

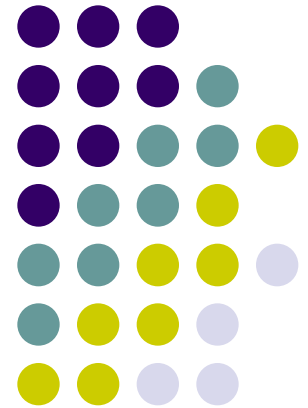
Indoor Bioaerosols

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Additional Qualification in Environmental Medicine

Travel Medical Health Advice



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AWMF is a network of Scientific Medical Societies in Germany.

AWMF Mold Guideline

"Medical clinical diagnostics in indoor mold exposition" - AWMF Registry No. 161/001 - Final Version, *German only*

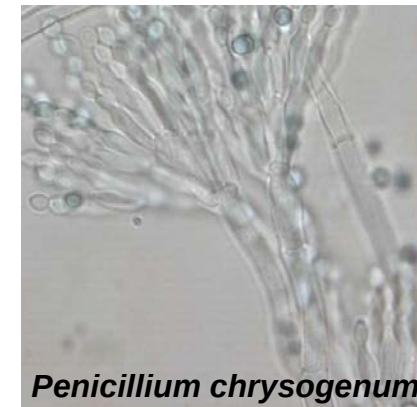
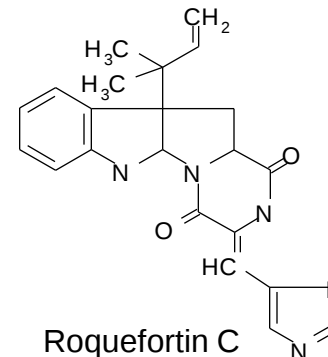
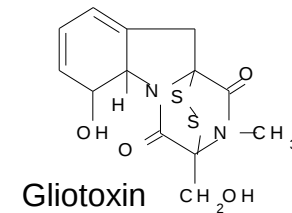
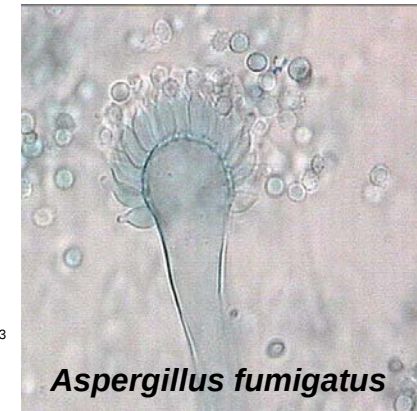
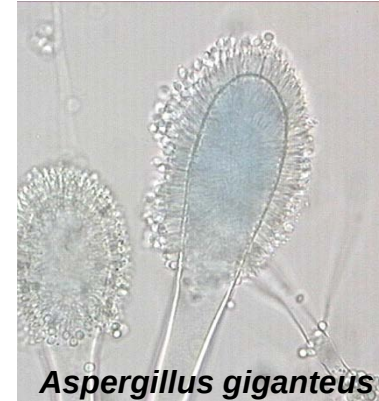
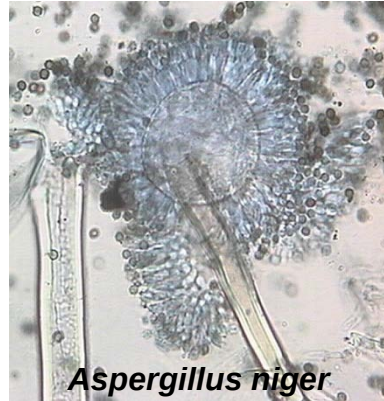
Gerhard A. Wiesmüller^{1,2,a,b*}, Birger Heinzow^{3,a,b}, Ute Aurbach^{4,a},
Karl-Christian Bergmann^{5,a,b}, Albrecht Bufe^{6,b}, Walter Buzina^{7,a,b}, Oliver A. Cornely^{8,a,b},
Steffen Engelhart^{9,a,b}, Guido Fischer^{10,a}, Thomas Gabrio^{11,a}, Werner Heinz^{12,a},
Caroline E.W. Herr^{13,14,a,b}, Jörg Kleine-Tebbe^{15,a,b}, Ludger Klimek^{16,a,b},
Martin Köberle^{17,a,b}, Herbert Lichtnecker^{18,a}, Thomas Lob-Corzilius^{19,a,b}, Rolf Merget^{20,a,b},
Norbert Mülleneisen^{21,a,b}, Dennis Nowak^{22,a,b}, Uta Rabe^{23,a,b}, Monika Raulf^{20,a,b},
Hans Peter Seidl^{24,a,b}, Jens-Oliver Steiß^{25,26,a,b}, Regine Szewczyk^{27,a,b},
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<http://www.awmf.org/leitlinien/detail/II/161-001.html>

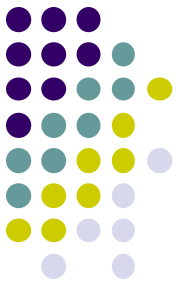
Health risks due to mold exposure indoors



- Infections
- Sensitization and allergies
- Toxic reactions
- Olfactory effects
- Impairment of well-being

