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Review

Medical diagnostics for indoor mold exposure

Julia Hurraß^{a,*}, Birger Heinzow^b, Ute Aurbach^c, Karl-Christian Bergmann^d,
Albrecht Bufe^e, Walter Buzina^f, Oliver A. Cornely^g, Steffen Engelhart^h, Guido Fischerⁱ,
Thomas Gabrio^j, Werner Heinz^k, Caroline E.W. Herr^{l,m}, Jörg Kleine-Tebbeⁿ,
Ludger Klimek^o, Martin Köberle^p, Herbert Lichtnecker^q, Thomas Lob-Corzilius^r,
Rolf Merget^s, Norbert Mülleneisen^t, Dennis Nowak^u, Uta Rabe^v, Monika Raulf^s,
Hans Peter Seidl^w, Jens-Oliver Steiß^x, Regine Szewczyk^y, Peter Thomas^z,
Kerttu Valtanen^y, Gerhard A. Wiesmüller^{a,A}

^a Abteilung Infektions- und Umwelthygiene, Gesundheitsamt der Stadt Köln, Germany

^b Formerly: Landesamt für soziale Dienste (LASD) Schleswig-Holstein, Kiel, Germany

^c Abteilung Mikrobiologie und Mykologie, Labor Dr. Wisplinghoff, Köln, Germany

^d Allergie-Centrum-Charité, Charité Universitätsmedizin Berlin, Germany

^e Experimentelle Pneumologie, Ruhr-Universität Bochum, Germany

^f Institut für Hygiene, Mikrobiologie und Umweltmedizin, Medizinische Universität Graz, Austria

^g Klinik I für Innere Medizin, ZKS Köln und Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Universität zu Köln, Germany

^h Institut für Hygiene und Öffentliche Gesundheit, Universitätsklinikum Bonn, Germany

ⁱ Currently: Landesgesundheitsamt Baden-Württemberg im Regierungspräsidium Stuttgart, Germany

^j Formerly: Landesgesundheitsamt Baden-Württemberg im Regierungspräsidium Stuttgart, Germany

^k Medizinische Klinik und Poliklinik II, Schwerpunkt Infektiologie, Universitätsklinikum Würzburg, Germany

^l Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit, München, Germany

^m Ludwig-Maximilians-Universität München, apl. Prof. "Hygiene und Umweltmedizin", Germany

ⁿ Allergie- und Asthma-Zentrum Westend, Berlin, Germany

^o Zentrums für Rhinologie und Allergologie, Wiesbaden, Germany

^p Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Germany

^q Institut für Umwelt- und Arbeitsmedizin MIU GmbH, Erkrath, Germany

^r Christliches Kinderhospital Osnabrück, Germany

^s Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung, Institut der Ruhr-Universität Bochum (IPA), Germany

^t Asthma und Allergiezentrum Leverkusen, Germany

^u Institut und Poliklinik für Arbeits-, Sozial- und Umweltmedizin, Mitglied Deutsches Zentrum für Lungenforschung, Klinikum der Universität München, Germany

^v Zentrum für Allergologie und Asthma, Johanniter-Krankenhaus im Fläming Treuenbrietzen GmbH, Treuenbrietzen, Germany

^w Formerly: Lehrstuhl für Mikrobiologie sowie Dermatologische Klinik der Technischen Universität München, Germany

^x Zentrum für Kinderheilkunde und Jugendmedizin, Universitätsklinikum Gießen und Marburg GmbH, Gießen, Germany

^y Umweltbundesamt, FG II 1.4 Mikrobiologische Risiken, Berlin, Germany

^z Klinik und Poliklinik für Dermatologie und Allergologie der Ludwig-Maximilians-Universität München, Germany

^A Institut für Arbeitsmedizin und Sozialmedizin, Medizinische Fakultät der RWTH Aachen, Germany

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ABSTRACT

In April 2016, the German Society of Hygiene, Environmental Medicine and Preventative Medicine (Gesellschaft für Hygiene, Umweltmedizin und Präventivmedizin (GHUP)) together with other scientific medical societies, German and Austrian medical societies, physician unions and experts has provided an AWMF (Association of the Scientific Medical Societies) guideline 'Medical diagnostics for indoor mold exposure'. This guideline shall help physicians to advise and treat patients exposed indoors to mold. Indoor mold growth is a potential health risk, even without a quantitative and/or causal association between the occurrence of individual mold species and health effects. Apart from the allergic bronchopulmonary aspergillosis (ABPA) and the mycoses caused by mold, there is only sufficient evidence for the following associations between moisture/mold damages and different health effects: Allergic respiratory diseases, asthma (manifestation, progression, exacerbation), allergic rhinitis, exogenous allergic

* Corresponding author.

E-mail address: julia.hurraß@stadt-koeln.de (J. Hurraß).

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alveolitis and respiratory tract infections/bronchitis. In comparison to other environmental allergens, the sensitizing potential of molds is estimated to be low. Recent studies show a prevalence of sensitization of 3–10% in the total population of Europe. The evidence for associations to mucous membrane irritation and atopic eczema (manifestation, progression, exacerbation) is classified as limited or suspected. Inadequate or insufficient evidence for an association is given for COPD, acute idiopathic pulmonary hemorrhage in children, rheumatism/arthritis, sarcoidosis, and cancer. The risk of infections from indoor molds is low for healthy individuals. Only molds that are capable to form toxins can cause intoxications. The environmental and growth conditions and especially the substrate determine whether toxin formation occurs, but indoor air concentrations are always very low. In the case of indoor moisture/mold damages, everyone can be affected by odor effects and/or impairment of well-being. Predisposing factors for odor effects can be given by genetic and hormonal influences, imprinting, context and adaptation effects. Predisposing factors for impairment of well-being are environmental concerns, anxieties, conditioning and attributions as well as a variety of diseases. Risk groups that must be protected are patients with immunosuppression and with mucoviscidosis (cystic fibrosis) with regard to infections and individuals with mucoviscidosis and asthma with regard to allergies. If an association between mold exposure and health effects is suspected, the medical diagnosis includes medical history, physical examination, conventional allergy diagnosis, and if indicated, provocation tests. For the treatment of mold infections, it is referred to the AWMF guidelines for diagnosis and treatment of invasive *Aspergillus* infections. Regarding mycotoxins, there are currently no validated test methods that could be used in clinical diagnostics. From the perspective of preventive medicine, it is important that mold damages cannot be tolerated in indoor environments.

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Contents

1.	Introduction.....	00
1.1.	Aim of the guideline.....	00
1.2.	Methodology.....	00
2.	Key messages of the guideline.....	00
3.	Sources of mold and mold derived fragments or metabolites.....	00
3.1.	Sources of elevated mold exposure.....	00
3.2.	Cell wall components and metabolites.....	00
3.3.	Mycotoxins.....	00
4.	Mold-associated health effects and diseases.....	00
4.1.	Disease entities and health disturbances.....	00
4.1.1.	Allergic rhinitis.....	00
4.1.2.	Invasive and non-invasive rhinosinusitis.....	00
4.1.3.	Allergic asthma.....	00
4.1.4.	Atopic dermatitis.....	00
4.1.5.	Urticaria.....	00
4.1.6.	Hypersensitivity pneumonitis.....	00
4.1.7.	Allergic bronchopulmonary aspergillosis.....	00
4.1.8.	Infectious diseases due to mold (mycoses).....	00
4.1.9.	Organic dust toxic syndrome.....	00
4.1.10.	Acute idiopathic pulmonary hemosiderosis.....	00
4.1.11.	Susceptibility to infection.....	00
4.1.12.	Mucous Membranes Irritation, chronic bronchitis.....	00
4.1.13.	Sarcoidosis.....	00
4.1.14.	Rheumatism.....	00
4.1.15.	Mycotoxicosis.....	00
4.1.16.	Effects of mold odors.....	00
4.1.17.	Impairment of well-being and mood, non-specific symptoms.....	00
4.1.18.	Neuropsychological, neurotoxic effects.....	00
4.1.19.	Gastrointestinal effects, renal effects, teratogenicity, cancer.....	00
4.2.	Risk analysis and assessment.....	00
4.2.1.	Infection risk.....	00
4.2.2.	Sensitization/allergy risk.....	00
4.2.3.	Risk of toxic/irritative effects.....	00
4.2.4.	Risk of odor effects and impairment of well-being and mood.....	00
5.	Diagnostic tools.....	00
5.1.	Reasons for counseling.....	00
5.2.	General procedures, medical history (anamnesis) and physical examination.....	00
5.2.1.	Medical history.....	00
5.2.2.	Physical examination.....	00
5.3.	Markers of mold exposure.....	00
5.3.1.	Environmental monitoring.....	00
5.4.	Clinical diagnosis.....	00
5.4.1.	Allergy diagnosis.....	00

5.4.2.	Systemic or invasive fungal infection diagnosis	00
5.4.3.	Toxicological diagnostics	00
5.4.4.	Unconventional diagnostic methods	00
6.	Therapy	00
6.1.	General pharmacological treatment and specific immunotherapy (hyposensitization)	00
6.2.	Cessation of exposure	00
6.3.	Unconventional treatment methods and therapies	00
7.	Remediation of living spaces (buildings) with moisture problems and mold growth	00
8.	Prevention	00
	References	00

1. Introduction

Indoor mold exposure is a major health issue. For the persons affected, this problem is often associated with high uncertainty.

Scientific knowledge on the topic “health effects of mold” is still rare in many areas, and only few physicians have the necessary knowledge of possible health risks of indoor mold exposure, their diagnosis and therapy of mold-induced diseases.

Required objective approach to possible health effects of indoor mold exposure is difficult because of partly unexplained nosology and lack of a comprehensive diagnostic guideline. The AWMF (Association of the Scientific Medical Societies) guideline “Medical diagnostics for indoor mold exposure” (<http://www.awmf.org/leitlinien/detail/II/161-001.html>), that has been published in German, intends to close some of these gaps and to help physicians to advise and treat patients exposed to indoor molds. Diagnosis and treatment of mycoses are not covered by this guideline.

Here, we summarize the main findings and recommendations. For this report, we updated some references and, if possible, current international literature is considered in the passages, where only German literature is cited in the original guideline.

“Mold” is a collective term for various fungi which may occur as visible mold in indoor environments. Mold is a natural, ubiquitous part of our environment. Mold spreads and reproduces by producing spores. Prerequisite for the growth of mold is sufficient moisture in the material or on surfaces. Thus, mold growth is favored by high humidity, lack of ventilation and cold surfaces (condensation will form on a surface that is below the dew point). Structural deficiencies, water damage, rising damp, leaks, accidents, etc. can also lead to increased moisture and promote mold growth. Mold can grow indoors on a variety of materials (e.g., wood, paper, cardboard, plastics, rubber, and carpeting) and in a wide temperature range (WHO, 2009b). Mold growth indoors is always a moisture problem. This cause must be removed to avoid long-lasting exposure of indoor users. Mold spores can survive harsh environmental conditions, such as dry conditions, that do not support normal mold growth.

Dampness and mold exposures may be due to visible or invisible damages with microbiological colonization, especially mold infestation with active mold growth (viable) or with desiccated mold (non-viable). Under these conditions, an increased release of mold components (spores, mycelium, etc.) and other biomaterials is likely.

Since individual sensitivity and exposure to mold spores vary widely, no threshold value (CFU/m³) for indoor environments can be determined. Quantitative health risk assessment is not possible. Nevertheless, from a hygienic-preventive point of view, such damages must be classified as critical and always remediated properly because of their potential health risks.

Moisture damages (with increased mold and bacterial growth) are linked to different effects in humans. Symptoms and signs as well as illnesses that may occur in connection with indoor mold exposure, are:

– Allergies

Type I allergy: Allergic rhino-conjunctivitis, asthma, urticaria
Type I allergy: Allergic rhino-conjunctivitis, asthma, urticaria
Type I and Type III allergy: Allergic bronchopulmonary aspergillosis (ABPA)
Type III and Type IV allergy: Hypersensitivity pneumonitis (HP), farmer's lung
Atopic eczema

- Susceptibility to infection (chronic bronchitis)
- Systemic mycoses
- Mycotoxicoses
- Toxic alveolitis, Organic Dust Toxic Syndrome (ODTS) (only at workplaces)
- Mucous Membrane Irritation (MMI), sometimes named Mucous Membrane Irritation Syndrome (MMIS)
- Odor effects
- Impairment of well-being

The answer to the question of patients, which health risks are associated with the detection of mold in their living environment, is primarily a medical task. To assess a health hazard due to indoor mold, on the one hand the health status of the exposed person (predisposition), and on the other hand the extent of mold infestation and the release of mold spores or other fungal components (e.g., metabolic products, cell constituents) must be taken into account.

In practice, medical history and general and specialist medical clinical assessment of the patient are most critical. It is important to check firstly whether the complaints or diseases may be caused by mold exposure, whether there is evidence of indoor mold exposure that goes beyond the ubiquitous background exposure, and whether in the exposed person a predisposition to possible mold effects exists.

Based on current knowledge, mucous membrane irritations of eyes and the respiratory tract as well as allergic reactions are probably the most frequently observed effects among the mold-associated health disorders (WHO, 2009b).

At very high bioaerosol concentrations that occur only at certain workplaces and not indoors, serious toxic effects (Organic Dust Toxic Syndrome, ODTS) can be observed (Seifert et al., 2003). Occupational exposures and the associated medical conditions are not covered by this guideline, but are addressed where it appeared reasonable.

From a preventive point of view, indoor mold growth must be considered as a potential health risk, even without a trusted quantitative and causal relationship between the occurrence of individual mold species and health complaints. From a health care point of view, moisture damage and/or mold growth indoors are always a hygienic problem that – even without present health disorders – must not be tolerated and therefore must be precautionary minimized or terminated if possible. The most important preventive

measure for indoor mold exposure is to identify the cause of the moisture/water damage and the proper remediation.

1.1. Aim of the guideline

The presented guideline shall close the existing gap for rational and efficient medical diagnostics of indoor mold exposure. So far, there are only guidelines for building-related approaches in case of moisture damage in Germany from the Federal Environment Agency ([Innenraumlufthygiene-Kommission des Umweltbundesamtes, 2002, 2005](#)) and review articles on associated diseases ([IOM, 2004; WHO, 2009b](#)), but there is no comprehensive guideline concerning patient-related diagnostic procedures.

Work-related diseases or specific workplace exposures, ingestion of mold or mold components, and diseases caused by yeasts and dermatophytes are not covered by this guideline.

The scientific literature on fungi is extensive and published mostly in English. In epidemiological studies, the residential exposure is often categorized by the terms “dampness and mold” that means that there is no distinction between moisture damage with or without mold indoors. This is reasonable, as there are no specific health markers for quantitative mold exposure. “Mold” (or British-English “mould”) is understood as “visible” mold structures, whereas “visible” also includes hidden mold. This guideline refers to “dampness/moisture and mold”.

In the following, the key messages of the guideline are listed which contain also the core recommendations of the guideline. The strength of the recommendations is expressed by the following terms: strong recommendation: “shall”; recommendation: “should”; open recommendation: “may”.

1.2. Methodology

For the preparation of the guideline, a nationwide network of experts of the GHUP was created. The guideline is based on the statements of the German RKI Commission *Environmental Medicine (Kommission, Methoden und Qualitätssicherung in der Umweltmedizin des Robert Koch-Instituts, 2007)*, the WHO Guideline *Dampness and Mould (WHO, 2009b)* and the consensus of four workshops ‘Mold and Health’ of the GHUP annual meetings 2009–2012 ([Wiesmüller et al., 2010, 2011, 2013, 2014](#)).

The guideline has been prepared in accordance with the methodology for development of guidelines for diagnosis and treatment of the Association of the Scientific Medical Societies (AWMF) and corresponds to the 3-stage concept of an AWMF S2K guideline. The guideline is based on a comprehensive and systematic literature search, which however does not formally meet the requirements of S2K guidelines, as no clinical studies existed. Determination of levels of evidence for recommendations was therefore not possible and not useful.

Search in the Cochrane database with the terms “mold”, “mould” and/or “dampness” yielded three results. Two reviews dealt with specific immunotherapy in asthma and rhinitis and one review analyzed the preventive effect of the remediation of moisture and mold damage to respiratory disease ([Sauni et al., 2013](#)).

A conceptual stepped Medline (Medical Literature Analysis and Retrieval System Online) search yielded 1949 citations. No thematically comprehensive or overall review on medical diagnosis of indoor mold and moisture exposure was found, instead papers only referred to individual issues of the searched topic (e.g. [Tischer and Heinrich, 2013; Vesper and Wymer, 2016](#)).

Search was performed in German language by search engines of the Web (Google) and in English language in the database Medline.

As basic evidence, reviews of an association between mold exposure and defined diseases, publications of the World Health

Organization ([WHO, 2009b](#)), of the Institute of Medicine ([IOM, 2004](#)) and a review by [Palaty and Shum \(2012\)](#) were used.

For individual topics, mainly concerning diagnoses, German guidelines focusing on inhalative mold exposure, allergic rhinoconjunctivitis, allergic rhinitis, rhinosinusitis, asthma, urticaria, hypersensitivity pneumonitis, allergic bronchopulmonary alveolitis (ABPA), invasive mold infections, sarcoidosis, rheumatoid arthritis, diagnosis of chronic cough, *in vitro* allergy diagnosis, *in vivo* allergy diagnosis, skin tests, nasal provocation tests, bronchial provocation tests, workplace-related inhalation tests, specific immunotherapy and allergy prevention were considered.

2. Key messages of the guideline

The problem of indoor mold exposure requires objectification.

1. Mold infestation in a relevant degree must not be tolerated indoors for precautionary reasons.
2. Most important measures for indoor mold exposure are the clarification of the underlying causes and proper remediation.
3. Mold measurements indoors are rarely useful for medical reasons. Usually, in case of visible mold exposure both quantitative and qualitative measurements of mold species are dispensable. Rather, causes of infestation must be clarified and then mold infestation and primary causes must be eliminated.
4. In general, mold exposure can induce mucous membrane irritation (MMI), odor effects and impairment of well-being.
5. Specific disorders due to indoor mold exposure are allergies and mold infections (mycoses)
6. There is a doctor's duty to provide objective and careful deliberation in cases of suspected relationships of moisture damage or indoor mold exposure and gastrointestinal or renal disease, reproductive disorders, teratogenicity or cancer.
7. Risk groups that must be specially protected are:
 - a) Immunosuppressed patients according to the classification of the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) at the Robert Koch Institute (RKI) ([KRINKO, 2010](#))
 - b) Individuals with mucoviscidosis (cystic fibrosis)
 - c) Individuals with asthma
8. The risk for development of asthma (“allergic march”) is increased by:
 - a) Individuals with allergic rhinoconjunctivitis
 - b) Individuals with allergic rhinosinusitis
 - c) Individuals with atopy
9. Probably, all mold species are likely to cause sensitization and allergies. Compared to other environmental allergens, the allergenic potential of mold species is estimated to be low ([Heinzerling et al., 2009](#)).
10. Individuals with atopy (people with a disposition to hypersensitivity reactions upon contact to environmental substances, responding with (among others) allergic rhinitis (hay fever), allergic asthma or atopic dermatitis) are often poly-sensitized and also produce IgE antibodies against mold, not necessarily with pathological significance.
11. Key elements of the diagnosis of allergies are medical history, skin tests (e.g., skin prick test) and *in vitro* serological tests to detect specific IgE antibodies in case of type I sensitization or specific IgG antibodies only in case of hypersensitivity pneumonitis (very rare due to non-occupational indoor exposures) and provocation tests.
12. Detection of specific IgE means that a specific sensitization to relevant allergens is present. However, just like a positive reaction in skin prick test, this does not equate with a clinically relevant allergy.

13. Negative *in vitro* and *in vivo* tests cannot exclude sensitization or allergy to mold.
14. Determination of specific IgG antibodies in connection with the diagnosis of a mold allergy of the immediate type (type I allergy) has no diagnostic value and is therefore not recommended.
15. Lymphocyte transformation tests (LTT) on mold are not indicated as diagnostic procedures.
16. Infections by molds are rare and most likely occur by inhalation. In practice, from those mold species classified in the risk groups 2 and 3 of the German Technical Guideline for Biological Agents 460 (TRBA 460) (TRBA 460, 2016), *Aspergillus fumigatus* is the main causative agent of mycosis. Individuals with local or general immune deficiencies are predominantly affected.
17. Key elements of mold infection diagnosis are microbiological, immunological, molecular biological and radiological procedures.
18. Persons with mold allergy and individuals with diseases that weaken the immune system should be informed objectively about the dangers of indoor mold exposure and on measures to prevent and minimize such exposures.

