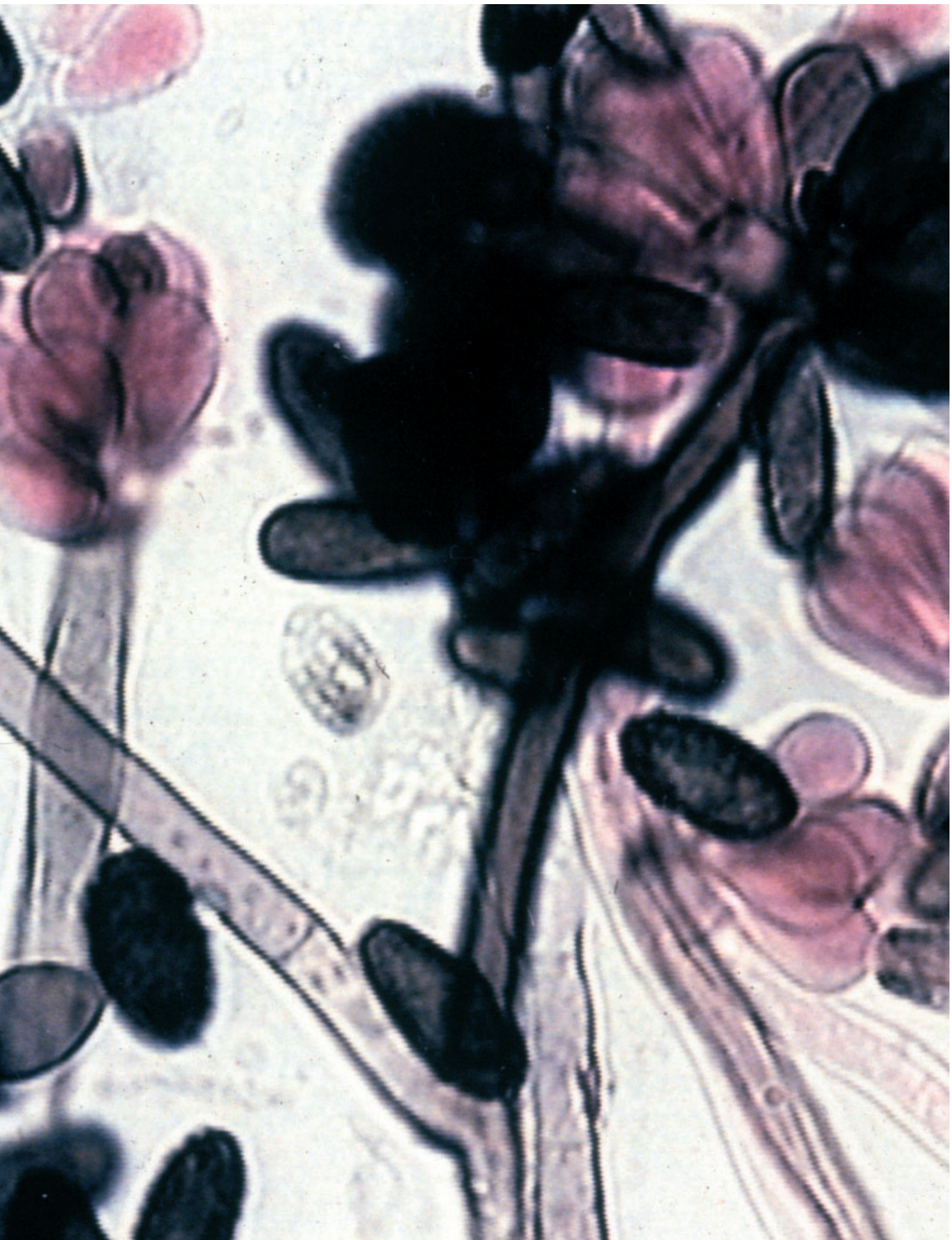
Ph.D. thesis

Mould growth on building materials

Secondary metabolites, mycotoxins and biomarkers



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Statens Byggeforskningsinstitut
Danish Building and Urban Research

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Kristian Fog Nielsen

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PREFACE

This publication includes the Ph.D. thesis of Kristian Fog Nielsen exclusive the published peer reviewed papers.

The Danish Building Research Institute financed the Ph.D. project. It was agreed upon in 1998 between the Research Academy, Technical University of Denmark (DTU) and the Danish Building Research Institute (SBI) – now Danish Building and Urban Research (By og Byg).

Kristian Fog Nielsen M. Sc. (Chem. & Biotech. Eng) commenced his studies in June 1998 and defended his thesis at a public hearing and evaluation on December 7, 2001.

A major part of the chemical and mycological work was performed in the Mycology Group at BioCentrum – DTU.

Dr. Maija Riitta Hirvonen and dr. Aino Nevalainen, the National Public Health Institute, Kuopio, Finland and dr. Olaf Adan, TNO Bouw, Delft, the Netherlands are gratefully acknowledged for their hospitality to Kristian Fog Nielsen, thereby giving him a broader perspective on his project.

The institute wants to thank the principal supervisor Ulf Thrane, associate professor, Ph.D. for the inspiring, valuable and always positive collaboration during the three years.

DANISH BUILDING AND URBAN RESEARCH
Division of Energy and Indoor Climate
June 2002

Erik Christophersen
Head of Division

Mould growth on building materials

Secondary metabolites, mycotoxins and biomarkers

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This thesis was defended at 14 o'clock the 7. December 2001, in auditorium 51, building 208, Technical University of Denmark.

AUTHOR'S PREFACE

More than seven ago years ago I was introduced to the fascinating world of fungi and mycotoxins by Ole Filtenborg and Thomas O. Larsen. The opportunity to work on my own with an array of sophisticated equipment, made me stay in the Mycology Group, and led to my M.Sc. project where Suzanne Gravesen and Thomas convinced me to work with *satratoxins in buildings*. Successfully ending this work, it resulted in my Ph.D. project financed by the Danish Building Research Institute where Erik Christophersen organised the funds for the project as well as the many travels.

However, it has also been frustrating to work in a field where you are unable to help people, often socially disadvantaged, who are forced to move from their mouldy homes due to massive symptoms, often victims of the ignorance of the authorities.

Working in such a multidisciplinary area requires help from a lot of people, and at the Danish Building Research Institute I would like to thank the librarians, especially Lillian Nielsen who have been a tremendous help in ordering scientific papers. Gunnar Holm has been a great help in constructing experimental set-ups, Lotte P. Uttrup and Per Hansen have prepared material samples, Jan Carl Westphall helped with various photographic problems, Yelva Jensen has been a good secretary, and Solveig Nissen with the language revision of some of the papers as well as this thesis. Peter A. Nielsen is acknowledged for the fruitful discussions on health and building related issues.

Jørgen Ø. Madsen, Department of Organic Chemistry, in preparing the 4-D_2-ergosterol was a great help in making the ergosterol analytical method work.

The private consultants Mikael Ø. Hansen and Peter Thompson have kindly supplied me with "real" mouldy materials, interesting field observations, and taken their time to show me the real mouldy world outside the laboratories.

I would like to thank Dr. Aino Nevalainen, Dr. Maija-Riitta Hirvonen, and their helpful Ph.D. students for letting me work in their laboratories at the National Public Health Institute, Kuopio, Finland.

Working at TNO Bouw, The Netherlands, with Dr. Olaf Adan and Gerben van der Wel helped me understand the importance of instationary environmental conditions for mould growth.

Having Professor Bruce B. Jarvis in our group for a year raised the level of my work on *Stachybotrys* and natural products significantly and introduced me to a number of other research groups.

The help of colleagues in the Mycology group, in particular Elisabeth Krøger, Kir Lyhne, Flemming Lund, Thomas O. Larsen, Jørn Smedsgaard, Jens C. Frisvad and Birgitte Andersen has been encouraging. Ulf Thrane has been the perfect Ph.D. supervisor who always had time - if needed, and on the other hand never intervened much in my work.

Thanks to Suzanne Gravesen who believed so much in my work and have taught me so much about so many different things and introduced me to so many people as well as helping with the language revision of this report.

The support and understanding of my beloved wife Hanne - especially during my stays in Finland, Holland and various conference as well as the acceptance of the large piles of papers, CD, books etc. during my project cannot be overestimated.

Lyngby, June 2001

Kristian Fog Nielsen

ABSTRACT

The aim of this study was to document if the moulds produce mycotoxins and other biologically active metabolites when growing in buildings, as well as investigate the influence of environmental conditions on the production of these metabolites. The growth of moulds under various humidities should also be investigated along with the use of chemical biomarkers for quantitation of mould growth.

It was shown that *Stachybotrys chartarum* produced a number of mycotoxins when growing in buildings. These components were produced in significantly higher quantities than by other moulds investigated in this study. Only 35% of the isolates from buildings produced the extremely cytotoxic satratoxins. Actually these metabolites are probably not responsible for idiopathic pulmonary hemosiderosis in infants, which is probably caused by other *S. chartarum* metabolites.

For the first time ever *Stachybotrys* metabolites were found in air-samples, where several classes of spiriocyclic drimanes and satratoxins were detected.

Aspergillus versicolor produced high quantities of the carcinogenic mycotoxin, sterigmatocystin at water activities (a_w) > 0.95. At lower a_w more than 10 unknown metabolites were produced, including at least 5 metabolites also produced by *A. ochraceus*. *A. versicolor* was often growing in mixed cultures with others moulds where it sporulated poorly, meaning that it may evade detection based on cultivating methods. The *A. ustus* isolates from buildings were macro-morphologically and chemically very different from the cereal isolates, and should be described as a new species.

Penicillium chrysogenum produced few detectable metabolites and often none when growing on materials. Combined with the no observed effects on persons experimentally exposed to high quantities of the spores, these observations implies that this species may not be important and is actually obscuring the detection of more toxic genera and species. *P. brevicompactum* produced mycophenolic acid and *P. polonicum* the tremorgenic verrucosidin when they were inoculated on water-damaged materials.

Chaetomium globosum produced high quantities of chaetoglobosins whereas *Trichoderma* species did not produce detectable quantities of trichothecenes when growing on materials. Even on laboratory media <1% of the isolates produced trichodermol or esters of it.

Ergosterol content of building materials was quickly and precisely quantified by isotope dilution GC-MS/MS. Determination of ergosterol is only needed as a supplement for assessing mould growth on test materials, as visual assessment, especially supported by dissection microscopy generally was just as sensitive. The minimal RH for growth on wood based materials and material containing starch was just below 80% at room temperature, and increased to about 90% at 5°C. On paper-mineral composites such as gypsumboard the minimal RH was approx. 90% RH from room temperature to 5°C. Pure mineral based materials with few organic additives seem to be able to support growth at RH ≥ 0.90, although ≥95% RH was needed to generate chemical detectable quantities of biomass.

The phylloplane *Cladosporium* was able to outgrow *P. chrysogenum* on materials under transient humidities. This is presumably why phylloplanes like *Cladosporium, Ulocladium, Phoma* and *Aureobasidium* are very common in bathrooms and other places with instationary humidity conditions.

Mould growth in buildings is causing various health effects among the occupants, however the causal components is still partly unknown making scientifically based guidelines for "how much is too much" and cost efficient remediation of mouldy buildings almost impossible.

RESUME

Målet med dette studium var at dokumentere om skimmelsvampe producerer mykotoksiner og andre biologisk aktive stoffer, når de vokser på byggematerialer. Anvendelse af kemiske markører til kvantificering af den producerede biomasse skulle også undersøges sammen med svampenes vækst og metabolisme under forskellige temperatur- og fugtforhold.

Stachybotrys chartarum producerede en række mykotoksiner, når den voksede på byggematerialer. Mængderne af disse stoffer i svampepartiklerne, der blev frigjort ved en let vakuum opsamling, var klart større end de mængder, der blev produceret af andre skimmelsvampe. Kun 35% af isolater fra vandskadede bygninger producerede de celledræbende satratoxiner, og inhalationen af netop disse synes næppe at være årsagen til lungeblødninger hos spædbørn; men kunne derimod skyldes andre stoffer fra *Stachybotrys*, eks. de spiriocykliske drimaner. For første gang blev *Stachybotrys* metabolitter fundet i luftprøver. Her blev flere typer af spiriocykliske drimaner samt satratoxiner påvist.

Aspergillus versicolor producerede meget store mængder af de kræftfremkaldende sterigmatocystiner når vandaktiviteten (a_w) > 0.95, hvorimod den ved lavere a_w i stedet producerer mindst 10 ukendte metabolitter. Heraf er 5 tidligere set i kulturekstrakter fra *A. ochraceus*.

A. versicolor gror oftest i blandede kulturer med mange andre svampe, og da den sporulerer dårligt vil den oftest ikke blive påvist ved dyrkning på vækstmedier. *A. ustus* isolater fra bygninger var både kemisk og makro-morfologisk forskellige fra stammer isoleret fra korn og bør derfor beskrives som en ny art.

Penicillium chrysogenum producerer stort set ingen påviselige metabolitter, når den gror på byggematerialer. Sammenholdt med de ikke observerede effekter efter patienters eksponering for meget store mængder luftbårne sporer i et enkelt forsøg indikerer det, at den langtfra har det samme toksiske potentiale som *A. versicolor* og *S. chartarum*. I stedet forhindrer den påvisning af mere vigtige arter. *P. brevicompactum* producerede mycophenolsyre og *P. polonicum* det tremorgene verrucosidin, når de voksede på vandskadede materialer. Under samme forhold producerede *Chaetomium globosum* store mængder af de toksiske chaetoglobosiner, hvorimod *Trichoderma* spp. ikke producerede påviselige mængder trichothecener på materialer, og selv på laboratoriesubstrater producerede <1% af isolaterne trichodermol eller estre af denne.

Ergosterol-indholdet i materialer kunne hurtigt og præcist blive kvantificeret med isotop fortynding GC-MS/MS. Dette er kun nødvendigt som et supplement til bestemmelse af biomasse på testmaterialer, idet visuel bestemmelse kombineret med stereomikroskopi generelt er lige så følsomt. Den minimale relative fugtighed (RH) for at der kan opstå vækst af skimmelsvampe ligger lige under 80% ved stuetemperatur og stiger til ca. 90% RH ved 5°C. På gipsplader kræver skimmelsvampene ca. 90% RH for at kunne vokse. Beton med nogle organiske additiver kan tilsyneladende give anledning til meget minimal vækst ved RH > 90%, og ved RH > 95% kan der blive produceret ikke ubetydelige mængder biomasse på dette materiale. Den phylloplane *Cladosporium* kan udkonkurrere *P. chrysogenum* på materialer under transiente fugtforhold, og det er sandsynligvis årsagen til at phylloplaner som *Cladosporium, Ulocladium, Phoma* og *Aureobasidium* dominerer i badeværelser og andre steder, hvor der er skiftende fugtforhold.

Skimmelsvampevækst i bygninger er sundhedsskadeligt, med en del af de aktive stoffer og mekanismer en endnu ukendte. Derfor er det ikke muligt at fastsætte hygiejniske grænseværdier for skimmelsvampe i bygninger, ligesom det ikke endnu er muligt at renovere angrebne bygninger økonomisk effektivt, idet man ikke ved hvor langt man skal gå.

ABBREVIATIONS AND TERMS

AFB_1	Aflatoxin B_1
ALK	Alkaloid forming agar
Antibiotic	Activity against microorganisms, usually against bacteria
a_w	Water activity
CE	Capillary electrophoresis
CFU	Colony forming unit
Conidia	Asexual production structure from fungi /moulds.
CYA	Czapek yeast extract agar
DAD	Diode array detection
DAS	Diacetoxyscirpentriol, a type A trichothecene
DG18	Dichloran 18% glycerol agar
DON	Deoxynivalenol, a type B trichothecene
EI^+	Positive ion, electron impact ionisation
ESI	Electrospray ionisation, method used extensively in LC-MS
FLD	Fluorescence detection
GC	Gas chromatography
HFB	Heptafluorobuturyl, derivative-group $-CO-CF_2-CF_2-CF_3$.
HPLC	High performance liquid chromatography, also referred to as LC
IL-1	Interleukin 1, a cytokine
IL-6	Interleukin 6, a cytokine
IPH	Idiopathic pulmonary hemosiderosis
LC	Liquid chromatography
LC_{50}	Concentration lethal to 50% of the test organisms
LD_{50}	Dose lethal to 50% of the test organisms
MEA	Malt extract agar
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
MTR	Macrocyclic trichothecene
MVOC	Microbial volatile organic compound
MW	Molecular mass (Da)
NICI	Negative ion chemical ionisation
NIV	Nivalenol, a type B trichothecene
NO	Nitrogen oxide, as inflammatory mediator
OAT	Oatmeal agar
PCR	Polymerase chain reaction
PFP	Pentafluoropropionyl, derivative group, $-CO-CF_2-CF_3$.
PSA	Potato sucrose agar
RE	Roridin E, a macrocyclic trichothecene
RH	Relative humidity (%)
RI	Retention index
RT	Retention time
ROS	Reactive oxygen species
SG	Satratoxin G, a macrocyclic trichothecene
SH	Satratoxin H, a macrocyclic trichothecene
SPE	Solid phase extraction, chemical clean-up method

Spore	Reproductive structure of fungi/moulds and certain bacteria
ST	Sterigmatocystin
5ST	5-methoxysterigmatocystin
T-2	T-2 toxin, a type a trichothecene
TA	Type A trichothecene
TB	Type B trichothecene
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMS	Trimethylsilyl, derivative group, -$Si(CH3)_3$
TNFα	Tumor necrosis factor α, a cytokine
TR	Trichothecene
V8	V8 juice agar
VB	Verrucarin B, a macrocyclic trichothecene
VJ	Verrucarin J, a macrocyclic trichothecene
Water-damaged	Floating water present, $a_w \approx 1$
WP	Wallpaper
YES	Yeast extract sucrose agar

PAPERS PREPARED IN CONNECTION WITH THIS THESIS

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7. Peltola J, Niessen L, Nielsen KF, Jarvis BB, Salkinoja-Salonen M, Möller E. Genetic diversity of *Stachybotrys chartarum* and relatedness to toxicity (submitted).
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11. Wilkins KC, Nielsen KF, Din SL. 2002. Patterns of volatile metabolites and trichothecenes produced by Stachybotrys and other trichothecene producing molds. Environmental Science & Pollution Research (in press).
12. Reelsev M, Miller M, Nielsen, KF. Quantifying mold biomass on building materials: A comparison of ergosterol and MycoMeter-test (submitted).
13. van der Wel GK, Nielsen KF, Adan O. Mould growth and metabolism on building materials under constant and transient humidities. (in prep, crude draft)

Appendix A lists the conference proceedings and non peer-reviewed publications prepared during this Ph.D. thesis.

1 INTRODUCTION

During the last 10 years several studies have shown that people living and working in damp or mouldy buildings have an increased risk of airways infections, adverse health effects, respiratory problems such as asthma, and CNS symptoms[1-9]. However concern of mould growth in buildings is not a new problem, already in the Bible (Leviticus Chapter 14, 33-48) it is written that contaminated spots on walls should be removed, and if consistently reappearing the house should be torn down.

The estimated proportion of dwellings with microfungal problems in Northern Europe and North America is perhaps as high as 20-40% based on data from the United Kingdom with 30-45%[1,10], the Netherlands with 20-25%[6,11,12], Finland with 20-30%[9,13], USA with up to 40%[2] and Canada with up to 30%[3] buildings affected. No data exist for dwellings in Denmark, but the majority of schools and day-care centres build in the late 1960s and 1970s seem to have problems.

Mould growth only occurs in water-damaged and humid constructions. Consequently the major part of the problems in Scandinavia and North America are due to poorly manufactured constructions and inadequate maintenance[14-16].

The health problems observed in mouldy or damp buildings can be grouped into three major categories as seen in Table 1.

Table 1
Health problems associated with mouldy and damp buildings

General symptoms incl. CNS-symptoms	Mucosal symptoms	Lung symptoms
• Extreme fatigue[7,8,17-20]. • Lack of concentration and memory[7,8,17-20], in extreme cases as cognitive impairment[21]. • Nausea[1,7,8,17,18] • Lowered immune function due to a misbalance in the lymphocytes sub-populations or chronic stimulation of some of the these[22,23].	• Blocked nose.[1,5,12,19] • Itching eyes[19,24,25] • Burning sensation of the skin[7,8,17,18,24,25] • Hoarseness.[1,7,8,17,18] • Recurrent airway infections, especially sinusitis[7,8,17,18,24,25].	• Wheeze[1,2,4] • Cough[2,3,5,6,8,12] • Bronchitis[2,3] • Asthma[2,4,6,8] • Pulmonary hemosiderosis in infants[26-28].

