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What effect do mycotoxins, cell wall components, enzymes and other mold components and metabolites have on our health?

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Abstract The AWMF (Association of the Scientific Medical Societies) mold guideline "Medical clinical diagnostics for indoor mold exposure"—Update 2023 [44] concludes that there is limited or presumed evidence of a link between indoor dampness/mold exposure and health problems. However, there is inadequate or insufficient evidence for an association between indoor dampness/mold exposure and the environmental medical syndromes sick building syndrome (SBS), multiple chemical sensitivity (MCS) and chronic fatigue syndrome (CFS). Newly coined terms, such as biotoxicosis and mold and vapor hypersensitivity syndrome (MDHS) or volatoxins, suggest a nosological specificity of a pathophysiological connection for which, however, there is no evidence to date. The background to this assessment is presented in this paper.

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Abbreviations

BRI	Building Related Illness
CFS	Chronic Fatigue Syndrome
DHS	Dermatophytes, yeasts, molds
IEI	Idiopathic Environmental Intolerance
LPS	Lipopolysaccharides
MCS	Multiple Chemical Sensitivity
MDHS	Mold and Dampness Hypersensitivity Syndrome
MVOC	Microbial volatile organic compounds
SBS	Sick Building Syndrome

Introduction

Disorders of well-being play a significant role in environmentally associated health disorders in general [12, 14] as well as in indoor-associated health disorders in particular [12–14]. Environmentally associated health disorders can be presented as environmental medical syndromes (group of similar disease symptoms, similar phenotype) [125]. Environmental medical syndromes include sick building syndrome (SBS), multiple chemical sensitivity (MCS) and chronic fatigue syndrome (CFS) [126]. A possible connection to indoor dampness/mold damage is discussed for both mood disorders and environmental medical syndromes [44]. There is more or less strong evidence for such a connection. The reasons for this are described in more detail below.

Molds, mycotoxins, cell wall components, enzymes and other mold components and metabolites

In taxonomy, fungi used to be subsumed under plants, but today they represent their own kingdom as fungi.

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Fungi belong to the eukaryotes and have cell walls made of chitin and other glucans, whereas the cell walls of plants consist of cellulose.

Another important difference to plants is that fungi, as heterotrophic organisms, have no chlorophyll, do not carry out photosynthesis and must obtain their energy from organic substances of other organisms [39]. In addition, they do not perform active locomotion.

The nomenclature of fungi is binominal, i.e. each organism has a genus and a species name. However, changes in the names of fungi are relatively frequent due to new findings and taxonomic classifications. Until a few years ago, taxonomic classifications were mainly based on morphological characteristics. New taxonomic descriptions are based on a combination of morphology, physiology and genetic characteristics [20, 98, 99]. The use of molecular biological techniques to identify molds has provided new insights into the phylogeny of different mold species. It has been shown, for example, that many organisms that were previously grouped together as a single species, although morphologically and physiologically almost identical, are usually closely related but are genetically too different to belong to a single species. Currently, phylogenetically closely related species are regarded as species complexes.

For example, molecular biology has so far identified 15 species that were previously grouped morphologically under "*Aspergillus versicolor*", an indicator organism for moisture damage. The species delimitation within this complex has not yet been conclusively clarified. The species of this complex isolated indoors were predominantly identified as *Aspergillus jensenii, A. versicolor, A. protuberus* or *A. creber.* For many complexes, identification of the molds down to the species level is only possible by molecular biology. For the general, hygienic assessment of mold fungi indoors using the Federal Environment Agency's guideline "On the prevention, detection and remediation of mold infestation in buildings" [47], classification as belonging to the *A. versicolor* complex is sufficient. In test reports and expert opinions, the different species of the *Aspergillus versicolor* complex can therefore be summarized by stating the identification criteria used or the literature used [30].

Aspergilli with asexual and sexual stages previously had a separate name for each stage, for example *Eurotium* and *Aspergillus*. There are currently discussions about naming both stages after the asexual form, i.e. ***Aspergillus*** for the *Eurotium* and *Aspergillus* structures.

This can lead to communication problems if, for example, doctors list indoor mold species in their reports that are named differently according to the new nomenclature and include them in their assessment of possible health problems. In scientific articles and expert reports, the currently valid name for the designation of a mold should therefore be used wherever possible, for example the scientifically correct designation *Penicillium chrysogenum* instead of *Penicillium notatum*, a name still frequently used in the medical field.

In MycoBank, an online database, the current names and combinations as well as associated data, for example descriptions and illustrations, are accessible (https://www.mycobank.org/).