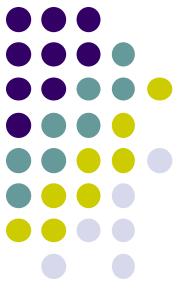


General diagnostic procedure

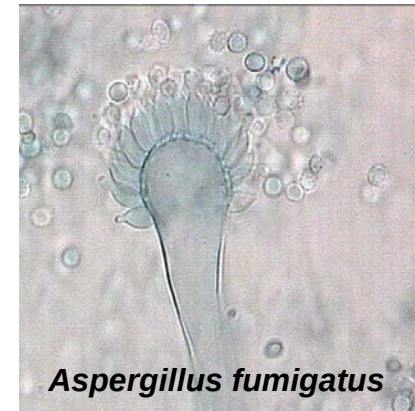
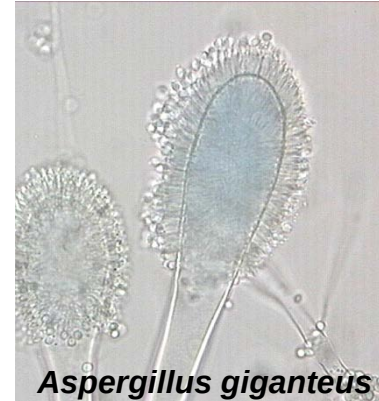


- **Medical history (anamnesis)**
- **Physical examination**
- **Objective information about:**
 - up-to-date knowledge of possible health effects of indoor mold exposure
 - Examination possibilities and limits of such health effects
 - Treatment options and limits of such health effects

Health risks due to mold exposure indoors

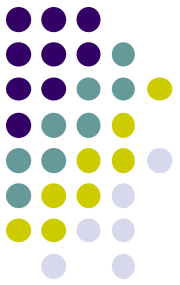


- **Infections**
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- Toxic reactions
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- Impairment of well-being



Infections

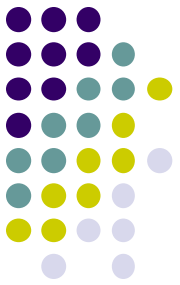
due to mold exposure indoors



- Molds classified in the risk groups 2 and 3 according to the German Technical Rules for Biological Working Substances (TRBA) 460
- Especially molds with **optimum growth temperature of 37°C**, such as most **aspergilli**, many **mucorales**, such as e. g., *Rhizopus oryzae*, *Rhizomucor sp.*, *Mycocladius corymbiferus*
- **Infection risk increases** in the following order:
 - No potential pathogens
 - Emerging pathogens (*Fusarium*, Zygomycetes [*Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia*, *Cunninghamella*])
 - Many *Aspergillus* species
 - *Aspergillus fumigatus*

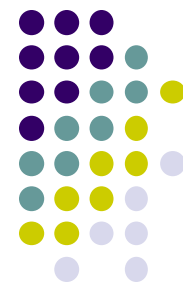
Infections

due to mold exposure indoors



- **Patients** with (listing **in decreasing risk order**):
 - **Cancer**, esp. **hemato-oncological diseases**, such as leukemia, lymphoma
 - Acute myeloid leukemia (**AML**) **more** affected **than** with acute lymphoblastic leukemia (**ALL**)
 - **Allogeneic more than autologous stem cell transplantation**
 - **Solid organ transplantation**
 - **HIV infection**
 - **Other immunosuppression**, e. g., prolonged high-dose therapy with glucocorticoids
 - **Aplastic anemia**, and much more

German Commission for Hospital Hygiene and Infectious Disease Prevention (CHH) of the Robert Koch Institute (RKI)



Empfehlung

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*[Hygiene requirements
for medical care of
immunocompromised
patients]*

Kommission für Krankenhaushygiene und Infektionsprävention
beim Robert Koch-Institut (RKI)

Anforderungen an die Hygiene bei der medizinischen Versorgung von immunsupprimierten Patienten

Empfehlung der Kommission für Kranken-
haushygiene und Infektionsprävention beim
Robert Koch-Institut (RKI)

Risk Group 1 (moderate immunosuppression / -deficiency)

- Granulocytopenia $< 0.5 \times 10^9/l$ ($< 500/\mu l$) up to 10 days (analog leukopenia $< 1 \times 10^9/l$; $< 1000/\mu l$)
- Deficiency of CD4-positive T-helper cells $< 250/\mu l$ (cave: age-appropriate normative values for children); autologous stem cell transplantation until three months after the intensive phase of therapy

Patients who have more than one criterion listed under Risk Group 1 of immunosuppression / -deficiency are classified into Risk Group 2.