To cope effectively with the health problems it is essential to identify the causative agents and the cellular mechanisms as it would lead to:

- Clinically valid analyses documenting the patients' complaints.
- Targeted analysis of causative compounds in buildings suspected of having mould problems
- Consent guidelines for "how much is too much".
- Economically sound cleaning procedures.

However, very little knowledge have been established on peoples' specific exposures and the non-immunologic mechanisms, especially toxic reactions, after exposure to moulds[8,29,30]. Non-immune mediated chronic activation of immune competent cells[22,30,31] have been suggested as the major mechanisms.

From the agricultural occupational environment exposure-effect data exist. Here inhalation of fungal spores have been shown to cause cancer[32,33], premature birth[34] and farmers lung[25]. However the levels of spores and metabolites are magnitudes higher than in indoor air[35].

A number of potentially causative agents produced by moulds in the water-damaged buildings have been suggested:

- **Proteins** causing the well-known immediate allergic reactions within minutes of exposure (Type I allergy) [24,25,36] and in rare incidences type III allergy[25].
- **β-(1,3)-d-glucans** triggering inflammatory reactions very similar to symptoms observed on exposure to endotoxin[37-39].
- **Microbial volatile organic compounds** (MVOC) released from the fungi during growth[40-43].
- **Mycotoxins** released from fungal spores and fragments after inhalation[19,40,44-49].

Compounds from other organisms associated with moulds such as mites[6] and bacteria[50-53] should also be considered as they may play an important role in the ecosystem of the infested materials. Additional bacteria growing on building materials also produces a number of very potent bacterial toxins[54].

The work carried out during the study and this report, focused on the secondary metabolites and mycotoxins produced by moulds during growth on building materials, as these metabolites are potential risk factors for the adverse health effects observed in mouldy buildings.
Consequently, a major part of the following literature review will focus on fungal growth on materials and the different metabolites produced by moulds during their growth in buildings.

2 MOULDS IN BUILDINGS

Viable mould spores and bacteria are ubiquitous in buildings[10,55] and are well adapted to inhabit this ecological niche if just sufficient water is available[10,55-57].
The moulds growing on a particular material are referred to as the *associated funga*[58], and have been divided into three groups by Grand et al[55] following their water requirements on laboratory substrates:

- **Primary colonisers** capable of growth below a water activity (a_w) of 0.8 including species of *Wallemia*, *Penicillium*, *Aspergillus* and *Eurotium*[59].
- **Secondary colonisers,** with a minimal a_w between 0.8 and 0.9 including species of the phylloplanes: *Cladosporium, Phoma, Ulocladium* and *Alternaria*.
- **Tertiary colonisers**, demanding a_w of at least 0.9, including genera such as: *Stachybotrys*, *Chaetomium, Trichoderma*, *Auraeobasidium*[40,60] as well as actinomycetes and other bacteria[57,61]. These conditions are generally only met by incoming water and not just high humidity or condensation on indoor surfaces[25,55].

2.1.1 The building associated funga

The associated funga reported from different countries varies considerable for a number of reasons, such as different climates, materials, different isolation procedures and difficulties in identifying the isolates to species level especially in *Penicillium, Aspergillus* and *Cladosporium*[59,62-64]. In Table 2, the most common fungal species isolated in buildings have been compiled.
In Europe*, P. chrysogenum* is the most abundant[59,63,65], whereas it seems to be *Penicillium aurantiogriseum* and *P. viridicatum* in North America. However, this is probably due to misidentification with other species from the *P. aurantiogriseum* complex.
For the genus *Aspergillus* consensus seems to exists with *A. versicolor* being the absolutely most frequently isolated species, followed by *A. sydowii* and *A. ustus*[63,64].

Table 2
The most common part of the building associated funga*

Genus	Species	Natural habitat	Common on
Water damage moulds			
Chaetomium	*globosum*	Soil, straw, wood	Mostly on wood and cellulose containing materials
Stachybotrys	*chartarum*	Hay and straw[66], paper, soil	Gypsum boards, pipe insulation
Ulocladium	*chartarum* and *atrum*	Soil, dung, grasses	Wood, wallpaper, gypsum boards
Trichoderma	*harzianum, citrinoviride, atroviride* and *longibrachiatum*	Wet wood, soil	Mostly on wood
Alternaria	*tenuissima*	Saprophyte on plants, foods Cereals, leaves	Wallpaper, gypsum
Aureobasidium	*pullulans*	Soil, leaves, cereals	Paint especially in bathrooms, window frames, paint
Rhodulotorula	*rubra*		Paints, wood
Phoma	*sp.*	Plant material, soil,	Paints, wood, wall papers, caulkings, especially in bathrooms
High relative humidity moulds			

Table 2 The most common part of the building associated funga*			
Genus	Species	Natural habitat	Common on
Aspergillus	*versicolor*	Cheese, cereals, spices, dried meat products	Most materials, primary coloniser, grows in dust
Penicillium	*chrysogenum*	Various foods, spices, dry cereals	All materials
Penicillium	*brevicompactum*	Soil, nuts, fruits and juices	Especially wooden materials
Penicillium	*corylophilum*	Various foods	Most materials, primary coloniser
Aspergillus	*Sydowii*	Soil, cotton, beans, nuts and straw	Most materials, primary coloniser
Aspergillus	*ustus*	Soil, cereals, groundnuts	
Cladosporium	*sphaerospermum*	Dead plants	Paints, wood, wall papers, caulkings, especially in bathrooms
Cladosporium	*herbarum*	Dead plans, stored fruits	Paints, wood, wall papers, caulkings, especially in bathrooms
Penicillium	*palitans*	Cheese, wood	Most materials, but especially wooden
Eurotium	*repens*	Cakes, dried food, cereals	
Wallemia	*sebi*	Dried foods, jam, cakes, dates, salted fish, sugar, chocolate	
Paecilomyces	*variotii*	Compost	
Penicillium	*polonicum*	Cereals, meat products	
Aspergillus	*niger*	Dried food, spices	
Penicillium	*expansum*	Nuts, fruits (apples)	Wood

*References[14,16,40,49,59,63,65,67,67-72]

When measuring viable fungi, as colony-forming units (CFU), the laboratory media will always favour certain genera and species[65], thus several media are needed for covering the majority of the building associated funga. Dichloran 18% glycerol agar (DG18) is generally considered the best media for xerophilic fungi (moulds who can grow a_w <0.85[73]), and low nutrient high a_w media as V8 juice agar (V8), malt extract agar (MEA) or rose Bengal agar[74-76] for the secondary and tertiary colonisers[77]. However MEA can be supplemented with cellulose agar to enhance detection of *Stachybotrys* who have difficulties competing with species of *Aspergillus* and *Penicillium* as well as having many sterile spores[49,78].

2.1.1.1 Air measurements

For investigating moulds associated health problems, air measurements would provide the best exposure data. However, as the causal agents have not been identified, it has not been established what should actually be measured. Four main techniques are used for air measurements: i) cultivation of viable spores; ii) collecting spores and counting them microscopically[79]; iii) detecting chemical markers[80,81]; iv) using different molecular-biological (DNA) techniques[82]. In sections 2.5 and 2.6.3 measurements of biomarkers, including mycotoxins, will be dealt with in detail.

A major problem with cultivating techniques is that a major part of the spores may not be viable[83]. In addition, hyphal and spore fragments are also released from the mouldy materials[84]. Aggressive air sampling methods are generally preferred over sedimentation plates which are unreliable [40,59,77].

Even in rooms with visible mould growth aggressive sampling may give low counts[85-87] although other authors have found clear relationships[10]. Especially if the ratio between outdoors and indoors is used and speciation of the collected moulds is performed, a clear relationship between infested areas and air measurements can be found[14]. Determining the ratio

of *Penicillium* and *Aspergillus* versus outdoors phylloplane moulds as *Cladosporium* and *Alternaria* has been successful for indicating a humid environment[40,87,88].
A totally different and very elegant approach, is to measures the personal exposure and response by determining inflammatory mediators, such as IL-1, IL-6, TNFα, NO, eosinophil cationic protein and myeloperoxidase in nasal lavage fluid[89-91].
Nevertheless interpretation and knowledge of the limitations of the different techniques is crucial[78] and generally no single method will provide the full picture of mould exposure and presence in a building[69].

2.2 Growth of moulds on building materials

Moulds can grow on laboratory media at temperatures as low as -7°C[92] and some wood associated cladosporia and penicillia are able to grow at temperatures as low as -5°C on wood, but seem to require at least 0°C to germinate[93]. In comparison *Aspergillus restrictus*[94] requires 9°C, and *A. versicolor* 4°C[25] for growth on a high nutrient substrate such as MEA, indicating that temperature cannot be used to avoid fungal growth in buildings.
The associated funga is also selected by a_w, light[92] and especially the composition of the material, including organic carbon, pH, nutrients like trace metals, nitrogen, phosphor and sulphur[10,56,57,92,95,96], consequently the most important of these factors will be reviewed in the next subchapters.

2.2.1 "Water - the key factor"[11]

This is undoubtedly the most important factor for determining if mould growth will start in a building[11]. Most of the moulds have their optimal a_w at 0.96-0.98 even though some are able to grow at much lower a_w[11,95,97]. Some xerophilic fungi like *Eurotium* spp. and *Wallemia* will not grow at such high a_w[65,73].
The germination process requires a slightly (approx. 0.02) higher a_w than the critical a_w for growth[57,94,98-101], older spores also require longer time to germinate[99].
In Table 3, data on the minimal a_w for growth on food products and agar media have been compiled. On agar media the a_w was usually regulated by adding glycerol or occasionally sugars to the media.

Table 3
Minimal a_w for fungal growth of selected species

Medium	*Aspergillus versicolor*	*Eurotium* spp.	*Penicillium* spp.	*Cladosporium* spp.	*Rhodotorula* spp.	*Alternaria* spp.	*Stachybotrys chartarum*
Food products[73]	0.78	0.70-0.72	0.78-0.84				
MEA[94]		0.71	0.74				
MEA[99]			0.81				
MEA[100]		0.71	0.79-0.82				0.94
MEA[102]				0.81		0.85	
Different agars[56]	0.80	0.70	0.80				
MEA[94]	0.74	0.71					
MEA[103]	0.81	0.76	0.82	0.85	0.92	0.89	0.95
DRBC*[103]	0.81	0.77	0.83	0.86	0.93	0.89	0.95

* Dichloran Rose Bengal chloramphenicol agar.

Table 4 compiles data on selected mould growth on different building related materials, as the minimal a_w on these are higher than on the more nutrient rich agar substrates.

Table 4
Minimal water activity for fungal growth on materials of selected species and genera

Medium	*Aspergillus versicolor*	*Eurotium* spp.	*Penicillium* spp.	*Trichoderma* spp.	*Cladosporium* spp.	*Rhodotorula* spp.	*Alternaria* spp.	*Stachybotrys chartarum*
Ceiling tile[104]			0.85-0-90					
Fibre glass[104]			0.85-0-90					
Wood chip paper, 25°C[55]	0.84		0.84-0.89		0.96			no growth
Viscose [105]	0.80	0.80	0.80-0.85	0.85-0.90	0.90			0.90
Woodchip paper, at 12°C[55]	0.91		0.91-0.87		0.97			no growth
Painted woodchip paper, 25°C[55]	0.79		0.84		0.93			0.97
Painted woodchip paper at 12°C[55]	0.87		0.87		0.87-0.91			0.96
Fibre glass earth cont.[106]	0.69-0.72		0.53-0.60		0.85-0.87			
Fibre glass[106]	0.85-0.87				0.96-0.98			
Wallpaper and paper[107]								0.78-0.81
Gypsum[107]								0.84-0.89
Cellulose filter[108]								0.84-0.89
Woodchip wallpaper[103]	0.85	0.77	0.86		0.89	0.93	0.90	0.97

Table 5 shows data on building materials, where the moulds were applied as a mixture, the natural contamination was used or where moulds growing were not identified, often referred to as mildew.

Table 5
Minimal water activity for fungal growth of mixtures or unidentified fungi (mildew)

Medium	Mixture
Pinewood , planned[109]	0.80
Painted wood[109]	0.80
Hardened paint[109]	No growth
Distempered wood[109]	0.80
Brick[109]	0.88
Cement rendered brick[109]	0.80 (but almost no growth)
OSB, MDF, Particle board, Fibre board, wood[110]	Growth at 0.70 (after 8 weeks)
Glass wool and cotton[111]	0.92-0.96
Cotton fabrics[112]	0.70
Wood and wool[111]	0.85
Leather[111]	0.76
Different wood[113]	0.80, 0.90 when temp < 5°C
White brick[109,109]	0.80

It is clear from Tables 4 and 5 that no consensus exists on the minimal a_w for fungal growth on materials. It is however generally known that the humidity calibrations in many studies are not correct[11]. Hence studies are needed with more precisely controlled humidity and other environmental conditions.

2.2.1.1 Humidity - some definitions

The water activity is called equilibrated relative humidity in some papers[103] and is the same as the RH/100 (at steady state). A_w is considered a better descriptor of available water[57,114] than the absolute water contents in the material[56,57,105]. This is perhaps seen more clearly when the a_w relation to the *osmotic pressure* is shown[56,57,114], as it is the difference between this pressure and the osmotic pressure in their own cytoplasma the moulds have to maintain:

$$Osmotic\ pressure = \frac{-R \times T \times \ln(a_w)}{V}$$

Where *T* is the absolute temperature, *R* the gas constant, and *V* the partial molal volume of water.

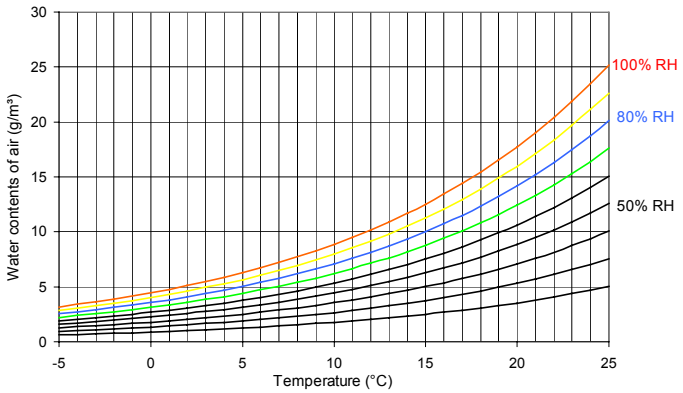

Figure 5. Relations between air temperature, relative humidity and absolute humidity.

Large local differences in ventilation and surface temperatures, especially on thermal bridges, can generate *micro climates* with very high a_w, even in rooms with low RH. This is due to the large temperature dependency of RH and the water contents of air as illustrated in Figure 1. For example, if the indoor air temperature is 22°C and the RH is 50%. The RH at a cold wall of 15°C can be estimated to about 80% RH, which is at the RH point where moulds starts to grow.

Precise measurements of the humidity in materials and the air is difficult especially at RH > 90%. Especially if the measurements are calibrated against sulfuric acid it gives inaccurate determinations[11,57].

2.2.1.2 Transient conditions

Physical parameters including humidity and temperature are not constant in buildings, and greatly influence the mould growth[11,115-117]. A bathroom is one of the extreme examples of this, and in this environment the funga is different than in environments with more constant environmental conditions[65,118] as it is being dominated by phylloplane fungi such as *Phoma, Aureobasidium*, and *Cladosporium.* This field observation is explained by data of Park[119] who showed that after drying for one week, phylloplane fungi were able to re-attain growth from the hyphal tip within 60 min, whereas storage moulds (*Penicillium* spp.) and soil fungi (*Fusarium* spp., *Verticillium*, and *Trichoderma*) needed 1-2 days, meaning that the phylloplanes can cope with a few hours of humid environment in the bathroom.

Adan[11], who worked with mould growth on plaster and painted materials, introduced the term *Time-of-wetness* (TOW) defined as the ratio between the wet period (RH ≥ 80%) and the total period, and the term f, for the number of cycles per day. It was shown that using air dryer than 65% during the dry period did not affect the growth, and that growth increased slowly with TOW from TOW=0.17 to 0.5, with a dramatic increase of higher TOWs. The parameter f had only very limited effect on growth, unless very high values were used (f>4). Viitanen[116,120] also showed that when short time fluctuations were applied (0.25 days) the growth occurred more slowly compared with longer periods (1, 2, 7 and 14 days).

2.2.2 The impact of the material on the mould growth

Moulds are able to degrade almost all natural and many man made materials[25,65], especially if they are hygroscopic[11,111]. Even totally inorganic materials will still get mouldy as they over time absorb dust which is a good medium for especially *A. fumigatus*[25] and *A. versicolor*[121,122].

Wood is still one of the most commonly used materials, and is highly susceptible to mould growth[116,123,124]. It may become infested with *Cladosporium*, *P. brevicompactum* and *P. expansum*, already at the sawmill[93]. Kiln drying makes the surface of the wood more susceptible to mould growth[116,120], as the surface will get a higher content of nitrogen and low molecular carbohydrates[125]. A number of modified wood materials are commonly used, and materials such as OSB, plywood and MDF are more susceptible to growth of *Aspergillus*, *Trichoderma* and *Penicillium* than solid wood, particleboard[110], acylated wood[126] and wood-polyethylene composites[127].

Prefabricated gypsum board is the most commonly used inner-wall material in new Danish buildings. However due to the paper, used to reinforce the material, the boards are highly susceptible to growth of moulds especially the cellulytic *S. chartarum*[14,25,72,107,128]. The gypsum itself (used to plaster walls) can also support fungal growth and the susceptibility is then correlated to the relative nutrient content of gypsum[11] and additives who make it more hygroscopic at lower humidities[129].

Many indoor surfaces are wallpapered and this increases the susceptibility of the walls, as paper and the glue are very good media for most indoor moulds[55,64,72].

Plastic materials are being increasingly used, and polyethylene and PVC are vulnerable to mould growth, as the moulds utilise most plasticizers[130]. Already in 1957, Berk, et al[131] showed that 90 of 127 different plasticizers could be degraded by moulds commonly found on indoor surfaces. Even fibre glass insulation[106,132] and fibre glass ceiling tiles (10% urea phenol-formaldehyde resin)[104] support fungal growth of especially *A. versicolor* and *Penicillium* sp. Polyurethanes has been used in many composites as well as insulation materials, and some of them are highly susceptible to mould attack[133] and they should be routinely tested for microbial degradation. Especially *Paecilomyces variotii, T. harzianum*, and *Penicillium* spp. are frequently growing on urea-formaldehyde foam insulation materials[72].

Paints can both increase and decrease the susceptibility of a given base material. Waterborne paints, which are the most commonly used in Europe due to occupational health problems with organic solvents, are highly susceptible to mould growth and should be routinely tested[11,134]. However the base material for paint is also important for the mould growth[11,55]. *Aureobasidium pullulans* is the absolutely most common mould on paints which it deteriorates in contrast to *Penicillium* and *Aspergillus* species which grow superficially on the paints[135]. Actually *A. pullulans* is often succeeding *Aspergillus*, *Alternaria* and *Cladosporium* on acrylic paints[136].

Mould growth in air filters[137] and in ventilation ducts[138] is of special concern, as the ventilation system will act as an effective carrier of the spores. In the ventilation ducts growth generally occurs on painted surfaces and especially in dust[139], although certain fibre glass insulation materials may support growth[16,140].

2.2.3 Modelling mould growth on materials

Validated models which can predict fungal growth under different environmental conditions on building materials are extremely important as they can be interfaced with many of the

current PC programs which can model humidity conditions on materials, and simulate real buildings. However only a very few models for growth on materials have been published:

- Rowan[103] predicted RH limit for growth of *S. chartarum*, *A. versicolor* and *Eurotium herbariorum*, as a function of temperature (3rd order polynomial), and interfaced this simple model for transient temperature and humidity conditions in buildings.
- Hukka & Viitanen[141] have an almost identical model, and have improved it[120,141] to include also growth under transient temperature and humidity conditions.