3. Sources of mold and mold derived fragments or metabolites

3.1. Sources of elevated mold exposure

While not being a taxonomical definition, “mold” is widely used as a collective term for spore forming hyphomycetes. Molds are a ubiquitous part of our biosphere, their spores being present in varying numbers in outdoor and indoor air, as well as in specific workplace environments.

Mold infestation (mold-infested material) is a construction material or inventory that is overgrown (colonized) by mold. If not readily visible to the naked eye, it is detected by microscopic identification of hyphae and more or less developed conidiophores and conidia, regardless of whether the molds are still vital and active or already dead. In addition to mold, other biomaterials such as bacteria may be present.

Mold contamination is a contamination above general background level of surfaces or materials (e.g., with fungal spores) that entered from outside (e.g., in house dust, airborne spores).

Mold growth is understood as a process that includes biological activity and therefore depends on moisture. It is characterized by cell division, hyphae/mycelium growth and sometimes sporulation.

Moisture damage is a visible, measurable or perceived consequence of increased water content of interior rooms or construction components.

As a practical matter, it makes sense that increased exposure to mold and other factors associated with increased humidity indoors such as yeasts, bacteria (actinobacteria) and mites is summed up as moisture/mold damage. The concentration and species composition of mold in outdoor air are highly dependent on geographic region, season, climate, weather conditions and local mold reservoirs. Levels of the individual parameters are subject to wide temporal and spatial variability. Therefore, the spore concentration and species composition in outside air are used as a reference to identify mold sources (infested materials, house dust) indoors. They have to be considered when measurements of indoor air are evaluated, because its mold content depends on primary fungal sources, i.e. infested materials as well as secondary sources (e.g., sedimented fungal spores in house dust). As with outside air, the concentrations of the individual parameters show large variability in both temporal and spatial resolution.

Mold growth requires (increased) humidity as an essential criterion. Depending on humidity, temperature and nutrients, certain species have individual growth advantages and such can be associated with certain causes/sources (WHO, 2009b).

3.2. Cell wall components and metabolites

Besides mold spores and mycotoxins, exposures to other metabolites and cell wall components such as microbial volatile organic compounds (MVOC), β -glucans, mannans and ergosterol play a role; MVOC being responsible for the typical mold odor.

Ergosterol is a metabolite (steroid alcohol) of yeasts, molds and mushrooms. It is produced in different amounts as a cell membrane component.

Moisture damage is also accompanied by further microbial factors (e.g., in house dust), like the lysosomal enzyme *N*-acetyl- β -D-glucosaminidase and bacterial endotoxins. It is not clear yet, whether these markers (cell fragments, β -glucan, ergosterol) correlate better with health effects of the affected individuals than cultural characteristics of the molds (Choi et al., 2014; Frankel et al., 2014; Górny et al., 2002; Hirvonen et al., 2005; Rao et al., 2005; Rylander, 1997; Tischler and Heinrich, 2013).

Until now, 77 mold allergens (excluding dermatophytes and yeasts) have been described and officially recognized (WHO/IUIS, 2016). They are members of protein families with clearly distinct biochemical and structural properties as compared to pollen, food and animal epithelium allergen families. The most prominent mold allergens are categorized as:

- Proteases (n = 18, including 16 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)
- Manganese superoxide dismutases (MnSOD; n = 2)
- Flavodoxins (n = 2)

Further mold allergens are found among mitoglinins, cyclophilins, fibrinogen-binding proteins and proteins with unknown function.

3.3. Mycotoxins

Mycotoxins are secondary metabolites produced by molds that may have toxic effects on diverse cellular systems of vertebrates at low concentrations ($\mu\text{g/kg}$ food), depending on the type of toxin and eating habits (Fischer et al., 2006). Mycotoxins are to be distinguished from fungal toxins of fruit-bodies of macrofungi (toadstools/mushrooms). Numerous mold genera (among others *Aspergillus*, *Penicillium*, *Fusarium*, *Alternaria* and *Stachybotrys*) can form mycotoxins. The formation of mycotoxins depends on the fungal species and environmental factors such as substrate composition, moisture, pH, light wavelength and nutrient competition. Mycotoxins are generally low molecular weight compounds, many of them formed in the polyketide metabolism, while fungal toxins are mostly oligopeptides. In general, mycotoxins of important indoor molds can be detected in extremely low concentrations (ppt) in house dust, in bio-aerosols and on building materials (Bloom et al., 2009). Mycotoxins are non-volatile, and airborne mycotoxins are always bound to spores, cell fragments and other particles.

Because mycotoxins are products of secondary metabolism, to our current knowledge they have no physiological significance for

fungal metabolism. They are “waste products” that got an ecological importance in the course of evolution (antibiotic substances inhibit competitors). Mycotoxins in concentrations relevant for human health occur almost exclusively in mold colonized food and forage.

It has been shown in cell culture and animal experiments that mycotoxins have cytotoxic (Schulz et al., 2004) and immunomodulatory effects (Müller et al., 2002). The cytotoxic effects of some mycotoxins on lung cells are concentration dependent. The data available so far suggest that the indoor concentrations of most airborne mycotoxins have no acute toxic effects. Only the most toxic compounds, trichothecenes and gliotoxin, could be present in relevant concentrations in mold infested indoor materials. There is some evidence that effective concentrations by pulmonary uptake are one to two orders of magnitude below those of oral exposure. The anticipated maximum concentrations of individual mycotoxins *in situ* (bioaerosols) apparently cannot induce cytotoxic effects. Synergistic effects of various mycotoxins together with other cell components (e.g., glucans or endotoxins) are considered responsible for toxicity. Insights into potential effects were primarily generated in cell culture and animal experiments. However, even when taking into account the higher sensitivity of e.g., primary lung epithelial cells (factor 10 compared to immortalized cell line A549), the anticipated exposure concentrations in indoor air are below their effective concentrations in the cell culture-based approach by about a factor of 100 (Fischer et al., 2006; Nevalainen et al., 2015). The only exceptions where effective exposure concentrations under extreme exposure conditions could be reached are the *A. fumigatus* gliotoxin (rarely indoor-relevant) and the satratoxins of *Stachybotrys chartarum*. Still, it cannot be ruled out so far that airborne mycotoxins reach concentrations of a magnitude that could possibly be responsible for immunomodulatory effects and thus might promote susceptibility to infection or allergy development (Pestka et al., 2008). Further research is needed, particularly regarding possible effects and synergies of various noxious agents such as mycotoxins in conjunction with LPS (lipopolysaccharide, bacterial endotoxin), β -glucans (cell wall components of fungi) or other organisms (e.g., Actinobacteria) (Peitzsch et al., 2012; Täubel et al., 2011).

4. Mold-associated health effects and diseases

Epidemiological studies consistently show a relationship between indoor mold damage and health effects, especially eye, nose and throat irritation, blocked nose, wheezing, dry cough, and tiredness (Rylander, 1998). In this review, we focus essentially on diseases and less on symptoms.

The known evidence levels for associations between mold damage and the different health effects are shown in Table 1. For individuals, it is not possible to prove unambiguous causality between mold exposure and particular health complaints or diseases.

Health risks due to mold exposure above all depend on the disposition of the affected persons. Risk groups, which should be protected, are:

- Individuals with immunosuppression according to the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) at the Robert Koch Institute (RKI) (KRINKO, 2010)
- Individuals with cystic fibrosis
- Individuals with bronchial asthma

Irrespective of whether or not there is sufficient evidence for an association, housing conditions must be hygienically safe for individuals with chronic diseases. If there are indications for mold exposure, from a preventive perspective the mold (infested materi-

Table 1

Evidence for an association between exposure to moisture/mold damage indoors and diseases without mold mycoses, modified according to (Fisk et al., 2007, 2010; Mendell et al., 2011; Palaty and Shum, 2012; WHO, 2009b).

Causal relationship
No evidence
Sufficient evidence for an association
Allergic respiratory diseases
Asthma (manifestation, progression, exacerbation)
Allergic rhinitis
Hypersensitivity pneumonitis (HP)/Exogenous allergic alveolitis (EAA)
Promoting respiratory infections, bronchitis
Restricted or suspected evidence for an association
Mucous membrane irritation (MMI)
Atopic eczema (atopic dermatitis; manifestation, progression, exacerbation)
Inadequate or insufficient evidence for an association
Chronic obstructive pulmonary disease (COPD)
Acute idiopathic pulmonary hemorrhage in children
Rheumatism
Arthritis
Sarcoidosis
Cancer
Neurotoxic effects

als) must be removed, and the primary reasons for the mold damage must be remediated (DHSS (NIOSH), 2012).

4.1. Disease entities and health disturbances

The different health effects associated with dampness and/or mold exposure cannot be explained by a single mechanism or factor (Bush et al., 2006; Mendell et al., 2011; Seltzer and Fedoruk, 2007). The epidemiological findings point to both allergological and non-IgE-mediated immunological and toxic, immunomodulatory mechanisms. For both atopics and non-atopics persons, moisture damage or mold growth may cause adverse effects (Cox-Ganser et al., 2005; Dales et al., 2010; Douwes and Pearce, 2003; Kuyucu et al., 2006). The order of the diseases below is not meant to represent a weighting of clinical importance.

4.1.1. Allergic rhinitis

Allergic rhinitis (AR) is defined as a symptomatic IgE-mediated inflammatory disease of the nose. It may occur as seasonal or perennial AR. AR may be further subdivided in occupational or non-occupational. According to (Brozek et al., 2010), AR may be assigned to intermittent or persistent forms. It is known that atopic patients show higher sensitization rates to molds than non-atopics, thus sensitizations to molds occur mostly in patients with multiple sensitizations to various allergens. The rates of subjects with sensitizations due to mold vary between about 2.7–19% among patients with allergic rhinitis, depending on the study populations, regions and test materials (Mari et al., 2003; Reijula et al., 2003; Torres-Rodríguez et al., 2012). The mold spectrum is dominated by seasonal outdoor molds, e.g., *Alternaria alternata*, with lower frequency *Cladosporium herbarum*, *Botrytis cinerea*, *Mucor* sp., *Penicillium* sp. and *Aspergillus* sp. (Mari et al., 2003; Reijula et al., 2003; Torres-Rodríguez et al., 2012). Dampness and indoor mold exposures are consistently associated with AR in epidemiological studies (Jaakkola et al., 2013; Mendell et al., 2011), but mono-sensitizations to indoor molds are rare.

4.1.2. Invasive and non-invasive rhinosinusitis

Rhinosinusitis (RS) is defined as an inflammatory disorder of the nose and sinus. Its chronic form (CRS), which is defined by duration of symptoms of at least 12 weeks, may occur with or without nasal polyposis. Although detailed numbers are not available, it is considered one of the most frequent chronic diseases worldwide. Five clinical entities of mold-induced RS may be differentiated: (1) acute invasive fungal RS, (2) chronic invasive RS, (3) granuloma-

tous invasive RS, (4) non-invasive allergic fungal RS (AFRS), and (5) RS with the presentation of a spherical mycetoma (see also Section 4.1.10), i.e. a non-invasive accumulation of dense conglomeration of fungal hyphae (fungus ball), mostly affecting only one sinus cavity (Chakrabarti et al., 2009; Fokkens et al., 2009). Invasive forms of RS are typically diagnosed in severely immunocompromised subjects. In its acute form it may be fatal within a few weeks, but in less immunocompromised subjects (e.g., patients with diabetes) the duration may be much longer. The granulomatous invasive forms of RS have primarily been described in Africa, Saudi Arabia and Arabic Gulf States. AFRS has similarities with allergic bronchopulmonary aspergillosis (ABPA; see Section 4.1.7). It is characterized by generalized sinonasal inflammation in combination with viscous allergic mucin that effectively obstructs the normal drainage pathway. Often *Aspergillus* spp. and increased numbers of eosinophils are detected in the affected sinus. As it is known that molds may occur in a high number of control subjects (including those with CRS) (Ebbens and Fokkens, 2008), it becomes clear that a modified immune response is the primary trigger for the disease. Consequently, therapy with antifungal substances is not recommended for non-invasive forms, and also randomized controlled studies were unable to find positive effects of antifungal therapy in patients with AFRS. (Ebbens and Fokkens, 2008; Fokkens et al., 2012). A pathogenetic role of biofilms, a community of microorganisms encased within a self-produced, extracellular, polymeric substance as a major factor in CRS has been hypothesized, and the use of confocal scanning laser microscopy with fluorescent *in situ* hybridization in combination with common culture techniques for the diagnosis of AFRS has been recommended (Keir et al., 2011).

4.1.3. Allergic asthma

As in allergic rhinitis, allergic asthma due to molds is mostly a seasonal disease. It is predominantly induced by seasonal outdoor molds like *Alternaria* or in rarer cases *Cladosporium*, *Epicoccum*, *Fusarium*. Rarely indoor molds like *Aspergillus* sp. or *Penicillium* sp. may cause perennial asthma (Reponen et al., 2012). A causal relationship between dampness or mold exposure and asthma prevalence and asthma exacerbations, especially in children, is strongly suggestive (Hägerhed-Engman et al., 2009; Iossifova et al., 2009; Mendell et al., 2011; Pekkanen et al., 2007; Tischer et al., 2011). The prevalence of asthma as well as asthma severity have been associated with exposure especially to *Alternaria alternata* (Halonen et al., 1997; Licorish et al., 1985; Meng et al., 2012; Schultze-Werninghaus et al., 1987; Zureik et al., 2002). Often, allergy to *Alternaria alternata* occurs in subjects with sensitization to pollen, but rarely seasonal allergy with mono-sensitization to *Alternaria alternata* may occur with symptoms from June to September (Koch et al., 2000). Asthma occurs frequently in subjects with further atopic diseases like rhinitis or atopic dermatitis (Toskala and Kennedy, 2015). Subjects with allergic asthma to molds showed sensitizations to further environmental allergens in 95% (Iversen and Dahl, 1995), but mono-sensitizations to molds may occur in rare cases. The latter is especially true for indoor molds. This study suggested that sensitization to molds mostly occurs in patients with a high potential for being sensitized to common inhalation allergens and that sensitization to molds is not related to damp dwellings. It is believed that molds have a low sensitizing potential and genetic factors are of higher importance than exposure (Iversen and Dahl, 1995; Tarlo et al., 1988).

4.1.4. Atopic dermatitis

Mold allergens have been considered as triggers of atopic dermatitis (Kim et al., 2015). There is some evidence that dampness or mold exposures are associated with eczema (Mendell et al., 2011). Skin reactions have been described after exposure to molds, e.g., dryness, itching and dermatitis, but it is not clear whether these

reactions may be interpreted as immunologic reactions to indoor molds (Seltzer and Fedoruk, 2007).

4.1.5. Urticaria

There are rare cases of urticaria after ingestion of mold-containing food (Maibach, 1995), e.g., mold in beverages, bakery products or salami (Hoff et al., 2003; Maibach, 1995; Morisset et al., 2003). Inhalation of molds as a cause of urticaria has not been reported (Palaty and Shum, 2012) or is at best an extremely rare event (Shelly and Florence, 1961). Immunologically mediated occupational contact urticaria has been described due to molds on a salami casing (Maibach, 1995).

4.1.6. Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease which combines elements of a type III and a type IV reaction. The diagnosis is sometimes difficult to establish, especially in chronic HP (Quirce et al., 2016). HP has an incidence of about 2–4 cases per 100,000 subjects and thus is a rare disease (Griese et al., 2013). HP occurs rarely in smokers. Its occurrence is well documented in susceptible subjects with mold or bacterial exposure (IOM, 2004). Bird antigens are the most frequent antigens, but indoor mold from contaminated material e.g., water-damaged walls, air-conditioning systems, humidifiers or tabletop fountains have to be considered. A summary of antigens has been published recently (Quirce et al., 2016). HP due to molds occurs predominantly as an occupational disease (Quirce et al., 2016), but HP after exposure to birds and molds has been described repeatedly in the non-occupational setting as well (Morell et al., 2008; Greenberger, 2004; Baxi et al., 2016). The occupations with occurrence of HP have given their names to the disease, e.g., farmers' lung, cheese washers' lung, cork workers' lung etc. (Quirce et al., 2016).

4.1.7. Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a rare immunologic lung disease with sensitization (IgE and IgG) to *Aspergillus* antigens. There is no evidence that indoor dampness or exposure to mold is associated with ABPA, although it is probable that mold exposures may induce symptoms or possibly modify prognosis. Occasionally, sensitization may be detected to *Helminthosporium*, *Candida* sp. or other fungi. Whereas specific IgE- and IgG antibodies to mold antigens can be detected, the occurrence of molds (e.g., *Aspergillus* sp.) in sputum or bronchial lavage fluids is less frequent. ABPA should be considered if two of the following criteria are fulfilled: cystic fibrosis, asthma, eosinophilia with unknown origin, pulmonary infiltrates detected by radiological methods which do not resolve after antibiotic therapy, central bronchiectasis, the occurrence of *Aspergillus* in sputum, expectoration of brown sputum, and cutaneous late reaction to *Aspergillus*. The diagnosis of ABPA can be corroborated if total serum IgE is above 1000 kU/L and specific IgE antibody concentrations to recombinant *Aspergillus* single allergens rAsp f 4 and rAsp f 6 with high specificity and moderate sensitivity (Crameri et al., 1998; Fricker-Hidalgo et al., 2010; Rosenberg et al., 1977). Oral steroids are the most effective therapy, antifungal therapy cannot be recommended with the available information, although data are sparse. Omalizumab may help to lower the steroid dose. Early detection and therapy are recommended in order to decrease severe long-term consequences (Shah and Panjabi, 2016).

4.1.8. Infectious diseases due to mold (mycoses)

Infectious diseases due to environmental molds are called mycoses. Diagnosis and treatment of mycoses are not covered by this guideline, but the risk assessment of exposure to indoor molds in order to prevent mycoses and to give advice to patients

with increased susceptibility. Mycoses increased in frequency during recent years (Ruhnke et al., 2012). A high incidence has been reported especially in patients with malignant diseases after chemotherapy and longer periods of neutropenia or allogeneic stem cell transplantation. Similarly, less severe immunosuppression may be followed by mycoses, e.g., after systemic steroid medication, interstitial lung diseases, tuberculosis (Anon, 1970; Sonnenberg et al., 2001), COPD or a combination of such diseases. Mycoses are among the most frequent causes of death by infections in patients with malignant diseases, and the number of such patients is increasing (IARC, 2016). Primary infections develop mostly in the lungs, rarely in the nasal sinus, the ear or the skin. Afterwards mycoses may spread to other organs (Koehler et al., in press).

Increased numbers of thermo-tolerant *Aspergillus* sp. rarely occur in indoor environments, but may be detected near compost and waste processing facilities. Occasionally, these molds may be transferred to indoor environments by further anthropogenic activities, e.g., farming. Mycoses due to opportunistic molds are well-known (Ramani et al., 1993; Torres-Rodríguez et al., 1998). The most prominent molds of outbreaks of mycoses in susceptible subjects are *Aspergillus* sp. Community-acquired mycoses were reported repeatedly, and in some of the affected patients there was no or only mild immunosuppression. A causal link with building activities like demolition works and increased concentrations of mold spores has been demonstrated (Barreiros et al., 2015).

Nosocomial mycoses occur after the inhalation of contaminated materials, after building activities, or by potted plants. The predominant molds are *Aspergillus* and *Mucor* sp.

4.1.8.1. Invasive aspergillosis. Invasive infections by *Aspergillus* sp. are an important cause of morbidity and mortality in immunocompromised subjects (Fernández-Ruiz et al., 2012; Hope et al., 2005). The number of severe infections due to *Aspergillus* sp. is estimated to 200,000 per year worldwide.

4.1.8.2. Aspergilloma. Aspergilloma (synonymous: mycetoma) is a localized form of aspergillosis with agglomeration of mold mycelia to form a fungal ball. It usually develops in preformed air spaces, e.g., tuberculous caverns, bronchiectasis, or malignant diseases (Latgé, 1999; Stevens et al., 2000).

4.1.9. Organic dust toxic syndrome

Organic dust toxic syndrome (ODTS) is defined by an acute systemic illness with flu-like symptoms after acute inhalation of high concentrations of bioaerosols ($>10^9$ spores/m³) possibly less for *Aspergillus fumigatus* (Herr et al., 1999), which occur almost exclusively occupationally. Thus ODTS is not an indoor disease. However, the pathomechanism is not fully understood. (Seifert et al., 2003). ODTS occurs with higher frequencies than HP, but it may be diagnostically difficult to separate ODTS from HP (see Section 4.1.6).