Risk Group 2 (severe immunosuppression / -deficiency)

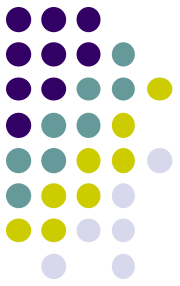
- Granulocytopenia $< 0.5 \times 10^9/l$ ($< 500/\mu l$) over more than 10 days (analog leukopenia $1 \times 10^9/l$; $< 1000/\mu l$)
- Severe aplastic anemia or macrophage activation syndrome during an intensive immunosuppressive therapy
- Allogeneic bone marrow and / or stem cell transplantation until 6 months after completion of the intensive treatment phase (important: extent of graft-versus-host disease (GVHD) and persistent iatrogenic immunosuppression)
- Acute inpatient phase of treatment, autologous stem cell transplantation or after solid organ transplantation (until dismissal)

Risk Group 3 (very severe immunosuppression / -deficiency)

- Allogeneic bone marrow transplantation / peripheral blood stem cell transplants (PBSCT) in intensive treatment phase (until engraftment = regeneration of granulopoiesis)
- Severe GVHD grade III or IV under intensive immunosuppression

The decision on the classification in group 3 of patients after allogeneic stem cell transplantation is ultimately made in summary of all test results of the attending oncologist.

Infections due to mold exposure indoors



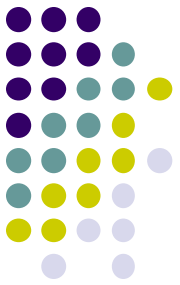
- **Children** have **NO increased risk for mold infections** !



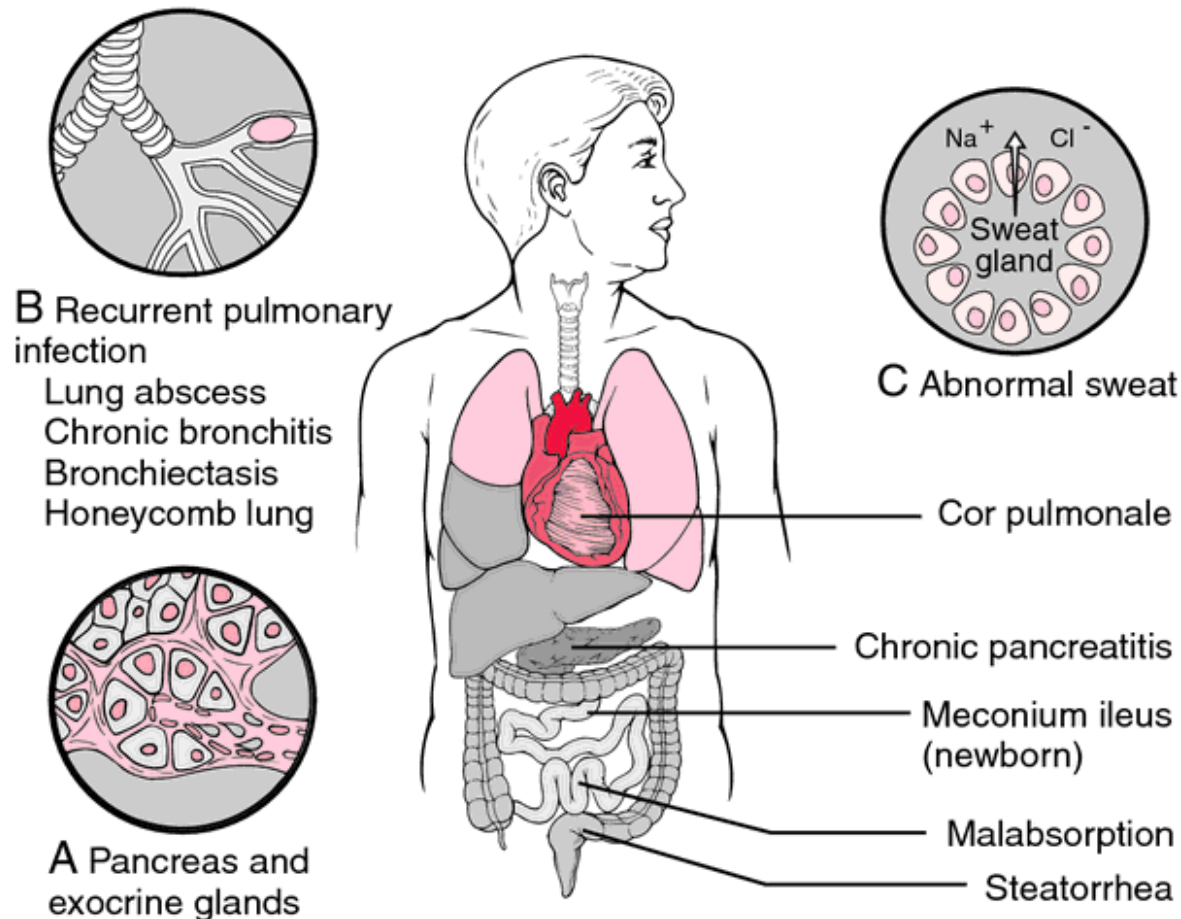
- **Newborns < 1 500 g birth weight** have **in hospitals** an increased risk of infection with *Aspergillus*

Infections

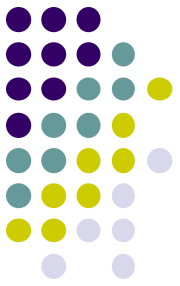
due to mold exposure indoors



- Children with **mucoviscidosis (cystic fibrosis)**



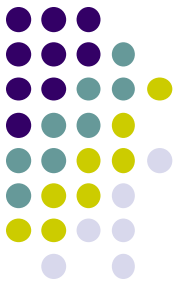
Infections **due to mold exposure indoors**



Mold infections
are counted among the most frequently causes of death
due to infectious diseases
in hemato-oncological patients
and become more important.