However, none of these models have been validated on a large number of real buildings with and without mould problems, which is the only way to validate these models.
Adan[11] have developed several models for comparing the susceptibility with building materials to both constant and transient humidity conditions. These are however more sophisticated and they are based on a non-linear logistic model, which is able to cope with the non-linear, 6-point scale, used to compare the susceptibility of different materials.

2.3 Health problems associated with airborne moulds

A number of different approaches exist for studying the health effects associated with mouldy buildings. The two major approaches are: i) comparing the toxicity or biological activity, based on in vitro and in vivo data, with the actual exposures in the buildings; ii) epidemiological studies where symptoms in a large population are correlated to exposure in normal and mouldy buildings.

In the first studies of health problems related to mouldy buildings it was believed that people were type I allergic[25,142], meaning that IgE antibodies are formed against specific proteins, called allergens, from the fungal spores[25]. Type I allergy can be precisely diagnosed by the classic skin prick testing (SPT) or in serum if extracts of the appropriate allergens exist[25]. SPT panels and antibody-allergen-kits for the outdoor air moulds, *Alternaria* and *Cladosporium*, as well as some penicillia and aspergilli have been commercially available for a number of years, but are not available for many of the building associated moulds. Allergic persons are often genetically predisposed[25] and may develop asthma due to inflammation of the lung as a results of large quantities of inflammatory mediators released from the different lung granolocytes. However, as type I allergy is not the main cause of the health problems observed in mouldy buildings[22,30], the use of SPT or specific IgE in serum has a very limited diagnostic value when working with mouldy buildings.
A number of other types of antibodies, including the IgG antibodies, are naturally produced against most "non-self" proteins and help clearing these from the body. Detection of specific IgG antibodies against these "non-self" proteins can hence be used do determine if a person have actually been exposed to a specific mould. However only positive results can be used, as not all people will develop detectable quantities of IgG antibodies[23].
High exposures to protein dust may result in such high levels of antigen-antibody complexes, in the blood vessels, that these are deposited in such quantities that they may trigger an immune response (allergic alvolistis / hypersensitivity pneumonitis) seen as malaise, elevated temperature, pains in joints and even astma[25,143].

2.3.1 In vivo and in vitro effect of fungal spores

As earlier mentioned, the vehicle for exposure to mycotoxins in the indoor environment seems to be the fungal spores[46] and fragments of these and the mycelia[84]. Hence, studies of

the effects of whole spores are important as they contain the whole "mixture" of metabolites and structural components as well as the particle effect of the spores[144].
An interesting study showed that rats exposed to naturally released spores of *A. versicolor* (up to 10×10^6 CFU/m^3) originating from growth on the walls, during one month developed severe lung damages including granulomatous lesions, partly due to high production of IL-1 from the macrophages[145].
Instillation of *P. chrysogenum* spores in mice[146] revealed similar results, and in addition showed that 10^4 spores instilled twice a week increased total IgE in serum and IL-4 in the lung bronchoalveolar lavage, interestingly this was not seen when the spores were treated with methanol to kill them or extract metabolites.
Shahan et al[147] showed that spores from different fungal species induced very different responses in rat macrophages, measured as mRNA induction of TNFα and other inflammatory mediators. Spores from *A. terreus* and *P. spinulosum* did not stimulate any inflammatory response, in contrast to *A. fumigatus, A. candidus*, *A. niger*, *Eurotium amstelodami*, and *C. cladosporioides* which stimulated production of several inflammatory mediators.
Ruotsalainen[148] showed that *Stachybotrys* isolates (21 different) induced either strong inflammation, by releasing NO, TNFα, IL-6 and reactive oxygen species (ROS), or cytotoxicity (induced by satratoxins producing isolates) in macrophages. *In vitro* studies with instilled *Stachybotrys* spores in mice have showed similar results[45,45] and will be dealt with in details in section 2.4.1.
The cytotoxicity of *Penicillium* and *Aspergillus* isolates from damp buildings in Scotland cultured on MEA was studied at it was found that about 50% of the investigated isolates were cytotoxic to the fibroblasts[149,150]. Such cytotoxicity may cause severe lung damage, especially if the fibroblasts and perhaps also macrophages die by necrosis, as the latter subsequently will liberate high quantities of inflammatory mediators.
However there seems to be many different mechanisms associated with the effects in cell cultures, especially when both cytotoxicity and inflammatory potential are tested simultaneously [151]. Generally many mould spores will kill macrophages before they are able to respond with an inflammatory response.
These studies indicate that the lung damage induced by fungal spores may be partly or fully due to the inflammation induced by the macrophages as it has been shown that excess induction of some cytokines, NO and ROS may play an important role in the pathogenesis of inflammatory diseases such as asthma[152-154]. It is also notable, that isolates/species specific metabolites are involved. However, except for the first, they have all used spores from agar culture, which is seriously biased as moulds usually produces much higher quantities of metabolites on these media[64].
Literature on *in vitro* and *in vivo* studies of specific metabolites will be found in respective mould species in section 2.4.

2.3.2 Epidemiological studies

Epidemiological studies have been widely used to study health effects in mouldy buildings[6,9,155], especially combined with questionnaires to determine symptoms and/or if the home or workplace has been damp or mouldy. However several studies have concluded that objective measures are needed to obtain statistically significant results[6,30,86,88].
A large number of studies on general health problems and the association dampness and mould growth have been published (see Table 1, p. 1), however reviewing these is outside

the scope of this work, and only case studies of specific moulds will be further dealt with, as they may be correlated to specific fungal metabolites.

Johanning et al[23,156] studied an office building heavily infested with *S. chartarum*. Only two persons were IgE positive to *S. chartarum*, these persons worked in the same area and some had abnormal complement function and composition of T and B lymphocytes, $CD3^+$ T cell (CD3 is a protein found on both $T_{cytotoxic}$ and T_{helper} cells[143]) concentrations were lower among the employees than among controls. IgG measurements showed only small differences between exposed and non-exposed employees and were not significantly correlated with symptoms. In later papers[20,157], they reported several more cases from the clinic with corresponding surveys of their homes for mould occurrence. Specific IgG antibodies could only be used as exposure markers but was only positive in 25% of the cases of actual exposure.

In a 10 years old building with severe water damages Hodgson et al[19] found that the occupants had significantly more pulmonary problems, as eye irritations, stuffy nose, and especially flue like symptoms, than normal. Air samples in one of the rooms revealed up to 8000 CFU/m^3 of especially *A. versicolor*, and in an other room up to 129 CFU/m^3 but with up to 50% of the colonies being *S. chartarum*.

2.3.2.1 Idiopathic pulmonary hemosiderosis cases

A dramatic escalation in the symptoms observed in mouldy buildings has been reported from the Cleveland, Ohio, area[158,159]. Here idiopathic pulmonary hemosiderosis (IPH) in infants (< 6 months old) was associated with growth of *S. chartarum* in the homes. It should be noted that IPH is extremely rare in infants, with a general prevalence of 0.2-1.2 per 10^6 children per year in the Western world[160]. Reports of such life threatening conditions including fatal cases have great legal implications, especially in the USA, as well as economic importance for the rest of the world as it could lead to guidelines not accepting growth of *S. chartarum* in buildings.

The first 10 IPH cases from Cleveland were reported in December 1994 by the US CDC[161] however with no plausible reason. Later CDC reported additional 27 cases from Cleveland[158,159], and at this time it was concluded that IPH was associated with growth of *S. chartarum*. Additional 7-9 cases were identified in Chicago[162] and 6 from Detroit[163], however no mould investigation of the houses has been published.

An overview of the IPH cases in USA has been made by Dearborn et al[26], who found 138 IPH cases in USA the period 1993-1995, and that the IPH incident rate in Cleveland was 1.5 IPH per 10^3 infants per year in the period. The association between IPH and *Stachybotrys* exposure has been questioned by the CDC[164], after a anonymous review to which the investigators have not been able to respond.

An additional case has been reported from Kansas city[165,166] in a home with a mould infested ventilation system, yielding 420 *Stachybotrys* spores/m^3 (counted by microscopy) from the bedroom of the infant, however also extremely high counts of *Penicillium* and *Aspergillus* (11250 spores/m^3 counted by microscopy) in the air was detected.

From Houston a case has also been described[28], and here *Stachybotrys* (= Houston strain[167]) was isolated from the lung of a 7 years old white boy with IPH, chronic cough, and chronic fatigue.

From Cleveland an additional case has been reported[168] with no abnormal clinical tests except from the hemosiderin laden macrophages (showing that the bleedings had been occur-

ring over some time) recovered from the lung. The bedroom of the child was heavily infested with *S. chartarum* and air samples revealed 6×10^4 CFU/m^3 of the fungus.
From St. Louis there is also a report[27] on a case of IPH in an infant, who was exposed to fungi during a 2 weeks holiday. On the return trip the infant developed the hemorrhage upon exposure to tobacco smoke. Low quantities of hemosiderin in macrophages in the lung indicated no preceding bleedings. During the vacation (14 days) the infant had resided in a room with visible mould growth of *Trichoderma*, *Penicillium*, *Cladosporium* and *Ulocladium*.
Recently a fatal IPH case has been discovered in Belgium (N. Nolard, personal communication), in this case airborne spores were detected, they were released in high numbers due to constructional work in the bathroom.

2.4 *Biologically active metabolites from moulds*

Microfungi have the ability to produce a high number of secondary metabolites, which they for various reasons need in their natural habitat[169,170]. Most of these are produced as a response to other organisms especially other fungi[171]. Some of these metabolites can cause a toxic response "when introduced by a natural route in low concentrations to higher vertebrates and animals" and are referred to as mycotoxins[172].
Sorenson[173] and Miller[69] were some of the first to realise the implications of mycotoxins in the indoor environment. The latter emphasises that moulds generally produce several mycotoxins and synergizers, which are not toxic themselves, but enhance the toxicity of some mycotoxins[174]. It is also stressed that repeated low concentration exposure of airborne mycotoxins would be very difficult to diagnose.
When trying to predict which biologically active compounds of microfungal origin may be present in water-damaged buildings - at least five problems have to be addressed:

- Most secondary metabolites and mycotoxins are species specific making identification of isolates to the species level extremely important. Changes in taxonomy including introduction of new species and synonomisation of others have further complicated this work[62,175].
- False positive findings of mycotoxins are often common from laboratories which use insufficiently specific methods, or which are not experienced in mycotoxin analysis and the large number of interfering compounds produced by moulds[62].
- Even in fungal extracts of species, which have been extensively studied for their metabolites as e.g. *Aspergillus flavus, A. fumigatus,* and *Fusarium graminearum*, unknown biologically active metabolites are still present[69].
- A large number of the secondary metabolites described in the literature have been tested in a very few assays, and extremely few compounds have been tested in full animal studies. The latter method is unfortunately often the only way of finding defects in the offspring or reveal metabolites which are activated in special organs such as liver or kidney[144,176]. For exposure assessment even fewer metabolites have been tested in inhalation studies where some metabolites have been magnitudes more potent[177].
- The produced metabolites vary considerably between media, so the moulds may produce very different metabolites when growing on building materials[63,178].

It should be considered that on naturally infested materials the moulds do not grow in pure cultures, but in mixed cultures with other moulds and often also bacteria. These conditions may induce production of other metabolites than in pure cultures[50].
The following review will target the potential fungal metabolites produced in buildings by the building associated funga, and may have a varying detailing level. This reflects where most of the experimental work has been concentrated and where less known species and genera have been reviewed.
The tables of the metabolites reported from the reviewed species have been moved to Appendix B, as many of them run over several pages, and hence will diminish the readability of this thesis.

2.4.1 *Stachybotrys*

Stachybotrys chartarum (Ehrenberg ex Link) Hughes (= *S. atra* Corda, and *S. alternans* Bonord.) is the only species from this genus which has been found in buildings.
Jong & Davis[179] made a revision of the genus in 1976 based on available cultures and found that the genus comprised additional ten species: *S. albipes, S. bisbyi, S. cylindrospora, S. dichroa, S. kampalensis, S. microspora, S. nephrospora, S. parvispora, S. oenanthes* and *S. theobromae*. Later McKenzie[180] described three new species from decaying leaves, and Dorai & Vittal [181] and Hua-zhong[182], Miyazaki et al[183] additional species.
Most interest of *S. chartarum* has been due to its capacity to deteriorate organic fabric fibres[179] and its ability to produce the highly cytotoxic macrocyclic trichothecenes[184,185] which have given significant problems in mouldy straw in Eastern and Northern Europe[184,186-188].
Stachybotryotoxicosis was first described in the 1930s by Russian researchers[189], and later by Forgacs in the English written literature[187,190]. He assisted Russian veterinarians during World War II, where stachybotryotoxicosis in horses was a severe problem for the Russian army[191]. Russian researchers showed that horses were very susceptible to *Stachybotrys* infested straws[192]. Forgacs describes two types of toxicosis: i) A typical form with inflammation of the stomach, and the mouth as well as necrosis of some areas, followed by a decreasing number of thrombocytes and a decreases in the blood clotting, followed by a decreasing number of leukocytes and an almost total absence of blood clotting[192]; ii) An atypical form, characterised by nervous disorders, as loss of reflexes, elevated body temperatures, and altered cardiac action[192].
The link to indoor air appeared in 1986, when Croft et al[47] described a household in Chicago, where the occupants suffered from symptoms similar to stachybotryotoxicosis. Filters from air sampling in this home was black after sampling due to the many *Stachybotrys* spores (B. B. Jarvis, personal communication).

2.4.1.1 Trichothecenes

In 1973, Eppley & Bailey[184] were the first to isolate trichothecenes from *S. chartarum*, they found the known components, trichodermol and roridin E (RE) and three novel components, named satratoxins H, G and F[193]. These three components were first structure elucidated 4-7 years later[185,194]. All trichothecenes produced by *Stachybotrys* species have been compiled in Table 1 in Appendix B.
The trichothecenes (TR) are divided into the following four groups[195].

- Type A trichothecenes (TA), easily described as the trichothecenes (TR) not included in the following three groups. These trichothecenes have been isolated from species within

the fungal genera *Memnoniella, Trichoderma, Trichothecium, Myrothecium, Stachybotrys,* and *Fusarium,* are highly cytotoxic.

- Type B trichothecenes (TB) are characterised by the C_8-keto group. This group is approximately only 10% as toxic as the TA[176,196] and is only produced by *Fusarium* species.
- Type C trichothecenes are characterised by the ring from R^2 to the R^3 alcohol group and are generally referred to as macrocyclic trichothecenes (MTR). These are at least 10 times more cytotoxic than the type A, and are produced by species of *Stachybotrys* and *Myrothecium*.
- The very rare type D trichothecenes are characterised by a C-7,8 or C-9,10 epoxy group.

The sesquiterpenoid pathway of the trichothecenes produced by *Fusarium* has been examined in detail (see Figure) due to the economical importance of this genus[197]. An important step in the biosynthesis is the then cyclization to trichodiene by trichodiene synthase, encoded by the *TRI5* gene[197-199], which has been characterised in *Fusarium*, *Myrothecium* and *Stachybotrys*[197,200,201]. Trichodiene is volatile and can be used as an indicator for the synthesis of trichothecenes[202,203]. The MTR is the synthesised over trichodermin and the trichoverroids as seen in Figure [197,204].

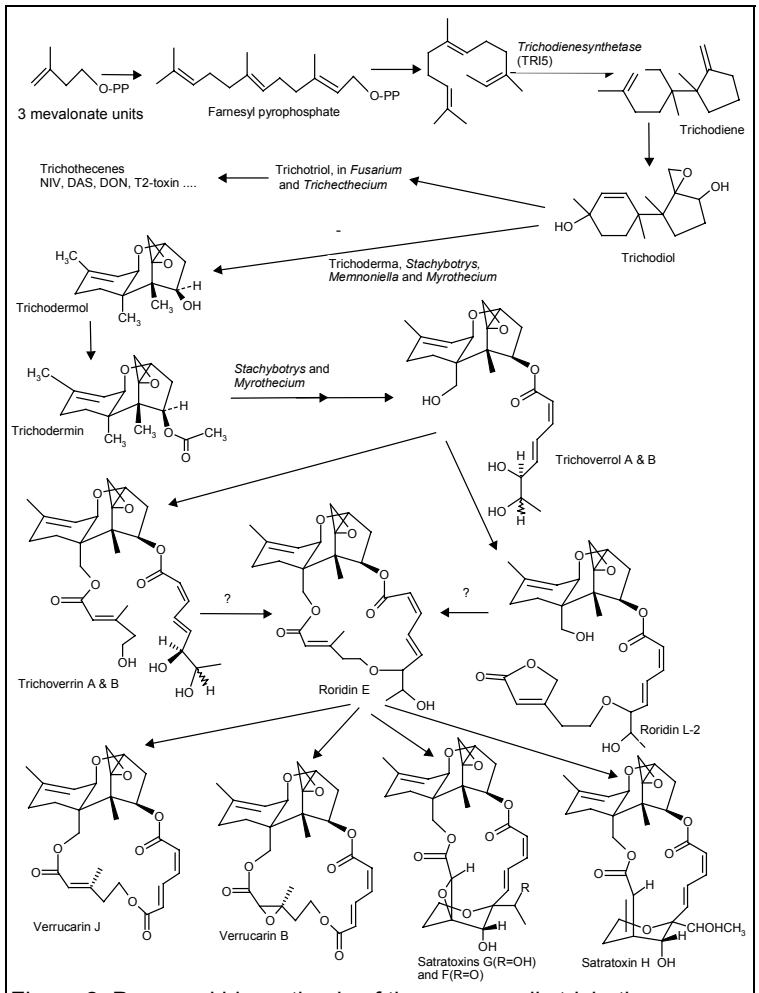

Figure 2. Purposed biosynthesis of the macrocyclic trichothecenes.

Several studies have shown that *S. chartarum* strains isolated from cereals can produce MTR[107,108,205] when grown on building materials and air filters. In naturally infested materials MTR have been detected by Croft et al[47] who found, satratoxin H (SH), verrucarin B (VB), verrucarin J (VJ), and the trichoverrins. Several later studies have verified these findings[50,165,206]. From an exposure point of view, Sorenson[46] has shown that the spores from MTR producing isolates contained approx. 10-40 ppm of the MTR ≈ 40 fg MTR per spore, whereas Nikulin et al[45] found 140 fg/spore.

Not all S. chartarum strains produces satratoxins, Korpinen & Uoti[188], showed that 67% of the *S. chartarum* strains isolated from toxic feed in Finland were cytotoxic to fibroblasts (presumably producing satratoxins). Andrienko & Zaichenko[207], showed that Russian *S. chartarum* isolates grown on seeds, could be grouped in four: i) 19% with highly dermatoxic properties (presumable being satratoxin produces); ii) 4% with only antifungal activities; iii) 47% strains with antifungal and antibacterial activity also being dermatoxic; iv) 26% with no biological activity. Jarvis et al[208] found that 80% of the strains isolated from stachybotrytoxicosis cases in farm animals from Eastern

Europe produced MTR. This is significantly different from the strains isolated in water-damaged buildings in the USA where only 30-40%, of the isolates from the IPH case homes produced MTR[44,209] and from Finland[148] where about 50% of the strains were highly cytotoxic to murine macrophages, resembling the biological activity of MTR producing strains.

Toxicology of the trichothecenes

It has long been known that the TR generally inhibited the protein synthesis[196], where some inhibited the ribosomal termination or the elongation of the translation process. Later both TR and MTR have been shown also to induce apoptosis in cells, by activating SAPK/JNK and p38 MARK kinases by ribosome binding inhibiting the protein synthesis[196,210]. Interestingly trichodermol and trichodermin are the only TR that are non-cytotoxic[196].

Parent-Massin & Parchment[211] grouped haematoxicity, abnormal blood cell grouping or malfunction, of mycotoxins in three groups:

- Haematoxicity not described in literature: patuline, verrucosidin, and fumonisins.
- Compounds able to cause adverse haematoxic effects, but with the principal mechanism not being haematoxic: ochratoxin, aflatoxin and zearalenone.
- Compounds giving severe haematoxic effects, with minor symptoms, like the trichothecenes.

At high concentrations (10-20 mM) T-2 (the most toxic TA) induces haemolysis of red blood cells of rodents, pigs, dogs, horses and humans. Single doses of DAS (a TA) given to humans as anti-cancer drug (Phase I test), resulted in vomiting and central nervous toxification. TR have a significantly lower LD_{50} value in new borne animals (mice, lowered by approx. 100 $\times$) in which the pathologists found severe lesions of bone marrow, thymus and spleen.