In medical mycology, however, fungi are classified clinically and independently of taxonomy into dermatophytes, yeasts, and molds. Although the DHS system (DHS, dermatophytes, yeasts, molds) is a practicable classification, this classification is misleading and incorrect from a biological (taxonomic) point of view because molds do not represent a taxonomic unit and most "yeasts" (shoot fungi), like dermatophytes, belong taxonomically to the *Ascomycota*.

Microbiologically, molds should generally be taxonomically indicated as genus and species. If only the Latin genus name and then sp. or spp. are given, the species or the individual species have not been further differentiated.

Mycotoxins

Mycotoxins are secondary metabolites of molds that can have toxic effects on various cell systems of vertebrates in low concentrations (µg/kg food), depending on the type of toxin and consumption habits: Mycotoxins are to be distinguished from the fungal toxins of basidiomycetes (stator fungi). Numerous mold genera (including *Aspergillus, Penicillium, Fusarium, Alternaria, Stachybotrys*) can form mycotoxins. Mycotoxin formation depends on the species and on environmental factors such as substrate composition, humidity, pH value, light wavelength, and nutrient competition [27]. Mycotoxins are mostly low molecular weight compounds, many of which are formed in polyketide metabolism; the fungal toxins of basidiomycetes are usually oligopeptides.

In general, mycotoxins from indoor molds can be found in low concentrations (ppt) in house dust [11], in bioaerosols and on building materials. Mycotoxins can also occur in human blood [5]. However, the mycotoxins detected here (aflatoxins, ochratoxins, citrinin, patulin, various trichothecenes from *Fusarium* species) are only produced by food-relevant molds, but not by indoor-relevant species. The only exception is sterigmatocystin [5], which is formed as an intermediate product in the aflatoxin biosynthesis of "yellow" aspergilli *(A. flavus* group) and can also be formed as an end product by the *Aspergillus versicolor* complex and has been detected in house dust [21, 23]. Since the concentration of mycotoxins in food is 100 to 1000 times higher than in house dust and bioaerosols, it can be assumed that the mycotoxins in the human body were primarily absorbed via the food pathway. Against this background, it is much more likely that possible internal exposure to sterigmatocystin in humans is acquired via the food pathway than via the

inhalation pathway (indoor exposure). However, a differentiated human biomonitoring study on this is still lacking. Mycotoxins are not volatile, but occur in the air bound to spores, cell fragments and other particles.

As mycotoxins arise from secondary metabolism, they have no physiological significance in the metabolism of the fungus according to current knowledge. They are "waste products" that have only acquired an ecological significance in the course of evolution (e.g., the antibiotically or antimycotically active substances inhibit competitors in the biotope). Mycotoxins are generally only found in health-relevant concentrations in food and animal feed if these have been colonized by molds. A distinction must be made between so-called field pests (primarily *Fusarium* species), which produce mycotoxins on crops, and storage pests (*Aspergillus* and *Penicillium*), which synthesize mycotoxins under warm and humid conditions during storage.

As has been shown in cell culture and animal experiments, mycotoxins trigger cytotoxic effects [26, 102] and have immunomodulatory effects [75]. The cytotoxic effect of some mycotoxins on lung cells depends on their concentration. The data available to date allow the conclusion that the concentrations of most airborne mycotoxins to be expected indoors have no acute toxic effect. Only the most potent toxic compounds, such as the satratoxins (trichothecenes) of *Stachybotrys* species, could be present in indoor environments in their active concentrations due to mold-infested materials [25]. Individual studies indicate that the effective concentration of, for example, aflatoxin, which is detectable in house dust but is not produced by indoor-relevant fungal species, in cell systems from the lungs (pulmonary uptake, humans) is about an order of magnitude (factor 10) below the effective concentration in kidney cells (oral exposure, animals) [26].

However, the maximum expected concentrations of individual mycotoxins *in situ* (bioaerosols) cannot explain the cytotoxic effects alone. Rather, synergistic effects of different mycotoxins or of mycotoxins with other cell components (e.g., glucans, endotoxins) appear to be responsible for the effects [55].

Even taking into account the higher sensitivity of, for example, primary lung epithelial cells (factor 10 compared to immortalized cells, A 549), the expected exposure concentrations in the air are about a factor of 100 below the effect concentrations in the cell culture-based approach [27, 79]. The only exception here are the satratoxins (trichothecenes) of *Stachybotrys chartarum*, which could possibly be in the order of magnitude of the effect concentration under extreme exposure conditions (e.g., during indoor refurbishment). It cannot yet be ruled out that aerogenic concentrations reach a magnitude that could be responsible for immunomodulatory effects and thus possibly promote susceptibility to infection or allergy development or allergy intensification [87].