Infections

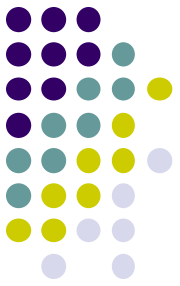
due to mold exposure indoors



Special diagnostic and therapeutic procedure

- ✓ Guideline-compliant diagnostic and therapeutic procedure

Causal connection between indoor mold exposure and possible infections



Infections

Incubation time

Entry into the body

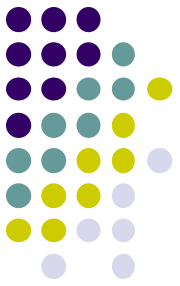
First infection complaints with appropriate health vulnerability (disposition)



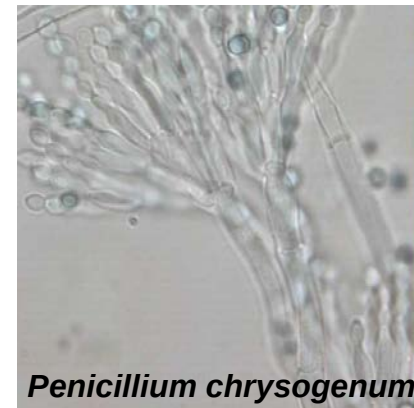
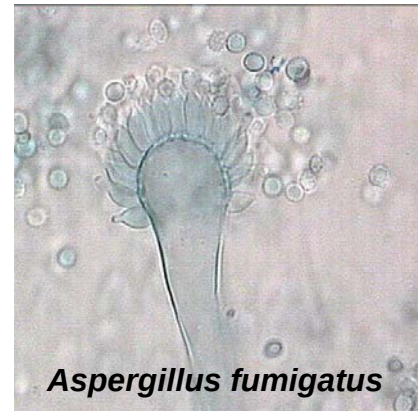
Incubation time

Time

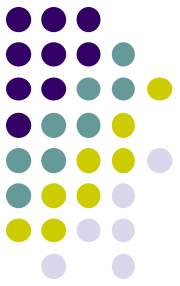
Health risks due to mold exposure indoors



- Infections
- Sensitization and allergies
- Toxic reactions
- Olfactory effects
- Impairment of well-being

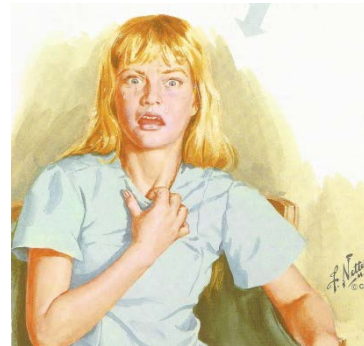


Sensitization, allergies due to mold exposure indoors

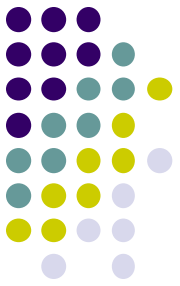


- Mainly allergic clinical pictures / allergic reactions to molds relevant in environmental medicine:

- Allergic conjunctivitis
- Allergic rhinitis
- Allergic rhinosinusitis
- Allergic bronchial asthma
- Urtikaria
- As aeroallergen triggering factor for atopic dermatitis (atopic eczema, neurodermatitis)



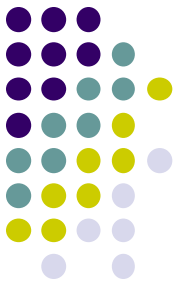
Sensitization, allergies due to mold exposure indoors



- **Hypersensitivity pneumonitis (HP; exogenous allergic alveolitis (EAA))**; rare allergic disease, mainly at workplace, accepted as occupational disease in Germany (**BK Nr. 4201**))
- **Allergic bronchopulmonary aspergillosis (ABPA)**; rare, in relation to existing asthma or mucoviscidosis (cystic fibrosis (CF))
- **Aspergilloma** (i. a. in caverns after tuberculosis, bronchiectasis and malignant diseases).

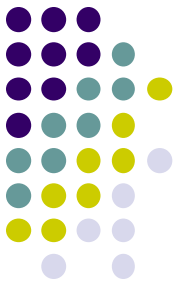
Sensitization, allergies

due to mold exposure indoors



- **Predisposing factors** of mold allergy are the following:
 - **Familial** (genetic) **disposition** for **immediate allergies**
 - Existence of **sensitizations** and **existence** of one or more atopic diseases
 - **Difficult to treat allergic rhinitis**
 - **Difficult to treat sinusitis**
 - **Difficult to treat asthma**
 - **Asthma exacerbation because of unclear reasons**
- In case of **hypersensitivity pneumonitis** (**exogenous allergic alveolitis**) by molds, mainly **non-smokers** are affected.