As only few MTR are commercially available, only few studies on these components exist. However Hughes et al[212] studied the effect of 11 different MTR on the immune system of mice. They were administered, once, with half the LD_{50} dose and sacrificed after 4 days. White blood cell concentration decrease upon exposure to VJ and RE, but some of the others MTR had the opposite effects. This might be due to more circulating white blood cells at the start. ELISA showed a decreased production of antibodies against sheep red blood cells for some components.

Pestka & Bondy[213] who showed that mice exposed to TR had up to a 10 000 lower LD_{50} to *Salmonella typhimurium* exposure. This is presumably due to the fact that leukocytes (white blood cells) are affected at far lower concentrations than the acute ones[211]. Especially TA, are cytotoxic to granulocyte, monocyte and erythroblast progenitors[211] at concentrations higher than 5×10^{-8} M. Effects at this level includes inhibition of antibody production, delayed skin graft rejection, and inhibiting phagocytosis of murine macrophages[144].

These symptoms resemble the ones observed in humans from *Stachybotrys* infested buildings reported by Johanning et al[23,156] (see section 2.3.2), especially when combined with the data of Creasia et al[177,214] who showed that the acute effects of the TR T-2 toxin in rodents was 10-20 time stronger when it was inhaled than when it was administrated through the feed. However Pang et al[215] was not able to verify this effect in pigs.

Animal studies on the inhalation of *Stachybotrys* spores

The association of IPH cases with *S. chartarum*[26] has of course triggered a number of projects on the influence of *S. chartarum* spores on cell cultures and whole animals.

Lung mycotoxicosis in mice was demonstrated by Nikulin et. al.[45] who used two *S. chartarum* strains, isolates #72(=CBS 414.95 = IBT 9460) and #29 (=CBS 413.95 = IBT9472). It was shown that #72 induced much more severe haemorrhage in the mice than #29. The first iso-

late produced satratoxins and high quantities of stachybotrylacetones and the later strain produced only minor quantities of the latter type. The same group[216] also instilled mice with 10^3 and 10^5 spores of the same two *S. chartarum* isolates 6 times during 3 weeks. In the mice instilled with the highest dose, severe inflammatory changes were observed in the lungs. The mice administered with spores from #72 developed much more severe inflammations than the mice instilled with spores from #29. At the lowest level only the mice instilled with the spores from the satratoxin producing isolate, #72, developed inflammatory changes in the lungs. However due to the few isolates used and the variation in both MTR and stachybotrylacetone production the study remains partly inconclusive on the responsible components.

This is the same for the study of Mason et al[217,218] who instilled *S. chartarum* spores and isosatratoxin F in the lungs of mice, and observed that both obstructed the lung homeostasis whereas *Cladosporium* spores did not. However the *S. chartarum* spores and the pure toxin induced very different surfactant production (P60 and P100 phosphor lipids), but no chemical analyses were performed on the strain so it is unknown if it produced MTR.

Rao et al[219] instilled spores in rat lungs, and showed that when spores from a highly cytotoxic (presumably a MTR producer) of *S. chartarum* was methanol extracted, the toxicity of the spores almost disappeared compared with unextracted spores. This clearly shows that the pulmonary toxicity is due to extractable metabolites as MTR or most of the metabolites described in the following subchapter.

The conclusion drawn from these studies is that *S. chartarum* spores indeed contains a number of metabolites which can induce severe inflammation, haemorrhage and death in animals. However there is no evidence that these effects are only caused by the MTR.

2.4.1.2 Non trichothecene metabolites

Most species in *Stachybotrys* and especially *S. chartarum* produces high quantities of a number of spiriocyclic drimanes[183,220] as shown in Figure 3. These components have a number of biological properties, *inter alia* inhibition of TNFα liberation from human macrophages[221], complement inhibition[183,222] and antiviral activity[223]. When considering that one of the most common symptoms in mouldy buildings is recurrent airway infections, metabolites which inhibits the complement system are interesting, as the complemet system is an important part of our defence against bacteria[143]. A number of triprenyl phenol metabolites (see Figure 3) have been described from several *Stachybotrys* species. They are precursors of the spiriocyclic drimanes, as the triprenyl can be cyclizied into the drimane part. These metabolites can activate and enhance the plasminogen-mediated fibrinolysis (at levels down to 100 µM)[224-226] and could in that way be plausible components responsible for IPH, as this could account for the brittle blood vessels in the lungs.

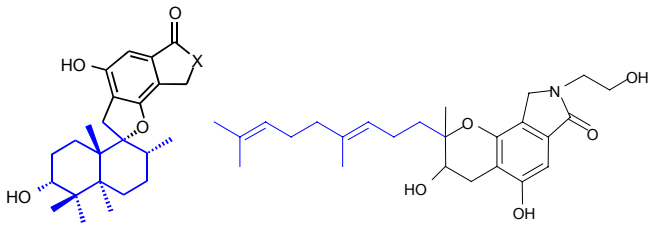

Figure 3. Left, the spiriocyclic drimanes, stachybotrylactone (X=O) and stachybotrylactam (X=NH). Right, SMTP-1, one of their precursors.

Both the triprenyl phenols and the spiriocyclic drimanes are produced by two mixed biosynthetic pathways, partly by the sesquiterpenoid pathway (shown in blue on Figure 3) and partly by the polyketide pathway. Reviewing the literature on these components has been troublesome as Russian groups have published known structures under new names, data on the stereochemistry is often not available, and a significant number of the publications have

been Japanese patents and patent applications. Chemical and biological data on the spirio-cyclic drimanes and other non-trichotehcene metabolites are given in Table 2, Appendix B.
A new type of metabolites has been isolated from non-satratoxin producing isolates of *S. chartarum*, and has been named atranones[209]. They are [227] biosynthetically related to the dolabellanes[228] and altogether 8 atranones and two dolabellanes have been isolated from the *S. chartarum* cultures[209,227]. Three of these metabolites (6β-hydroxydolabella-3E,8E,12-trien-14-one, atranones B and C) have also been detected in material samples from a IPH case home in Cleveland[229]. However the biological activity revealed until now on these components has been rather limited, but with the number of enzymatic steps used to synthesise such complicated components[228] they must have a biological activity.
A component belonging to the immunosuppressing cyclosporin family has also been isolated from a *Stachybotrys* sp.[230], and is of course interesting due to many infections experienced by people living in mouldy buildings. Also components, shown not to be TR, damaging the cell membrane of boar sperm cells has also been described[231] from *S. chartarum*, however it has not been cleaned up and characterised.
Vesper et al[232] tested the haemolytic activity[229] of *S. chartarum* isolates from the Cleveland IPH cases, grown on gypsum boards. Haemolysis was correlated to growth at 35°C and not at 23°C, and a higher percentage of the spores from IPH case homes were haemolytic. The responsible component has just been partly charecterised[233] as a novel haemolytic protein, stachylysin. Additionally the group has showed that the *S. chartarum* strains from the IPH case homes produces higher quantities of siderophores than strains from non-IPH case homes[167]. Iron is a key component for pathogens and iron binding proteins and peptides excreted from pathogenic bacteria[234] and fungi[235] are well known. The authors seem to indicate that a mechanism might be partly due to actual growth of *Stachybotrys* in the lung tissue of the infants.
All these findings clearly show that the biologically active components from *S. chartarum* are far from known, and even when they are all known there will still be much left to do in determining the actual exposure to these in mouldy buildings.

2.4.2 Aspergillus

As the genus of *Aspergillus* Mich. ex Fr. is one of the anamorph genera placed in the family *Trichocomaceae,* where it is associated with 8 holomorph genera. This is new in comparison with the last monograph by Raper & Fennell[236], which is still extensively used, although it should only be used in combination with "Integration of modern taxonomic methods from *Penicillium* and *Aspergillus* classification" and “Modern concepts in *Penicillium* and *Aspergillus* classification” from 2000[237] and 1990[238] respectively.
The following sub chapter has been divided into subsections on the most important species.

2.4.2.1 A. versicolor

A. versicolor (Vuillemin) Tiraboschi belong to the subgenus »Nidulantes« section »Versicolores«, with no known teleomorphs. This species is common in many dry environments and is one of the few aspergilli, which are also common in temperate and cold environments[25]. It is the absolutely most common *Aspergillus* in damp and water-damaged buildings.
Together with several streptomycetes[239] and *Chaetomium globosum*[240] it may be one of the major producers of the mouldy smelling component, geosmin, in buildings[241].

Fragments which are significantly smaller than the spores are liberated from *A. versicolor* infested building materials[84] and may account for the health problems in buildings where it is the predominant species on the materials without being so in cultivation based air-samples.
Prolonged exposure may lead to significant lung damage, maybe as a secondary effect of IL-1 liberation[145], as discussed earlier in the report.

Sterigmatocystin

Sterigmatocystin (ST) is considered the most important toxic metabolite of *A. versicolor* and as seen in Table 3 in Appendix B, a number of analogues have been isolated including a number of precursors that are also biologically active.
The biosynthesis of ST has been studied in detail, as ST is only two enzymatic steps from aflatoxin B_1 (AFB_1) which is of great economical importance for the agriculture industry. ST is deca polyketide synthesised over a C_{20} precursor, which is then transformed to norsoloric acid, averatin, 1'hydroxyversicolorone, versiconal hemiacetate acetate, versicolorin A and finally ST[242], meaning that findings of ST would also imply the presence of a significant number biologically active precursors.
ST is cytotoxic by itself, but the major problem is the carcinogenic properties after activation in the liver by the cytochrome P450 mono-oxidase system, to the 8,9-epoxide analogue which then preferable reacts with guanine as seen in Figure 4, just as for AFB_1 [176,243].
ST has been shown to be a very strong inhibitor of the of chicken tracheal cilia[244], and as this is one of the important ways we clean our upper airways, inhibition of this system may increase the risk of upper airways infections.
No studies of airborne ST have been found. However several exist for AFB_1, which in rats and mice (one dose 17 mg/kg) suppressed the macrophage phagocytosis for 2 weeks as well as their release of TNFα upon exposure to endotoxin. Airborne dust containing AFB_1 has been shown to increase the risk of liver cancer in workers handling ABF_1 infected animal feed by two- to threefold with a 10 years latency[32,33]. Later studies have shown that the AFB_1-guanine-adduct is an important exposure biomarker[243].

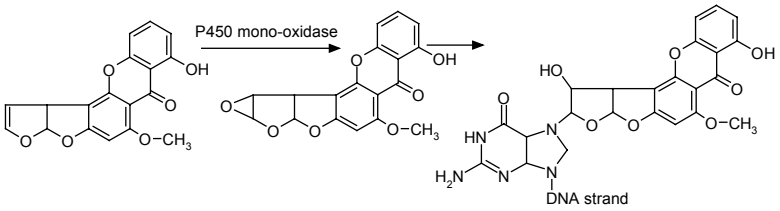

Figure 4. Activation of sterigmatocystin and formation of the guanine adduct.

ST production is influenced by the humidity on cereals, as was only detected at RH over 88.5% and the maximum production of the toxin as well as biomass occurred at 93% RH[245], and hence the same phenomena may be found in buildings.

Other metabolites

A. versicolor produces a number of other metabolites shown in Appendix B, table 4, but their toxicity is generally not very well described. The production of cyclopiazonic acid by *A. versicolor* reported by Ohmomo et al[246] was due to misidentification with *A. oryzae*[62] and isolation of griseofulvin, dechlorogriseofulvin, and 3,8-dihydroxy-6-methoxy-1-methylxanthone from *A. versicolor* reported by Kingston et al[247] must be due to a misidentification or contamination with a griseofulvin producing *Penicillium* (J. C. Frisvad, personal communication).

2.4.2.2 A. ustus

Aspergillus ustus (Bainer) Thom & Church, also belongs to the subgenus »Nidulantes« but is placed in the section »Usti«, and has no known teleomorphs.

The most extensive work on *A. ustus* metabolites have been done in South Africa by the group of Steyn and Vleggaar, due to problems with mycotoxicosis in cattle caused by *A. ustus* infections of grains[248-250]. And as seen in Appendix B, Table 5 the austamides and austdiols[251,252] are acute toxic and the austocystins both toxic and carcinogenic[253]. The later group is also deca polyketides and closely related to AFB_1 and ST both in structure and biological activity[242] also notable is the production of versicolorin C[254] which is one of the precursors to ST.

Aspergillus ustus var. *pseudodeflectus* is very different from *A. ustus* sensu strictu and produces pergillins, the TMC-120's and the ophibolins all showing various biological activities[255] (Appendix 5, Table 5)[254,256,257].

However no studies of airborne *A. ustus* spores or metabolites have been published, and hence the data on airborne AFB_1 found in the *A. versicolor* section is the best when concerning the austocystins.

2.4.2.3 A. niger complex

The *Aspergillus* section *Nigri*, found in the subgenus Circumdati, is also called the Black *Aspergilli*, and contains 8 species*: A. heteromorphus, A. ellipticus, A. niger, A. bubingensis, A. brasiliensis, A. japonicus, A. carbonarious* and *A. aculeatus*[258].

The literature review on metabolites deals with the first 6 species, as they are very difficult to differentiate and seem to produce very similar metabolites (J.C. Frisvad, personal communication), and can be seen in Appendix B, Table 6.

When a Niger is found in buildings, there are usually significant quantities of biomass but it is not that common that a full overview of its preferred materials has been established.

Extracts of *A. niger* generally contains significant quantities of the low toxic[259] tetra-cyclic compounds and naphtho-γ-pyrones [65], but the distribution of strains producing the highly cytotoxic malformins[260] not known. This together with the low number of isolates which actually produces the highly nephrotoxic component ochratoxin A, makes a this a species which could pose a significant indoor problems if these two latter types of metabolites are produced in buildings.

2.4.2.4 Other aspergilli

A number of other aspergilli are also found in buildings especially the teleomorph *Eurotium repens* de Bary (*A. glaucus group in* Raper & Fennell[236]), often isolated from wood containing products and in roof construction which are getting very hot during the day. *Eurotium* is not recognised as a mycotoxin-producing genus[65], but has however never been tested for their inhalation toxicity. Many of them can grow at 37°C and may cause infections in immunosuppressed persons.

A. ochraceus is relatively rare in buildings, but in a household with indoor air problems, growth of *A. ochraceus* was found, and subsequently ochratoxin A was detected in dust using several highly selective analytical methods[261]. This means that growth of this species in a building should be considered a very serious problem.

Two studies[262] have both shown that *A. flavus* does not produce aflatoxins when growing on different building materials. The isolates used with both studies were capable of producing

theses toxins on laboratory media[262,263]. However this species produces a number of other metabolites which many pose a health risk.
A. fumigatus, is commonly found in dust and thus isolated frequently on dusty materials, but rarely found growing on materials[25]. When cultivated on wood pieces, it produces tremorgenic components[264], but the responsible components were not detected. Later, Ren et al[262] showed that two isolates capable of producing verruculogen and helvolic acid, failed to produce these when growing on different materials. This species is the most common infectious mould, growing in the lungs of immunosuppressed persons.

2.4.3 Penicillium

The genus of *Penicillium* Link ex Fr. is one of the anamorph genera placed in the family *Trichocomaceae.* It is associated to the holomorph genera, *Eupenicillium* and *Talaromyces*[265]. In the last 10-15 years, the use of secondary metabolite profiles, isoenzyme patterns, and genetic approaches has drastically altered the taxonomy of this genus, previously classified on the basis of morphology. At present 225 accepted species exist in *Penicillium.* These include approx. 3 times as many synonymisized species[265], reflecting the difficulties experienced when identifying and classifying *Penicillium* species.
Especially the terverticillate penicillia are difficult to identify to species level as they are very closely related, and secondary metabolite profiling seems to be most the accurate method[266]. Unfortunately misidentification of production cultures has obscured the connection between species and secondary metabolites[62,267,268].

2.4.3.1 P. chrysogenum

Penicillium chrysogenum Thom, is placed the series *Chrysogena* Raper & Thom ex Stolk & Samson[269] in the subgenus *Penicillium.*
P. chrysogenum has 16 synonomised species[269]:

- *P. griseoroseum* Dierckx
- *P. brunneorubrum* Dierckx
- *P. citreoroseum* Dierckx,
- *P. baculatum* Westling
- *P. notatum* Westling
- *P. meleagrinum* Biourge
- *P. flavidomarginatum* Biourge
- *P. cyaneofulvum* Biourge
- *P. roseocitreum* Biourge
- *P. rubens* Biourge
- *P. camerunense* Heim apud Heim
- *P. chrysogenum* var. *brevisterigma* Romankova
- *P. harmonense* Baghdadi
- *P. verrucosum* var. *cyclopium* strain *ananas-olens* Ramire

P. chrysogenum is found in dry habitats and can grow at temperatures as low as 5°C[270]. It is known to produce a large number of metabolites especially antibacterial as shown in Table 7 in Appendix B. However, this also reflects the many screening projects including this species due to its original production of penicillin. The most toxic metabolites isolated have been the neurotoxic roquefortine C but it may also produce secalonic acid D[176,271-273] which is produced by the closely related *P. oxalicum,* (J.C. Frisvad, personal communication).
PR-toxin have been reported from this species by Frisvad & Filtenborg[274] and by Dai et al[275], but these findings are still discussed (J.C. Frisvad, personal communication).
An inflammatory mediator may be present in the spores, as methanol extracted spores were non active compared with non-extracted spores[146].

2.4.3.2 P. brevicompactum

Penicillium brevicompactum Dierckx[265] is now placed in the series *Olsonii*[269] in the subgenus *Penicillium.* It is common on wood, some fruits, tropical soil and can grow at a lower a_w than other penicillia[124,269].

P. *brevicompactum* has 9 synonomised species[269]:

- *P. griseobrunneum* Dierckx
- *P. stolenifererum* Thom
- *P. tabescens* Westling
- *P. szaferi* K.M. Zalessky
- *P. hagemiii* K.M. Zalessky
- *P. biolowiezense* K.M. Zalessky
- *P. patris-meii* K.M. Zalessky
- *P. brunneostoloiferum* Abe
- *P. brunneostoloiferum* Abe ex Ramirez

As seen from Table 8 in Appendix B, this fungus is capable of producing a high number of biologically active metabolites, from which mycophenolic acid is the most well known and most consistently produced[268,276]. This component was the first mould metabolite to be purified and crystallised, as early as in 1893[277]. It is being used as both an antibacterial and immunosuppressant drug. The most toxic component is the mytagenic botryodiploidin[278-280], but it has not been prooven to be the principle component for a number of mycotoxicosis cases where this species has been the primary contaminant (J.C. Frisvad, personal communication). However most of the biologically active components seem to be able to interact with the growth of plants[281-283].

2.4.3.3 P. polonicum

Penicillium polonicum K.M. Zalessky also found in the subgenus Penicillium, but the series *Viridicata*, some times refereed to as the *Penicillium aurantiogriseum* complex. The series are generally found on cereals and produces a high number of secondary metabolites[269].

P. polonium has 2 synonomised species:

- *P. aurantigriseum* var. *polonicum* (K.M. Zalessky) Frisvad
- P. *carneolutescens* G. Smidth

Some of the most toxic *Penicillium* species are found in the *aurantiogriseum* complex, but it is extremely difficult to distinguish the individual species by other means than metabolite profiling. Consequently literature has been obscured especially in this complex and the literature review will mostly be based on the paper of Frisvad & Lund[284,285], and can be seen in Table 9, Appendix B.

P. polonicum produces at least the groups of highly toxic components, the verrucosidins[286] who are tremorgenic, the cytotoxic penicillic acid, which is extremely active against rodent lung macrophages (*in vitro*)[287], and nephrotoxic glycopeptides which may be involved in the Balkan nephropathy endemic [288].

2.4.3.4 P. expansum

P. expansum is occasionally isolated in buildings, where it is often isolated from wood[63]. On this substrate, Land and Hult[289] showed that some *P. expansum* could produce patulin. This mycotoxin is one of the most toxic *Penicillium* metabolites, being very highly cytotoxic and has a high inhibitory effect on the activity of mouse peritoneal macrophages[290], as well as increases the susceptibility of fungal and bacterial infections[213].