4.1.10. Acute idiopathic pulmonary hemosiderosis

Acute idiopathic pulmonary hemosiderosis (AIPH) is a rare disease of unknown origin (IOM, 2004). The Centers for Disease Control and Prevention (CDC) concluded that there is no evidence that AIPH in newborns is caused by mold exposures, esp. *Stachybotrys chartarum*. This conclusion is shared by the WHO and others (IOM, 2004; Kuhn and Ghannoum, 2003; WHO, 2009a,b).

4.1.11. Susceptibility to infection

There is evidence of an association between dampness or indoor mold exposures and physician-diagnosed common cold, bronchitis or infections of the airways (Fisk et al., 2010; Mendell et al., 2011). *Penicillium* sp., *Cladosporium* sp., *Zygomycetes* and *Alternaria* sp. showed the strongest associations. The mechanism remains

unknown, but it is obviously not an allergic reaction (Stark et al., 2003).

4.1.12. Mucous Membranes Irritation, chronic bronchitis

Mucous Membranes Irritation (MMI), synonymous with Mucous Membranes Irritation Syndrome (MMIS) and chronic bronchitis were found to be associated with dampness or indoor mold exposures (Baser et al., 2003; Ebbehøj et al., 2005; Mendell et al., 2006). The rates of subjects with MMI among those with occupational or environmental exposure to bioaerosols were reported between 20 and 30% (Herr et al., 2003; Radon et al., 2001; Reijula, 1998), but there are no valid data about indoor mold exposures and MMI. Typical symptoms of MMI are burning or itching eyes, lacrimation, sneezing, runny nose, nasal obstruction, dryness of the throat, frequent clearing of the throat, or cough (Baser et al., 2003). Typically, symptoms resolve quickly after exposure cessation. It is believed that MMI is caused by products of mold metabolism or constituents of the cell walls or a combination of these substances (Douwes et al., 1999; Douwes et al., 2000; Frankel et al., 2014; Hirvonen et al., 2005; Johannessen et al., 2005; Rylander, 1998).

4.1.13. Sarcoidosis

Sarcoidosis is a systemic granulomatous disease that affects predominantly the lungs. Granulomatous disease is generally linked with infection or reactions to foreign bodies (Heffner, 2007), thus it has been discussed whether sarcoidosis may represent a microbial-induced disease (Marshall and Marshall, 2004; Tercelj et al., 2008). Case reports with bacterial or fungal infections in patients with sarcoidosis were published, and microbial DNA or proteins were found in samples from sarcoidosis patients (Eishi et al., 2002; McFarland and Goodman, 1963; Rizik, 1965; Shields, 1959). Also a number of case series reported an increased prevalence of sarcoidosis in occupations known to be associated with mold exposures (Kern et al., 1993; Kucera et al., 2003; Laney et al., 2009; Prezant et al., 1999). There are also interventional studies which seem to demonstrate the effectiveness of antibiotic (Marshall and Marshall, 2004) or antifungal therapies (Tercelj et al., 2011). Extending diagnostic measures beyond standard procedures to mold-specific diagnosis cannot be recommended.

4.1.14. Rheumatism

An association between inflammatory rheumatic diseases and infections has been hypothesized since many years. There are also reports about dampness and rheumatic complaints (Lorenz et al., 2013; Luosujärvi et al., 2003; Myllykangas-Luosujärvi et al., 2002; Nevalainen and Seuri, 2005). However, these observations were made by one group of researchers and further evidence is not available. Extending diagnostic measures beyond standard procedures cannot be recommended.

4.1.15. Mycotoxicosis

Intoxications due to oral ingestion of mycotoxins in food products have been well documented (Stoev, 2015), but there is no data about the consequences of indoor mold inhalation and mycotoxicosis. There is still a need for clarification whether mycotoxin concentrations indoors are systemically relevant. So far, this does not seem to be the case.

4.1.16. Effects of mold odors

Mold metabolites are known to cause relevant odors (Palaty and Shum, 2012; Portnoy et al., 2005). Such odors should prompt a search for dampness and mold exposures. Microbial volatile organic compounds (MVOC) consist of organic compounds that are released from bacteria and molds. It must be taken into account that for many so-called MVOC other sources (e.g., tobacco smoke, cooking, baking, roasting, potted earth, composting bucket) also

exist beside mold infested materials (Schleibinger et al., 2004). It is unknown whether indoor MVOC with concentrations in a low $\mu\text{g}/\text{m}^3$ range may induce biological effects. Psychic reactions with nonspecific symptoms are considered plausible, but toxic or direct physiological reactions are not. Typical symptoms after relevant unpleasant odor nuisance are fatigue, reduced power of concentration, headache, nausea and insomnia (Portnoy et al., 2005). These symptoms show high inter-individual variability, with a high number of modifying factors (Dearborn et al., 2002).

4.1.17. Impairment of well-being and mood, non-specific symptoms

Complaints are presented as impairment of mental, physical and social well-being and feeling of subjective impaired productivity. As emotional experience, they can be described as annoyance reactions that include cognitive evaluation of specific environmental stimuli. Impairments of well-being play a major role in environment-associated disorders in general and in indoor-associated health disorders in particular (Wiesmüller et al., 2003). To explain the mode of action of such environment-associated psychological impairments, the following three models are used (Bullinger, 1989):

a) Pollutant Model:

Physiological relationship between environmental factor and human reaction, e.g., by a psychotropic substance

b) Model of Attribution:

A health condition attributed to an environmental factor after a cognitive assessment process

c) Stress Model:

An environmental factor is consciously perceived and experienced as unpleasant, harmful or threatening; stress reactions can result in physical dysfunction, mood changes, and productivity impairment a triggering of environmental-associated impairment of well-being and mood by mold is principally possible, e. g. by odors (Sucker et al., 2009).

4.1.18. Neuropsychological, neurotoxic effects

Hitherto, there are no systematic reviews on this controversial topic available.

On various occasions, exposure to toxin producing molds (“toxic mold”) indoors has been associated with neurotoxic effects, and cognitive or emotional problems have been causally related to mycotoxins (“black toxic mold syndrome”) (Baldo et al., 2002; Crago et al., 2003; Gordon et al., 1999; Gordon et al., 2004; Singer, 2011) and toxin detoxifying therapies have been propagated. However, these works were criticized because of methodological weaknesses (McCaffrey and Yantz, 2005). No consistent proof can be deduced from the literature that the toxin concentrations occurring indoors can cause neurotoxic effects (Bush et al., 2006; Chapman et al., 2003; Gordon et al., 2004, 2006; Khalili et al., 2005; Lees-Haley, 2003; Terr, 2009).

4.1.19. Gastrointestinal effects, renal effects, teratogenicity, cancer

In single cases, hypotheses about relationships between fungi and many other different diseases are postulated with the consequence of frightened patients who “inform” themselves via internet. Additionally, mold is incorrectly equated with “intestinal fungi” (commensal colonization by *Candida albicans*).

Hitherto, no systematic examinations or case reports are available that show or suggest an association with moisture damage or mold indoors and gastrointestinal or renal disease, reproductive disorders, teratogenicity or cancers (see also (Mazur and Kim, 2006; Palaty and Shum, 2012)).

It is a medical task, to provide objective information for concerned patients in such cases.

4.2. Risk analysis and assessment

4.2.1. Infection risk

Infection risk of indoor mold species is low for healthy individuals. Most species are classified into the risk group 1 and only few into the risk group 2 (*Aspergillus fumigatus*, *A. flavus*) of the German Biological Agents Regulation (TRBA 460, 2016).

For professional activities (handling) with molds, the current German Biological Agents Regulation (BAR) is in force, in which the risk of infection by biological agents is divided into four risk groups (BioStoffV, 2013), whereas mold species are only classified into the risk groups 1 and 2:

Risk group 1: Biological agents which are unlikely to cause illness in humans.

Risk group 2: Biological agents that can cause human disease and may be a hazard to workers; substance dispersal among the general population is unlikely; effective preventive measures or treatment is normally possible.

Risk group 3: Biological agents that can cause severe human disease and present a serious hazard to workers; there can be a risk of spreading to the general population, but there is usually effective prophylaxis or treatment available.

Risk group 4: Biological agents that cause severe human disease and present a serious hazard to workers; the risk of spreading to the general population is large in several circumstances; usually effective prophylaxis or treatment is not available (risk group 4 includes no mold species).

Similarly, the CDC recommends handling of miscellaneous molds under biosafety level 2 conditions (DHHS (CDC), 2009).

Mycoses are opportunistic infections. They require a decreased immune status of the exposed individuals. Thermo-tolerant mold species of the risk group 2 (e.g., *A. fumigatus*, *A. terreus*, *A. niger*, *A. flavus*, *Emmericella nidulans* or mesophilic *Fusarium* sp.) of the German “TRBA 460: Classification of mold in risk groups” (TRBA 460, 2016) of the German Biological Agents Regulation (BioStoffV, 2013) only rarely cause infections in healthy, immunocompetent persons, but can cause invasive mycoses in humans whose immune system is incompetent due to illness or other circumstances (Raad et al., 2002).

According to the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) at Robert Koch Institute (KRINKO, 2010) immunosuppressed individuals are divided into three risk groups (Table 2).

Particularly at risk are (in order of decreasing risk) patients with tumor disease, esp. with underlying hemato-oncological disease (e.g., leukemia, lymphoma), acute myelogenous leukemia (AML), acute lymphatic leukemia (ALL), allogenic stem cell transplantation, autologous stem cell transplantation, solid organ transplantation, HIV infection, other immunosuppression (e.g., prolonged high-dose glucocorticoid therapy), aplastic anemia, cystic fibrosis and many others (Nagano et al., 2007). Acute myelogenous leukemia (AML) is associated with the highest incidence of invasive mold infections (about 12%) and with the highest frequency of mold infections (about 8%). This is followed by acute lymphatic leukemia (about 4%). Within the treatment procedures, allogenic hematopoietic stem cell transplantation (alloSCT) is associated with a very high incidence of mold infections (Baddley et al., 2001; Bhatti et al., 2006).

Table 2
Risk groups according to the German Commission for Hospital Hygiene and Infection Prevention immunosuppression (KRINKO) at Robert Koch Institute (KRINKO, 2010).

Risk Group 1 (moderate immunosuppression) - Granulocytopenia $<0.5 \times 10^9/l$ ($<500/\mu l$) up to 10 days (analog leukopenia $<1 \times 10^9/l$; $<1000/\mu l$) - Lack of CD4-positive T-helper cells $<250/\mu l$ (Cave: age-matched normal values in children); autologous stem cell transplantation up to three months after intensive treatment phase <i>Patients who manifest more than 1 symptom of immunosuppression listed under Risk Group 1 belong to Risk Group 2</i> Risk Group 2 (severe immunosuppression) - Granulocytopenia $<0.5 \times 10^9/l$ ($<500/\mu l$) over more than 10 days (analog leukopenia $<1 \times 10^9/l$; $<1000/\mu l$) - Severe aplastic anemia or macrophage activation syndrome during an intensive immunosuppressive therapy - Allogenic bone marrow or stem cell transplantation up to 6 months after completion of the intensive phase of therapy (important: degree of graft-versus-host disease (GVHD) and the ongoing iatrogenic immunosuppression) - Acute inpatient therapy phase with autologous stem cell transplantation or after transplantation of solid organs (until discharge) Risk Group 3 (very severe immunosuppression) - Allogenic bone marrow transplantation (BMT)/peripheral blood stem cell transplantation (PBSCT) in intensive therapy phase (up to engraftment = regeneration of granulopoiesis) - Severe GVHD grade III or IV with intensive immunosuppression <i>The decision on classification in Group 3 in patients after allogenic stem cell transplantation is eventually taken in synopsis of all results of the treating oncologist</i>
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Due to continuous increase of the proportion of immunosuppressed patients in the general population and the longer survival of those affected it cannot currently be ruled out that mold infections may be an increasing risk factor for the health of this subpopulation.

A numerical risk cannot be derived on the basis of current knowledge. Fig. 1 shows a semi-quantitative risk assessment for the risk of infection by indoor mold exposure.

4.2.2. Sensitization/allergy risk

Principally, there is always the possibility of sensitization and induction of a clinically symptomatic allergy by inhalation of spores and other mold components (e.g., mycelium) for healthy individuals. The sensitizing potential of molds is considered significantly lower in comparison to other environmental allergens, such as allergens of fur-bearing pets, grass and tree pollen or house dust mites (about 15–30%) (Immonen et al., 2001; Nevalainen and Seuri, 2005; Taskinen et al., 1997; Taskinen et al., 1999; Zöllner et al., 2005). Recent studies – both population- and patient-related (Heinzerling et al., 2009) – show a comparatively low sensitization prevalence of 3–10% in the general European population (Burbach et al., 2009). Generally, it should be noted that sensitization – also to mold – cannot be equated with a clinically relevant allergy. It is generally assumed that there are over one million mold species. So far about 350 species of mold have been listed under www.allergome.org as potentially sensitizing. The proportion of sensitizing mold species as a whole cannot be deduced from this statement. The WHO/IUIS (World Health Organization and International Union of Immunological Societies) criteria for the classification of an allergen is met currently by 107 mold proteins from 43 mold species (WHO/IUIS, 2016). Only few mold species are available as test allergen solutions and typical indoor fungal allergen extracts are largely missing (Kespohl and Raulf, 2014; Zahradnik et al., 2013). From an allergological point of view, after sensitization, a dose dependency of the exposure to mold (measured as CFU/m³) of a patient is generally not alone decisive for the clinical response. Sensitization with formation of specific IgE antibodies and induction of allergic reactions occur due to proteins and peptide components (epitopes). Thus, it is not necessary that complete spores or intact mold mycelium are present.

In individuals with atopy, rhinoconjunctivitis, rhinosinusitis exposure to damp indoor environments represents a risk factor for the formation of asthma. For rhinosinusitis associated with mold exposure, the risk for the development of asthma doubles (OR: 2.2; CI: 1.3–3.6) (Park et al., 2012). Infants with atopy are at

increased risk for the development of asthma when a moisture damage or mold infestation is present in their bedroom or living room (Karvonen et al., 2015).

A numerical risk cannot be deduced on the basis of current knowledge. Fig. 2 shows a semi-quantitative risk assessment for sensitizing/allergy by mold indoors.

4.2.3. Risk of toxic/irritative effects

Only mold species that are potentially able to produce toxic substances can induce intoxication. Whether toxin formation is taking place in individual cases is determined by environmental and growth conditions, especially the available substrate (Mazur and Kim, 2006; Trout, 1998).

In humans, no predisposing factors for intoxication by mycotoxins are known. However, predispositions are imaginable on the level of the affected organ. For example, it is conceivable that a pre-damaged liver (e.g., chronic hepatitis, liver cirrhosis) may be a predisposition factor to hepatotoxic aflatoxin effects after ingestion of this toxin (Wild and Montesano, 2009). Whether this is also applicable to airborne toxin exposures, is still unclear.

A numerical risk cannot be derived based on current knowledge (Bush et al., 2006).

So far it is unclear whether individuals suffering from mucous membrane irritation (MMI) or chronic bronchitis are particularly susceptible persons who react at lower doses, or whether sensitized persons may react dose-independently and differently than non-sensitized individuals (Bascom, 1991). Possible predisposing factors for MMI and chronic bronchitis can be other inflammatory processes in the mucous membranes of the eyes and the respiratory tract, such as infections, atopic mucosal diseases, keratoconjunctivitis sicca and dry nasal mucosa (Shusterman et al., 2003).

4.2.4. Risk of odor effects and impairment of well-being and mood

In damp/moldy interiors, principally everybody can be affected by odor effects and/or well-being and mood impairment. These reactions do not indicate acute health hazard. Genetic and hormonal influences, genetic imprinting, context, and adaptation effects can be predisposing factors for olfactory effects (Dalton and Hummel, 2000). Environmental concerns, environmental fears, environmental conditioning, and environmental attribution as well as a variety of diseases can be predisposing factors for mood disorders (Hurraß et al., 2014; Wiesmüller et al., 2013).

Predisposition Mold species	No immuno- suppression	Moderate immuno- suppression	Severe immuno- suppression	Very severe immuno- suppression
Usually non-infectious mold species, e.g.: <i>C. herbarum</i> , <i>C. cladosporioides</i>				
Rarely opportunistic infectious mold species (risk group 1 according to BAR (TRBA 460, 2016)), e.g.: <i>A. niger</i> , <i>A. clavatus</i> , <i>Alternaria alternata</i>				
Opportunistic infectious mold species (risk group 2 according to BAR (TRBA 460, 2016)), e.g.: <i>A. fumigatus</i> , <i>A. flavus</i>				

Fig. 1. Infection risk by mold (The darker one box, the greater the potential health risk.); German BAR = Biological Agents Regulation.

Predisposition Mold species	No allergy and no familial disposition	No allergy but familial disposition	Allergy* without mold allergy	Allergy* to mold	Allergy* to specific mold species
Mold species with sensitizing / allergenic effect e.g.: <i>Alternaria alternata</i> , <i>A. fumigatus</i> , <i>P. chrysogenum</i> , <i>Cladosporium</i> sp.					

Fig. 2. Sensitization/allergy risk by indoor mold (The darker one box, the greater the potential health risk.) (* = Evidence of clinical relevance of the performed allergy test is needed!).

5. Diagnostic tools

5.1. Reasons for counseling

Concerning an association between mold exposure and health effects, patients usually look for medical advice for the following reasons (Storey et al., 2004):

1. Patients with health problems suggesting a relation to moisture damage and/or mold exposure
2. Patients with impairment of well-being and non-specific symptoms showing a clear temporal relation to specific environmental/ambient conditions or activities.
3. Patients who are concerned about a possible mold exposure
4. There are already measurement results indicating a mold exposure
5. Medical assistance is sought in tenancy or building construction disputes or litigation

5.2. General procedures, medical history (anamnesis) and physical examination

Basic elements of every medical diagnosis are medical history and physical examination (Warrell et al., 2016). On this basis, depending on the question to be answered, further specialized examination methods of appropriate medical disciplines may be employed. In environmental and occupational medicine, tests for internal exposure (human biomonitoring as an exposure and/or effect monitoring) and/or for external exposure (home visits/site

inspection, environmental monitoring) also can be carried out wherever possible and indicated.

5.2.1. Medical history

In taking a medical history, a holistic approach shall be carried out, which is not confined to environmental burden and aspects of physical illness, but equally recognizes the psycho-social dimension of the health problems. This approach which is necessary because of the high expectations of the patients to the doctors should be explained to the patient. The inclusion of mental and social aspects rarely results in difficulties if this is explained properly to the patient.

On suspicion of possible health problems caused by mold the following elements of medical history shall be considered:

- Exposure in the living indoor environment
- Exposure at the workplace
- Exposure in the leisure sector
- Infectiological anamnesis including predisposing factors
- Allergological anamnesis including predisposing factors
- Anamnesis focusing on irritative-toxic effects
- Anamnesis regarding odor effects
- Anamnesis about impairment of well-being and mood

In the following some aspects are described in more detail. Where no literature is cited, only experiences from daily medical practice are available.

Medical history in case of suspected mold-related diseases consists of an environmental medical and allergological anamnesis.

Personal medical history including family history should be assessed (atopy). Conclusions of experienced allergologists based on the medical history of temporal and spatial exposure to allergens, coincide up to about 50% with the results of allergy testing (Siles and Hsieh, 2011). Systematic environmental and allergological anamnesis in case of mold growth is particularly useful to indicate further diagnostic steps and to detect competing allergens.

Only with the synopsis of medical history, clinical symptoms and signs, allergen-detection and provocation testing where necessary, a reliable allergological diagnosis is possible.

The allergological history is taken by asking two sets of questions. Firstly, pre-existing diseases, symptoms and signs are asked. Secondly, the anamnesis is completed by questions concerning possible mold allergens, competing allergens as well as temporal and spatial associations of complaints to allergen exposure. In addition, non-allergic symptom complexes are assessed and confined. These include impairment of well-being, neuropsychological symptoms, odor effects, and toxic-irritative effects of molds, their components and of bacteria.