Sensitization, allergies due to mold exposure indoors



Special diagnostic procedure with regard to sensitization

✓ Guideline-compliant allergy testing:

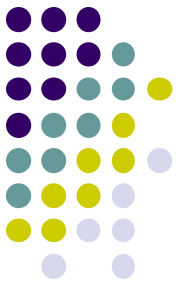
✓ Skin tests



✓ Analysis of specific IgE antibodies

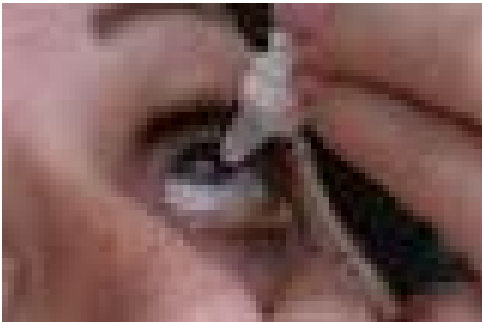
✓ In case of suspected allergic bronchopulmonary aspergillosis (ABPA) or hypersensitivity pneumonitis (HP; exogenous allergic alveolitis (EAA)) additional analysis of specific IgG antibodies in serum

Sensitization, allergies due to mold exposure indoors

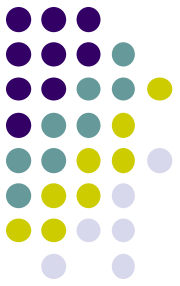


Special diagnostic procedure regarding IgE-mediated allergy

- ✓ Medical history (anamnesis)
- ✓ Guideline-compliant
conjunctival, nasal and / or bronchial provocation



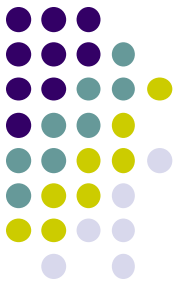
Sensitization, allergies **due to mold exposure indoors**



NOTE

**For most of the molds
occurring with moisture damage indoors,
no commercially available test extracts
are available for allergy testing!**

Sensitization, allergies due to mold exposure indoors



Special serological tests

- Cytokines, Eosinophilic Cationic Protein (ECP)
- Immune complexes

No indication

No routine method

Special cellulare test systems

- Basophil Degranulation Test and Histamine Release, HLT = Histamine Liberation Test
- Basophil Activation Test using Flow Cytometry (Flow CAST)
- Analysis of other effector cell mediators (Leukotriene Release Test, Cellular Antigen Stimulation Test (CAST))
- Lymphocyte transformation test (LTT)

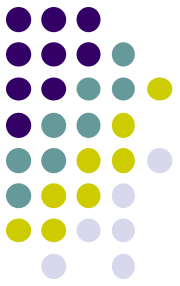
No indication

No routine method

No routine method

No indication

Sensitization, allergies **due to mold exposure indoors**



Special therapeutic procedure

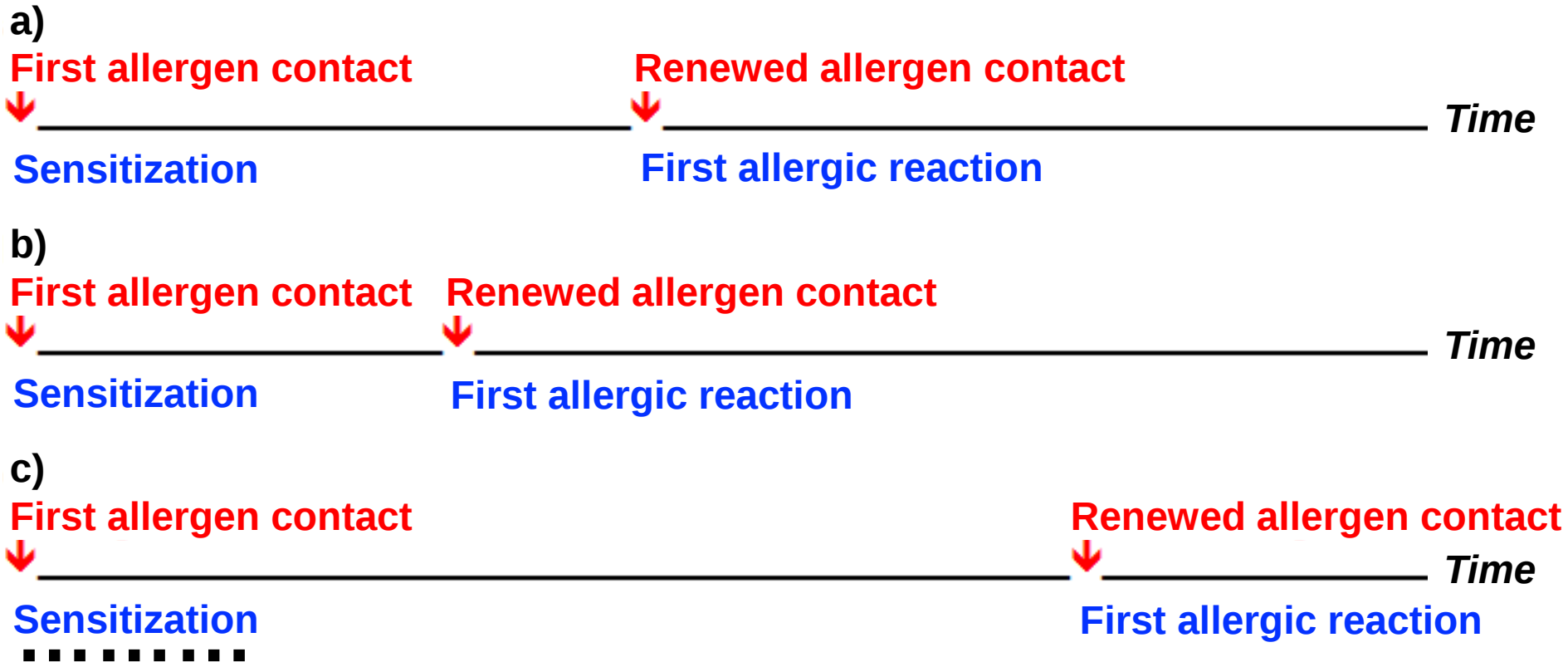
- ✓ **Restriction / Elimination of exposure**
- ✓ General drug therapie
- ✓ Guideline-compliant immunotherapy, if possible