However on agar substrates this species produces patulin, citrinin, chaetoglobosin C, roquefortine C, and the communisins A and B, one of the most toxic mixtures in this genus[65].

2.4.4 Trichoderma

Trichoderma Pers. ex Fr. is common on water-damaged wood containing materials, and from Danish buildings six different species have been isolated: *T. longibrachiatum, T. harzianum, T. citrinoviride, T. atroviride, T. viride* and *T. harmatum*[71].

Trichoderma was originally known for producing trichodermin and trichodermol which was originally isolated from a *T. viride* strain, and crystallised for the X-ray structure determination as the first TR by Godtfredsen & Vangedal[291,292]. Later another ester, Harzianum A, of trichodermol has been isolated[293]. As trichodermol and esters of it are not commercially available, very few surveys for these metabolites have been performed, probably also due to its very low toxicity.

Cvetnic & Pepelnjak[294] have reported the production of DAS from *T. viride* using TLC, but it has not been possible to obtain any of the strains, for verification of this very unlikely finding.

As seen in Appendix B, Table 10, the majority of the non-peptabol metabolites seems to be antibiotic and especially antifungal, and a large number of these seem to be small pyrones and lactones (<300 g/mol) often being volatile. Production of gliotoxin and viridin have also been reported from several *Trichoderma* species, but these have always been shown to be *T. virens*[295] which has not been found in mouldy buildings[65].

The major group of biologically active metabolites are the peptabols, and cyclic peptides, Appendix B, Table 11, who often works by making pores in the cell membranes of the target organisms giving free passage of ions over the cell membrane. These metabolites have both antibacterial, and antifungal properties, but few reports exists of their effect on mammalian cells as most of the work on *Trichoderma* has been done to identify new antibacterial, and antifungal components. A number of proteins with severe biological properties ribosome inactivation[296] and high toxicity[297,298] have also been described.

No studies on the inhalation toxicity of these species or their peptabols exist, but they may be significantly more potent when inhaled.

2.4.5 Memnoniella

Only one species from the genus *Memnoniella* Höhnel has been identified in buildings and that is *M. echinata* Galloway, which is closely related to *Stachybotrys*[179,299]. As seen in Appendix B, Table 12, a number of biosynthetic groups are produced by this species. The griseofulvins which is a known type of antibiotics[44] and are commercially used as such, can inhibit the polymerisation of turbulin in mammalian cells[176].

Two mycophenolic acid analogues; memnoconol and memnoconone[300] have also been isolated along with a number of spiriocyclic drimanes very similar to the ones produced by *S. chartarum*[223,300-303] also the production of the simple trichothecenes; trichodermol and trichodermin are common with *Stachybotrys*[304].

2.4.6 Alternaria

The genus of *Alternaria* Nees ex Fr. comprises more than 40 species[270] and is very common in soil and the phylloplane species *A. alternata* and *A. tenuissima* are found in very high numbers in the outdoors air during the summer[25]. The toxicology of the *Alternaria* toxins have been reviewed thoroughly by Woody & Chu[305]. The acute toxicity (LD_{50}) in rodents of alternariols seems to be in the range of 400 mg/kg, which is quite low even though they are reported teratogenic at 10 lower levels. They are mutagenic in the Ames test, but only few data in higher animals exists. Tenuazonic acid (LD_{50} 10-200 mg/kg in rodents) is more toxic

and the altertoxins are about 1000 more toxic (LD_{50}, 200 µg/kg in rodents). In Appendix B, Table 13 the biologically active metabolites of this groups have been compiled. It should be noted that *A. alternata* in grains may to be associated to esophageal-canser in China.
The most potent mycotoxins produced by this genus, are the AAL toxins which are related to the fumonisins[306,307] *Alternaria alternata* f.sp. lycopersici infecting tomato plants, but these strains have not been linked to buildings.
Ren et al[308] showed that only alternariols were produced on various building materials, whereas the altertoxins were not produced in detectable quantities.
However if species of this genus should be the cause of the health problems observed in mouldy buildings, very different metabolites should be produced selectively in buildings,

2.4.7 Chaetomium

The teleomorph genus of *Chaetomium* Kunze ex Fr. comprises about 160-180 species[270] and has the genus of *Acremonium* Link ex Fr. as anamorph genus.
The genus one of the most important deteriorators of cotton and cellulose containing materials[270] and in buildings *C. globosum* Kunze ex Steud. is the most common species[16].
C. globosum is known from the cytohalasin mycotoxins, which are also produced by several *Penicillium* species, and who inhibit cytoplasmatic cleavage, and inhibit glucose transport in the tissue[176]. However the knowledge of toxicity of these components during inhalation is not known.
The major work done on the metabolites has been performed in Japan[309], but as seen in Tabel 14 from Appendix B, many other metabolites are produced by species of the genus, especially the highly cytotoxic chaetomin which inhibits protein synthesis, the cytotoxic chaetocins, the mutagenic mollicellins and the chaetochromins who are cytotoxic, teratogenic and induces liver injuries[310].
Interestingly some species also produce sterigmatocystins[311] but these species have not been found in buildings.

2.4.8 Cladosporium

Cladosporium Link ex Fr. is a phylloplane genus and during the summer there can be as many as 10 000 spores per. m^3 air of *C. cladosporioides* and *C. herbarum*[25], and both contains many of the same allergenic proteins[312].
On indoor surfaces C. *sphaerospermum* Penz. and some times also *C. herbarum* (Pers.) Link ex Gray is frequently isolated from bathrooms and silicone caulkings[11,25].
As seen in Appendix B, Table 15 no papers on real mycotoxins have been found from this genus, but a number of antifungal metabolites have been isolated along with a few plant growth inhibitors.

2.4.9 Ulocladium

The genus of *Ulocladium* (Thüm.) Simmons is often isolated from water-damaged materials together with *Stachybotrys*, and generally it is *Ulocladium chartarum* and *U. atrum* which are two commonly species of this genus in buildings[16,63].
Although this genus is morphologically similar to *Alternaria* and share the same major-allergen, almost no secondary metabolites have been isolated as seen in Table 16 in Appendix B.

2.4.10 Paecilomyces

From the genus Paecilomyces Bain. two species are found in water damaged buildings, *P. variotii* Bain. and *P. lilacinus* (Thom) Samson, with the first being the most abundant.
P. variotii is capable of growing on very low nutrient substrates as optical lenses, whereas *P. lilacinus* seems to prefer protein rich media[270].
P. variotii can produce the strongly cytotoxic mycotoxins patulin and viriditoxin[65] as well the metabolites: ferrirubin, variotin, fusigen and indole-3-acetic acid[25].

2.5 Biomarkers of mould growth

As earlier mentioned, not all spores are viable and hence a number of methods for measuring chemical and molecular biological markers are needed. These methods can also provide much faster measurements for mould determination and significantly better quantification. For determination of moulds, four different principles can be used for material samples or air filters:

- **Determination of the activity of fungal enzymes**. Here two methods have been used: i) Fluorescein diacetate hydrolytic activity (by determining fluorescein) will both detect the presence of bacteria and/or moulds in wooden samples[125,313]; ii) Determination of the activity of β-N-acetylglucosaminidase[314] (a enzyme in the chitinase partway) which is now commercially available as the Mycometer Test™. Both methods have the advantage that the samples can be incubated for as long time as wanted, and hence a very high sensitivity can be obtained as many molecules of reactant can be obtained from each enzyme molecule. However these methods only detect functional enzymes.
- **Chemical markers, which can be genus, species, or isolate specific**. These include: i) extracellular polysaccharides from *Penicillium* and *Aspergillus*[30,315];ii) 18:2ω-phosphorlipid fatty acids[314];iii) β-glucan from the cell wall, also being an important inflammatory marker[37,39]; iv) mycotoxins or secondary metabolites who are species specific[47]; v) MVOC's in the air[41,316]; vi) chitin from the cell wall [317]; and finally the cell membrane material ergosterol [318,319]. All these metabolites can principally be detected using various analytical methods as described for metabolites in section 2.6.
- **PCR-based methods, detecting specific parts of the fungal DNA**, enabling even isolate recondition if needed, and also recently quantitation[229]. These methods will undoubtedly be very important in the future especially when the DNA-chip technology comes down in price.
- **Bioassay detection**, either by detection cytotoxicity[320,321] or more specific *mode of action*, as the protein translation inhibition which is highly selective against trichothecenes[322]. Such methods give health relevant data but do not give any information on the producing mould.

All these methods are significantly faster than cultivation techniques and can also detect dead spores and mycelia, and will be the predominant methods in the future.

2.5.1 Ergosterol

Ergosterol (Erg) is the predominant compound in the fungal cell membrane, making it a suitable indicator for fungal growth, although it should be noted that also some amoebae and green algae are capable of producing Erg[323].

Erg is partially bound as different esters[324], and thus three different extractions can be performed: *Free Erg*, extracted without saponification; *Total free Erg* by saponification of the esters after extraction; and *Total Erg* by saponification of the sample during extraction[325-327,327-330]. In plant tissue extraction has shown some matrix dependency due to instability of Erg under various conditions, as exposure to sunlight or low pH[327,328,331].
Extraction has included reflux in methanol-water with or without NaOH/KOH for 30-90 min, generally being labour intensive compared with the microwave-assisted extraction for total Erg developed by Young[330] and the extraction method of Larsson and co-workers[318,332,333]. These methods have been able to detect quantities down to 500 pg, corresponding to 200 spores[81,88].
Erg is an excellent marker for quantification of fungal biomass on building materials[318,334] and can also be used as exposure marker in air or dust, where especially Larsson et al[332,335] and Miller et al[22,81,88,336] have used it. However here it was found not to correlate with questionnaire data on mould in the home and not with as self-reported symptoms[81].

2.6 Detection of fungal metabolites

Although perhaps more than half the time of the present work has been spent on developing analytical methods and trouble shooting on instruments, this subchapter will only give an overview of the analytical methods, as a more detailed literature review can be found in the papers 1-13.

2.6.1 Chromatographic methods for detection of mycotoxins

Fungal metabolites can be detected by various methods, often combined with chromatographic methods[337,338].

2.6.1.1 Thin layer chromatography

Thin layer chromatography (TLC) is the oldest of the chromatographic method, and requires less expensive and advanced equipment than the other chromatographic methods[274] and a considerable sample speed can be achieved compared with other methods, unless 2-D TLC is used[337,339].
Target components can after separation be detected visually or instrumentally under light or under UV-light, the latter being very sensitive to fluorescent components. Usually the target components can be more or less selectively coloured by spraying with various reagents[274,337].
Antimicrobially components can be found by spraying the plate with a suspension of microorganisms in a growth substrate and after incubation for some days spots with no growth can be detected.
Mass spectrometric methods such as MALDI-TOF and FAB-MS can also be used as detection methods of TLC[339] although it seems more troublesome and slower than LC-MS and will probably only be used for very special applications.
TLC is not specific enough for detection of TR[340] although a number of "selective" colouring methods have been published[341,342].
For sterigmatocystins, spraying with $AlCl_3$ is considered quite specific when combined with sample preparation methods removing quinones and related components[343].

2.6.1.2 Gas chromatography

As previously mentioned, mycotoxins are generally not volatile and hence gas chromatographic detection of them will always have to face instability problems during injection and chromatography[344]. On the other hand capillary GC gives 10-100 times higher separation power[345] than LC (packed column) and runs very stable with flame ionisation, electron capture detection (ECD), and MS, which are significantly more sensitive than UV and refraction index detectors used in LC.

Almost all GC methods for mycotoxins start with derivatisation of free OH and N-H groups[346] to decrease the thermal lability. Acid groups are usually methylated, and alcohol groups are reacted to their TMS ether or esterficied to their acetyl or pentafluoropropionyl esters[340,344].

GC methods on most mycotoxins have been published, *inter alia* AFB_1 and ST[346], *Alternaria* mycotoxins[347], penicillic acid[348], patulin[349], the backbone of the AAL toxins and the fumonisins[350], and especially the TR[340]. The latter, is the only group where GC-MS or GC-ECD has been the primary analytical method.[351-365].

2.6.1.2.1 GC-MS for trichothecenes

The use of MS detection of the pentafluoropropionyl- (PFP) or heptafluorobuturyl (HPB) esters will give the highest sensitivity if the MS has a mass range > m/z 800[340]. These derivatives can be formed by the imidazoles PFPI and HFBI respectively or acid anhydrides PFPA and HFBA respectively, although the latter needs a nucleophilic catalyst such as triethylamine, dimethylaminopyridin or imidazole[340]. Unfortunately the TB react slowly with both types of reagents and can undergo isomerisation giving more than one peak[352]. The fluorinated derivatives can be detected selectively to very low levels using negative ion chemical ionisation (NICI)-MS or ECD, but also positive electron impact ionisation (EI^+)-MS or positive chemical ionisation (PCI)-MS can been used[360,366,367].

TR lacking free OH groups cannot be detected using NICI and ECD unless they are hydrolysed to their parent alcohols prior to derivatisation[353,360].

2.6.1.2.2 GC-MS for sterols

GC-MS has also been used, usually based on an internal standard, such as cholesterol or dehydrocholesterol[335,368], as a isotope substituted standard is not commercially available. Erg has usually been derivatised to its tertiary-butyldimethylsilyl or trimethylsilyl (TMS) ether to reduce decomposition during injection and chromatography. On-column injection can also be used to further reduce decomposition[330], but this method requires cleaner samples and is not as robust as splitless injection[368].

2.6.1.3 High performance liquid chromatography

Since the late 1980s and the start of the 1990s HPLC have been the most important analytical method for mycotoxins[337,369,370].

The success of HPLC compared with the other methods have several reasons. Firstly the instruments have decreased in price as well as getting easier to maintain. They are easily automated and PCs can sample and do automated detection of target compounds. Many column materials are available from many different manufactures, and significantly larger samples can be injected than in a GC. More over samples do generally not demand derivatisation as GC does.

From the mid 1990s the use of HPLC with MS detection employing atmospheric pressure ionisation techniques (API)[371] such as electrospray[372] and atmospheric pressure chemical

ionisation (APCI) have greatly expanded the use of HPLC for mycotoxins[372,373]. As toxins previously transparent to UV detectors can now be detected, e.g. the fumonisins which previously needed OPA derivatisation[374,375], small peptides[376,377], and especially the TR[378].

2.6.1.4 Capillary electrophoresis

Capillary electrophoresis (CE) has been used for detection of mycotoxins and low molecular-mass compounds since the late 1990s, due to the extreme separation power exceeding capillary GC by several magnitudes, as well as providing very fast separation[379-381].
The method has, however, a number of limitations as uncharged components cannot be separated unless micellar CE is being used which greatly lowers its separation power[382]. The very small sample volume (<<1 µl) which can be loaded on to the column gives detection-limit problems even though several pre-concentration methods exists[380,383]. This means that CE is still generally used with very sensitive detectors such as Laser-Induced Fluorescence detection[384,385]. CE-MS methods have been used for low molecular-mass compounds but it has not yet been possible to use it in combination with micellar CE[371,371,381].

2.6.1.5 Immunochemical methods

For routine analysis, enzyme linked immunoassay (ELISA) is used for detection of AFB_1, the TB DON, ochratoxin A and zearalenone in cereals[386,387].
An increasingly important and very specific technique is to combine chromatographic detection methods with immunoaffinity clean-up[388].
Monoclonal antibodies have also been prepared for the TB 3- and 15-acetyl-DON[389,390], sporidesmin A[391], the MTR roridin A[392], the TA DAS[393,394] and presumable a number of other mycotoxins.
A roridin A ELISA has been used to detect SG and SH in building material samples[320], as the assay cross-reacts with SG (4-7%) and SH (15-19%)[392,394]. Also the MTR hydrolysis product verrucarol, was detected in serum using DAS-ELISA samples after it was derivatised to diacetyl-verrucarol which is structurally similar to DAS.

2.6.1.6 Bioassay for detection of mycotoxins

The first assays for measuring *Stachybotrys* toxins, were rabbit skin test which later have been shown to be highly sensitive for TR[66,188,395]. However due to ethical reasons this method is not used any more, as *in vitro* cultivated cell lines of human or animal origin can provide the same sensitivity and specificity[321]. Cell cultures are the most common assay for cytotoxicity testing, and have been very successful for detection of the cytotoxic trichothecenes[20,321,396] and cytotoxic indoor air organisms[148,149]. It should be noted that great differences in sensitivity and specificity of different cell types exist[321]. Most of the methods are used in combination with the MTT test, which measures if the mitochondria are functioning using a simple colormetric detection[321,397]. The cell assays can also be used for measuring other reactions than cytotoxicity, e.g. induction of inflammatory mediators such as NO and different interleukins[152,398].
The major problem with mammalian cell cultures is the need for cultivation in highly sterile environments and frequent sub-cultivation which is very time and material-consuming. Hence a more simple solution can be used, e.g. sperm cells[50,399-401] who are available from local insemination centres, blood cells which can assayed for haemolysis[229] and/or rings from chicken trachea where the movement of the cilia can be monitored[402]. A very simples assays is the brine shrimp *Arthemia salina*[184,403] which has been extensively used for TR and other

mycotoxins as the aflatoxins[403]. Engler et al[404] used the yeast *Kluyveromyces marxianus* grown in microtitre plates for detection of TR by monitoring its expression of β-galactosidase. An assay measuring protein translation inhibition have has reported by Yike et al[322]. This assay has detection limits 20-400 times lower than cell cultures.

2.6.2 Sample preparation

The most time-consuming part of analysing for mycotoxins and other fungal metabolites, is extraction and especially the sample clean-up.

2.6.2.1 Trichothecenes

TR range from polar compounds like nivalenol (NIV) extracted with methanol-water or acetonitril-water mixtures to apolar compounds such as diacetoxyscirpentriol (DAS) and T-2 toxin (T-2) extracted with mixtures of chloroform, dichloromethane and ethyl acetate. Thus no method can provide full extraction (≈ > 80%) of all TR unless multiple extractions are performed [340].

The MTR can be extracted using water-methanol to dichloromethane-methanol mixtures, but the first mixture should extract fewer interfering components[405].

At least one solid phase extraction (SPE) step has to be included before the TR can be detected. Most successful are normal phases, such as silica gel, florisil, charcoal-alumina or MycoSep columns[340,359]. Reversed phase has also been published[351],[406] but due to the large difference in polarity of the TR and the time-consuming evaporation of water these methods have not been as popular as the normal phase ones. For the MTR the PEI silica has proven to be superior, as it selectively removes the spiriocyclic drimanes, phenolic compounds and the brownish gum always present in extracts from *Stachybotrys*[405,407].

For the polar TB immunoaffinity clean-up is also widely used, as they are soluble in the water-acetonitrile mixtures used for loading immunoaffinity columns[340,390], and can be detected using HPLC with UV detection.

2.6.3 Detection of mycotoxins in air and settled dust

To estimate the human exposure to mycotoxins, these have to be measured and quantified directly in air samples or in settled dust. But as spores and airborne dust contain interfering components and the spore concentration is very low [408](usually << 5000 m^{-3}), detection of airborne mycotoxins will be very difficult due to the very low quantities. Until now, airborne mycotoxins have only been detected in environments with high concentrations of airborne spores, such as the agricultural industry and the feed-handling industry. Here several studies have demonstrated airborne AFB_1 when handling materials infested *with A. flavus*[32,409].

Richard et al[261] detected ochratoxin A in dust from a dwelling with growth of *A. ochraceus*, using LC-MS and HPLC-FLD from samples cleaned up using immunoaffinity clean-up.

Sorenson[46] showed that spores released from a *S. chartarum* isolates growing on rice, contained ≈ 4×10^{-14} g MTR per spore, meaning that about 1500 spores (450 spores using the data of Nikulin et al[45]) should be collected, if assuming 80% extraction efficiency and 50 pg detection limit in sample, however as there are different MTR present (unless they are hydrolysed to verrucarol) and rice and MEA are good substrate for MTR production significant more spores may be needed.

Smoragiewicz et al[410] reported that dust from a ventilation system contained the TR roridin A, T-2 tetraol, T-2 toxin, and DAS. They also reported TR from cultures of the non-TR producing

genera *Penicillium*, *Aspergillus*, *Alternaria*, and *Ulocladium*, which demonstrates that all their results must be false positives.

Yike et al[229,322] demonstrated that dust and air samples from houses infested with *S. chartarum* inhibited their protein translation assay, which strongly suggested the presence of trichothecenes in the air.