In the first step of medical history, organ-related symptoms and signs, their onset, intensity and duration are assessed. There are no specific anamnestic symptoms that allow an unambiguous identification of mold exposure as the cause of an allergy. The severity of allergic diseases induced by immediate-type sensitization is independent of the specific causative allergen. The severity of the allergic symptoms and signs is modulated by a variety of endogenous and exogenous factors (e.g., tobacco smoking). Stress can aggravate allergic symptoms and signs; it may include emotional conflicts in the partnership, the family or at work. The stress load as it occurs, for example, after water damage and mold growth indoors can exacerbate allergic symptom severity. In women, but also in men, the allergic reaction and its organ localization can also change depending on hormonal balance.

In the second step of medical history, the relationship of place, time and allergen to the complaints are to be determined. For this purpose, the symptoms with respect to their beginning, their course and severity at different locations should be inquired. According to the ecology of molds, complaints also have to be checked in relation to the weather, seasonal variations, staying in the flat, in air-conditioned rooms or in the bedroom (Note: molds occur together with mites in the bedroom). Focus is on questions about “mold smell”, a visible mold growth or mold contamination indoors. The smell of mold growth is often described as musty, moldy and sourly. Moisture damage, thermal bridges, condensation, waste management, handling of organic waste and garbage, compost storage, animal keeping, presence of indoor plants, hobbies, behavior of the room users and defects and deficiencies of the construction have to be inquired. Living conditions and user behavior may represent decisive factors. At this point, heating and ventilation facilities of the building or dwelling, the year of construction, roof construction, attic and basement shall be considered. Also demolition, construction or renovation works in the building and the surroundings can contribute to mold allergen load (Barnes and Rogers, 1989; Burwen et al., 2001; Iwen et al., 1994; Loo et al., 1996; Thio et al., 2000). Isopods (lat. *Oniscidea*), silverfishes (lat. *Lepisma saccharina*) and especially barklice (lat. *Psocoptera*), which feed on “mold lawn”, can serve as indications for increased moisture.

The transfer of molds and their components also may be relevant due to the mobilization of rotting biological material (leaves, grass, soil, and wood). This can happen by motor fans for cleaning, gardening and landscaping works as well as in strong wind in a dry period after humid weather. Ventilation and air conditioning systems, which are not serviced regularly, are important, but often not easily recognizable mold reservoirs.

It is of vital importance to find the source, if typical symptoms of possible health effects of mold exposure occur in a spatial and temporal relation to certain rooms or activities. As part of the diagnostic procedure, a period of exposure rest, meaning a temporary leave of the suspected areas and a subsequent re-exposure, can give important notes.

To determine the spatial and temporal dependencies of complaints, the reporting of symptoms in a diary by the patient can be useful.

Medical history shall identify most vulnerable and sensitive persons like immunocompromised individuals, allergic (atopic) persons and individuals with pre-existing pulmonary diseases like asthma, COPD, cystic fibrosis (CF; mucoviscidosis) (Dearborn, 2014; Nagano et al., 2007). CF patients have an increased risk for ABPA. Predisposing factors for mold allergy are familial predisposition to type I allergies, existing sensitizations and the presence of one or more atopic diseases. The significance of these predispositions increases in the order shown. For a sensitization and atopic disease, the predisposition is all the more pronounced the more mold-specific it is.

Other predisposing factors are:

- Difficult to treat allergic rhinitis
- Difficult to treat sinusitis
- Difficult to treat asthma
- Exacerbation of asthma for unknown reasons

Occupational exposure to mold qualitatively and quantitatively depends on the different activities. In Germany, after the amendment of the Biological Agents Regulation in 2013, which represents the national implementation of Directive 2000/54/EC, the classification of infection risk is omitted for activities, for which a sensitizing effect is assumed predominant. This concerns occupational mold exposure. Generally, occupational mold exposure is considered to be given in the following areas of activity:

- Activities in the waste sector (waste management, composting, waste separation, waste incineration, waste sorting)
- Remediation of mold-infested indoor spaces
- Professional sampling and inspection of molds indoors
- Stay in archives, libraries, depots and magazines (old paper or mold infestation)
- Activity in agriculture (hay, straw, animal husbandry)
- Gardeners, landscapers, florists, tree work
- Millers and bakers
- Wineries (esp. when destalking of grapes)
- Breweries
- Paper and wood production and processing
- Handling coolants (aerosols with bacteria and mold)
- Building renovators (upholsterer, plumber)
- Feed production and handling feed
- Ventilation/air conditioning maintenance

If there are workplace-related complaints when a worker is dealing with mold-contaminated materials, that indicate a mold allergy, firstly the exposure (frequency, quantity, quality) as a part of the risk assessment must be considered. Technical measures are to be taken if necessary. Personal protective equipment has to be provided if necessary. In Germany, employers and physicians are required to report the suspicion of an occupational disease to the responsible accident insurance.

5.2.2. Physical examination

Each medical history includes a complete or at least symptom and sign oriented physical examination. Methodology of physical

examination relies on inspection, palpation, percussion, auscultation and functional testing. The target organs suspected in the medical history are preferentially to be investigated.

Particular attention should be paid to the mucous membranes of the eyes and the upper respiratory tract as well as to the skin, because patients often complain of non-specific symptoms of these organs. Generally, physical examination should be carried out in a structured and standardized way and be adequately documented.

5.3. Markers of mold exposure

Measurements of mold exposure are carried out due to different objectives. Some of these analyses are expedient, for others it is postulated that they can demonstrate a causal association between mold exposure and potential health effects. These time-consuming and expensive investigations often do not meet the expectations set in them. In addition, it must be distinguished between analyses which are used in practice and those for scientific purposes.

A distinction has to be made between environmental (ambient) monitoring and analyses in biological material (biomonitoring) to assess exposure. Analyses in biological material may also be part of biomonitoring of effects and susceptibilities. In the following, we focus on environmental monitoring.

Effect and susceptibility biomonitoring are part of the medical diagnosis and are described in Section 5.4.

5.3.1. Environmental monitoring

Usually, there is no medical indication for the determination of mold indoors or on building materials or furnishings.

Epidemiological studies show a relationship between humidity/mold damage indoors and health complaints of indoor users (WHO, 2009b). The observed health problems are obviously related to the microorganisms that have multiplied on and possibly in the moist materials. But, it could not yet be clarified which specific biological agents are particularly relevant in this context (WHO, 2009b). In moisture damages, together with molds also bacteria multiply, especially actinobacteria. They themselves, but also metabolites and cellular constituents of microorganisms such as toxins, allergens, MVOCs, β -glucans, endotoxins and fragments of molds (particles) or bacteria can be health hazards. In connection with humidity/mold damages, mites and amoeba often occur, therefore an increased health impact of these parasites and microbes also can be expected. There is no simple causal relationship between single noxious agents mentioned above and health effects (DHSS (NIOSH), 2012; Eduard, 2009). With a correspondingly high exposure, both cultivable and non-cultivable mold spores can be responsible for health effects. The same applies to mycelium fragments. This means e.g., that even after disinfection measures, allergenic mold components still can be detected.

The intake pathways of the various mold components into the possible biological materials are different. Airborne MVOCs, mold spores, mycelium fragments of molds and bacteria, mycotoxins, endotoxins and allergens are inhaled. These toxicants can, however, also be ingested with foods or absorbed percutaneously via contact e.g., with infested building materials.

Even the most comprehensive analyses on the identification and quantification of fungi and other noxious substances occurring in connection with moisture/mold damage in indoor environments are of little use for the diagnosis and treatment for the treating physician. This is since there is no simple causal relationship between individual health complaints and the observed mold infestation (DHSS (NIOSH), 2012; Eduard, 2009) and because the repertoire of mold allergen extracts for allergy diagnosis, which are commercially available, is very limited and mainly includes typical outdoor species.

From a medical perspective, the on-site inspection of mold infestations is sufficient to induce medically justified measures. In the case of visible mold growth, increased material moisture or physical/structural abnormalities (“moisture or water damage”), the identification and quantification of fungal species in the affected indoor spaces is not indicated from a medical diagnostic or a therapeutic point of view (Wiesmüller et al., 2013).

For the health assessment of mold exposure, the differential diagnosis is of high priority. Since the health effects stemming from mold exposures mainly depend on the disposition of the person concerned, a time delay to take protective measures caused by mold measurements can result in an increased risk for people who must particularly be protected with respect to mold exposure (see Section 4.2). For these risk groups, mold analyses for risk assessment may be medically indicated in some cases, if there are any suspicions of hidden mold exposure, solely for reasons of prevention.

A summary presentation of current measurement methods for mold exposure assessment indoors can be found in Hurraß et al. (2016). This presentation aims to provide in-depth knowledge about expedient or not expedient application and the validity of the various measuring and testing methods to physicians, but also to environmental mycologists, indoor experts, craftsmen, architects and building experts, so that they have a solid basis for ordering and evaluating the appropriate investigations. To look further into this issue, it is referred to the corresponding literature (e.g., DHSS (NIOSH), 2012).

5.4. Clinical diagnosis

The basis for allergy diagnosis according to the pyramid model is the history or anamnesis followed by skin prick testing and the determination of allergen specific IgE. On top of this scheme is the organ-specific provocation test. This mentioned pyramid model suggests two things: the higher up the diagnostic procedure is in the pyramid, the greater is the impact, and the smaller the area, the indication decreases.

5.4.1. Allergy diagnosis

In general, there is no difference between the diagnosis of mold allergy and the diagnosis of other allergic diseases. As usual, a step-by-step approach according to the classic level scheme is carried out taking into account the individual factors: anamnesis/physical examination – skin prick test – analysis of sera or additional *in vitro* methods – provocation.

Allergic diseases by mold allergens can manifest essentially as conjunctivitis, rhinitis, rhinosinusitis, allergic asthma, urticaria, hypersensitivity pneumonitis or allergic bronchopulmonary aspergillosis (ABPA). Therefore, differential diagnosis with anamnesis and *in vitro*–*in vivo*–diagnosis is of central importance. In each individual case, it is necessary to confirm the allergic reaction and to identify the responsible trigger of the allergic reaction. A wide variety of *in vitro* tests, using different cellular and/or humoral parameters of the allergic reaction on different levels exist. The repertoire of commercially available mold allergen extracts is very limited and includes more or less only typical outdoor mold species.

Especially for the interpretation of *in vitro* tests it has to be considered that e.g., increased mold-specific IgE concentrations indicate sensitization against mold allergens, but this cannot be equated with an allergic disease. A correct interpretation of the results necessitates further diagnostic information from anamnesis, physical examination and technical tests, e.g. the demonstration of sensitization and/or an organ-specific provocation test. Sensitization to molds has to be interpreted carefully in the causality assessment regarding the possible exposures (ubiquitous outdoor-, indoor-, or occupational exposures). In practice, reliable confirmation of the causal relation between mold sensitizations, indoor

mold exposure and the specific related sensitization and disease (rhinitis, conjunctivitis, asthma) is scarce (Larenas-Linnemann et al., 2016).

The following requirements for the diagnosis of mold allergy must exist:

- A pathogenic mold antigen is found in the environment.
- A confident temporal relation between the onset of allergic symptoms and the exposure against the mold allergen exists.
- Atopic predisposition exists.
- An evidence for specific IgE-production against mold antigens is present.
- Cessation of mold exposure obviously shows beneficial effects.

Fundamentally, for the diagnosis of a mold allergy the same recommendations and guidelines apply as described for other allergens inducing an immediate-type allergy (Pfaar et al., 2014).

5.4.1.1. Serological testing. In case of an IgE-mediated type I sensitization the serological *in vitro* testing includes the detection of allergen-specific IgE-antibodies or in case of a hypersensitivity pneumonitis (HP) (Type III) the determination of allergen specific IgG-antibodies. The evidence of increased specific antibodies is a clear indication of sensitization but cannot be equated with the clinical relevance, whereby with an increasing sensitization degree the predictive value of clinical relevance increases (van Kampen et al., 2008).

a) Detection of mold-specific IgE-antibodies

The undoubtedly most important and most practicable *in vitro* test is the serological determination of allergen specific IgE-antibodies (sIgE). Although a variety of tests of different manufacturers exists, the repertoire of indoor-relevant mold test extracts is very limited. The test equipment of the several manufacturers differs not just because of the test implementation (including the use of different detection equipment like ELISA, FEIA, RIA, the use of different allergen carriers, e.g., chemically activated paper discs, micro titer plates, ImmunoCAP, chip technique or the use of liquid allergens) but also due to various raw materials, allergen extraction procedures and their standardization. The significance of the *in vitro* diagnosis is determined by the diagnostic sensitivity and specificity of the test method and therefore the significance of the allergy diagnosis highly depends on the quality of the allergen extracts used for testing (Kespohl et al., 2016), but also on the method of testing. In spite of the numerous so far characterized mold allergens, currently only eight recombinant single allergens of the three species *Alternaria alternata* (rAlt a 1, rAlt a 6), *Aspergillus fumigatus* (rAsp f 1, 2, 3, 4, 6) and *Cladosporium herbarum* (rClah 8) are available for the molecular diagnosis (Kespohl and Raulf, 2014). An improved mold-IgE diagnosis by the use of mold-typical marker allergens with strong IgE binding would be desirable.

According to several German allergy diagnosis guidelines, the determination of total IgE is useful in connection with specific IgE determination as an additional parameter for the evaluation and the interpretation of the specific IgE-values, but it cannot exclude or verify a specific sensitization.

For the diagnosis of allergic bronchopulmonary aspergillosis (ABPA), a type of allergy with components of type I-, type III- and type IV-reaction, mostly caused at least partially by *A. fumigatus*, the determination of *A. fumigatus*-specific IgE as well as the determination of total IgE and *A. fumigatus*-specific IgG, are useful (see specific IgG-determination). Recombinant *A. fumigatus* single allergens (rAsp f 1–10) are useful for complementary differential diagnosis. As an indicator for ABPA the combination of rAsp f 2 + rAsp f 4 + rAsp f 6 is typical, whereas a sensitization against

rAsp f 1 and/or rAsp f 3 does not represent a clear indication of an allergic asthma. Serologic positive results to rAsp f-allergens can also occur in other diseases like cystic fibrosis (Cramer, 1998).

The following points are important for the test evaluation:

- Detection of allergen-specific IgE indicates specific sensitization but not necessarily a disease; the result can just be interpreted correctly in connection with anamnesis, medical examination and the outcome of the organ-specific provocation test. Positive reactions caused by cross-sensitizations need to be considered.
- Quantitative comparison of the results obtained from different test systems is difficult (therefore necessity of international standardization).
- Improvement of the quality of the reagents via allergen standardization and definition of minimum requirements for allergen carrier material (determination of the diagnostic efficiency) must be demanded.
- Extracts of indoor-relevant molds should also be commercially available in sufficient quality.
- The repertoire of available single allergens of relevant molds should be enlarged.

b) Determination of mold specific IgG

The determination of specific IgG-antibodies in connection with the diagnosis of an immediate type allergy (type I-allergy) to molds has no diagnostic relevance, because IgG-antibodies are produced as a physiological response of the immune system to foreign antigen exposure and rarely have a pathogenetic relevance. Therefore in these cases mold-specific IgG-determination is not recommended (Kleine-Tebbe, 2009).

Only upon suspicion of an allergic bronchopulmonary aspergillosis (type I-, III-allergy) or hypersensitivity pneumonitis (type III-, IV-allergy) determination of mold-specific IgG-antibodies is a useful part of the diagnosis and therefore recommended (Shah and Panjabi, 2016).

In addition to increases of total IgE- and *A. fumigatus*-specific IgE levels in patients with allergic bronchopulmonary aspergillosis (ABPA), the levels of *A. fumigatus*-specific IgG are also increased. In comparison to patients with an allergic *A. fumigatus* sensitization, *A. fumigatus*-specific IgG levels are significantly increased in ABPA patients and thereby useful for differential diagnosis.

For quantitative assessment of specific IgG-concentrations (mg/L) no defined cut-off-values exist, which definitely refer to pathological alterations. The cut-off-values have to be determined individually for each measurement method and for each allergen based on results of controls' and patients' sera.

c) Cytokines, eosinophilic cationic protein (ECP)

Increased ECP-concentrations reflect the activation status of eosinophils, but do not permit an allocation or clarification of specific diseases. There is no indication for the measurement of this nonspecific activation and recruitment marker of eosinophilic granulocytes in mold allergy.

d) Immune complexes

The determination of immune complexes is limited to special diseases like HP (type III reactions) and furthermore no indication exists in the diagnosis of mold exposure (see above mold-specific IgG-determination).

e) Serological determination of galactomannan (GM)

Galactomannan, a heteropolysaccharide, is a constituent of the cell wall of the mold genus *Aspergillus* and can circulate in the blood in the case of invasive aspergillosis (IA). For the assay of galactomannan, serological testing methods are available. For the antigen detection the classical sandwich-ELISA technique is used. The microtiter plates are coated with monoclonal antibodies, which bind the antigen in sera or bronchoalveolar lavage fluid. The test is only indicated for diagnosis of invasive aspergillosis (Mayo Clinic, 2015; Verdaguer et al., 2007). In addition, quantitative real-time PCR (qPCR) assays have been developed for the detection of invasive pulmonary aspergillosis.

f) Serological detection of (1 → 3)-β-D-glucan

The principle test method bases on a modification of the Limulus-amoebocyte-lysate-test. It includes a microtiter plate-based detection system for the detection of (1 → 3)-β-D-glucan in sera. Briefly, a chromogen reagent is used, which eliminates in the pro-coagulation system of the Limulus-amoebocyte-lysate-pathway the factor C. If (1 → 3)-β-D-glucan is present, Factor G, a serine protease zymogen, can be activated. The inactive pro-coagulation system is activated, which breaks down a chromogenic peptide substrate whereby a light absorbing chromophore develops.

The test is technically sophisticated and may be useful for the diagnosis of invasive mycoses; an application in connection with indoor mold exposure is not indicated (Fontana et al., 2012).

g) Serological detection of mycotoxins

With regard to intoxication due to airborne mold toxins a diagnosis is only partially possible. In the USA macrocyclic trichothecenes were detected in sera from individuals which had indoor *Stachybotrys chartarum* exposure (van Emon et al., 2003). For the detection a Trichothecene-ELISA was used and 23 sera from patients but also one control serum were positive (Brasel et al., 2004; Hooper et al., 2009; Straus, 2009). Although the ELISA is a very sensitive method with detection limits in the range of ppb (equates to ng/ml or g), nonspecific reactions and cross-reactions cannot be excluded.

Due to the current state of analytical technology, mycotoxin indoor exposure can neither be validly specified nor evaluated by human biomonitoring. For routine analysis in practical medicine determination of mycotoxins in blood, serum or urine makes no sense and has to be limited currently to scientific research studies.

5.4.1.2. Cellular test systems. For all cellular test systems applies so far: they are methodically complicated, expensive, usually unsuitable for sample shipment and demanding in execution and interpretation. In addition, using cellular tests based on stimulation of basophil granulocytes, the quality of the test outcome depends on the availability and/or quality of the extract. In routine diagnostics, they are mostly not suitable but can represent a useful supplement in individual cases. They should be reserved for specialized in vitro allergy diagnosis in the case of a clear suspicion of an IgE-mediated allergy and unclear diagnostic findings and/or scientific research questions.

In addition, the repertoire of commercially available mold allergen extracts, which can be used as stimuli, is limited also for these tests and here again, the result of the test will depend on the quality of the used antigen (extract or single allergen).

Of course, it is necessary to differentiate between cellular test systems which are based on basophil granulocytes or mast cells and those which are based on T-cells (lymphocyte transformation test or proliferation test).

Cellular test systems based on IgE-sensitized basophil granulocytes use different parameters ('readouts') for test evaluation, but have identical bases: Positive results after titrated incubation with the allergen serve as indirect measure for the cell bound specific IgE. The significant excess of bound IgE on basophils and its high affinity to the FcεRI-receptor determine an extremely high analytical sensitivity of these test systems that by far exceeds serological quantification of specific IgE as well as skin tests. Samples with extremely low total IgE and negative serological test results on antigen specific IgE represent rare indications for these tests with 'basophils' as target cells, when sensitization (e.g., to exotic allergens) is suspected nevertheless.

a) Basophil degranulation test and histamine release, HLT = Histamin-Liberation-Test

The histamine release serves as indirect measure for cellular-bound specific IgE (see above), which has got a longer half-life in comparison to free IgE in serum. Histamine determinations (e.g., via ELISA) are complex; automated fluorimetric histamine determinations are not offered for routine in Germany. HLT is not useful for the diagnosis of mold allergy.

b) Basophil activation test using flow cytometry (Flow CAST)

A quantitative determination of CD63 (or another cell membrane marker of basophil-activation like CD203c), expressed on allergen stimulated isolated basophils, via flow cytometry may be performed; a further development represents the so called Flow2CAST using anti-CCR3 for a better discrimination of the basophils. This test is useful for inhalation allergens especially in cases where skin tests and measurements of specific IgE cannot be executed. Rare indications therefore represent samples with low total IgE, negative specific serological IgE detection and/or negative skin test for the assumed sensitization or exotic allergens.

c) Determination of other effector cell mediators (Leukotriene release testing, cellular antigen stimulation test (CAST))

This test is based on allergen-specific cell stimulation and on the quantification of released peptidoleukotrienes via immunoassay.