There is a particular need for research into the possible effects and synergies of various noxins, such as mycotoxins in combination with LPS (lipopolysaccharides of bacteria, endotoxins), with β-glucans (cell wall components of fungi) or other groups of organisms (e.g., actinobacteria) [86, 113].

Cell wall components, enzymes and other mold components and metabolic products

In addition to mold spores and mycotoxins, other mold components and metabolites, such as microbial volatile organic compounds (MVOCs), ß-glucans, mannans and ergosterol, also play a role in exposures to molds [73, 74], whereby the MVOCs are responsible for the typical mold odor.

Ergosterol (ergosterol) is a metabolic product (sterol) of yeasts, molds, and edible fungi. It is formed in varying quantities as a membrane component, toxic properties are not known.

In connection with moisture damage, other microbiological components such as the lysosomal enzyme N-acetyl-β-D-glucosaminidase and lipopolysaccharides of gram-negative bacteria (LPS, endotoxin) are also increasingly present (e.g., in house dust) [72]. It is not clear whether these markers (cell fragments, β-glucan, ergosterol) correlate better with health effects than mold or spore concentrations [16, 28, 32, 41, 88, 91, 116].

To date, 77 proteins have been described and officially recognized as allergens of molds (excluding dermatophytes and yeasts) (www.allergen.org). The associated protein families differ significantly biochemically and structurally from the allergen families in pollen, food, or animal epithelia [50].

The most prominent representatives of mold allergens are [26, 50]:

- Proteases ($n = 18$, 16 of which are serine proteases)
- Ribosomal proteins ($n = 9$)
- Enolases ($n = 5$)
- Dehydrogenases ($n = 4$)
- Thioredoxins ($n = 3$)
- Heat shock proteins (HSP 70/90) ($n = 3$)
- Peroxisomal proteins ($n = 2$)
- Isomerases ($n = 2$)
- Superoxide dismutases MnSOD ($n = 2$)
- Flavodoxins ($n = 2$)

Other mold allergens can be found among the mitogilins, cyclophilins, fibrinogen-binding proteins and proteins with no known biochemical function [50].

A working group led by Olynych [83] demonstrated an immunomodulatory and proinflammatory effect of zymosan. They showed that zymosan leads to increased leukotriene production in mast cells via a dectin-dependent mechanism.

Mood disorders, unspecific symptoms

Disorders of well-being are defined as "deteriorations in psychological, physical and social well-being as well as the feeling of subjective performance. As an emotional experience, they are to be distinguished from annoyance reactions that involve a cognitive evaluation of specific environmental stimuli" [12, 14]. Disturbances of well-being play a significant role in environment-associated health disorders in general and in indoor-associated health disorders in particular [125]. The following three models are used to explain the mechanisms of action of such environment-associated mood disorders [12, 14]:

a. Model of the noxe:
   – Physiological relationship between an environmental factor and a person's reaction, for example to a psychotropic substance.
b. Model of attribution:
   – A health condition is attributed to an environmental factor according to a cognitive assessment process.
c. Stress model:
   – An environmental factor is consciously perceived and experienced as unpleasant, harmful, or threatening. Stress reactions can manifest themselves as physical dysfunctions, changes in well-being and impaired performance.

Changes in well-being can include anxiety, depression, impaired concentration and memory, psychophysiological activation reactions of blood pressure and hormone concentrations as well as vegetative complaints such as headaches and exhaustion.

The triggering of environmental-associated mood disorders due to moisture damage and mold is possible in principle, for example through the visual, cognitive and/or odor-related perception of a possible mold infestation [125].

In principle, anyone can be affected by discomfort caused by damp/mold damage indoors. This is a nuisance, not a health hazard.

Predisposing factors for mood disorders can be environmental concerns, fears, conditioning, and attributions as well as a variety of illnesses [124].

Environmental medical syndromes

Syndromes are widespread in medicine. In addition to the syndrome, the disease also requires a clear and unambiguous determination of the cause [34, 63]. A syndrome (Greek: σύγδρομος = convergence) is a specific constellation of symptoms (or abnormalities) of a clinical picture,

1. the cause(s) of which may be currently or generally unknown
2. which can have various causes
3. which cannot be differentiated from other symptom constellations or cannot be differentiated with certainty, or
4. which are rather rare [34, 63].

