pain. 2005; 114: 131–140.
[33] Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. The New England Journal of Medicine. 2015; 373: 163–172.
[34] Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. Immunological Reviews. 2018; 282: 121–150.
[35] Theoharides TC, Tsilioni I, Patel AB, Doyle R. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. Translational Psychiatry. 2016; 6: e844.
[36] Theoharides TC. Autism spectrum disorders and mastocytosis. International Journal of Immunopathology and Pharmacology. 2009; 22: 859–865.
[37] Georgin-Lavialle S, Gaillard R, Moura D, Hermine O. Mastocytosis in adulthood and neuropsychiatric disorders. Translational Research: the Journal of Laboratory and Clinical Medicine. 2016; 174: 77–85.e1.
[38] Moura DS, Sultan S, Georgin-Lavialle S, Barete S, Lortholary O, Gaillard R, *et al*. Evidence for cognitive impairment in mastocytosis: prevalence, features and correlations to depression. PLoS ONE. 2012; 7: e39468.
[39] Saluja R, Metz M, Maurer M. Role and relevance of mast cells in fungal infections. Frontiers in Immunology. 2012; 3: 146.
[40] von Tobel JS, Antinori P, Zurich MG, Rosset R, Aschner M, Glück F, *et al*. Repeated exposure to Ochratoxin A generates a neuroinflammatory response, characterized by neurodegenerative M1 microglial phenotype. Neurotoxicology. 2014; 44: 61–70.
[41] Ratnaseelan AM, Tsilioni I, Theoharides TC. Effects of Mycotoxins on Neuropsychiatric Symptoms and Immune Processes. Clinical Therapeutics. 2018; 40: 903–917.
[42] Patel R, Hossain MA, German N, Al-Ahmad AJ. Gliotoxin penetrates and impairs the integrity of the human blood-brain barrier in vitro. Mycotoxin Research. 2018; 34: 257–268.
[43] Dai C, Xiao X, Sun F, Zhang Y, Hoyer D, Shen J, *et al*. T-2 toxin neurotoxicity: role of oxidative stress and mitochondrial dysfunction. Archives of Toxicology. 2019; 93: 3041–3056.
[44] Fang H, Wu Y, Guo J, Rong J, Ma L, Zhao Z, *et al*. T-2 toxin induces apoptosis in differentiated murine embryonic stem cells through reactive oxygen species-mediated mitochondrial pathway. Apoptosis: an International Journal on Programmed Cell Death. 2012; 17: 895–907.
[45] Campbell AW, Thrasher JD, Madison RA, Vojdani A, Gray MR, Johnson A. Neural autoantibodies and neurophysiologic abnormalities in patients exposed to molds in water-damaged buildings. Archives of Environmental Health. 2003; 58: 464–474.

[46] Campbell AW, Anyanwu EC, Vojdani A. Combination of high-dose intravenous immunoglobulins and itraconozole in treating chronic mycotic demyelinating optic neuritis. TheScientificWorldJournal. 2003; 3: 640–646.
[47] Vickers NJ. Animal Communication: When I'm Calling You, Will You Answer Too? Current Biology: CB. 2017; 27: R713–R715.
[48] Ménard A, Amouri R, Dobránsky T, Charriaut-Marlangue C, Pierig R, Cifuentes-Diaz C, *et al*. A gliotoxic factor and multiple sclerosis. Journal of the Neurological Sciences. 1998; 154: 209–221.
[49] Brasel TL, Campbell AW, Demers RE, Ferguson BS, Fink J, Vojdani A, *et al*. Detection of trichothecene mycotoxins in sera from individuals exposed to Stachybotrys chartarum in indoor environments. Archives of Environmental Health. 2004; 59: 317–323.
[50] Vojdani A, Thrasher JD, Madison RA, Gray MR, Heuser G, Campbell AW. Antibodies to molds and satratoxin in individuals exposed in water-damaged buildings. Archives of Environmental Health. 2003; 58: 421–432.
[51] De Santis B, Brera C, Mezzelani A, Soricelli S, Ciceri F, Moretti G, *et al*. Role of mycotoxins in the pathobiology of autism: A first evidence. Nutritional Neuroscience. 2019; 22: 132–144.
[52] Theoharides TC, Kavalioti M, Martinotti R. Factors adversely influencing neurodevelopment. Journal of Biological Regulators and Homeostatic Agents. 2019; 33: 1663–1667.
[53] Theoharides TC, Kavalioti M, Tsilioni I. Mast Cells, Stress, Fear and Autism Spectrum Disorder. International Journal of Molecular Sciences. 2019; 20: 3611.