A positive reaction to an allergen, i.e. the indirect evidence of a sensitization, is indicative for clinical relevant allergy only within an explicit anamnestic context and/or in combination with a positive provocation test. Furthermore, this test has a complex implementation and is not useful for routine diagnosis.

d) Lymphocyte stimulation test (LST) or lymphocyte transformation test (LTT)

The lymphocyte transformation test (LTT) is a laboratory procedure for the detection of antigen-specific T-lymphocytes which is used in the immune function diagnosis in medicine. During the last years the test was also used in allergological *in vitro* diagnostics for the detection of certain allergic reactions of the delayed type IV (e.g., drug allergy). A principle problem of the LTT is that it cannot distinguish between a 'physiological' answer to an antigen and an 'allergic' T-cell answer. The proliferation is thus just an expression of a normal reaction of the organism with an (already known) antigen and therefore no indicator for a clinically relevant sensitization. Indications for LTT are usually in basic research. However, it should be noted that endotoxin contaminations of the antigen used for stimulation can induce a false-positive proliferation. As mold allergens don't lead to a type IV-sensitization, lymphocyte

transformation tests (LTT) with mold extracts are not indicated for diagnosis of mold allergy.

5.4.1.3. Provocation tests. If history, physical examination and serology do not provide a clear diagnosis to confirm a mold allergy, a provocation test may be indicated if important consequences arise for treatment, prevention and/or compensation. In this, the patient is confronted with the potential allergens in a natural way in order to provoke under controlled conditions an immediate (type I) allergic reaction with the typical corresponding symptoms. An organ-related provocation test is intended to confirm the clinical relevance of existing sensitizations or allegedly observed symptoms.

A study by O'Driscoll et al. (2009) found that the correlation between skin test results and the specific IgE test results is unsatisfactory in mold allergy diagnosis. It is therefore recommended to include all available methods, both skin testing and serological tests, for specific diagnosis and also to use test extracts – if available – from different manufacturers. Use of serological IgE determination alone to demonstrate mold sensitization does not appear sufficient with regard to sensitivity.

Tests with commercial extracts should not be omitted though, as these are easy to use and biological quality is monitored by batch tests by the Paul Ehrlich Institute.

Combinations of fixed test series have proven useful for certain queries. The choice of aeroallergens for standard testing must take into account individual, occupational and regional circumstances. False-negative results often arise when comparing the history and skin testing.

In particular, the results of tests with rare allergens and unstable mold allergens should be assessed critically.

Consequently, negative *in vitro* and *in vivo* test results do not exclude sensitization or allergy to mold.

Mold allergy is a rarity if there is a complete absence of IgE-mediated sensitization to the largely standardized skin test solutions of common environmental allergens.

With every provocation test there is a risk for a severe allergic reaction and for anaphylactic shock in the worst case. Doctors and nursing staff must therefore have appropriate experience, provide emergency equipment during testing and provocation and be familiar with the treatment of emergencies. Provocation tests should not be performed when there is a high degree of sensitization, acute inflammatory diseases of the nose, acute allergic reactions in other organs, severe general reactions, with use of medications that increase the risk of intolerance reactions (ACE inhibitors, beta-blockers) and generally not in children less than 5 years.

5.4.1.3.1. Test materials. Currently only a few commercial mold allergen extracts are offered from individual manufacturers. As studies from Kespohl et al., 2013, 2016) via detailed biochemical and immunological and also *in vivo* (SPT) analysis demonstrated, mold allergen extracts show very high variability in the allergen composition and preparations of the same mold species from different manufacturers are not comparable. An exception represent the skin test extracts of the outdoor air mold *Alternaria*. Storage and durability of the mold test extracts are the same as for other ubiquitous allergen skin test extracts (storage of the extracts in the refrigerator at a mean temperature of 4 °C, notice of expiration dates of the test solutions). In rules of the EU-directive 2001/83/EC, article 1 (4b) test allergens are defined as medicinal products. Therefore they require a certification procedure, which tends to decrease commercial availability, especially of mold extracts with time-consuming and costly production procedures. To avoid this gap, in the patients' interest, useful strategies for the future should be found as soon as possible.

a) Skin tests

Second to medical history, skin tests constitute the basis of allergy diagnosis and can be performed quickly and relatively cheaply. They are usually sufficiently valid and have a low complication rate. Skin tests should be performed in accordance with the corresponding German or European position papers.

A distinction is made between epicutaneous (patch test, rub test) and cutaneous tests (scratch, prick, intracutaneous test). The allergen concentration of solutions for intracutaneous tests is usually lower by a factor of 100–1000 than for prick test solutions. Currently (June 2015), however, commercial intracutaneous test solutions are no longer available so this diagnostic test is not applicable for demonstrating mold allergy. An allergic reaction is produced by introducing an allergen dose onto or into the skin. A prick test will usually be performed when inhaled allergies to mold spores are suspected.

The size and type of the reacting area (erythema, wheal) are used as a measure of the organism's degree of sensitization. Maximum histamine reaction occurs within 15 min. Allergen-induced reactions reach their maximum after 15–20 min. Regression usually takes place within 1–2 h. Delayed immediate-type reactions can occur a few hours later, appearing as a wheal or erythema. Late-type reactions, which appear within hours to a few days after the test are also possible, e.g., as erythematous papules or eczema. With all tests these late-type reactions can occur both with a negative and a positive immediate reaction as a delayed reaction (after 6–24 h) or as a late reaction (up to 48 h) so the observation period should not be less than 24 h (patient self-observation is possible). A positive skin test result requires both functioning immunological mechanisms and the skin's ability to react. The result becomes doubtful if the patient takes medications that influence the immune reaction (such as antihistamines, corticosteroids) and in the case of eczematous or urticarial skin diseases.

The inside of the forearm or the back are suitable areas for skin testing.

b) Nasal provocation test (NPT)

The nasal provocation test (NPT) allows reproduction of an allergic reaction in the manifestation organ under standardized conditions and is regarded as a simple and safe procedure with high specificity and sensitivity. Persistent respiratory symptoms usually occur with inhalational allergies to mold spores. This can make a clear relation with the history difficult. In this situation, the NPT can confirm or refute the suspected diagnosis of an allergic reaction of the respiratory tract. The NPT is also indicated when a skin test is contraindicated, when local allergic rhinitis (LAR) is suspected and for monitoring therapy such as allergen-specific immunotherapy (SIT).

When provocation has been carried out with a positive result, the next test can be performed 48 h later at the earliest. A range of medications interferes with the results of nasal provocation so a waiting period must be observed for these substances. Contraindications summarized in Table 3 should be considered.

5.4.1.3.2. Procedure. The disadvantage of the NPT is its time-consuming nature for both the investigator and the patient. Testing of one allergen alone takes about 35–45 min. Another allergen can be tested only when the outcome of the previous challenge was negative; if the test result is positive, testing on this day must be stopped. If several allergens are to be tested, repeated sessions must therefore be scheduled.

Since allergic late-phase reactions of the nasal mucosa do not occur during a normal examination period but after 4–6 h, the patient should be given a self-observation questionnaire for the first 24 h after the test. When evaluating this information, however, it

Table 3

Contraindications to a nasal provocation test NPT (modified according to Akerlund et al. (2005) and Chapman et al. (2008).

Relative contraindication to the NPT
- Particularly high degree of sensitization
- Pregnancy
- Children under 5 years
Absolute contraindications to the NPT
- Acute inflammatory diseases of the nose or sinuses
- Surgery on the nasal cavity or paranasal sinuses less than 8 weeks previously
- Severe systemic disease
- Poorly medication-controlled or uncontrolled bronchial asthma
- Medications that increase the risk of intolerance reactions (β -blockers and ACE inhibitors)
- Vaccinations should be carried out at least one week ago

Table 4

Stage I–IV according to the conjunctival provocation test (CPT).

Stage I	Foreign body sensation, conjunctival erythema, incipient pruritus
Stage II	As I, plus tearing, more severe pruritus, erythema of the tarsal conjunctiva of the lower lid
Stage III	As II, plus erythema of the tarsal conjunctiva of the upper lid, severe pruritus, blepharospasm
Stage IV	As III, plus chemosis, lid swelling, irresistible pruritus

must be borne in mind that the patient is in an uncontrolled environment after the ambulant testing and external environmental influences may well play a part.

The results of the NPTs are false-negative in an estimated one fifth of allergic patients. The causes were:

- Previous medication consumption
- Nasal volume flow too small at the start of the examination when the nose is highly obstructed, e.g., due to polyposis
- Insufficient adaptation to the room conditions
- Prior physical exertion
- Previous endonasal operation with partial removal of the nasal mucosa
- Non reactivity of the nasal mucosa of other origin

Other sources of error in the use of the NPT are technical errors, sympathetic stimulation of the nasal mucosa and occurrence of and failure to identify a late reaction.

c) Conjunctival provocation test (CPT)

The CPT should be performed only when the patient is asymptomatic; standardized prick test solutions are generally used in a 1:10 and possibly higher dilution. A control solution is first instilled in the inferior conjunctival sac, with 10 min waiting for a possible reaction (control eye). A drop of the allergen test solution is then instilled in the inferior conjunctival sac of the other eye (test eye). A positive test result consists of progressive pruritus, increased tear secretion, foreign body sensation, photophobia, etc. (Table 4).

As soon as stage II–III has been reached, the test is regarded as positive and the patient should be spared further, more severe reactions by irrigating the conjunctival sac with normal saline and by instilling eye drops (antihistamines, vasoconstricting agents).

The CPT is much more poorly standardized than the NPT, and also does not record the reaction of the respiratory mucosa directly as manifestation organ with aeroallergens. Hence, it is not a standard test method.

A CPT can be indicated when

- The symptoms are predominantly conjunctival.

- There are nasal symptoms but an NPT is not possible on account of contraindications (Table 3).

d) Bronchial provocation test (BPT)

A bronchial provocation test can be indicated when the diagnosis cannot be made by a combination of exposure assessment and less invasive diagnostic tools such as asthma symptoms, antibody detection and skin testing. Especially in the case of the perennially occurring indoor molds, the history is usually not specific. Confirmation of the diagnosis may be indicated prior to hyposensitization, and if an association of symptoms with a certain exposure is subject of expert evidence in legal matters. In analogy with other inhaled allergens, the degree of sensitization can be considered as guidance. In this respect, the bronchial provocation test is highly important when allergic perennial asthma due to indoor molds is suspected. The choice of allergen should be guided by the sensitization spectrum. The evidence for provocation testing in the absence of proof of sensitization is insufficient; therefore no recommendation can be made in this regard.

Allergen extracts from molds are suitable for provocation tests due to their adequate solubility. Since, in addition, adequate quantification of molds in native materials cannot be achieved with acceptable expense, testing with native material in the laboratory is not a suitable method. Testing in and outside potentially contaminated rooms can deliver evidence of an allergen source but is not assessable regarding the causative agent.

The repertoire of commercial extracts for provocation tests is becoming increasingly limited. They must be performed adhering to the corresponding guideline.

When assessing provocation tests with allergens, both false-positive and false-negative reactions may occur. In the absence of a clinically significant gold standard, a statement about sensitivity and specificity is generally problematic and in the case of molds it is made particularly difficult by the inadequate studies of the quality of the test extracts. More recent studies from Finland of individuals with occupational exposure to mold show that provocation testing with commercial mold extracts is possibly much more sensitive than gaining evidence of sensitization (Karvala et al., 2010). These data require confirmation. Assessment of the provocation reaction to mold provocation is a challenge in this respect, especially as isolated late reactions have been described frequently.

5.4.1.4. Differential allergy diagnosis (pollen, house dust mites, indoor allergens). When nonspecific health complaints are linked to visible or hidden mold damage, it should be noted that the symptoms reported in these cases (e.g., fatigue, headaches, mucosal irritation) can also occur with a variety of other diseases and in association with other indoor pollutants (e.g., VOC, formaldehyde, wood preservatives, insecticides, tobacco smoke). A house visit can be recommended in principle for orientation, if feasible together with indoor hygiene and building experts.

Since molds indoors usually occur simultaneously with other allergens, distinguishing effects specific for molds is problematic. It has been shown, for instance, that early exposure to house dust mites possibly leads to symptoms in the first year of life corresponding to obstruction of the upper respiratory tract. House dust mite antigens, the Fel d 1 cat antigen, antigens introduced from outside as well as bacteria and endotoxins must also be considered. House dust mites (and also bacteria) represent a particular confounder as they occur more frequently in rooms with greater air and material humidity, just like molds. It is especially problematic that numerous allergens of biological origin are subject to a seasonal cycle similar to that of typical outdoor molds. For instance, not only are more mold spores (esp. *Cladosporium* sp. and *Alternaria* sp.) found in outdoor and indoor air, precisely in summer and late summer,

but also numerous grass and weed pollens. Diagnostic investigation for further indoor allergens is therefore useful, e.g., by specific IgE determination or by a skin test.

5.4.2. Systemic or invasive fungal infection diagnosis

Diagnostic procedures in invasive mold infection are covered by the respective guideline (Ruhnke et al., 2012).

5.4.3. Toxicological diagnostics

At present, there are no useful and validated testing procedures that could be used in clinical practice.

5.4.4. Unconventional diagnostic methods

Often unconventional diagnostic methods are demanded by patients but also propagated by doctors and therapists from various disciplines. It is noticeable that scientific methods suitable to tackle other questions, such as human biomonitoring are being misused to give an appearance of science. The same is true for the imaginative names of some applications. Without performing a method criticism with the patients in detail, their protection against costly and nonsensical procedures must be a concern of environmental health counseling. The right to a pluralism of directions of thought and methods shall remain inviolated.

Unconventional diagnostic methods must be tested and evaluated according to the current state of scientific knowledge, as it is done for all medical procedures.

In addition, unequivocal statements of experts, professional societies and institutions shall be made to these procedures in scientific journals, lay press, and television programs. Moreover, statutory and private health insurances shall only cover the costs for unconventional diagnostic methods, if their value has been demonstrated (Eis, 1998/99).

Table 5 shows examples of unconventionally used and unconventional diagnostic methods (Eis, 1998/99). They are not recommended due to lack of evidence.

6. Therapy

Even when a causal association between symptoms/findings/diseases and the presence of mold/damp indoors cannot be found, the first “therapeutic” measure in the presence of damage caused by damp/mold, from the preventive and hygiene standpoint, is prompt and correct remediation and swift minimization of exposure in the case of serious diseases with a high health risk (immunosuppression, cystic fibrosis, asthma).

6.1. General pharmacological treatment and specific immunotherapy (hyposensitization)

Topical and/or systemic therapy is indicated in allergy to molds depending on the specific organ involved.

The pharmacological treatment of allergic diseases (rhinitis, conjunctivitis, sinusitis, asthma) associated with exposure to mold does not differ from treatment of allergic diseases due to further allergens (e.g., pollen).

Specific immunotherapy (SIT) is the only causal therapy with an immune modulating function for allergies. Delivery of therapeutic allergens activates specific blocking antibodies, tolerance-inducing cells and messenger substances. This leads to attenuation of the immune response caused by allergens. The body's inflammatory reaction responsible for the allergic complaints subsequently regresses (Pfaar et al., 2014).

Specific immunotherapy (SIT) with mold extracts should be delivered as soon as possible in the course of the disease, especially when pharmacological treatment measures and allergen avoidance have not led to symptom control (Brehler et al., 2013).

The corresponding mold allergens must be clearly confirmed diagnostically as the cause of the allergic complaints. Proof of allergen-specific and clinically significant IgE sensitization is a precondition for SIT. The combination of different test methods, together with the history, provides an adequate basis for SIT.

Hyposensitization assumes that the diagnosis is confirmed. Please refer to the current guideline (Pfaar et al., 2014).

Eleven single test allergen extracts and two mold mixtures are currently licensed for skin testing according to the therapeutic allergen regulation (Paul-Ehrlich-Institut, 2016). These were withdrawn from the market by the manufacturer, however. For prick testing, single and mixed allergens from different manufacturers are still available, but mainly for outdoor molds (see Section 5.4.1.3). For provocation according to the guidelines prior to specific immunotherapy, only 12 single allergen extracts and two mixed allergen extracts that comply with the therapeutic allergen regulation (TAV) are available (as of 3/15). The hyposensitization solution should as far as possible be obtained from the same manufacturer as the test solution employed. Mixtures of different therapeutic mold allergens are possible. A narrow allergen spectrum probably increases the success of the SIT.

Preparations for subcutaneous immunotherapy (SCIT) and for sublingual immunotherapy (SLIT) are available for hyposensitization. Non-modified allergens are used for SCIT as aqueous or physically coupled (semidepot) extracts and as chemically modified extracts (allergoids) as semidepot extracts. The predominantly unmodified allergen extracts for SLIT are used as aqueous solutions. Preparations that contain frequent allergens are subject to licensing according to the therapeutic allergen regulation (TAV). Therapeutic allergens according to the TAV for the rare mold allergens are available for neither SLIT nor SCIT (Paul-Ehrlich-Institut, 2016). They cannot be mixed with the allergens that comply with the TAV.

Injections for SCIT are given by a doctor who has experience with this form of treatment and can deliver emergency treatment in the event of an allergological incident. Prior informed consent with documentation is required (observe patients' rights and comply with guideline).

The individual success of hyposensitization can be tracked from the severity of the clinical symptoms. A symptom questionnaire has proved useful. Regular monitoring by means of rhinomanometry or lung function is recommended.

According to recent studies, the efficacy of SCIT for the outdoor mold *Alternaria alternata* and *Cladosporium herbarum* has been confirmed by a few studies (Larenas-Linnemann et al., 2016). A DBPC study in *Alternaria*-sensitized children (Kuna et al., 2011) confirms that this form of allergy can be treated successfully with classic specific immunotherapy (SIT) by regular injections of an *Alternaria* allergen extract.

The efficacy of SLIT with regard to hyposensitization against indoor molds has not yet been adequately confirmed.

6.2. Cessation of exposure

As for all allergic diseases, the elimination or reduction of exposure has priority. However, an early medication is necessary in order to avoid that allergic symptoms recur after a symptom-free period.

The elimination of the causes of moisture as the basis for mold growth indoors is paramount. The evidence for the success of remediation of buildings damaged by dampness and mold in relation to asthma and respiratory symptoms as well as the frequency of common colds in adults and children is moderate (Sauni et al., 2011). Together with other studies (Burr et al., 2007; Heinrich, 2011; Krieger et al., 2010; Tischer and Heinrich, 2013), there is sufficient evidence that an intervention that improves the living conditions

Table 5

Unconventionally used and unconventional diagnostic methods in environmental medicine (Eis, 1998/99).

Unconventionally used diagnostic methods in environmental medicine	
Stress tests in body media	e.g., mold species in blood
Allergological tests	e.g., serial dilution titration, cytotoxic blood tests, analysis of IgG and IgA antibodies to mold species in case of type I allergy
Examination of immune system disturbances	e.g., lymphocyte stimulation tests (LTT)
Unconventional diagnostic methods in environmental medicine	
Holistic or bioenergetic diagnostic methods	e.g., electro-acupuncture according to Voll, bioresonance, Vega test, decoder dermatography, biotonometry, biotensor, Kirlian photography (plasma print process, energy terminal point diagnostic), regulation thermography according to Rost, auriculo-diagnostic, kinesiology, aura scopy
Methods of “clinical ecology”	e.g., cytotoxic blood tests, provocation and neutralization test (PN-test)

in terms of humidity and mold growth, positively affects the morbidity of asthma and respiratory allergies (Sauni et al., 2015).

For patients at risk (cystic fibrosis), the avoidance of damp rooms and rooms with mold growth and the timely remediation of each mold infestation are recommended (Rocchi et al., 2015).