Causal connection between indoor mold exposure and possible sensitization and allergies



Sensitization and allergies

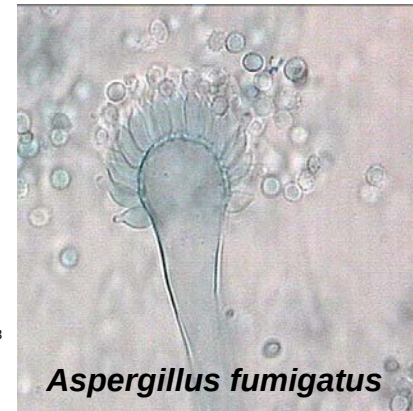
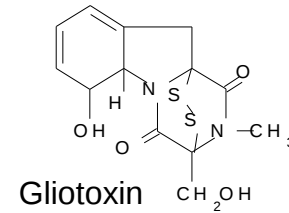
Variability of a possible temporal relationship between sensitization and first allergic reaction



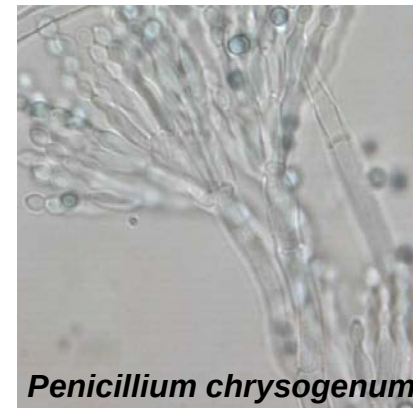
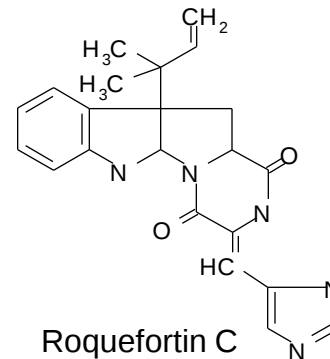
Health risks due to mold exposure indoors



- Infections
- Sensitization and allergies
- **Toxic reactions**
- Olfactory effects
- Impairment of well-being

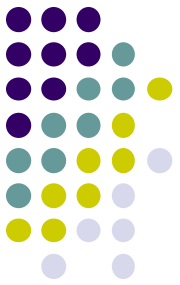


Aspergillus fumigatus



Penicillium chrysogenum

Toxic reactions **due to mold exposure indoors**



Generally,

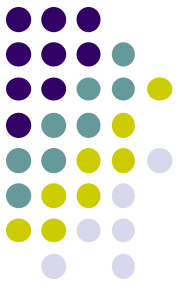
irritative effects (Mucous Membrane Irritation - MMI)

as well as

chronic inflammatory reactions of the respiratory tract

are possible

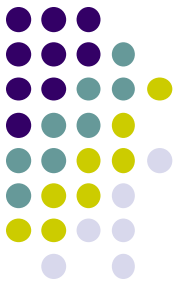
Toxic reactions due to mold exposure indoors



Microbial Volatile Organic Compounds (MVOC)

- It is still **unclear** whether MVOC elicits **biological signaling effects** at concentrations occurring indoors.
- For MVOC, there are **other indoor sources** than microorganisms.
- **MVOC analyses in indoor air** is **NOT** useful for medical diagnostics.

Toxic reactions due to mold exposure indoors



Mycotoxins

- **No reliable knowledge** of airborne intoxications by mycotoxins in the interior
- **Need to clarification** whether mycotoxin concentrations arising in indoor air are systemically toxicologically relevant
- According to the information available so far, this does not seem to be the case

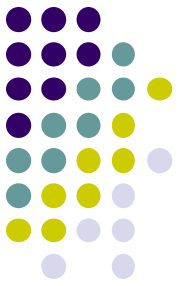
Human biomonitoring

- Analyses of mycotoxins in blood or urine have **NO significance for medical practice**
- Restriction to scientific research

Environmental monitoring

- At the present state of analytical possibilities, **mycotoxins indoors can neither be reliably determined nor assessed.**

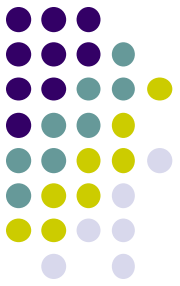
Toxic reactions due to mold exposure indoors