To conclude it should be possible to detect mycotoxins in air samples, but no validated sampling and clean-up procedures exist, meaning that this major problem has to be addressed first.

3 OVERVIEW OF EXPERIMENTAL WORK

The details of the experiments performed during this study can be found in the papers 1-13. However results of a number of small experiments not included in the papers can be found in the discussion part and identification of components initially reported as unknown.

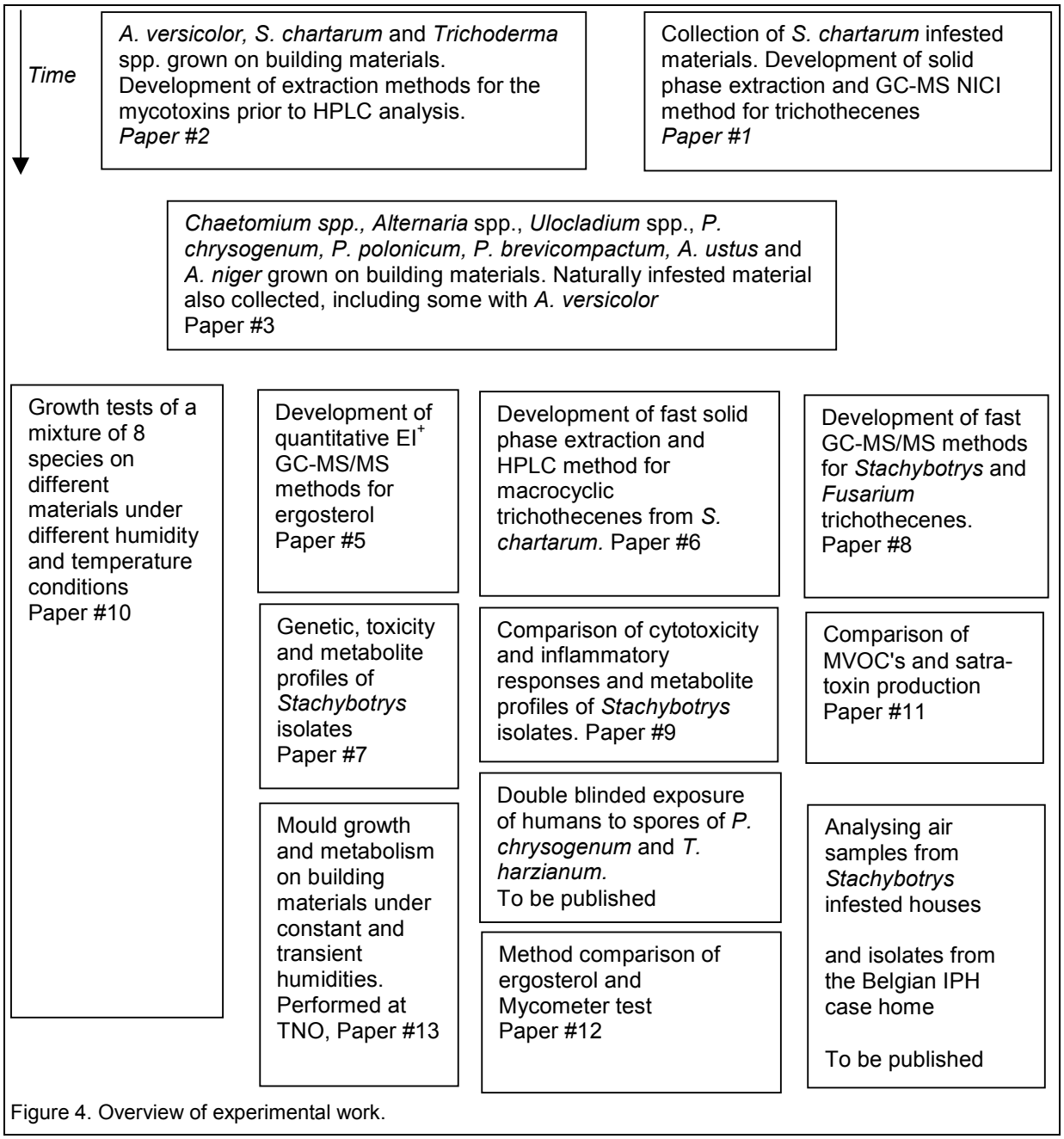

Figure 4. Overview of experimental work.

4 RESULTS AND DISCUSSION

The reason for the more detailed comments and results included in the thesis, is that a number of them would not fit into any scientific papers, but that I feel they should be documented somewhere.

4.1 The building associated funga

As mentioned in paragraph 2.1.1 the associated funga reported from different countries varies considerably. Unfortunately this study has not analysed field samples enough to make definite conclusions on this issue. However a number of observations are still interesting:

- It was not possible to get any material samples with *Alternaria* infestation, all were instead infested with *Ulocladium.* Although > 15 field samples which should contain Alternaria were received).
- Almost all (>50%) of the material samples received were at least partly infested with *P. chrysogenum* and *A. versicolor*, although the presence of the latter could only be revealed by chemical detection of sterigmatocystin (ST), see section 4.3.2.1, page 44.
- When *Trichoderma* spp. or *Chaetomium* spp. were present on a material they grew in almost pure culture and with significant biomass.

4.1.1 *Penicillium* and *Aspergillus* cultures received from Finland

A number of *Aspergillus* and *Penicillium* isolates collected from both material and air samples were received from National Public Health Institute, Kuopio, Finland (KTL). They were cultivated on YES, CYA, CREA and MEA and identified by colony diameter and morphology. Isolates that could not be unquestionably identified were metabolite-profiled by HPLC-DAD (YEA and CYA).

Table 6

Aspergillus and *Penicillium* isolates (n=131) received from KTL[1]

Species	Frequency (%)	Species	Frequency (%)	Species	Frequency (%)
Aspergillus versicolor	23	*P. citreonigrum*	3	*Penicillium charlesii*	1
Penicillium brevicompactum	11	*Aspergillus ustus*[2]	2	*Penicillium commune*	1
Aspergillus fumigatus	10	*Penicillium crustosum*	2	*Penicillium echnilatum*	1
Penicillium corylophilum	5	*Penicillium solitum*	2	*Penicillium janczewskii*	1
Aspergillus sydowii	5	*Aspergillus niger*[3]	2	*Penicillium manginii*	1
Eurotium repens	5	*Penicillium decumbens*	2	*Penicillium purpugenum*	1
Penicillium chrysogenum	5	*Penicillium expansum*	2	*Penicillium rosepurureum*	1
Penicillium palitans	5	*Penicillium rugulosum*	2	*Penicillium variabel*	1
Penicillium glabrum	4	*Aspergillus flavus*	1	*Penicillium vinaceum*	1
Penicillium italicum	4	*Penicillium albocoremium*	1		

[1]From Anne Hyvärinen, National Public Health Institute, Kuopio, Finland. [2]Not a classic *A. ustus* but *Aspergillus ustus* var. *pseudodeflectus.* [3]Did not produce detectable quantities (HPLC-FLD) ochratoxin A on CYA or YES agar.

As seen in Table 6, *A. versicolor* was the most predominant mould almost contributing with 25% of the isolates and more than 50% of all aspergilli. Surprisingly *A. fumigatus* was very frequently isolated (10%) which might be due to sampling on dusty surfaces, as *A. fumigatus* is frequently recorded in Danish house dust (S. Gravesen, personal communication).

P. brevicompactum was the most frequently isolated *Penicillium*, confirming results from the on-going Danish School study, where *P. brevicompactum*, *P. corylophilum* and *P. chrysogenum* were the most common penicillia.

These results contradict results from North America, reporting *P. aurantiogriseum* and *P. viridicatum* as the most abundant *Penicillium* species. This might be due to misidentification with *P. palitans* and other species from the aurantiogriseum-complex (J.C. Frisvad, personal communication), but unfortunately it has not been possible to obtain any of these *Penicillium* isolates to verify the identification.

4.2 Fungal growth on materials

In papers 2 and 3, material samples were water-damaged ($a_w \approx 1$) and significantly higher number of spores were applied to the materials than naturally found in buildings. The moulds were usually able to cover the materials where they occur "naturally" within 4-10 days, clearly demonstrating that when water damages occur, action should be taken the same day if materials should be saved. This also complies with observations by several consultant engineers (M. Ø. Hansen, personal communication), who report complains from the inhabitants within 10-30 days after a single water damage, and complaints within 2-4 days in buildings with a known water damage history.

When using lower a_w (papers 10 and 13) the growth rate decreased dramatically and with very few exceptions only the primary and secondary colonisers were observed growing on the materials. At stationary conditions (paper 10), only *Penicillium* and *Aspergillus* species grew, with *P. chrysogenum* and *A. versicolor* being the most common species. However on wooden materials *A. flavus* and *Eurotium* spp. were observed quite frequently and always with significant biomass. At 5°C only *P. chrysogenum* and *A. versicolor* grew, with the latter producing conidiophores with very few conidia.

Wooden and wallpapered materials supported growth down to 78% RH (paper 10), which was lower than the other materials. It was seen that the planned pinewood was usually not infested on as much of the surface as the rough materials, but on the areas where growth occurred there was not significant difference in the produced biomass. At 5°C this limit was about 90% RH, whereas the results only indicates a limit between 80 and 90% RH. These results comply perfectly with the results of Hukka & Viitanen[141] and Grant et al[55], when the uncertainties of the RH measurements of both studies (±2%) are taken into account.

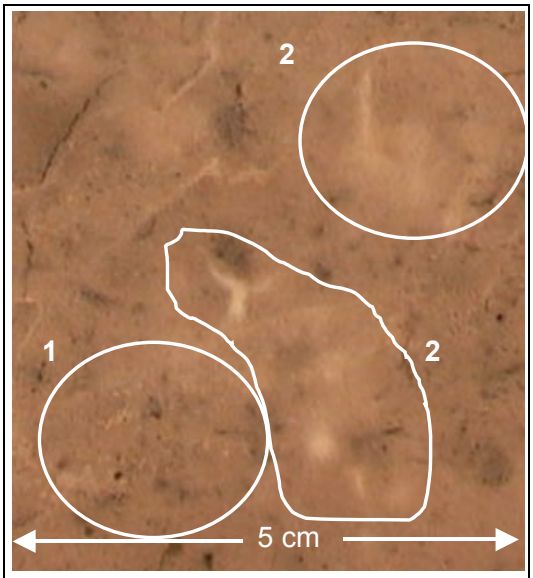

Figure 6. Concrete after 4 months at 95% RH and 10°C, at #1 can *A. versicolor* conidiophores be seen and at #2 sterile mycelia.

Interestingly, the gypsum boards did not support growth <90% RH, but did support production of significant quantities of biomass at 95% RH, it is also clear that the fibre-gypsum was less susceptible than the cardboard-gypsum, which is the most common type in Denmark. Paper insulation material did not support fungal growth at all due to the high contents of borates, although it should be noted that this material when damaged supports growth of several moulds including *Stachybotrys* (unpublished results). The almost totally

inorganic concrete materials partly supported germination of especially *A. versicolor* and sterilia mycelia at RH >90% and growth at 95%, as seen in Figure 6. This must be due to trace quantities of organic components in the concrete. As the concrete materials were cleaner than the ones used in buildings concrete based materials will probably support more growth under field conditions (paper 10).
When comparing Tables 2 and 3, it is clear that the temperature drop from 10 to 5°C had a dramatic effect on the fungal growth, showing no growth at 90% RH and 5°C, and that also here was wooden and the wallpapered materials the most susceptible (paper 10).

4.2.1 Methods for testing the susceptibility of materials

As mentioned in the literature part, testing materials for their susceptibility is difficult, even just controlling the humidity is difficult. As this was the first time such a test was performed at the Danish *Building Research Institute*, it was tried to keep the set-up as simple as possible (paper 10), and regard the study as a pilot project which should explore difficulties such as humidity range, inoculation, and especially assessment of the materials. This set-up is shown in Figure 7, and was primarily built by Gunnar Holm. Initial conditions may play an important role for the surface a_w of the materials, and as it was desired to use steel chamber and take the materials out for assesment, it was necessary to use the sample boxes for reasons occupational health. This meant that the surface a_w would be controlled by the RH of the incoming air to the sample box and primarily by the absorbance of water by the material until equilibrium, which small experiments had showed would take months. This meant that we had to add the quantity of liquid water to the materials, assuming that it would be equally distributed within a few days. Although this should tested in future experiments.

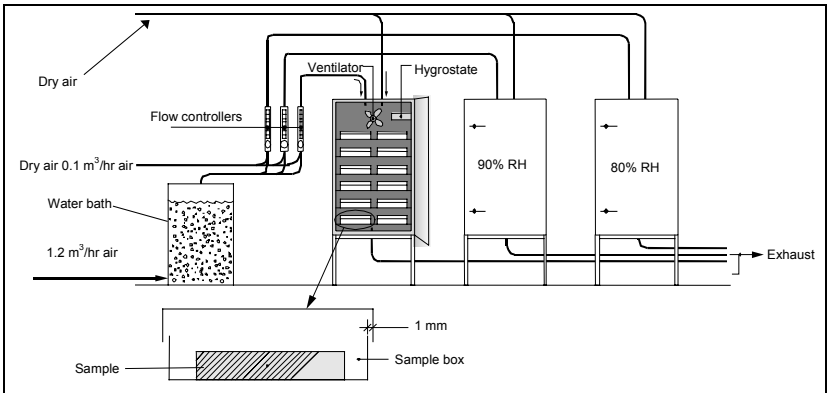

Figure 7. The fungal growth assesment set-up used in Paper 10.

I paper 13, the set-up at TNO Bouw was used, and the initial humidity was controlled by a high continuous airflow over the materials (see Figure 8). This means that the absorption of water from the airflow was so little that the change in humidity over the 10 materials in each channel could be neglected. However this approach created another problem as the air speed itself can inhibits growth if the speed is too high. This is illustrated in Figure 9, where the air speed was higher in one side of the channel than in the other.

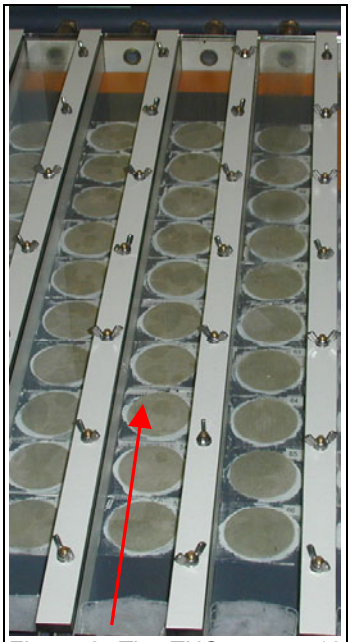
Figure 8. The TNO set-up, 10 material in each row. In this case infested with *P. chrysogenum*.

The TNO approach (paper 13) had another advantage, as it is possible to work with transient humidity conditions, and here it

was seen that the stress of using periods of high and low humidity during a day, trying to mimic a bathroom. This had a strong selectivity stress towards the phylloplane, *Cladosporium*, which under transient conditions was able to outgrow *P. chrysogenum*.

The instationary conditions, with and without surface condensation (paper 13), can cope with conditions which keeps the storage moulds away and still be too dry for the phylloplane. It can also cope with water accumulation in the surface of materials, especially when working with two to three layer systems, like a painted piece of cardboard gypsum (3-layer system)[11].

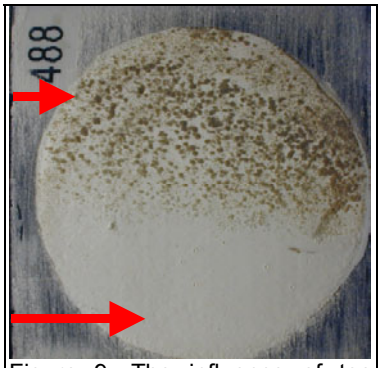

Figure 9. The influence of too high air velocity on *A. versicolor* growth in one side of the set-up.

Hence, the total growth behaviour of materials is extremely complicated, and to characterise a material well, the performance and associated funga under at least three different environmental conditions is needed:

- The lowest RH which supports growth.
- The performance under transient conditions.
- The performance under water damage.

4.2.2 Growth assessment

In paper 10, the materials had to be taken out of the set-up for assesment. This was very time consuming and obscured the environmental conditions for the samples. Using the approach of Adan[11] as in Paper 13 (see Figure 8), the materials can be assessed several times a day if required. The time resolution of this process describes the susceptibility - as how fast growth started - better than endpoint determinations of biomass. The latter parameter seems to describes how much of the substrate could be utilised (papers 10 and 13).

Visual inspection (paper 13) has a major problem, especially using the 5 point scale described by British Standard[411], as the assessed coverage area is the output parameter. This does not take the concentration of fungal biomass into account. Thus a material with very light coverage over all of the material will be assessed to have a higher value than a material with heavy growth over only a part of the material.

The use of image analysis was partly explored at the stay at TNO Bouw (unpublished), and this technique will undoubtedly help in future studies, as images for assessing the materials can be taken automatically several times a day. It can also cope with the high growth rate observed on some paints (where the materials had to be assessed 2-3 times per day, paper 13). Also a more standardized assessment including the fungal "concentration" can be made. However this will require that the image-analysis is calibrated carefully against very well-described samples. Here chemical markers could help to compare the appearance of different moulds.

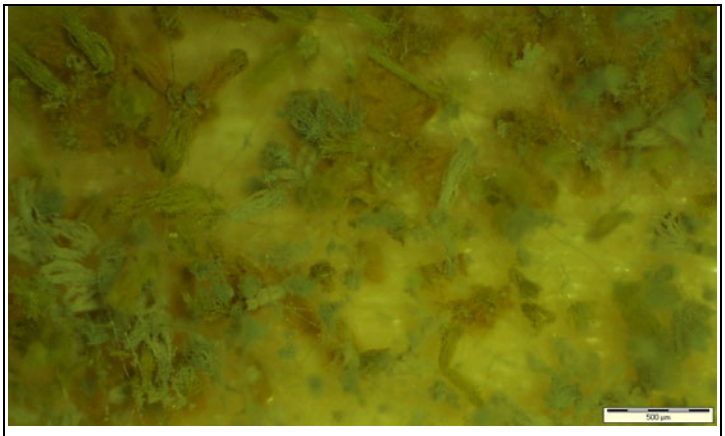
Figure 10. Mixture of *A. flavus, A. versicolor and P. chrysogenum*, growing on pinewood.

The use of dissection microscopy showed that the moulds often grew in mixtures (see Figure 10). Looking at materials with scarce growth and a fibrous surface was very difficult, and only sporulation could be detected. However it was possible to distin-

guish *A. versicolor,* often seen as white to olive conidiophores with very few spores and *P. chrysogenum,* often as light bluish or white conidiophores with very long chains of spores attached.
When no sporulation occurred on fibrous materials such as the pinewood or gypsum boards it was only the chemical markers which could detect growth, but in no case significant biomass overlooked.