By the use of special equipment for air purification and dehumidification, the concentrations of airborne mold components (bioaerosols) can be reduced (Bernstein and Levin, 2005). Whereas HEPA filters were effective in cat and dog allergy, there was no evidence of efficacy in house dust mite or mold allergies (Wood, 2002). A meta-analysis of 10 randomized controlled studies of air filtration from the years 1973–1999 found a small statistically significant improvement in overall symptoms and sleep disturbances when using air purifiers, but no improvement in nasal symptoms, medication use or peak expiratory flow (PEF) (McDonald et al., 2002).

Besides clearly indicated, professional constructional renovation to remove and avoid moisture and microbiological growth (see below), for additional technical measures (air filter, dehumidifier), which are occasionally recommended (Mazur and Kim, 2006), there is only insufficient evidence due to lack of studies (Singh and Jaiswal, 2013). “Air purifier” with ionizers must be considered problematic, as they can produce ozone levels which are harmful to health (Hubbard et al., 2005; Waring and Siegel, 2011).

Affected individuals themselves should respect the following recommendations:

Indoor air (DHSS (NIOSH), 2012)

- The living quarters are to be maintained dry by ventilation (three to four times daily for 5–15 min short, sharp ventilation, best done as cross-ventilation) and heating (relative humidity < 65 %, optimum room temperature approx. 20 °C).
- Sufficient ventilation, especially of wet rooms. Most of the moisture and thus mold growth can be found in the bathrooms. Dark stripes along the tile joints are a sign of mold growth (often *Alternaria* sp.). After showering or bathing the bathroom has to be adequately ventilated. Wipe and dry shower and bath tub. Wash shower curtains regularly and let them dry. Remove wet towels from the bathroom. No carpets in the bathroom.
- Sufficient air circulation between furniture and floor, ceiling and wall (10 cm from the outer wall).
- No humidifiers, no indoor fountains, no aquariums.
- Air-conditioning and ventilation systems require regular maintenance and cleaning.
- No storing of firewood indoors.
- Keep rooms dust-free (allergens are attached to dust).
- Remediation of sleeping area for mite allergy sufferers.
- No pot plants and cut flowers indoors, definitely not in the sleeping area (molds thrive in the soil).
- Do not keep wet shoes, clothes or leather products in wardrobes.
- Empty and clean frequently waste bins, especially compost bins.

Table 6

Examples of unconventionally used and unconventional therapeutic methods in environmental medicine (Eis, 1998/99).

Unconventionally used therapeutic methods in environmental medicine
Antifungal treatment
Detoxification, e.g., with colestyramine (CSM treatment)
Dietary changes
Homeopathic treatments
Symbiosis control
Unconventional therapeutic methods in environmental medicine
Bioresonance therapy (MORA therapy)
Self-blood and self-urine treatment
Holistic colon therapy
Methods of “clinical ecology” (e.g., provocation and neutralization test (PN test))

- Fur-bearing animals, especially long-haired dogs, may cause spore entry into indoor spaces. In their fur, *Alternaria* sp. develops, especially if the dog likes to go into the water. In addition, spores from the outdoor air are collected in the fur and transported into indoor spaces.
- Store pet food and bedding material dry.

Outdoor air (Diette et al., 2008)

- As generally observed for pollinosis, seasonal complaints may also exist for mold allergies, but they do not correlate with the usual pollen times. The concentration of mold spores in the air depends on the weather conditions. It is especially high in the late summer and early fall, whenever it is hot and humid, alternating thereafter.
- Seasonal complaints from July to September may indicate mold allergy, especially if they improve during prolonged good weather periods (heat waves) and deteriorate again after rainfall. However, on dry, windy days after a previous wet period, deposited spores may release from the ground into the air. During periods of high airborne spores concentrations (especially for dry and windy weather from May to October), staying outdoors should be reduced if possible.
- Avoid all activities with increased exposure to mold spores (gardening, handling with bark mulch or rotted leaves, compost piles).

6.3. Unconventional treatment methods and therapies

Often, patients call for unconventional treatments, but they were also propagated by physicians and therapists from various disciplines. It is noticeable that scientific founded methods such as an antifungal treatment are being misused to make the approaches appear scientific (Eis, 1998/99).

In Table 6, examples of unconventionally used and unconventional therapeutic methods are shown. Due to lack of evidence, they are not recommended.

Like all medical methods, unconventional therapeutic procedures must be verified and evaluated according to the current state

of scientific knowledge and will only be refunded, if the therapeutic benefit has been demonstrated.

7. Remediation of living spaces (buildings) with moisture problems and mold growth

A professional remediation of a moisture/mold damaged building includes the correction of the physical cause(s) in the building, the drying of the construction materials, the removal of all moldy materials, and a subsequent precision cleaning. The details and procedures are not part of this paper. In Germany, the requirements as well as detailed descriptions of the restoration processes are defined in special recommendations of the Federal Environment Agency (*Innenraumlufthygiene-Kommission des Umweltbundesamtes, 2002, 2005*), which are comparable to the recommendations given by the WHO (2009a).

Surveys of the German Federal Statistical Office and the Federal Ministry of Labor and Social Affairs have shown that frequent humidity/mold damages occur more frequently in homes of people with lower socioeconomic status than in the general population and that these people often suffer from energy poverty, i.e. they have not enough money to heat their living space efficiently. Thus, especially for people with low income, remediation measures in the case of moisture damages and prevention measures that avoid moisture and mold problems in advance would be important.

8. Prevention

The first important point is to inform and educate susceptible and immunosuppressed patients about risks and prevention measures associated to mold exposure in indoor environments (Mousset et al., 2014; Tacke et al., 2014), possibly supplemented by indoor measurements on the presence of *Aspergillus fumigatus* and *Aspergillus flavus* (rarely found indoors) (Rocchi et al., 2014).

For all health problems associated with exposure to environmental factors, prevention and elimination of exposure have priority. This particularly applies to molds. An indoor climate that promotes mold growth (high humidity, lack of ventilation and heating) must be avoided for allergy prevention (Rao and Phipatanakul, 2011).

The decisive prerequisite for the growth of mold and other microorganisms is moisture. Indoors, the following reasons inter alia may lead to increased humidity on surfaces of building materials or furnishings:

- Structural reasons
- Reasons according to the use of the rooms
- Water damages

When investigating the cause of moisture/mold damage in 217 homes by a consultant of the consumer protection service in Stuttgart, the following etiological factors were found:

- Construction defects 45%
- Increased air humidity 18%
- Incorrect furnishing 17%
- Leakages 20%

The nutrients necessary for mold growth are present in sufficient quantities on almost all surfaces, e.g., on wallpaper, wood surfaces, silicon joints, as well as in dust on plasters and in the organic additives contained in plasters.

References

- Akerlund, A., Andersson, M., Leflein, J., Lildholdt, T., Mygind, N., 2005. Clinical trial design, nasal allergen challenge models, and considerations of relevance to pediatrics nasal polyposis, and different classes of medication. *J. Allergy Clin. Immunol.* 115, S460–S482.
- Anon, 1970. Aspergilloma and residual tuberculous cavities – the results of a resurvey. *Tubercle* 51, 227–245.
- Baddley, J.W., Stroud, T.P., Salzman, D., Pappas, P.G., 2001. Invasive mold infections in allogeneic bone marrow transplant recipients. *Clin. Infect. Dis.* 32, 1319–1324.
- Baldo, J.V., Ahmad, L., Ruff, R., 2002. Neuropsychological performance of patients following mold exposure. *Appl. Neuropsychol.* 9, 193–202.
- Barnes, R.A., Rogers, T.R., 1989. Control of an outbreak of nosocomial aspergillosis by laminar air-flow isolation. *J. Hosp. Infect.* 14, 89–94.
- Barreiros, G., Akiti, T., Magalhães, A.C., Nouér, S.A., Nucci, M., 2015. Effect of the implosion and demolition of a hospital building on the concentration of fungi in the air. *Mycoses* 58, 707–713.
- Bascom, R., 1991. The upper respiratory tract: mucous membrane irritation. *Environ. Health Perspect.* 95, 39–44.
- Baser, S., Fisekci, F.E., Ozkurt, S., Zencir, M., 2003. Respiratory effects of chronic animal feed dust exposure. *J. Occup. Health* 45, 324–330.
- Baxi, S.N., Portnoy, J.M., Larenas-Linnemann, D., Phipatanakul, W., Environmental Allergens Workgroup, 2016. Exposure and health effects of fungi on humans. *J. Allergy Clin. Immunol. Pract.* 4, 396–404.
- Bernstein, J.A., Levin, L., 2005. A pilot study to investigate the effects of combined dehumidification and HEPA filtration on dew point and airborne mold spore counts in day care centers. *Indoor Air* 15, 402–407.
- Bhatti, Z., Shaikat, A., Almyroudis, N.G., Segal, B.H., 2006. Review of epidemiology, diagnosis, and treatment of invasive mould infections in allogeneic hematopoietic stem cell transplant recipients. *Mycopathologia* 162, 1–15.
- Verordnung über Sicherheit und Gesundheitsschutz bei Tätigkeiten mit Biologischen Arbeitsstoffen (Biostoffverordnung – BioStoffV). 15.07.2013 (BGBl. I S. 2514).
- Bloom, E., Grimsley, L.F., Pehrson, C., Lewis, J., Larsson, L., 2009. Molds and mycotoxins in dust from water-damaged homes in New Orleans after hurricane Katrina. *Indoor Air* 19, 153–158.
- Brasel, T.L., Campbell, A.W., Demers, R.E., Ferguson, B.S., Fink, J., Vojdani, A., Wilson, S.C., Straus, D.C., 2004. Detection of trichothecene mycotoxins in sera from individuals exposed to *Stachybotrys chartarum* in indoor environments. *Arch. Environ. Health* 59, 317–323.
- Brehler, R., Klimek, L., Kopp, M.V., Virchow, J.C., 2013. Specific immunotherapy – indications and mode of action. *Dtsch. Ärztebl. Int.* 110, 148–158.
- Brozek, J.L., Bousquet, J., Baena-Cagnani, C.E., Bonini, S., Canonica, G.W., Casale, T.B., van Wijk, R.G., Ohta, K., Zuberbier, T., Schünemann, H.J., Global Allergy and Asthma European Network, Grading of Recommendations Assessment, Development and Evaluation Working Group, 2010. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J. Allergy Clin. Immunol.* 126, 466–476.
- Bullinger, M., 1989. Relationships between air pollution and well-being. *Soz. Präventivmed.* 34, 231–238.
- Burbach, G.J., Heinzerling, L.M., Edenharter, G., Bachert, C., Bindslev-Jensen, C., Bonini, S., Bousquet, J., Bousquet-Rouanet, L., Bousquet, P.J., Bresciani, M., Bruno, A., Canonica, G.W., Darsow, U., Demoly, P., Durham, S., Fokkens, W.J., Giavi, S., Gjomarkaj, M., Gramiccioni, C., Haahela, T., Kowalski, M.L., Magyar, P., Muraközi, G., Orosz, M., Papadopoulos, N.G., Röhrl, G., Stingsl, G., Todo-Bom, A., von Mutius, E., Wiesner, A., Wöhr, S., Zuberbier, T., 2009. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. *Allergy* 64, 1507–1515.
- Burr, M.L., Matthews, I.P., Arthur, R.A., Watson, H.L., Gregory, C.J., Dunstan, F.D., Palmer, S.R., 2007. Effects on patients with asthma of eradicating visible indoor mould: a randomised controlled trial. *Thorax* 62, 767–772.
- Burwen, D.R., Lasker, B.A., Rao, N., Durry, E., Padhye, A.A., Jarvis, W.R., 2001. Invasive aspergillosis outbreak on a hematology-oncology ward. *Infect. Control. Hosp. Epidemiol.* 22, 45–48.
- Bush, R.K., Portnoy, J.M., Saxon, A., Terr, A.I., Wood, R.A., 2006. The medical effects of mold exposure. *J. Allergy Clin. Immunol.* 117, 326–333.
- Chakrabarti, A., Denning, D.W., Ferguson, B.J., Ponikau, J., Buzina, W., Kita, H., Marple, B., Panda, N., Vlaminck, S., Kauffmann-Lacroix, C., Das, A., Singh, P., Taj-Aldeen, S.J., Kantarcioglu, A.S., Handa, K.K., Gupta, A., Thungabathra, M., Shivaprakash, M.R., Bal, A., Fothergill, A., Radotra, B.D., 2009. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *Laryngoscope* 119, 1809–1818.
- Chapman, J.A., Terr, A.I., Jacobs, R.L., Charlesworth, E.N., Bardana Jr., E.J., 2003. Toxic mold: phantom risk vs science. *Ann. Allergy Asthma Immunol.* 91, 222–232.
- Chapman, M.D., Ferreira, F., Villalba, M., Cromwell, O., Bryan, D., Becker, W.M., Fernández-Rivas, M., Durham, S., Vieths, S., van Ree, R., 2008. CREATE consortium. The European Union CREATE project: a model for international standardization of allergy diagnostics and vaccines. *J. Allergy Clin. Immunol.* 122, 882–889.
- Choi, H., Byrne, S., Larsen, L.S., Sigsgaard, T., Thorne, P.S., Larsson, L., Sebastian, A., Bornehag, C.G., 2014. Residential cultural fungi, (1-3, 1-6)-beta-D-glucan, and ergosterol concentrations in dust are not associated with asthma, rhinitis, or eczema diagnoses in children. *Indoor Air* 24, 158–170.

- Cox-Ganser, J.M., White, S.K., Jones, R., Hilsbos, K., Storey, E., Enright, P.L., Rao, C.Y., Kreiss, K., 2005. Respiratory morbidity in office workers in a water-damaged building. *Environ. Health Perspect.* 113, 485–490.
- Crago, B.R., Gray, M.R., Nelson, L.A., Davis, M., Arnold, L., Thrasher, J.D., 2003. Psychological, neuropsychological, and electrocortical effects of mixed mold exposure. *Arch. Environ. Health* 58, 452–463.
- Cramer, R., Hemmann, S., Ismail, C., Menz, G., Blaser, K., 1998. Disease-specific recombinant allergens for the diagnosis of allergic bronchopulmonary aspergillosis. *Int. Immunol.* 10, 1211–1216.
- Cramer, R., 1998. Recombinant *Aspergillus fumigatus* allergens: from the nucleotide sequences to clinical applications. *Int. Arch. Allergy Immunol.* 115, 99–114.
- Dales, R., Ruest, K., Guay, M., Marro, L., Miller, J.D., 2010. Residential fungal growth and incidence of acute respiratory illness during the first two years of life. *Environ. Res.* 110, 692–698.
- Dalton, P., Hummel, T., 2000. Chemosensory function and response in idiopathic environmental intolerance. *Occup. Med.* 15 (3), 539–556.
- Dearborn, D.G., Smith, P.G., Dahms, B.B., Allan, T.M., Sorenson, W.G., Montana, E., Etzel, R.A., 2002. Clinical profile of 30 infants with acute pulmonary hemorrhage in Cleveland. *Pediatrics* 110, 627–637.
- Dearborn, D.G., 2014. Chapter 38 mold. In: Landrigan, P.J., Etzel, R.A. (Eds.), *Textbook of Children's Environmental Health*. Oxford University Press, Oxford.
- Department of Health and Human Services, Centers for Disease Control and Prevention, National Institutes of Health, 2009. Biosafety in Microbiological and Biomedical Laboratories, fifth ed. HHS Publication No. (CDC) 21–1112.
- Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, 2012. Preventing occupational respiratory disease from exposures caused by dampness in office buildings, schools, and other nonindustrial buildings. DHHS (NIOSH) Publication No. 2013–102.
- Diette, G.B., McCormack, M.C., Hansel, N.N., Breyse, P.N., Matsui, E.C., 2008. Environmental issues in managing asthma. *Respir. Care* 53, 602–615.
- Douwes, J., Pearce, N., 2003. Invited commentary: is indoor mold exposure a risk factor for asthma? *Am. J. Epidemiol.* 158, 203–206.
- Douwes, J., van der Sluis, B., Doekes, G., van Leusden, F., Wijnands, L., van Strien, R., Verhoef, A., Brunekreef, B., 1999. Fungal extracellular polysaccharides in house dust as a marker for exposure to fungi: relations with culturable fungi, reported home dampness, and respiratory symptoms. *J. Allergy Clin. Immunol.* 103, 494–500.
- Douwes, J., Zuidhof, A., Doekes, G., van der Zee, S.C., Wouters, I., Boezen, M.H., Brunekreef, B., 2000. (1→3)-beta-D-glucan and endotoxin in house dust and peak variability in children. *Am. J. Respir. Crit. Care Med.* 162, 1348–1354.
- Ebbens, F.A., Fokkens, W.J., 2008. The mold conundrum in chronic rhinosinusitis: where do we stand today? *Curr. Allergy Asthma Rep.* 8, 93–101.
- Ebbelohj, N.E., Meyer, H.W., et al., 2005. Molds in floor dust, building-related symptoms, and lung function among male and female schoolteachers. *Indoor Air* 15 (Suppl. 10), 7–16.
- Eduard, W., 2009. Fungal spores: a critical review of the toxicological and epidemiological evidence as a basis for occupational exposure limit setting. *Crit. Rev. Toxicol.* 39, 799–864.
- Eis, D., 1998/99. Clinical ecology – an unproved approach in the context of environmental medicine. *Zbl. Hyg. Umweltmed.* 202, 291–330.
- Eishi, Y., Suga, M., Ishige, I., Kobayashi, D., Yamada, T., Takemura, T., Takizawa, T., Koike, M., Kudoh, S., Costabel, U., Guzman, J., Rizzato, G., Gambacorta, M., du Bois, R., Nicholson, A.G., Sharma, O.P., Ando, M., 2002. Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. *J. Clin. Microbiol.* 40, 198–204.
- Fernández-Ruiz, M., Silva, J.T., San-Juan, R., de Dios, B., García-Luján, R., López-Medrano, F., Lizasoain, M., Aguado, J.M., 2012. *Aspergillus* tracheobronchitis: report of 8 cases and review of the literature. *Medicine (Baltimore)* 91, 261–273.
- Fischer, G., Thißen, R., Schmitz, C., Dott, W., 2006. Relevance of microfungi and their secondary metabolites (Mycotoxins) for indoor hygiene. *Proceedings of Healthy Buildings vol. 1*, 189–194.
- Fisk, W.J., Lei-Gomez, Q., Mendell, M.J., 2007. Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. *Indoor Air* 17, 284–296.
- Fisk, W.J., Eliseeva, E.A., Mendell, M.J., 2010. Association of residential dampness and mold with respiratory tract infections and bronchitis: a meta-analysis. *Environ. Health* 9, 72.
- Fokkens, W.J., Ebbens, F., van Drunen, C.M., 2009. Fungus: a role in pathophysiology of chronic rhinosinusitis, disease modifier, a treatment target, or no role at all? *Immunol. Allergy Clin. North Am.* 29, 677–688.
- Fokkens, W.J., van Drunen, C., Georgalas, C., Ebbens, F., 2012. Role of fungi in pathogenesis of chronic rhinosinusitis: the hypothesis rejected. *Curr. Opin. Otolaryngol. Head Neck Surg.* 20, 19–23.
- Fontana, C., Gaziano, R., Favaro, M., Casalini, I.A., Pistoia, E.S., Di Francesco, P., 2012. (1→3)-β-D-glucan vs galactomannan antigen in diagnosing invasive fungal infections (IFIs). *Open Microbiol. J.* 6, 70–73.
- Frankel, M., Hansen, E.W., Madsen, A.M., 2014. Effect of relative humidity on the aerosolization and total inflammatory potential of fungal particles from dust-inoculated gypsum boards. *Indoor Air* 24, 16–28.
- Fricker-Hidalgo, H., Coltey, B., Ilerena, C., Renversez, J.C., Grillot, R., Pin, I., Pelloux, H., Pinel, C., 2010. Recombinant allergens combined with biological markers in the diagnosis of allergic bronchopulmonary aspergillosis in cystic fibrosis patients. *Clin. Vaccine Immunol.* 17, 1330–1336.
- Górny, R.L., Reponen, T., Willeke, K., Schmechel, D., Robine, E., Boissier, M., Grinshpun, S.A., 2002. Fungal fragments as indoor air biocontaminants. *Appl. Environ. Microbiol.* 68, 3522–3531.
- Gordon, W.A., Johanning, E., Haddad, L., 1999. Cognitive impairment associated with exposure to toxigenic fungi. In: Johanning, E. (Ed.), *Bioaerosols, Fungi and Mycotoxins: Health Effects, Assessment, Prevention and Control*. Eastern New York Occup. Environ. Health, New York, pp. 94–98.
- Gordon, W.A., Cantor, J.B., Johanning, E., 2004. Cognitive impairment associated with toxigenic fungal exposure: a replication and extension of previous findings. *Appl. Neuropsych.* 11, 65–74.
- Gordon, W.A., Cantor, J.B., Spielman, L., Ashman, T.A., Johanning, E., 2006. Cognitive impairment associated with toxigenic fungal exposure: a response to two critiques. *Appl. Neuropsychol.* 13, 251–257.
- Greenberger, P.A., 2004. Mold-induced hypersensitivity pneumonitis. *Allergy Asthma Proc.* 25, 219–223.
- Griese, M., Haug, M., Hartl, D., Teusch, V., Glöckner-Pagel, J., Brasch, F., National Study Group, E.A.A., 2013. Hypersensitivity pneumonitis: lessons for diagnosis and treatment of a rare entity in children. *Orphanet J. Rare Dis.* 8, 121.
- Hägerhed-Engman, L., Sigsgaard, T., Samuelson, I., Sundell, J., Janson, S., Bornehag, C.G., 2009. Low home ventilation rate in combination with moldy odor from the building structure increase the risk for allergic symptoms in children. *Indoor Air* 19, 184–192.
- Halonen, M., Stern, D.A., Wright, A.L., Taussig, L.M., Martinez, F.D., 1997. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am. J. Respir. Crit. Care Med.* 155, 1356–1361.
- Heffner, D.K., 2007. The cause of sarcoidosis: the centurial enigma solved. *Ann. Diagn. Pathol.* 11, 142–152.
- Heinrich, J., 2011. Influence of indoor factors in dwellings on the development of childhood asthma. *Int. J. Hyg. Environ. Health* 214, 1–25.
- Heinzerling, L.M., Burbach, G.J., Edenharter, G., Bachert, C., Bindsløv-Jensen, C., Bonini, S., Bousquet, J., Bousquet-Rouanet, L., Bousquet, P.J., Bresciani, M., Bruno, A., Burney, P., Canonica, G.W., Darsow, U., Demoly, P., Durham, S., Fokkens, W.J., Gavi, S., Gjomarkaj, M., Gramiccioni, C., Haahela, T., Kowalski, M.L., Magyar, P., Muraközi, G., Orosz, M., Papadopoulos, N.G., Röhnlert, C., Stingl, G., Todo-Bom, A., von Mutius, E., Wiesner, A., Wöhr, S., Zuberbier, T., 2009. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy* 64, 1498–1506.
- Herr, C., Bittighofer, P.M., Bünger, J., Eikmann, T., Fischer, A.B., Grüner, C., Idel, H., zur Nieden, A., Palmgren, U., Seidel, H.J., Velcovsky, H.G., 1999. Effect of microbial aerosols on the human. *Schriftenr. Ver. Wasser Boden Lufthyg.* 104, 403–481.
- Herr, C.E., zur Nieden, A., Jankofsky, M., Stilianakis, N.I., Boedeker, R.H., Eikmann, T.F., 2003. Effects of bioaerosol polluted outdoor air on airways of residents: a cross sectional study. *Occup. Environ. Med.* 60, 336–342.
- Hirvonen, M.R., Huttunen, K., Roponen, M., 2005. Bacterial strains from moldy buildings are highly potent inducers of inflammatory and cytotoxic effects. *Indoor Air* 15, 65–70.
- Hoff, M., Trüeb, R.M., Ballmer-Weber, B.K., Vieths, S., Wuethrich, B., 2003. Immediate-type hypersensitivity reaction to ingestion of mycoprotein (Quorn) in a patient allergic to molds caused by acidic ribosomal protein P2. *J. Allergy Clin. Immunol.* 111, 1106–1110.
- Hooper, D.G., Bolton, V.E., Guilford, F.T., Straus, D.C., 2009. Mycotoxin detection in human samples from patients exposed to environmental molds. *Int. J. Mol. Sci.* 10, 1465–1475.
- Hope, W.W., Walsh, T.J., Denning, D.W., 2005. The invasive and saprophytic syndromes due to *Aspergillus* spp. *Med. Mycol.* 43, S207–S238.
- Hubbard, H.F., Coleman, B.K., Sarwar, G., Corsi, R.L., 2005. Effects of an ozone-generating air purifier on indoor secondary particles in three residential dwellings. *Indoor Air* 15, 432–444.
- Hurraß, J., Szewzyk, R., Baschien, C., Gabrio, T., Fischer, G., Grün, L., Heinzow, B., Hummel, T., Panaskova, J., Herr, C.E.W., Wiesmüller, G.A., 2014. Risk of olfactory effects and impairment of well-being resulting from mould exposure – Results of a workshop of the annual conference of the German Society of Hygiene, Environmental Medicine and Preventive Medicine held in Freiburg, Germany in 2012. In: *Proceedings of Indoor Air 2014, Hong Kong*, pp. 1–8, Paper ID HP0126.
- Hurraß, J., Gabrio, T., Herr, C.E.W., Raulf, M., Wiesmüller, G.A., 2016. Analytical methods for mold exposure assessment from an environmental medical point of view. In: *Proceedings of Indoor Air 2016, Ghent*, pp. 1–8, Paper 253.
- International Agency for Research on Cancer (IARC), 2016. Global Cancer Observatory. <http://gco.iarc.fr/>.
- Institute of Medicine (IOM), Committee on Damp Indoor Spaces and Health, Board of Health Promotion and Disease Prevention, 2004. *Damp Indoor Spaces and Health*. Academy of Science, The National Academies Press, Washington D.C.
- Immonen, J., Meklin, T., Taskinen, T., Nevalainen, A., Korppi, M., 2001. Skin-prick test findings in students from moisture- and mould-damaged schools: a 3-year follow-up study. *Pediatr. Allergy Immunol.* 12, 87–94.
- Innenraumlufthygiene-Kommission des Umweltbundesamtes, 2002. *Leitfaden zur Vorbeugung, Untersuchung, Bewertung und Sanierung von Schimmelpilzwachstum in Innenräumen (Schimmelpilz-Leitfaden)*. Umweltbundesamt, Berlin.
- Innenraumlufthygiene-Kommission des Umweltbundesamtes, 2005. *Leitfaden zur Ursachensuche und Sanierung bei Schimmelpilzwachstum in Innenräumen (Schimmelpilzsanierungs-Leitfaden)*. Umweltbundesamt, Berlin.