Problems of environmental monitoring of mycotoxins

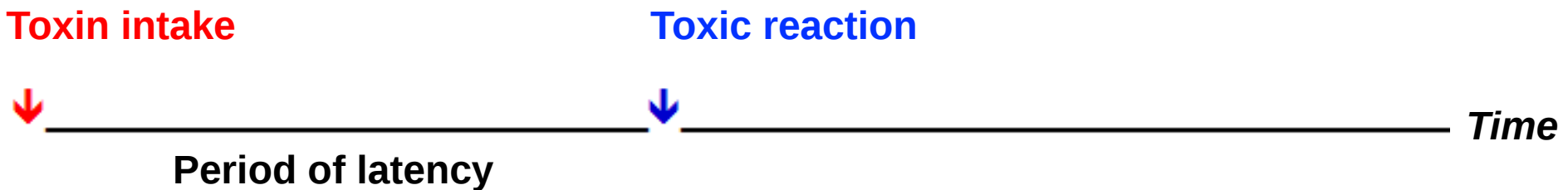
- The **concentrations** of mycotoxins in indoor air are usually **very low, near** or **below** the **limit of quantification**.
- There can be **many different toxins** for which there are **partly no analytical detection methods** available.
- In addition, **mycotoxins** are **particle-bound** in the air. Thus, the measured concentrations depend on mechanical activities in the room.
- **Analyses of mycotoxins in indoor air** are for the reasons mentioned afflicted with **significant errors** and **currently not routinely feasible**.
- Currently, **no reference values** can be derived.

Causal connection between indoor mold exposure and possible toxic reactions



Toxic effects

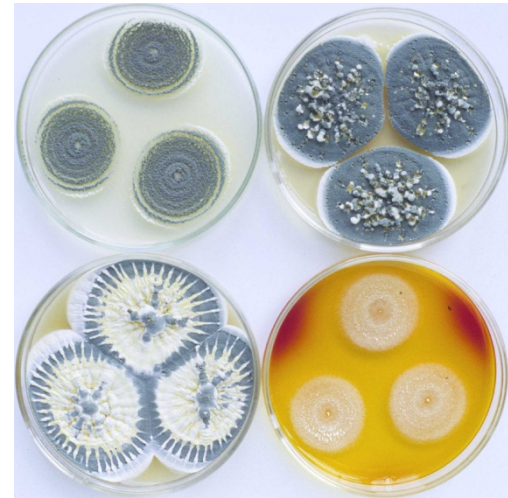
Period of latency



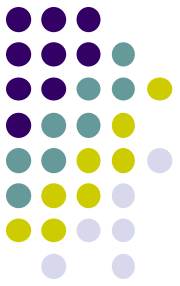
Health risks due to mold exposure indoors



- Infections
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- **Olfactory effects**
- Impairment of well-being



Olfactory effects due to mold exposure indoors



OVOC (Odour Active Volatile Organic Compounds)

- Metabolites of molds and bacteria
- MVOC are also among them
- Very low odor thresholds

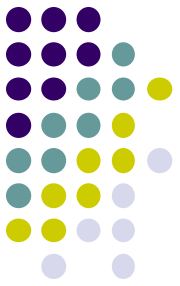
Health effects

- Odor perception as direct physiological effect
- Odor nuisance as emotional effect
- Indirect physiological effects as results of odor nuisance and associated chronic stress
- Impairment of well-being as result of odor nuisance and stress
- Impairment of well-being is precursor to physical dysfunctions

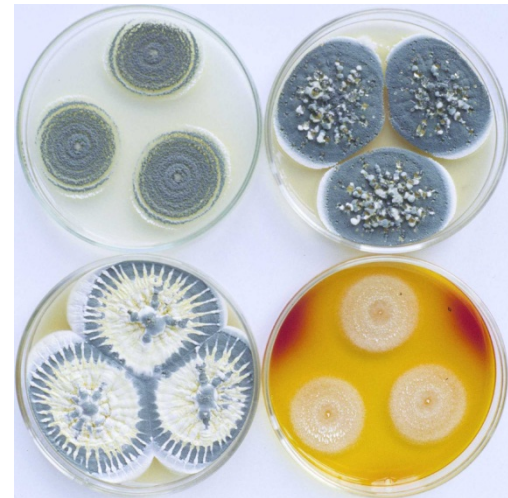
Predisposition

- Great interindividual differences of odor perception, cognitive evaluation, sensitivity to odors
- Genetic and hormonal influences, imprinting, context, adaptation effects

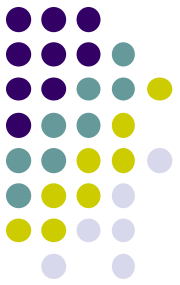
Health risks due to mold exposure indoors



- Infections
- Sensitization and allergies
- Toxic reactions
- Olfactory effects
- **Impairment of well-being**



Impairment of well-being due to mold exposure indoors



„Condition of diminishment of mental, physical and social well-being as well as of perceived performance and capability. As contents of perceptual experience they should be separated from nuisance reactions, which contain the cognitive assessment of specific environmental stimuli.“

Bullinger M (1992) Befindlichkeitsstörungen. [*Impairment of well-being*] In: Wichmann H-E, Schlipköter H-W and Füllgraf G, eds. Handbuch der Umweltmedizin [*Handbook of environmental medicine*]. ecomed Verlagsgesellschaft, Landsberg/Lech 1992, 1-12

Bullinger M (2002) Befindlichkeitsstörungen. [*Impairment of well-being*] In: Dott W, Merk HF, Neuser J and Osieka R, eds. Lehrbuch der Umweltmedizin. [*Textbook of environmental medicine*] Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, pp. 494–500.