4.2.2.1 Biological markers

One or both the biological markers ergosterol (Erg) and the Mycometer Test™ were used in papers 5, 10, 12 and 13.
Qualitative determination or Erg was easily performed by the standard HPLC and TLC methods already used at the department, but quantitative determination proved to be painstaking process. External standard quantitation using HPLC or GC-MS proved unreliable, especially using GC-MS where both splitless injection, various ion-trap phenomena, and the breakdown of the GCQ followed by it being rebuilt in USA, complicates things further (paper 5).
All the sterol standards obtained were almost transparent to the HPLC-DAD, leaving GC-MS with internal standard as the only possibility. LC-MS was not available at that time, and will probably not be an alternative, as the low-polar solvents used to elute it will give problems with the ionization process. Several sterols were tried as internal standard for GC-MS, but the high dynamics of the external ionisation ion-trap system did not give better standard deviations (SD) than 25% when working on standards. When using 4-D_2-ergosterol as internal standard, synthesised by Dr. J.Ø. Madsen, Erg could be determined with a SD of < 5%, as variation in the ionization and the dynamics of the gate lens is no longer interfering with the analysis.
In paper 5 it was shown that no SPE clean-up step was needed when using GC-MS/MS and that the sample did not need to be neutralised after the saponification when splitless injections was used. Microwave assisted extraction was proven to be a very powerful and fast technique but very dangerous, as the vials occasionally exploded and ripped open the microwave oven door.
As many samples could be hydrolysed in standard laboratory vials at the same time - this method was preferred. It was possible to reach 120 samples per day, although the GC-MS/MS can only analyse 60-65 samples per day. The SD ranged from 1-4% in spiked samples and in real samples SD ranged from 4-12%, with detection limits in the sample of 2-10 ng, which is fully sufficient as the variation of fungal growth on surfaces is much higher.
However during analyses of samples described in papers 10 and 13, this detection limits was difficult to reach and the general limit was 10-30 ng, which is significantly higher than reported in paper 5, which was already higher than reported elsewhere [318,330]. One of the major problems was the daughter ion-yield (number of daughter ions / number of the parent ion in the full scan chromatogram), decreased to 4-8% for unknown reasons, compared with a yield of > 50% of the PFP or HFB-trichothecene derivatives. The water and oxygen levels in the system ware extremely low, and various q-values, ion-source temperatures and CID voltages were explored as well as alternative tuning of the lenses, but with no increased sensitivity.
Sample decomposition during injection was a particular problem while running the sample described in paper 13, where the painted materials had a dramatic impact on the sensitivity due to deposits in the liner (not visible). In the future such samples should probably, after hydrolysis, be loaded (cold) onto a C_{18} cartridge which can be cleaned with water-methanol

mixtures, before the sterols can be eluted with methanol/dichloromethane, but would compromise sample preparation speed.
In paper 12, the m/ 363 and 365 were used as parent ions and m/z 157 and 159 as daughter ions for Erg and 4-D_2-Erg respectively, this combined with newly cleaned ion source assemble and new liners in the GC every 60 injections lowered the detection limit to 1 ng (20 pg injected).
In paper 10, both Erg and the Mycometer Test™ showed growth or no growth, but the correlation was obscured by the high variability of the fungal growth. This problem was overcome in paper 12, where the same sub-sample of material or agar were analysed for enzyme activity with the Mycometer Test™ and for ergosterol (Erg) using GC-MS/MS. Here it was noticed that the enzyme activity would usually be highest during the initial growth phase and usually decreased to about 50-80% whereas Erg would only decrease to 90-70% of it peak value, as illustrated in Figure 11. When comparing enzyme activity, Erg and dry weight of agar cultures it was noticed that these parameter did not always peak at the same time, probably due to different induction of the enzyme.

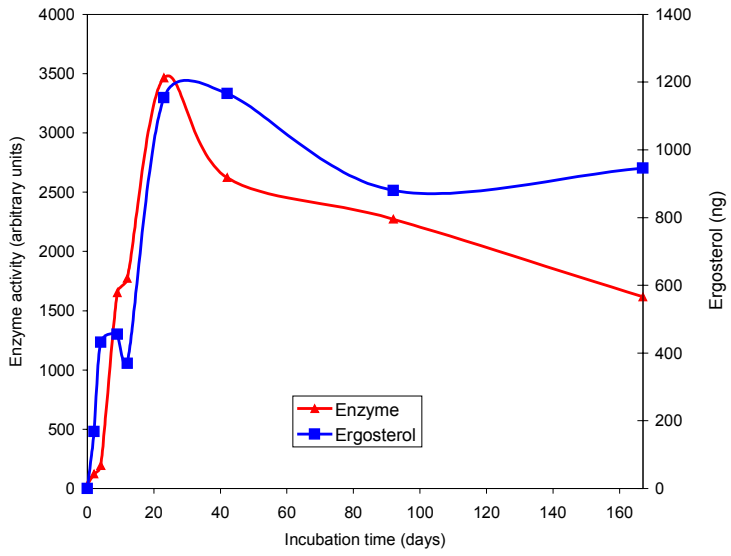

Figure 11. Comparison of Mycometer test and ergosterol determinations on gypsum board inoculated with *Stachybotrys chartarum* (IBT 9694).

Compared with visual inspection, paper 10, the chemical markers generally showed the same, but were a nice alternative on very fibrous surfaces where even the use of a stereomicroscope gave problems with distinguishing fungal growth from fibres. Erg has the advance of being an absolute method, which can be good for comparing different ratings of mould growth.
The secondary metabolites were very useful species-specific biomarkers, and in papers 3 and 10, significant growth of *A. versicolor* (see section 4.3.2.1, page 44) was hidden by *P. chrysogenum*.
Metabolites may also indicate how wet the materials have been, e.g. does the presence of the *A. versicolor* metabolites PE1, XOO and ROQ but not ST, indicates $0.95 > a_w > 0.90$, whereas ST indicates $a_w > 0.95$ (see section 4.3.2.1, page 44).

4.3 Growth and metabolite production

In this chapter the most important results of the different moulds and their growth and metabolites production will be discussed.

4.3.1 Stachybotrys

Experimental growth of *S. chartarum* IBT 7711 could be recognised after 5 days of incubation (paper 2) on new water-damaged ($a_w \approx 1$) gypsum boards, which is partly due to the high dose of spores (4×10^3 spores/cm^2), but still surprisingly fast. Growth of the other 4 isolates was not as fast, but the gypsum boards were still totally covered with the fungus after 14 days. None of the 5 isolates could grow on chipboard, acoustic ceiling tiles or pinewood pieces.

These findings are in accordance with field observations[14] and paper 4 where consistently wet gypsum boards seem to be the main substrate of *Stachybotrys* in buildings[25].

In paper 10 where mixtures of common moulds were inoculated under regulated humidities and temperatures (95-70% RH) *Stachybotrys* was only found on the three types of gypsum boards when RH ≥95, and here only with very limited production of biomass had occurred, as shown in Figure 12. This demonstrates that this species generally require water-damaged materials to produce significant quantities of biomass and compete with the penicillia and aspergilli. This is in accordance with the literature (see Table , p.5) where *Stachybotrys* is seen to require a_w 0.95 or more for growth, although Pasanen et al[107,108] have reported growth as low as a_w 0.78-0.81 which is highly unlikely. This is presumable due to the 1 ml spore suspension added to very small samples (down to 0.25 g), meaning that a_w of the samples would be higher than the RH in the air controlled by the saturated salt solutions for an unknown period.

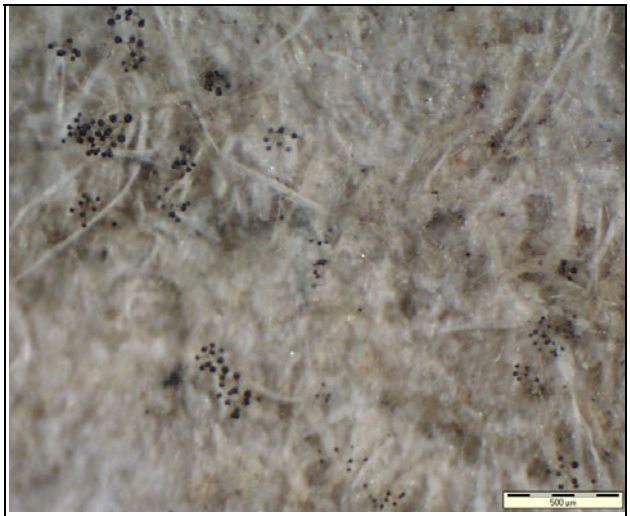

Figure 12. Scarce growth of *S. chartarum* on a gypsum board at 95% RH and 10°C after 4 months.

4.3.1.1 Analysis for trichothecenes

In papers 1 and 2, GC-MS negative ion chemical ionisation (NICI) was used successfully for detection of the trichothecenes (TR) as it gave excellent matrix suppression compared with EI^+ ionization, as illustrated i Figure 2 in paper 2. However, the matrix suppression could also be obtained with more polar extraction mixtures (methanol-water) and more effective removal of acid residues from the derivatised samples. Combined with a number of problems with NICI compared with EI^+ (paper 1, 2 and 8) the latter became the preferred as NICI gave the following problems:

- A decrease in sensitivity after 10-15 samples was observed. This could be avoided by changing the ion volume.
- After changing to the turbo pump, it took 1-2 hr to stabilise the ionisation gas.
- The MS got very dirty much quicker and needed to be cleaned every 2-3 months, which is very time consuming.
- Very short lifetime of the filament (1-2 months)
- The high pressure of methane, which was necessary to obtain a high sensitivity and high m/z ions, gave a poor mass resolution of approx. m/z 0.5-1 (10% valley), making automatic data processing very difficult.
- If the method should be used on the type A trichothecenes (TA) from *Fusarium*, the ion volume temperature should be raised to 120°C to avoid condensation. However this gave almost no high-mass ions (<m/z 300) especially not for the type B trichothecenes (TB).
- The number of ionised molecules is about 10 times as low in NICI as in EI^+, meaning than when MS/MS (which looses 10-90% of the ions) was used a significant drop in sensitivity was observed.

In EI^+ the daughter ion spectra were significantly more reproducible than the full scan spectra. Thus EI^+ ionisation combined with MS/MS (paper 8) was used in all other studies except papers 1 and 2.

In the study of TR produced by *Fusarium* (paper 8) it was observed that the methods used in papers 1 and 2, could not fully derivatise the type B trichothecenes (TB) and that a number of artefacts were produced. A number of methods using imidazole or acid anhydride based reagents and mixtures of these were tried but none were successful, until the method of Langseth et al[396] was applied. This method worked both with PFP and HFB esters, but the PFP was chosen as the HFB gives MW exceeding the upper mass range of the GCQ (m/z 1000).

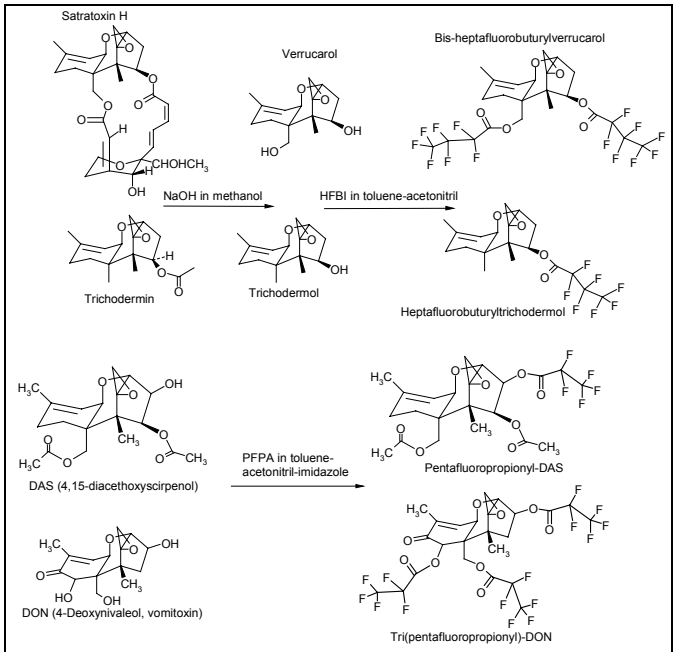

Figure 13. Derivatisation of the trichothecenes.

However this derivatisation method did not work for trichodermol and verrucarol as partly facilitated apotrichothecene rearrangements (ring breakage of the epoxy group)[412], so the original method (papers 1 and 2) using HFBI was not changed for these trichothecenes (Figure 13).

To speed up the hydrolysis step it was tried to pass the hydrolysed sample through a strong cat-ion exchanger for neutralisation of the NaOH[405], which worked fine on standards. However with fungal extracts huge quantities of interfering peaks and irreproducible derivatisation were observed, hence the liquid-liquid extraction seems to be a powerful clean-up step.

Parallel to changing the GC-MS method to EI^+, a clean-up method for HPLC detection was developed to detect the unhydrolysed macrocyclic trichothecenes (MTR). It was clear that reversed phase clean-up was not effective due to the polarity difference between the MTR a problem well known from the simple trichothecenes where normal phase clean-up is the most effective[340]. Silica and PEI silica (provided by B.B. Jarvis[407]) were tested, but it was clear that the latter was significantly better to remove the spiriocyclic drimanes. By dry-packing the PEI in syringes between two pieces of filter-support material stamped out by a sharp steel cylinder a SPE-PEI module could be manufactured on less than 30 sec. The dichloromethane sufficient to elute the macrocyclic trichothecenes could then be placed in the RVC (takes 24 vial) and evaporated in 2 hr giving a much higher sample throughput compared with the method of Hinkley & Jarvis[405]. The effect of cleaning up the extract on the PEI columns is illustrated in Figure 14, where the HPLC profiles of crude extract is compared with the cleaned up extracts on a MTR and an non-MTR producing *S. chartarum* on PSA agar.

It was noted that the sample should be totally dry before redissolving it in dichloromethane, as water or methanol traces facilitated the breakthrough of the spiriocyclic drimanes in the dichloromethane fraction. When trying to fractionate *Stachybotrys* extracts it was also noted that the dry solvent blanks from the PEI-columns were toxic to the boar sperm used by Peltola et al[231] and the human bronchoalveolar cells used by Norn et al[413].

To study the ratio between trichodermol and trichodermin in the crude extracts, unhydrolysed crude and PEI cleaned extracts were HFB derivatised and analysed using GC-MS/MS. The PEI clean-up step was necessary to avoid huge quantities of interfering peaks and unreproducible derivatisation. It was also shown that the trichodermol TR are predominantly present as trichodermin (paper 6-8).

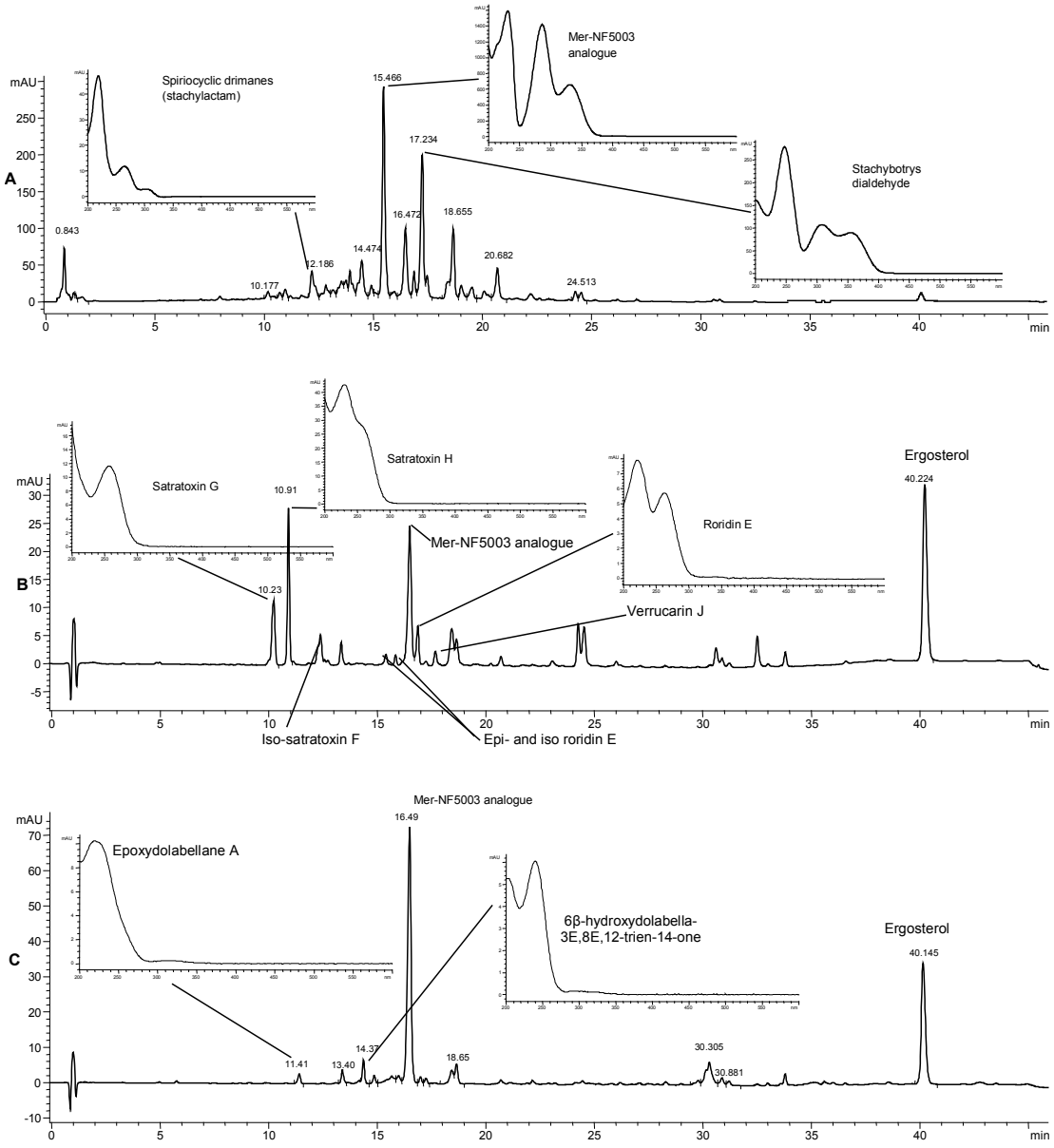

Figure 14. HPLC-DAD chromatograms (260 nm) of *Stachybotrys chartarum* extracts from PSA agar: a) crude extract (IBT 7711); b) PEI cleaned up extract from a satratoxin producing strain (IBT 7711); c) PEI cleaned up extract from an atranone producer (IBT 9466).

4.3.1.2 Metabolites produced by *Stachybotrys*

During the first part of study (papers 1 and 2) it was believed that most isolates would produce MTR[208]. This was, however later shown not to be true, papers 6-9 and Jarvis et al[44], as only 30-40% of the isolates produces MTR.

The samples collected in a school and a dwelling (paper 1) both yielded verrucarol upon hydrolysis (up to 15 ng/cm^2 SH equivalents) as well as trichodermol (not quantified). When incubating different strains on water-damaged new and old gypsum boards (paper 2), only 2 of 5 isolates yielded high quantities of verrucarol upon hydrolysis (up to 120 ng/cm^2 SH equiva-

lents), one isolate produced significantly less MTR. In extracts from the last two isolates verrucarol was perhaps present, but detection could only be performed on the non-specific m/z 213 ion, $[HFB\text{-}O]^-$, which was observed from many peaks of the chromatogram.

The satratoxin levels detected (15-120 ng/cm^2) are the same as reported by Johanning et al[23] who found 33 ng cm^{-2} satratoxin H in biomass scraped off from a infested building material, but lower than found by Nikulin et al[107] who detected 2-3.5 µg/cm^2 satratoxins from a highly toxic strain of *S. chartarum* (isolate #72 = IBT 9460).

Temperature and humidity did not seem to influence the production of the spiriocyclic drimanes (paper 10) when growing on gypsum boards, as these were detected in substantial quantities at 10°C and 95% RH at gypsum boards.

In papers 6, only *S. chartarum* produced satratoxins G, H and iso-F whereas *S. dichroa* stopped the trichothecene biosynthesis at roridin E (see Figure 2, p. 14). *S. oenanthes* produced trichodermol type TR. *S. bisbyi, S. albipes, S. microspora S. nilagrica S. parvispora, S. theobromae*, and *S. cylindrospora* did not produce any detectable quantities of TR. The latter species has been reported to produce trichodermol and trichodermin[414] and *El-Maghraby et al*[415] have reported that *S. albipes, S. kampalensis* and *S. microspora* produced MTR. Unfortunately these strains are not available in any culture collection. However as only 1-3 strains of each species were tested, the study is not big enough for major conclusions on these rare species, as it should also be noted that only ALK and PSA were used for these species.

In papers 6 and 8 it was observed that the strains capable of producing MTR did this on all solid substrates tested (CMA, V8, YES, PSA, OAT, PSA, DRYES, ALK, CYA and rice extracts agar), with PSA and ALK agar yielding the highest quantities. On the latter agar, enhanced production of stachybotrylactones and lactams was observed, often more than 20 different components with the UV spectra illustrated in Figure 14A. As these components are the main interfering components (removed by the PEI silica SPE clean-up), PSA agar was chosen as the standard substrate for chemotaxonomic studies of *S. chartarum*.

The rich substrates CYA and YES, where high quantities of biomass was produced, yielded surprisingly low quantities of MTR together with CMA, V8, OAT and rice extract agar. The low quantities of MTR produced on the latter substrate is surprising since whole rice is a very good substrate used extensively by Jarvis and co-workers[44,204,304]. The construction cardboard used in study 12 gave approx. as much of the MTR per area as PSA agar.