- Iossifova, Y.Y., Reponen, T., Ryan, P.H., Levin, L., Bernstein, D.I., Lockey, J.E., Khurana Hershey, G.K., Villareal, M., LeMasters, G., 2009. Mold exposure during infancy as a predictor of potential asthma development. *Ann. Allergy Asthma Immunol.* 102, 131–137.
- Iversen, M., Dahl, R., 1995. Characteristics of mold allergy. *J. Invest. Allergol. Clin. Immunol.* 5, 205–208.
- Iwen, P.C., Davis, J.C., Reed, E.C., Winfield, B.A., Hinrichs, S.H., 1994. Airborne mold spore monitoring in a protective environment during hospital construction, and correlation with an outbreak of invasive aspergillosis. *Infect. Control Hosp. Epidemiol.* 15, 303–306.
- Jaakkola, M.S., Quansah, R., Hugg, T.T., Heikkinen, S.A., Jaakkola, J.J., 2013. Association of indoor dampness and molds with rhinitis risk: a systematic review and metaanalysis. *J. Allergy Clin. Immunol.* 132, 1099–1110.
- Johannessen, L.N., Nilsen, A.M., Løvik, M., 2005. The mycotoxins citrinin and gliotoxin differentially affect production of the pro-inflammatory cytokines tumour necrosis factor- α and interleukin-6, and the anti-inflammatory cytokine interleukin-10. *Clin. Exp. Allergy* 35, 782–789.
- Karvala, K., Toskala, E., Luukkainen, R., Lappalainen, S., Uitti, J., Nordman, H., 2010. New-onset adult asthma in relation to damp and moldy workplaces. *Int. Arch. Occup. Environ. Health* 83, 855–865.
- Karvonen, A.M., Hyvärinen, A., Korppi, M., Haverinen-Shaughnessy, U., Renz, H., Pfefferle, P.I., Remes, S., Genuiteit, J., Pekkanen, J., 2015. Moisture damage and asthma: a birth cohort study. *Pediatrics* 135, e598–e606.
- Keir, J., Pedelty, L., Swift, A.C., 2011. Biofilms in chronic rhinosinusitis: systematic review and suggestions for future research. *J. Laryngol. Otol.* 125, 331–337.
- Kern, D.G., Neill, M.A., Wrenn, D.S., Varone, J.C., 1993. Investigation of a unique time-space cluster of sarcoidosis in firefighters. *Am. Rev. Respir. Dis.* 148, 974–980.
- Kespohl, S., Raulf, M., 2014. Mould allergens: how far has molecular allergy diagnosis come? Part 13 of the series Molecular Allergology. *Allergo J. Int.* 23, 120–125.
- Kespohl, S., Maryska, S., Zahradnik, E., Sander, I., Brüning, T., Raulf, M., 2013. Biochemical and immunological analysis of mould skin prick test solution: current status of standardization. *Clin. Exp. Allergy* 43, 1286–1296.
- Kespohl, S., Maryska, S., Bünger, J., Hagemeyer, O., Jakob, T., Joest, M., Knecht, R., Koschel, D., Kotschy-Lang, N., Merget, R., Mülleneisen, N.K., Rabe, U., Röseler, S., Sander, I., Stollwerck, D., Straube, H., Ulmer, H.M., van Kampen, V., Walusiak-Skorupa, J., Wiszniewska, M., Wurpts, G., Brüning, T., Raulf, M., 2016. How to diagnose mould allergy? Comparison of skin prick tests with specific IgE results. *Clin. Exp. Allergy* 46, 981–991.
- Khalili, B., Montanaro, M.T., Bardana Jr., E.J., 2005. Inhalational mold toxicity: fact or fiction? A clinical review of 50 cases. *Ann. Allergy Asthma Immunol.* 95, 239–246.
- Kim, H.J., Lee, E., Lee, S.H., Kang, M.J., Hong, S.J., 2015. Mold elicits atopic dermatitis by reactive oxygen species: epidemiology and mechanism studies. *Clin. Immunol.* 161, 384–390.
- Kleine-Tebbe, J., 2009. Supposed food allergy: unreasonable allergy test. *MMW Fortschr. Med.* 151, 6–7.
- Koch, A., Heilemann, K.J., Bischof, W., Heinrich, J., Wichmann, H.E., 2000. Indoor viable mold spores—a comparison between two cities, Erfurt (eastern Germany) and Hamburg (western Germany). *Allergy* 55, 176–180.
- Koehler, P., Hamprecht, A., Bader, O., Bekeredjian-Ding, I., Buchheidt, D., Doelken, G., et al., 2016. Epidemiology of Invasive Aspergillosis and azole resistance in patients with acute leukaemia—the SEPIA Study. *Int. J. Antimicrob. Agents*, in press.
- Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI), 2010. Anforderungen an die Hygiene bei der medizinischen Versorgung von immunsupprimierten Patienten. *Bundesgesundheitsbl.* 53, 357–388.
- Kommission Methoden und Qualitätssicherung in der Umweltmedizin des Robert Koch-Instituts (RKI), 2007. Schimmelpilzbelastung in Innenräumen – Befunderhebung, gesundheitliche Bewertung und Maßnahmen. *Bundesgesundheitsbl.* 50, 1308–1323.
- Krieger, J., Jacobs, D.E., Ashley, P.J., Baeder, A., Chew, G.L., Dearborn, D., Hynes, H.P., Miller, J.D., Morley, R., Rabito, F., Zeldin, D.C., 2010. Housing interventions and control of asthma-related indoor biologic agents: a review of the evidence. *J. Public Health Manag. Pract.* 16, S11–20.
- Kucera, G.P., Rybicki, B.A., Kirkey, K.L., Coon, S.W., Major, M.L., Maliarik, M.J., Iannuzzi, M.C., 2003. Occupational risk factors for sarcoidosis in African-American siblings. *Chest* 123, 1527–1535.
- Kuhn, D.M., Ghannoum, M.A., 2003. Review Indoor mold, toxigenic fungi, and *Stachybotrys chartarum*: infectious disease perspective. *Clin. Microbiol. Rev.* 16, 144–172.
- Kuna, P., Kaczmarek, J., Kupczyk, M.J., 2011. Efficacy and safety of immunotherapy for allergies to *Alternaria alternata* in children. *Allergy Clin. Immunol.* 127, 502–508.
- Kuyucu, S., Saraçlar, Y., Tuncer, A., Geyik, P.O., Adaloğlu, G., Akpınarlı, A., Sekerel, B.E., Sümbüloğlu, V., 2006. Epidemiologic characteristics of rhinitis in Turkish children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2. *Pediatr. Allergy Immunol.* 17, 269–277.
- Laney, A.S., Cragin, L.A., Blevins, L.Z., Sumner, A.D., Cox-Ganser, J.M., Kreiss, K., Moffatt, S.G., Lohff, C.J., 2009. Sarcoidosis, asthma, and asthma-like symptoms among occupants of a historically water-damaged office building. *Indoor Air* 19, 83–90.
- Larenas-Linnemann, D., Baxi, S., Phipatanakul, W., Portnoy, J.M., 2016. Environmental Allergens Workgroup Clinical evaluation and management of patients with suspected fungus sensitivity. *J. Allergy Clin. Immunol. Pract.* 4, 405–414.
- Latgé, J.P., 1999. *Aspergillus fumigatus* and aspergillosis. *Clin. Microbiol. Rev.* 12, 310–350.
- Lees-Haley, P.R., 2003. Toxic mold and mycotoxins in neurotoxicity cases: stachybotrys, fusarium, trichoderma, aspergillus, penicillium, cladosporeum, alternaria. *Trichothecenes. Psychol. Rep.* 93, 561–584.
- Licorish, K., Novey, H.S., Kozak, P., Fairshir, R.D., Wilson, A.F., 1985. Role of *Alternaria* and *Penicillium* spores in the pathogenesis of asthma. *J. Allergy Clin. Immunol.* 76, 819–825.
- Loo, V.G., Bertrand, C., Dixon, C., Vityé, D., DeSalis, B., McLean, A.P., Brox, A., Robson, H.G., 1996. Control of construction-associated nosocomial aspergillosis in an antiquated hematology unit. *Infect. Control Hosp. Epidemiol.* 17, 360–364.
- Lorenz, W., Buhrmann, C., Mobasher, A., Lueders, C., Shakibaei, M., 2013. Bacterial lipopolysaccharides form procollagenendotoxin complexes that trigger cartilage inflammation and degeneration: implications for the development of rheumatoid arthritis. *Arthritis Res. Ther.* 15, R111.
- Luosujärvi, R.A., Husman, T.M., Seuri, M., Pietikäinen, M.A., Pollari, P., Pelkonen, J., Hujakka, H.T., Kaipainen-Seppänen, O.A., Aho, K., 2003. Joint symptoms and diseases associated with moisture damage in a health center. *Clin. Rheumatol.* 22, 381–385.
- Müller, A., Lehmann, I., Seiffart, A., Diez, U., Wetzig, H., Borte, M., Herbarth, O., 2002. Increased incidence of allergic sensitization and respiratory diseases due to mould exposure: results of the Leipzig Allergy Risk children Study (LARS). *Int. J. Hyg. Environ. Health* 204, 363–365.
- Maibach, H.I., 1995. Contact urticaria syndrome from mold on salami casing. *Contact Dermat.* 32, 120–121.
- Mari, A., Schneider, P., Wally, V., Breitenbach, M., Simon-Nobbe, B., 2003. Sensitization to fungi: epidemiology, comparative skin tests, and IgE reactivity of fungal extracts. *Clin. Exp. Allergy* 33, 1429–1438.
- Marshall, T.G., Marshall, F.E., 2004. Sarcoidosis succumbs to antibiotics – implications for autoimmune disease. *Autoimmun. Rev.* 3, 295–300.
- Mayo Clinic, 2015. Test ID: ASPAG – Aspergillus (Galactomannan) Antigen, Serum. Mayo Medical Laboratories <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/84356>.
- Mazur, L.J., Kim, J., 2006. Spectrum of noninfectious health effects from molds. *Pediatrics* 118, e1909–1926.
- McCaffrey, R.J., Yantz, C.L., 2005. Cognitive impairment associated with toxigenic fungal exposure: a critique and critical analysis. *Appl. Neuropsychol.* 12, 134–137.
- McDonald, E., Cook, D., Newman, T., Griffith, L., Cox, G., Guyatt, G., 2002. Effect of air filtration systems on asthma: a systematic review of randomized trials. *Chest* 122, 1535–1542.
- McFarland, R.B., Goodman, S.B., 1963. Sporotrichosis and sarcoidosis Report of a case with comment upon possible relationships between sarcoidosis and fungus infections. *Arch. Intern. Med.* 112, 760–765.
- Mendell, M.J., Cozen, M., Lei-Gomez, Q., Brightman, H.S., Erdmann, C.A., Girman, J.R., Womble, S.E., 2006. Indicators of moisture and ventilation system contamination in US office buildings as risk factors for respiratory and mucous membrane symptoms: analyses of the EPA BASE data. *J. Occup. Environ. Hyg.* 3, 225–233.
- Mendell, M.J., Mirer, A.G., Cheung, K., Tong, M., Douwes, J., 2011. Respiratory and allergic health effects of dampness mold, and dampness-related agents: a review of the epidemiologic evidence. *Environ. Health Perspect.* 119, 748–756.
- Meng, J., Barnes, C.S., Rosenwasser, L.J., 2012. Identity of the fungal species present in the homes of asthmatic children. *Clin. Exp. Allergy* 42, 1448–1458.
- Morell, F., Roger, A., Reyes, L., Cruz, M.J., Murio, C., Muñoz, X., 2008. Bird fancier's lung: a series of 86 patients. *Medicine (Baltimore)* 87, 110–130.
- Morisset, M., Parisot, L., Kanny, G., Moneret-Vautrin, D.A., 2003. Food allergy to moulds: two cases observed after dry fermented sausage ingestion. *Allergy* 58, 1203–1204.
- Mousset, S., Buchheidt, D., Heinz, W., Ruhnke, M., Cornely, O.A., Egerer, G., Krüger, W., Link, H., Neumann, S., Ostermann, H., Panse, J., Penack, O., Rieger, C., Schmidt-Hieber, M., Silling, G., Südhoff, T., Ullmann, A.J., Wolf, H.H., Maschmeyer, G., Böhme, A., 2014. Treatment of invasive fungal infections in cancer patients—updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann. Hematol.* 93, 13–32.
- Myllkangas-Luosujärvi, R., Seuri, M., Husman, T., Korhonen, R., Pakkala, K., Aho, K., 2002. A cluster of inflammatory rheumatic diseases in a moisture-damaged office. *Clin. Exp. Rheumatol.* 20, 833–836.
- Nagano, Y., Millar, B.C., Johnson, E., Goldsmith, C.E., Elborn, J.S., Rendall, J., Moore, J.E., 2007. Fungal infections in patients with cystic fibrosis. *Rev. Med. Microbiol.* 18, 11–16.
- Nevalainen, A., Seuri, M., 2005. Of microbes and men. *Indoor Air* 15, S58–64.
- Nevalainen, A., Tåbe, M., Hyvärinen, A., 2015. Indoor fungi: companions and contaminants. *Indoor Air* 25, 125–156.
- O'Driscoll, B.R., Powell, G., Chew, F., Niven, R.M., Miles, J.F., Vyas, A., Denning, D.W., 2009. Comparison of skin prick tests with specific serum immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. *Clin. Exp. Allergy* 39, 1677–1683.
- Palaty, C., Shum, M., 2012. Health effects from mould exposure or dampness in indoor environments. In: Evidence Review. National Collaborating Centre for Environmental Health, Vancouver http://www.nccch.ca/sites/default/files/Mould_and_Health_Effects_Jul_2012.pdf.