Environmental medical syndromes include above all sick building syndrome (SBS) and multiple chemical sensitivity (syndrome) (MCS) and sometimes also chronic fatigue syndrome (CFS) [126].

Sick building syndrome

In numerous publications, mainly epidemiological studies, a possible connection between moisture/mold exposure and SBS (used synonymously: Building Related (Health) Symptoms; not correctly used as a synonym by definition: Building Related Illness[1]) is discussed [1–3, 6, 8, 17, 19, 22, 24, 29, 33, 35, 38, 40, 42, 48, 49, 51–54, 56, 58, 61, 62, 64–66, 69–71, 76, 77, 80–82, 84, 85, 89, 90, 92–97, 100, 101, 103, 105–108, 110, 111, 114, 115, 117, 119, 127], even with a pre-SBS [78].

However, a variety of physical, chemical, biological, psychosocial and personal factors are discussed as possible causes of SBS, without a clear etiology having been determined to date. It is therefore assumed to be a multifactorial process in which the simultaneous occurrence of various influences and thus variable combined effects leads to the development of the syndrome [9, 10].

Multiple Chemical Sensitivity (Syndrome) (MCS)/ Idiopathic Environmental Intolerance (IEI)

Some studies discuss a possible link between indoor damp/mold infestation and MCS [45, 46, 51, 59, 68, 81, 112, 118, 120, 122, 123, 128, 129]. Dampness and Mold Hypersensitivity Syndrome is also occasionally reported [120, 121] or Toxic Mold Syndrome [51, 60]; the latter not without contradiction [15].

However, MCS is an impressive example of the complex, often very individual and subjective interactions between body, psyche and environment [36, 37]. Despite the absence or low level of somatic findings, patients often suffer so much that it is almost impossible to cope with everyday life. This results in social and financial losses as well as high direct and indirect healthcare costs. The long-standing dualistic debate as to whether MCS is "physical" or "psychological" has unsettled many sufferers, wasted time and resources on searching for causes and attempting

[1] Definition of *Building Related Illness* (*BRI*): Clinically clearly defined clinical pictures (including humidifier fever, legionellosis, indoor-associated allergies, e.g., to house dust mites or molds, indoor-associated malignancies such as radon-associated lung carcinoma) [67, 104], for which the etiology, pathology, pathophysiology, diagnosis, therapy, prevention and prognosis are clearly known.

treatment, but has not brought about any satisfactory improvement in the situation of MCS patients. They often feel turned away by "conventional medicine", and doctor-patient relationships are regularly experienced as difficult. Those affected therefore often turn to alternative medical, scientifically unvalidated explanatory models and treatment methods, which may provide subjective relief, but rarely improve symptoms and participation and may be associated with dangerous side effects and high costs. From a scientific point of view, MCS is not yet a clearly definable clinical picture, but probably a special manifestation of a functional disease that is particularly stressful in individual cases [36, 37]. In particular, the lack of a causal relationship between exposure and symptoms, the chronic course and the comorbidities point to a general hypersensitivity that is not necessarily substance-related. However, their mechanisms of action, structural and functional correlates require further scientific substantiation, also with regard to their therapeutic modifiability. An understanding of MCS as a dysfunctional vicious circle of negative experiences and evaluations, psychophysiological tension and hyperreactivity offers both the patients themselves and their treating physicians a comprehensible psychoneurobehavioral model. It also implies at least potential reversibility and opens up concrete options for action, such as reviewing and relativizing threat expectations, focusing attention and avoidance behavior [36, 37].

Chronic fatigue syndrome

In contrast to the previously discussed syndromes, only a few studies address a possible link between indoor dampness/mold exposure and CFS [4, 31, 109].

Here, too, it must be taken into account that CFS is etiologically assumed to have a multifactorial genesis with biological, social and psychological factors [57]. In addition, the Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine has issued a 304-page statement on the subject of myalgic encephalomyelitis/chronic fatigue syndrome [18], in which terms such as mold, mycotoxins or MVOCs are not mentioned.

To date, there is insufficient evidence of an etiological link between the environmental medical syndromes SBS, MCS and CFS and indoor exposure to moisture/mold [43].

Conclusions

Based on the above, it can be concluded that neither the determination of MVOC and/or mycotoxins in indoor spaces nor human biomonitoring for mycotoxins is medically indicated due to suspected health problems or suspected SBS, MCS or CFS in connection with damp/mold damage in indoor spaces. Newly coined terms, such as biotoxicosis and mold and vapor hypersensitivity syndrome (MDHS) or volatoxins [7], suggest a nosological specificity of a pathophysiological connection for which, however, there is no evidence to date.

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