Impairment of well-being can be triggered by molds,
e. g. through odors

Wiesmüller G, Heinzow B, Aurbach U, Bergmann K, Buzina W, Cornely O, Engelhart S, Fischer G, Gabrio T, Heinz W, Herr C, Kleine-Tebbe J, Klimek L, Körberle M, Lichtnecker H, Lob-Corzilius T, Merget R, Mülleneisen N, Nowak D, Rabe U, Raulf M, Seidl H, Steiß J, Szewzyk R, Thomas P, Valtanen K, Hurraß J. Possibilities and limitations of health assessment of mould exposures indoors. Proceedings of Indoor Air 2016. Gent, Belgien (ISBN-13: 978-0-9846855-5-4) Paper ID 329, 1-8

Health risks due to mold exposure indoors

- Exposure measurements -

For medical diagnostics only in exceptional cases meaningful !



[Analytical methods for mold exposure assessment – an update]

Untersuchungsmethoden zur Erfassung einer Schimmelpilzexposition – ein Update

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²Institute für Hygiene und Umweltmedizin, Medizinische Fakultät der RWTH Aachen

³Gesundheitsamt der Stadt Köln

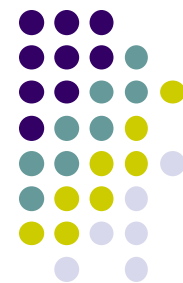
⁴Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit, München

⁵Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung,
Institut der Ruhr-Universität Bochum (IPA)

Umweltmed – Hygiene – Arbeitsmed **20** (3) 115 – 131 (2015)

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Hurraß J, Gabrio T, Herr C, Raulf M, Wiesmüller G. Analytical methods for mould exposure assessment from an environmental medical point of view. Proceedings of Indoor Air 2016. Ghent, Belgium (ISBN-13: 978-0-9846855-5-4) Paper ID 253, 1-8





Health risks due to mold exposure indoors

- Risk analysis and risk assessment -



Georges Seurat
Poseuse de profil 1886

Evidence for an association

between exposure to moisture / mold damage indoors
and diseases (without mold mycoses)



Causal relationship:

- NO evidence

Sufficient evidence for an association

- Allergic respiratory diseases
- Bronchial asthma (manifestation, progression, exacerbation)
- Allergic rhinitis
- Hypersensitivity pneumonitis (HP) / exogenous allergic alveolitis (EAA)
- Promoting respiratory infections, bronchitis

Restricted or suspected evidence for an association

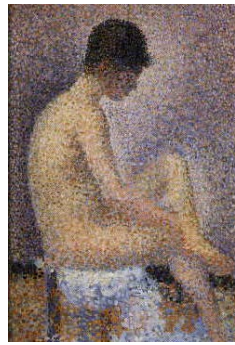
- Mucous Membrane Irritation (MMI)
- Atopic eczema (atopic dermatitis, neurodermatitis; manifestation, progression, exacerbation)

Inadequate or insufficient evidence for an association

- Chronic obstructive pulmonary disease (COPD)
- Acute Idiopathic Pulmonary Hemorrhage in children
- Rheumatism
- Arthritis
- Sarcoidosis
- Cancer

Risk assessment

of mold exposure indoors

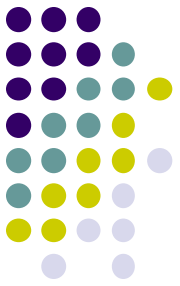


- **Infection risk**
 - Immunosuppression according to the 3 risk groups of the German Commission for Hospital Hygiene and Infectious Disease Prevention
- **Infection risk and allergic risk**
 - Mucoviscidosis (cystic fibrosis)
- **Allergic risk**
 - Bronchial asthma
- **Toxic effects**

(Mucous Membrane Irritation (MMI); Inflammatory reactions, esp. in the respiratory tract)

 - Especially patients with preexisting diseases of the mucous membranes of the eyes and respiratory tract are affected
 - No acute health risk
- **Olfactory effects and impairment of well-being**
 - Everybody can be affected
 - No acute health risk

General therapeutic procedure



First "therapeutic" measure

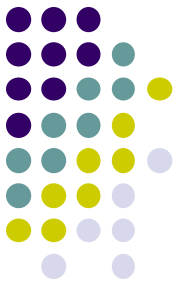
from a preventative and hygienic point of view

in the presence of moisture / mold damage:

- ✓ **Efficient professional and proper renovation**
- ✓ **In case of serious diseases with a high health risk, immediate minimization of exposure**

Network Mold Consulting

Locations of networks of mold advisory services in Germany



Source:

<http://www.umweltbundesamt.de/themen/gesundheit/umwelteinfluesse-auf-den-menschen/schimmel/netzwerk-schimmelpilzberatung>; *German only*

Thank you very much for your attention