- Park, J.H., Kreiss, K., Cox-Ganser, J.M., 2012. Rhinosinusitis and mold as risk factors for asthma symptoms in occupants of a water-damaged building. *Indoor Air* 396–404.
- Paul-Ehrlich-Institut, 2016. Authorised Allergens. http://www.pei.de/EN/home/node.html;jsessionid=46BFEA922EF678521AB8581A1B997441.1_cid329.
- Peitzsch, M., Suliyok, M., Täubel, M., Vishwanath, V., Krop, E., Borràs-Santos, A., Hyvärinen, A., Nevalainen, A., Krksa, R., Larsson, L., 2012. Microbial secondary metabolites in school buildings inspected for moisture damage in Finland, The Netherlands and Spain. *J. Environ. Monit.* 14, 2044–2053.
- Pekkanen, J., Hyvärinen, A., Haverinen-Shaughnessy, U., Korppi, M., Putus, T., Nevalainen, A., 2007. Moisture damage and childhood asthma: a population-based incident case-control study. *Eur. Respir. J.* 29, 509–515.
- Pestka, J.J., Yike, I., Dearborn, D.G., Ward, M.D., Harkema, J.R., 2008. *Stachybotrys chartarum*, trichothecene mycotoxins, and damp building-related illness: new insights into a public health enigma. *Toxicol. Sci.* 104, 4–26.
- Pfaar, O., Bachert, C., Bufe, A., Buhl, R., Ebner, C., Eng, P., Friedrichs, F., Fuchs, T., Hamelmann, E., Hartwig-Bade, D., Hering, T., Huttegger, L., Jung, K., Klimek, L., Kopp, M.V., Merk, H., Rabe, U., Saloga, J., Schmid-Grendelmeier, P., Schuster, A., Schwerk, N., Sitter, H., Umpfenbach, U., Wedi, B., Wöhrl, S., Worm, M., Kleine-Tebbe, J., Kaul, S., Schwalbenberg, A., 2014. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergy and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGhNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVJK), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J. Int.* 23, 282–319.
- Portnoy, J.M., Kwak, K., Dowling, P., VanOsdol, T., Barnes, C., 2005. Health effects of indoor fungi. *Ann. Allergy Asthma Immunol.* 94, 313–319.
- Prezant, D.J., Dhala, A., Goldstein, A., Janus, D., Ortiz, F., Aldrich, T.K., Kelly, K.J., 1999. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. *Chest* 116, 1183–1193.
- Quirce, S., Vandenplas, O., Campo, P., Cruz, M.J., de Blay, F., Koschel, D., Moscato, G., Pala, G., Raulf, M., Sastre, J., Siracusa, A., Tarlo, S.M., Walusiak-Skorupa, J., Cormier, Y., 2016. Occupational hypersensitivity pneumonitis: an EAACI position paper. *Allergy* 71, 765–779.
- Raad, I., Tarrand, J., Hanna, H., Albitar, M., Janssen, E., Boktour, M., Bodey, G., Mardani, M., Hachem, R., Kontoyiannis, D., Whimbey, E., Rolston, K., 2002. Epidemiology, molecular mycology, and environmental sources of *Fusarium* infection in patients with cancer. *Infect. Control Hosp. Epidemiol.* 23, 532–537.
- Radon, K., Danuser, B., Iversen, M., Jörres, R., Monso, E., Opravil, U., Weber, C., Donham, K.J., Nowak, D., 2001. Respiratory symptoms in European animal farmers. *Eur. Respir. J.* 17, 747–754.
- Ramani, R., Srinivas, C.R., Ramani, A., Kumari, T.G., Shivananda, P.G., 1993. Molds in onychomycosis. *Int. J. Dermatol.* 32, 877–878.
- Rao, D., Phipatanakul, W., 2011. Impact of environmental controls on childhood asthma. *Curr. Allergy Asthma Rep.* 11, 414–420.
- Rao, C.Y., Cox-Ganser, J.M., Chew, G.L., Doekes, G., White, S., 2005. Use of surrogate markers of biological agents in air and settled dust samples to evaluate a water-damaged hospital. *Indoor Air* 15, 589–597.
- Reijula, K., Leino, M., Mussalo-Rauhamaa, H., Nikulin, M., Alenius, H., Mikkola, J., Elg, P., Kari, O., Mäkinen-Kiljunen, S., Haahtela, T., 2003. IgE-mediated allergy to fungal allergens in Finland with special reference to *Alternaria alternata* and *Cladosporium herbarum*. *Ann. Allergy Asthma Immunol.* 91, 280–287.
- Reijula, K., 1998. Exposure to microorganisms: diseases and diagnosis. *Indoor Air* 8, 340–44.
- Reponen, T., Lockey, J., Bernstein, D.I., Vesper, S.J., Levin, L., Khurana Hershey, G.K., Zheng, S., Ryan, P., Grinshpun, S.A., Villareal, M., Lemasters, G., 2012. Infant origins of childhood asthma associated with specific molds. *J. Allergy Clin. Immunol.* 130, 639–644.
- Rizik, S.N., 1965. Acute anterior uveitis in a patient with sarcoidosis and high *Toxoplasma* dye test titre. *Br. J. Ophthalmol.* 49, 34–36.
- Rocchi, S., Reboux, G., Larosa, F., Scherer, E., Daguindeau, E., Berceanu, A., Deconinck, E., Millon, L., Bellanger, A.P., 2014. Evaluation of invasive aspergillosis risk of immunocompromised patients alternatively hospitalized in hematology intensive care unit and at home. *Indoor Air* 24, 652–661.
- Rocchi, S., Richaud-Thiriez, B., Barrera, C., Grenouillet, F., Dalphin, J.C., Millon, L., Reboux, G., 2015. Evaluation of mold exposure in cystic fibrosis patients' dwellings and allergic bronchopulmonary risk. *J. Cyst. Fibros.* 14, 242–247.
- Rosenberg, M., Patterson, R., Mintzer, R., Cooper, B.J., Roberts, M., Harris, K.E., 1977. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann. Intern. Med.* 86, 405–414.
- Ruhnke, M., Böhme, A., Buchheidt, D., Cornely, O.A., Donhuijsen, K., Einsele, H., Enzensberger, R., Hebart, H., Heussel, C.P., Horger, M., Hof, H., Karthaus, M., Krüger, W., Maschmeyer, G., Penack, O., Ritter, J., Schwartz, S., 2012. Diagnosis of invasive fungal infections in hematology and oncology—guidelines from the Infectious Diseases Working Party in Haematology and Oncology of the German Society for Haematology and Oncology (AGIHO). *Ann. Oncol.* 23, 823–833.
- Rylander, R., 1997. Airborne (1–3)β-D-glucan and airway disease in a day-care center before and after renovation. *Arch. Environ. Health* 52, 281–285.
- Rylander, R., 1998. Microbial cell wall constituents in indoor air and their relation to disease. *Indoor Air* 4, 559–68.
- Sauni, R., Uitti, J., Jauhiainen, M., Kreiss, K., Sigsgaard, T., Verbeek, J.H., 2011. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. *Cochrane Database Syst. Rev.* 2, CD007897.
- Sauni, R., Uitti, J., Jauhiainen, M., Kreiss, K., Sigsgaard, T., Verbeek, J.H., 2013. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. *Evid. Based. Child Health* 8, 944–1000.
- Sauni, R., Verbeek, J.H., Uitti, J., Jauhiainen, M., Kreiss, K., Sigsgaard, T., 2015. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. *Cochrane Database Syst. Rev.* 2, CD007897.
- Schleibinger, H., Laußmann, D., Eis, D., Samwer, H., Rüden, H., 2004. Sind MVOC geeignete Indikatoren für einen verdeckten Schimmelpilzbefall? *Umweltmed. Forsch. Prax.* 9, 151–161.
- Schultze-Werninghaus, G., Lévy, J., Bergmann, E.M., Kappos, A.D., Meier-Sydow, J., 1987. Clinical significance of airborne *Alternaria tenuis*-spores: seasonal symptoms, positive skin and bronchial challenge tests with *Alternaria* in subjects with asthma and rhinitis. *Experientia Suppl.* 51, 153–156.
- Schulz, T., Senkpiel, K., Ohgke, H., 2004. Comparison of the toxicity of reference mycotoxins and spore extracts of common indoor moulds. *Int. J. Hyg. Environ. Health* 207, 267–277.
- Seifert, S.A., Von Essen, S., Jacobitz, K., Crouch, R., Lintner, C.P., 2003. Organic dust toxic syndrome: a review. *J. Toxicol. Clin. Toxicol.* 41, 185–193.
- Seltzer, J.M., Fedoruk, M.J., 2007. Health effects of mold in children. *Pediatr. Clin. North Am.* 54, 309–333.
- Shah, A., Panjabi, C., 2016. Allergic bronchopulmonary aspergillosis: a perplexing clinical entity. *Allergy Asthma Immunol. Res.* 8, 282–297.
- Shelly, W.B., Florence, R., 1961. Chronic urticaria due to mold hypersensitivity. *Arch. Dermatol.* 83, 549–558.
- Shields, L.H., 1959. Disseminated cryptococcosis producing a sarcoid type reaction: the report of a case treated with amphotericin B. *Arch. Intern. Med.* 104, 763–770.
- Shusterman, D., Murphy, M.A., Balmes, J., 2003. Differences in nasal irritant sensitivity by age, gender, and allergic rhinitis status. *Int. Arch. Occup. Environ. Health* 76, 577–583.
- Siles, R.I., Hsieh, F.H., 2011. Allergy blood testing: a practical guide for clinicians. *Cleve. Clin. J. Med.* 78, 585–592.
- Singer, R., 2011. Chronic neurotoxicity from chronic mold exposure. In: 50th Annual Meeting of the Society of Toxicology, Washington <http://neurotox.blogspot.de/2011/03/chronic-neurotoxicity-from-chronic-mold.html>.
- Singh, M., Jaiswal, N., 2013. Dehumidifiers for chronic asthma. *Cochrane Database Syst. Rev.* 6, CD003563.
- Sonnenberg, P., Murray, J., Glynn, J.R., Shearer, S., Kambashi, B., Godfrey-Faussett, P., 2001. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 358, 1687–1693.
- Stark, P.C., Burge, H.A., Ryan, L.M., Milton, D.K., Gold, D.R., 2003. Fungal levels in the home and lower respiratory tract illnesses in the first year of life. *Am. J. Respir. Crit. Care Med.* 168, 232–237.
- Stevens, D.A., Kan, V.L., Judson, M.A., Morrison, V.A., Dummer, S., Denning, D.W., Bennett, J.E., Walsh, T.J., Patterson, T.F., Pankey, G.A., 2000. Practice guidelines for diseases caused by *Aspergillus*. *Infectious Diseases Society of America. Clin. Infect. Dis.* 30, 696–709.
- Stoev, S.D., 2015. Foodborne mycotoxicoses, risk assessment and underestimated hazard of masked mycotoxins and joint mycotoxin effects or interaction. *Environ. Toxicol. Pharmacol.* 39, 794–809.
- Storey, E., Dangman, K.H., Schenck, P., DeBernardo, R.L., Yang, C.S., Bracker, A., Hodgson, M.J., 2004. Guidance for Clinicians on the Recognition and Management of Health Effects Related to Mold Exposure and Moisture Indoors. University of Connecticut Health Center, Division of Occupational and Environmental Medicine, Center for Indoor Environments and Health <http://oehc.uchc.edu/clinser/mold%20guide.pdf>.
- Straus, D.C., 2009. Molds, mycotoxins, and sick building syndrome. *Toxicol. Ind. Health* 25, 617–635.
- Sucker, K., Both, R., Winneke, G., 2009. Review of adverse health effects of odours in field studies. *Water Sci. Technol.* 59, 1281–1289.
- Täubel, M., Suliyok, M., Vishwanath, V., Bloom, E., Turunen, M., Järvi, K., Kauhanen, E., Krksa, R., Hyvärinen, A., Larsson, L., Nevalainen, A., 2011. Co-occurrence of toxic bacterial and fungal secondary metabolites in moisture-damaged indoor environments. *Indoor Air* 21, 368–375.
- Technische Regel für Biologische Arbeitsstoffe 460 (TRBA 460), 2016. Einstufung von Pilzen in Risikogruppen. *BaRbL* 10.
- Tacke, D., Buchheidt, D., Karthaus, M., Krause, S.W., Maschmeyer, G., Neumann, S., Ostermann, H., Penack, O., Rieger, C., Ruhnke, M., Sandherr, M., Schweer, K.E., Ullmann, A.J., Cornely, O.A., 2014. Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. *Ann. Hematol.* 93, 1449–1456.
- Tarlo, S.M., Fradkin, A., Tobin, R.S., 1988. Skin testing with extracts of fungal species derived from the homes of allergy clinic patients in Toronto, Canada. *Clin. Allergy* 18, 45–52.

- Taskinen, T., Meklin, T., Nousiainen, M., Husman, T., Nevalainen, A., Korppi, M., 1997. Moisture and mould problems in schools and respiratory manifestations in schoolchildren: clinical and skin test findings. *Acta Paediatr.* 86, 1181–1187.
- Taskinen, T., Hyvärinen, A., Meklin, T., Husman, T., Nevalainen, A., Korppi, M., 1999. Asthma and respiratory infections in school children with special reference to moisture and mold problems in the school. *Acta Paediatr.* 88, 1373–1379.
- Tercelj, M., Salobir, B., Rylander, R., 2008. Microbial antigen treatment in sarcoidosis – a new paradigm? *Med. Hypotheses* 70, 831–834.
- Tercelj, M., Salobir, B., et al., 2011. Antifungal medication is efficient in the treatment of sarcoidosis. *Ther. Adv. Respir. Dis.* 5, 157–162.
- Terr, A.L., 2009. Sick Building Syndrome: is mould the cause? *Med. Mycol.* 47, S217–S222.
- Thio, C.L., Smith, D., Merz, W.G., Streifel, A.J., Bova, G., Gay, L., Miller, C.B., Perl, T.M., 2000. Refinements of environmental assessment during an outbreak investigation of invasive aspergillosis in a leukemia and bone marrow transplant unit. *Infect. Control Hosp. Epidemiol.* 21, 18–23.
- Tischer, C.G., Heinrich, J., 2013. Exposure assessment of residential mould, fungi and microbial components in relation to children's health: achievements and challenges. *Int. J. Hyg. Environ. Health* 216, 109–114.
- Tischer, C., Chen, C.M., Heinrich, J., 2011. Association between domestic mould and mould components: and asthma and allergy in children: a systematic review. *Eur. Respir. J.* 38, 812–824.
- Torres-Rodríguez, J.M., Madrenys-Brunet, N., Siddat, M., López-Jodra, O., Jimenez, T., 1998. *Aspergillus versicolor* cause of onychomycosis: report of 12 cases and susceptibility testing of antifungal drugs. *J. Eur. Acad. Dermatol. Venerol.* 11, 25–31.
- Torres-Rodríguez, J.M., Pulido-Marrero, Z., Vera-García, Y., 2012. Respiratory allergy to fungi in Barcelona, Spain: clinical aspects, diagnosis and specific treatment in a general allergy unit. *Allergol. Immunopathol. (Madr.)* 40, 295–300.
- Toskala, E., Kennedy, D.W., 2015. Asthma risk factors. *Int. Forum Allergy Rhinol.* 5, S11–16.
- Trout, D., 1998. Mycotoxins and building-related illness. *J. Occup. Environ. Med.* 40, 761–764.
- van Emon, J.M., Reed, A.W., Yike, I., Vesper, S.J., 2003. ELISA measurement of stachylysin in serum to quantify human exposures to the indoor mold *Stachybotrys chartarum*. *J. Occup. Environ. Med.* 45, 582–591.
- van Kampen, V., Rabstein, S., Sander, I., Merget, R., Brüning, T., Broding, H.C., Keller, C., Müskens, H., Overlack, A., Schultze-Werninghaus, G., Walusiak, J., Raulf-Heimsoth, M., 2008. Prediction of challenge test results by flour-specific IgE and skin prick test in symptomatic bakers. *Allergy* 63, 897–902.
- Verdaguer, V., Walsh, T.J., Hope, W., Cortez, K.J., 2007. Galactomannan antigen detection in the diagnosis of invasive aspergillosis. *Expert. Rev. Mol. Diagn.* 7, 21–32.
- Vesper, S., Wymer, L., 2016. The relationship between environmental relative moldiness index values and asthma. *Int. J. Hyg. Environ. Health* 219, 233–238.
- World Health Organization (WHO), 2009a. Damp and mould. In: *Health Risks, Prevention and Remedial Actions*. WHO, Copenhagen.
- World Health Organization (WHO), 2009b. Guidelines for Indoor Air Quality: Dampness and Mould. WHO, Copenhagen.
- World Health Organization International Union of Immunological Societies (WHO/IUIS), 2016. Allergen Nomenclature. WHO/IUIS Allergen Nomenclature Sub-Committee <http://www.allergen.org/>.
- Waring, M.S., Siegel, J.A., 2011. The effect of an ion generator on indoor air quality in a residential room. *Indoor Air* 21, 267–276.
- Warrell, D.A., Cox, T.M., Firth, J.D. (Eds.), 2016, fifth ed. Oxford University Press.
- Wiesmüller, G.A., Ebel, H., Hornberg, C., Kwan, O., Friel, J., 2003. Are syndromes in environmental medicine variants of somatoform disorders? *Med. Hypotheses* 61, 419–430.
- Wiesmüller, G.A., Szewzyk, R., Gabrio, T., Fischer, G., Lichtnecker, H., Merget, R., Ochmann, U., Nowak, D., Schultze-Werninghaus, G., Steiß, J.-O., Herr, C.E.W., 2012. Allergic risk of mold exposure – results of a GHUP workshop in Germany in 2010. In: *Proceedings of Healthy Buildings 2012, Brisbane*, pp. 1–6, Paper ID 5H.7.
- Wiesmüller, G.A., Szewzyk, R., Gabrio, T., Engelhart, S., Heinz, W.J., Cornely, O.A., Seidl, H.P., Fischer, G., Herr, C.E.W., 2011. Infection risk of mold exposure – results of a workshop of the annual conference of the German Society of Hygiene, Environmental Medicine and Preventive Medicine held in Stuttgart, Germany in 2009. *Proceedings of Indoor Air Austin*, 1–6, Paper ID 666.
- Wiesmüller, G.A., Szewzyk, R., Baschien, C., Gabrio, T., Fischer, G., Heinzow, B., Raulf-Heimsoth, M., Herr, C.E.W., 2014. Risk of toxic reactions to mould exposure – results of a workshop of the annual conference of the German Society of Hygiene Environmental Medicine and Preventive Medicine held in Munich, Germany, in 2011. In: *Proceedings of Indoor Air 2014, Hong Kong*, pp. 1–8, Paper ID HP044.
- Wiesmüller, G.A., Szewzyk, R., Baschien, C., Gabrio, T., Fischer, G., Cornely, O.A., Engelhart, S., Grün, L., Heinz, W.J., Heinzow, B., Hummel, T., Hurraß, J., Lichtnecker, H., Merget, R., Nowak, D., Ochmann, U., Panašková, J., Raulf-Heimsoth, M., Schultze-Werninghaus, G., Seidl, H.P., Steiß, J.-O., Herr, C.E.W., 2013. Frequently asked questions about possible health effects of indoor mold exposure – answers from a panel of experts at four workshops of the Society of Hygiene, Environmental Medicine and Preventive Medicine (GHUP). *Umweltmed. Hygiene Arbeitsmed.* 18, 249–274.
- Wild, C.P., Montesano, R., 2009. A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. *Cancer Lett.* 286, 22–28.
- Wood, R.A., 2002. Air filtration devices in the control of indoor allergens. *Curr. Allergy Asthma Rep.* 2, 397–400.
- Zöllner, I.K., Weiland, S.K., Piechotowski, I., Gabrio, T., von Mutius, E., Link, B., Pfaff, G., Kouros, B., Wuthe, J., 2005. No increase in the prevalence of asthma, allergies, and atopic sensitization among children in Germany: 1992–2001. *Thorax* 60, 545–548.
- Zahradnik, E., Kespohl, S., Sander, I., Schies, U., Khosravie-Hohn, J., Lorenz, W., Engelhart, S., Kolk, A., Schneider, G., Brüning, T., Raulf-Heimsoth, M., 2013. A new immunoassay to quantify fungal antigens from the indoor mould *Aspergillus versicolor*. *Environ. Sci. Process. Impacts* 15, 1162–1171.
- Zureik, M., Neukirch, C., Leynaert, B., Liard, R., Bousquet, J., Neukirch, F., European Community Respiratory Health Survey, 2002. Sensitization to airborne moulds and severity of asthma: cross-sectional study from European Community Respiratory Health Survey. *BMJ* 325, 411–414.