[54] Chauhdary Z, Rehman K, Akash MSH. Mechanistic insight of mycotoxin-induced neurological disorders and treatment strategies. Environmental Contaminants and Neurological Disorders. 2021; 125–146.
[55] Mathis S, Couratier P, Julian A, Corcia P, Le Masson G. Current view and perspectives in amyotrophic lateral sclerosis. Neural Regeneration Research. 2017; 12: 181–184.
[56] Norris PJ, Smith CC, De Belleroche J, Bradford HF, Mantle PG, Thomas AJ, *et al*. Actions of tremorgenic fungal toxins on neurotransmitter release. Journal of Neurochemistry. 1980; 34: 33–42.
[57] Bradford HF, Norris PJ, Smith CC. Changes in transmitter release patterns in vitro induced by tremorgenic mycotoxins. Journal of Environmental Pathology, Toxicology and Oncology: Official Organ of the International Society for Environmental Toxicology and Cancer. 1990; 10: 17–30.
[58] French PW, Ludowyke R, Guillemin GJ. Fungal Neurotoxins and Sporadic Amyotrophic Lateral Sclerosis. Neurotoxicity Research. 2019; 35: 969–980.
[59] Anyanwu E, Campbell AW, High W. Brainstem auditory evoked response in adolescents with acoustic mycotic neuroma due to environmental exposure to toxic molds. International Journal of Adolescent Medicine and Health. 2002; 14: 67–76.
[60] Anyanwu EC, Campbell AW, Vojdani A. Neurophysiological effects of chronic indoor environmental toxic mold exposure on children. The Scientific World Journal. 2003; 3: 281–290.
[61] Spengler JD, Jaakkola JJK, Parise H, Katsnelson BA, Privalova LI, Kosheleva AA. Housing characteristics and children's respiratory health in the Russian Federation. American Journal of Public Health. 2004; 94: 657–662.
[62] Zock JP, Jarvis D, Luczynska C, Sunyer J, Burney P, European Community Respiratory Health Survey. Housing characteristics, reported mold exposure, and asthma in the European Community Respiratory Health Survey. The Journal of Allergy and Clinical Immunology. 2002; 110: 285–292.
[63] Taskinen T, Hyvärinen A, Meklin T, Husman T, Nevalainen A, Korppi M. Asthma and respiratory infections in school children with special reference to moisture and mold problems in the school. Acta Paediatrica (Oslo, Norway: 1992). 1999; 88: 1373–1379.
[64] Belanger K, Beckett W, Triche E, Bracken MB, Holford T, Ren P, *et al*. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. American Journal of Epidemiology. 2003; 158: 195–202.
[65] McCall RB. Childhood IQ's as Predictors of Adult Educational and Occupational Status. Science (New York, N.Y.). 1977; 197: 482–483.
[66] Moffitt TE, Gabrielli WF, Mednick SA, Schulsinger F. Socioeconomic status, IQ, and delinquency. Journal of Abnormal Psychology. 1981; 90: 152–156.
[67] Guo M, Fang Y, Zhu J, Chen C, Zhang Z, Tian X, *et al*. Investigation of metabolic kinetics in different brain regions of awake rats using the [1H-13C]-NMR technique. Journal of Pharmaceutical and Biomedical Analysis. 2021; 204: 114240.
[68] Montaña E, Etzel RA, Allan T, Horgan TE, Dearborn DG. Environmental risk factors associated with pediatric idiopathic pulmonary hemorrhage and hemosiderosis in a Cleveland community. Pediatrics. 1997; 99: E5.
[69] Newsroom C. CDC estimates 1 in 68 children has been identified with autism spectrum disorder. Centers for Disease Control and Prevention. 2014.
[70] Geschwind DH, State MW. Gene hunting in autism spectrum disorder: on the path to precision medicine. The Lancet. Neurology. 2015; 14: 1109–1120.
[71] Willsey AJ, State MW. Autism spectrum disorders: from genes to neurobiology. Current Opinion in Neurobiology. 2015; 30: 92–99.
[72] De Santis B, Raggi ME, Moretti G, Facchiano F, Mezzelani A, Villa L, *et al*. Study on the Association among Mycotoxins and other Variables in Children with Autism. Toxins. 2017; 9: 203.
[73] Kilburn KH, Thrasher JD, Immers NB. Do terbutaline- and mold-associated impairments of the brain and lung relate to autism? Toxicology and Industrial Health. 2009; 25: 703–710.
[74] Casas L, Torrent M, Zock JP, Doekes G, Forns J, Guxens M, *et al*. Early life exposures to home dampness, pet ownership and farm animal contact and neuropsychological development in 4 years old children: a prospective birth cohort study. International Journal of Hygiene and Environmental Health. 2013; 216: 690–697.
[75] Gordon WA, Cantor JB, Johanning E, Charatz HJ, Ashman TA, Breeze JL, *et al*. Cognitive impairment associated with toxigenic fungal exposure: a replication and extension of previous findings. Applied Neuropsychology. 2004; 11: 65–74.
[76] Campbell AW, Thrasher JD, Gray MR, Vojdani A. Mold and mycotoxins: effects on the neurological and immune systems in humans. Advances in Applied Microbiology. 2004; 55: 375–406.
[77] Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: an overview of environmental risk factors. Environmental Health Perspectives. 2005; 113: 1250–1256.
[78] Baldo JV, Ahmad L, Ruff R. Neuropsychological performance of patients following mold exposure. Applied Neuropsychology. 2002; 9: 193–202.
[79] Gray MR, Thrasher JD, Crago R, Madison RA, Arnold L, Campbell AW, *et al*. Mixed mold mycotoxicosis: immunological changes in humans following exposure in water-damaged buildings. Archives of Environmental Health. 2003; 58: 410–420.
[80] Kilburn KH. Indoor mold exposure associated with neurobehavioral and pulmonary impairment: a preliminary report. Archives of Environmental Health. 2003; 58: 390–398.
[81] Rea WJ, Didriksen N, Simon TR, Pan Y, Fenyves EJ, Griffiths B. Effects of toxic exposure to molds and mycotoxins in building-

related illnesses. Archives of Environmental Health. 2003; 58: 399–405.
[82] Hyndman SJ. Housing dampness and health amongst British Bengalis in east London. Social Science & Medicine (1982). 1990; 30: 131–141.
[83] Packer CN, Stewart-Brown S, Fowle SE. Damp housing and adult health: results from a lifestyle study in Worcester, England. Journal of Epidemiology and Community Health. 1994; 48: 555–559.
[84] Reinhard MJ, Satz P, Scaglione CA, D'Elia LF, Rassovsky Y, Arita AA, *et al*. Neuropsychological exploration of alleged mold neurotoxicity. Archives of Clinical Neuropsychology: the Official Journal of the National Academy of Neuropsychologists. 2007; 22: 533–543.
[85] Platt SD, Martin CJ, Hunt SM, Lewis CW. Damp housing, mould growth, and symptomatic health state. BMJ (Clinical Research Ed.). 1989; 298: 1673–1678.
[86] Kilburn KH. Neurobehavioral and pulmonary impairment in 105 adults with indoor exposure to molds compared to 100 exposed to chemicals. Toxicology and Industrial Health. 2009; 25: 681–692.
[87] Griffin JM, Fuhrer R, Stansfeld SA, Marmot M. The importance of low control at work and home on depression and anxiety: do these effects vary by gender and social class? Social Science & Medicine (1982). 2002; 54: 783–798.
[88] Dunn JR, Hayes MV. Social inequality, population health, and housing: a study of two Vancouver neighborhoods. Social Science & Medicine (1982). 2000; 51: 563–587.
[89] Dales RE, Burnett R, Zwanenburg H. Adverse health effects among adults exposed to home dampness and molds. The American Review of Respiratory Disease. 1991; 143: 505–509.
[90] Hynes HP, Brugge D, Osgood ND, Snell J, Vallarino J, Spengler J. "Where does the damp come from?" Investigations into the indoor environment and respiratory health in Boston public housing. Journal of Public Health Policy. 2003; 24: 401–426.
[91] Mayer S, Twarużek M, Błajet-Kosicka A, Grajewski J. Occupational exposure to mould and microbial metabolites during onion sorting–insights into an overlooked workplace. Environmental Monitoring and Assessment. 2016; 188: 154.
[92] Viegas S, Veiga L, Figueiredo P, Almeida A, Carolino E, Viegas C. Assessment of workers' exposure to aflatoxin B1 in a Portuguese waste industry. The Annals of Occupational Hygiene. 2015; 59: 173–181.
[93] Elaridi J, Bassil M, Kharma JA, Daou F, Hassan HF. Analysis of Aflatoxin M_1 in Breast Milk and Its Association with Nutritional and Socioeconomic Status of Lactating Mothers in Lebanon. Journal of Food Protection. 2017; 80: 1737–1741.
[94] Leroy JL, Wang JS, Jones K. Serum aflatoxin B_1-lysine adduct level in adult women from Eastern Province in Kenya depends on household socio-economic status: A cross sectional study. Social Science & Medicine (1982). 2015; 146: 104–110.
[95] Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell research. 2020; 30: 492–506.
[96] Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology, -South Asia Edition-E-Book. 10th edn. Elsevier Health Sciences: Amsterdam, The Netherlands. 2021.