Three taxa was found among the isolates from buildings (paper 6): i) the MTR producing *S. chartarum* isolates; ii) the non MTR producing *S. chartarum* isolates; iii) a new undescribed species, referred to as *Stachybotrys* sp. type A.

The latter taxon did not show PCR amplification of the TR5 gene (paper 7) and did not produce detectable quantities of trichodermol. However this was not the same in paper 6, where 25% of the Type A isolates produced trichodermol or esters of it, which was also confirmed in paper 8, where trichodermol and trichodiene was detected from the type A isolate.

Study paper 6, 7 and 9 showed that and the non-MTR producing *S. chartarum* taxon and the Type A taxon consistently produced 6β-hydroxy-dolabella-3E,8E,12-trien-14-one and often also epoxydolabellane A (see Figure 14C), both precursors to the atranones[227]. Due to the lack of pure reference standards the identity of these had to be confirmed using LC-MS. This was kindly performed by Hanne Jakobsen, on the new Micromass LCT system using electrospray ionization (ESI) with the same or similar eluents as the general LC method[370]. In Figure 15) the ESI spectra of these two dolabellanes can be seen.

When growing on PSA agar, *S. chartarum* rarely produced the atranones themselves, which is different to growth on rice[227]. However, some of the isolates tested in the spring of 2001 also produced the atranones, indicating small changes in the PSA, may induce this.

Two extracts of atranone producing isolates on rice (Jarvis, B.B., Hinkley, S.F., Nielsen, K.F. et al, to be published) contained trace levels of verrucarol upon hydrolysis (GC-MS) and also were significant more toxic that the other atranone producing isolates although still being magnitudes less cytotoxic than the MTR producers. Trace level of verrucarol was also detected in the material sample from the Belgium IPH case home from which none of 6 isolates were MTR producers. When IBT 14915 (an atranone producer) in paper 2 was inoculated on gypsum boards trace level of verrucarol was also detected. Altogether these observations indicate that the atranone producers may be able to synthesise the verrucarol type TR. Hopefully a more sensitive LC-MS method can reveal if MTR are produced by these strains.

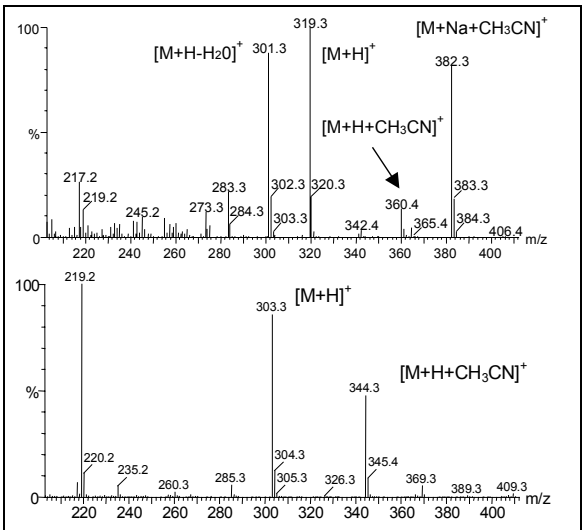

Figure 15. Positive ESI spectra of Epoxydolabellane A and 6β-hydroxydolabella-3E,8E,12-trien-14-one.

The very clear distinction of atranone producers and MTR-producers on agar substrates (papers 6-9) suggests that the genes from the atranone biosynthesis perhaps in inserted in, or near the genes coding for the enzymes used for synthesising trichodermin into verrucarol-type TR or epi-genetic changes (rearrangements in the 3D structure of the genes), so that only of these pathways is expressed.

The isolates studied by Ruotsalainen et al[148] were retrieved from Public Health Institute, Kuopio Finland (KTL). Originally two large groups of isolates were observed, one which was highly cytotoxic and one which induced inflammatory responses in the murine macrophages. When analysing (paper 9) the chemical profiles of the 20 isolates, it was shown that all the 11 isolates being cytotoxic, except one which was probably contaminated or confused by another isolate, belonged to the MTR producing taxon. All the isolates inducing inflammatory responses belonged to the atranone producing *S. chartarum* taxon. In the original study[148] it was also observed that as the only isolate HT16, did not induce the strong inflammatory response as well as not being cytotoxic at 10^5 spores/ml. This isolate was the only *Stachybotrys* sp. type A, suggesting that this taxon is not producing the inflammatory inducing substance(s) and that the effects is not due to the particle effects, as the spores are almost identical in size and shape (paper 6). The pure atranones B and D were did not induce any inflammatory response in the macrophages. Thus, the specific agent triggering the inflammatory response in the macrophages is still unidentified. The inflammatory agent(s) may be present in the MTR-producing isolates, but due to the extremely potent cytotoxins the macrophages are killed before they can respond or that the spores contains components inhibiting the induction of TNFα[221].

Identification of the component inducing the inflammatory response is of special interest since high induction of TNFα is known to be a significant factor of the induction for lung damage[153]. Nikulin et al[45,216] suggested that the MTR were the main reason of the lung tissue inflammation they observed when installing mice with *S. chartarum* spores from a MTR producer (#72) and a non-MTR producer (#29, later shown to produce atranones, paper 6).

However #29 also produced significantly smaller quantities of the spiriocyclic drimanes, making these components an alternative agent.

When looking at the number of papers dealing with possible causative agents to the IPH, it is surprising how little effort has been put into the spiriocyclic drimanes, which are produced at considerably higher levels than the atranones and trichothecenes, presumable 10-500 times more, based on their extension coefficient. Especially the spiriocyclic drimanes isolated from *S. microspora*[226,416] which enhances the plasminogen-mediated fibrinolysis should be taken into consideration as they might be produced by the *S. chartarum* isolates in buildings. The neurotoxic symptoms reported by Johanning et al[21,23] could be due to the neurotoxic as well as the nerve activator compounds[417,418].

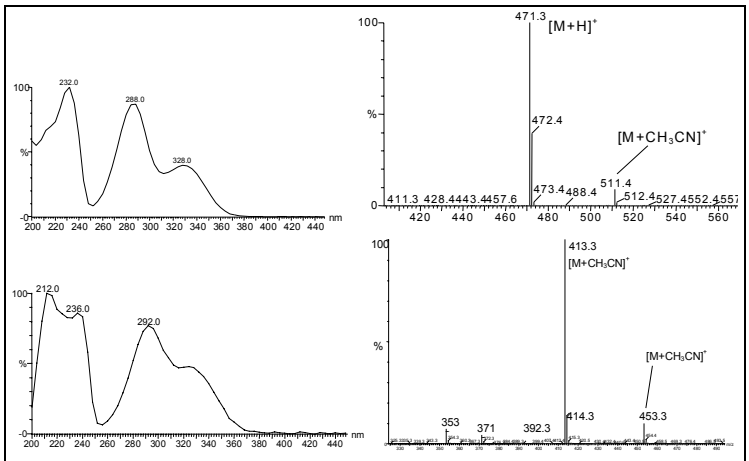

Figure 16. UV and ESI spectra of two MER-NF500 analogues.

It the present work attempts were not made to differentiate between the different spiriocyclic drimanes as their UV spectra are very similar. Furthermore there was only very limited time to run LC-MS analyses. A single subclass, including 5-7 analogues of the spiriocyclic drimanes was, however, tentatively identified (paper 6), by their distinct UV-spectra seen in Figure 16, as the Mer-NF5003[221] components. LC-MS analyses pointed at molecular masses (MW) of 470 Da of three analogues, two analogues of 412 Da, one with 368 Da. All with slightly higher MW than the reported B and E analogue[221], however one minor analogue also fitted MW, 386 Da, with the F analogue[221]. The attention was drawn to these components, as B.B. Jarvis had never seen these in *Stachybotrys* extracts from rice. These components are produced on most agar substrates, especially DRYES and PSA, as well as on hay (unpublished) and in crude extracts from the building materials (paper 1, 2, 10 and 11). In paper 10, it was shown that the spiriocyclic drimanes and atranones were produced at 10°C and 95% RH on several types of gypsum boards indicating that these metabolites are produced under most environmental conditions.

Airborne *Stachybotrys* metabolites

Late in the study a number of air samples (24 hr, 60 m^3/min) and material samples were received from E. Johanning. The filters and materials had already been shown to be highly cytotoxic in the pig kidney cell line used by Gareis et al[321], which indicated the presence of MTR. Analysis of these samples revealed that two air samples contained several spiriocyclic drimanes including Mer-NF5003 analogues as seen on Figure 17, and probably also satratoxins G and H (the UV spectra were very weak), which were confirmed by the presence of verrucarol in the two hydrolysed samples, detected by GC-MS and GC-MS/MS (Figure 18).

Based on HPLC-DAD detection of satratoxins G and H, the total MTR contents were estimated to 75 and 100 ng (± 50%), whereas GC-MS showed 130 and 150 ng (± 50%) respectively.

These quantities correspond to about 100 and 116 pg/m^3, as about 1.5% of the filter area was extracted, using the MTR contents of Sorenson et al[46] of 40 ppm in the spores from rice cultures which corresponds to about 0.04 pg/spore (assuming a density of 1 g/cm^3, and ellipsoidal shape of 11 x 4 µm) which correspond to about 2700 spores/m^3. Based on data of Nikulin et al[45] who found 0.14 pg/spore from MEA culture, this corresponds to 770 spores/m^3, which are high but realistic concentrations. Several of the material samples (vacuum cleaned onto the ALK filters) from the same building contained significantly higher quantities of the same drimanes as well as satratoxins G and H.

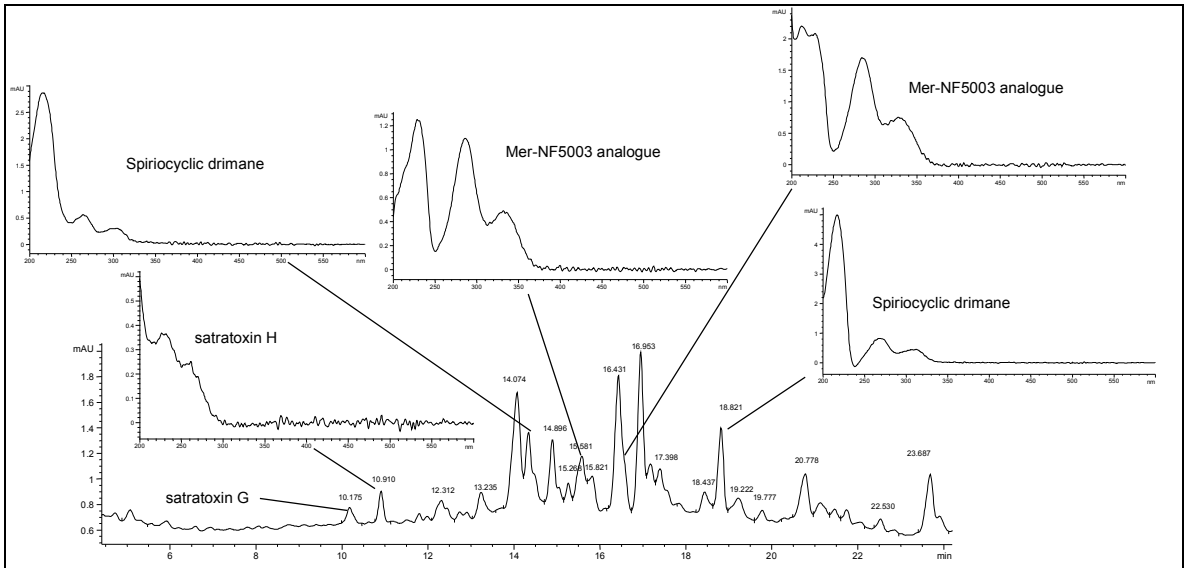

Figure 17. HPLC chromatogram (260nm) of air sample from a stachybotrys infested house. With the UV spectra of peaks corresponding to metabolites.

When working with these filters as well as samples from non problem buildings it was clear a significant quantities of black sticky material was also collected on the filters, and more method development is needed to clean-up these samples more efficiently.

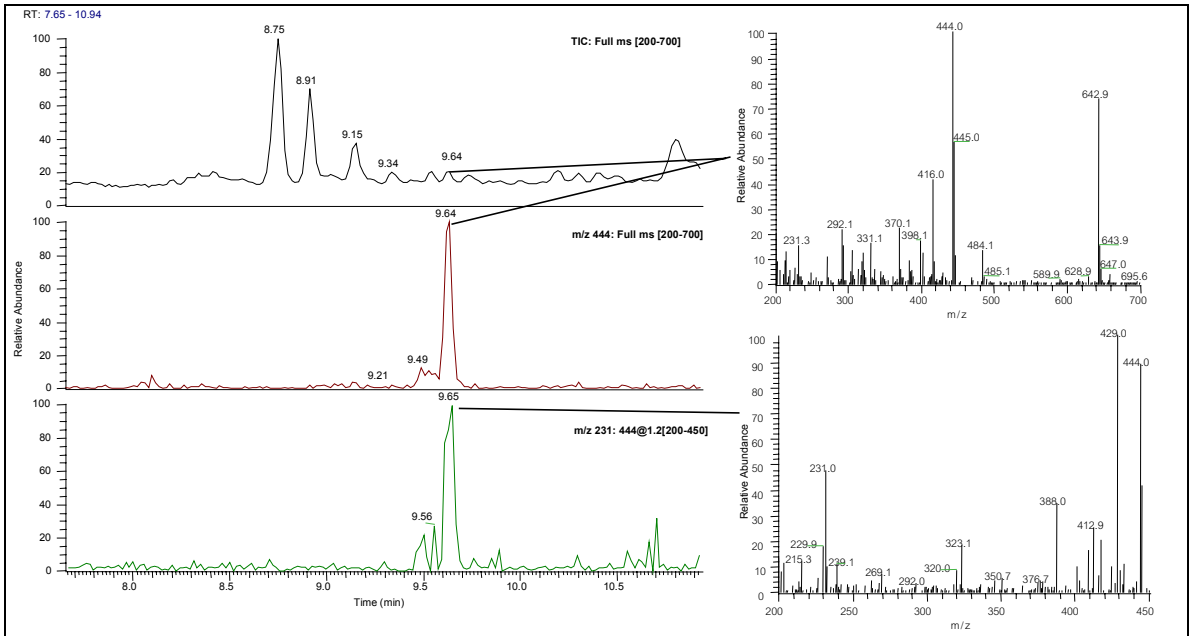

Figure 18. Chromatograms of HBF-derivatised hydrolysed air sample, from above: Total ion chromatogram; extracted ion (m/z 444) from the full scan event; extracted ion (m/z 231) from the MS/MS scan event on m/z 444. In the right side is the full-scan and MS/MS spectra inserted.

When comparing exposure data to animal studies, it seems for the non-toxicologist to be very high quantities that have been instilled in rats and mice. Often 10^5 to 10^6 spores in single doses[45,217-219,419] and down to 10^3 spores in several doses[216], and with the concentrations of *Stachybotrys* spores even in highly infested buildings generally <<1000 spores/m^3.
As seen in the literature part, many data on the toxicity of trichothecenes exist, however only af few studies take lung toxicity, particle effects, and other metabolites into account.
Using the data of Nikulin et al[45] who used 10^6 spores (containing 140 ng MTR) as a single dose, the death of 2 of 4 animals, resembles the LD_{50} value (not taking the statistical uncertainty into account). Directly transferred to a human (70 kg) assuming the same susceptibility per weight, corresponds to about 750 µg MTR or 3×10^9 spores.
As concentrations of *Stachybotrys* spores even in highly infested buildings, is generally below 1000 per m^3 (Hunter et al[10] have reported 20 times higher values) and with a human respiratory rate of 1.5 m^3/hr, about 36 000 spores can inhaled per day. This is so much lower than the LD_{50} value, that there is no reason to suspect lethal mycotoxicoses even if a 1000x lower LD_{50} is used, to cope with individual and species susceptibility as well as more toxic strains into account.
Workers handling infested materials, and not using the prescribed respiratory filters may be exposed to very high levels. Assuming up to 0.1-1 µg/cm^2 MTR and a LD_{50} of 750 µg MTR this corresponds to dust from 0.15-1.5 m^2, and it is not likely that any persons will inhale so much biomass even if working in a small unventilated room. But significant inflammation in the lungs and decrease in platelet concentration, as well as changes in the lymphocyte subpopulations may be possible. Such effects were observed in mice when instilling 6 dose over 3 weeks using 10^3 spores each time[216]. This corresponds to the dust from 2-15 cm^2 infested material per day. However these does not take the higher metabolism and shorter life span of the mice into account.
To asses the risk of people living in mouldy homes repetitive exposures of small doses is needed to estimate the *No observed adverse effect level* (NOAEL)[420]. This is especially important for the MTR, as they have immunosuppressing effects at far lower levels than the acute ones and should be combined with the other metabolites.
To conclude on this species, which is the far most investigated indoor contaminants, and still not been established any causal relationship to IPH, although is seems that the MTR are not the principle components. The general immunosuppression of people exposed to stachybotrys may also be explained by the spirocyclic drimanes, although exposure to MTR producing strains must be considered to be worse.
Significant is needed to characterise the health effects of spiriocyclic drimanes as they are the primary metabolites of *S. chartarum* when growing on building materials. More over they are also produced in its natural habitat, hay, and have been proven pharmacologically active in many assays (Appendix B, Table 2).

4.3.2 Aspergillus

4.3.2.1 A. versicolor

In paper 2, it was shown that this species was capable of growing on almost all the water-damaged materials, and that chipboard and wallpaper supported production of the most visible biomass. Furthermore (paper 13), it was observed that *A. versicolor* grew especially fast on paints, and transient humidity conditions greatly slowed its growth.

Two different growth patterns were seen: either low biomass production and heavy sporulation or high biomass production (white-red mycelia) with very low sporulation (papers 2, 3 and 10).

In paper 10, *A. versicolor* was one of the most frequently observed mould growing on the materials, even capable of growing at 5°C. This is contradictory to Smith & Hill[94], who observed that *A. versicolor* requires 9°C for growth on a high nutrient substrate such as MEA.

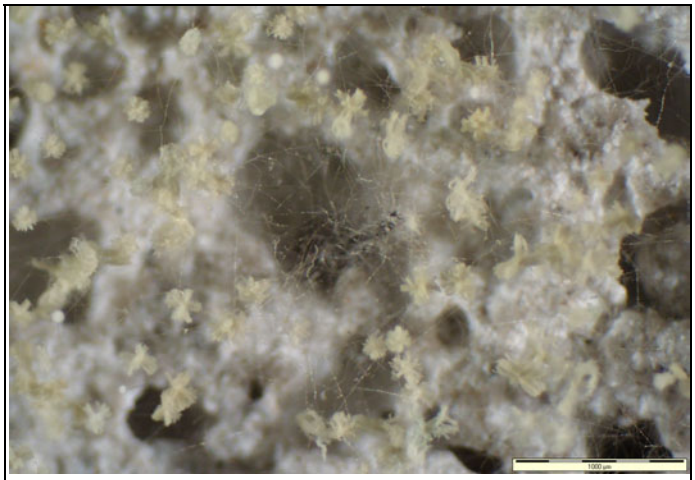

Figure 19. A "hotspot" of *A. versicolor* conidiophores on low density concrete (bar is 1 mm).

It was capable to grow on the three types of concrete at RH > 0.90 (paper 10), although the produced quantities of biomass were very low, except for a few hotspots (illustrated in Figure 19). It was notable, that it always was *A. versicolor* that grew on the concretes and never *P. chrysogenum,* which indicates that *A. versicolor* may require less nutrients or is better grow at high pH. This is confirmed by private consultants who often see *A. versicolor* growing in plaster (M. Ø. Hansen, personal communication).

In paper 2, it was shown that all the 5 isolates of *A. versicolor* from buildings produced, very high quantities of sterigmatocystins (ST) and 5-methoxysterigmatocystin (5ST), up to 30 µg/cm^2 on the material samples. In addition other ST analogues, versicolorins and other components from this biosynthetic pathway were usually also present in lower quantities estimated on the peak areas and the molar absorptivities. The amounts of biomass scraped from the materials were estimated to less than 100 mg, which means that the total contents of sterigmatocystins may have been more than 1% of the biomass. All the materials, especially wallpaper supported production of ST, which was positively correlated to the amount of visible biomass and negative correlated with sporulation. This is quite obvious, as substantial energy is put into sporulation.

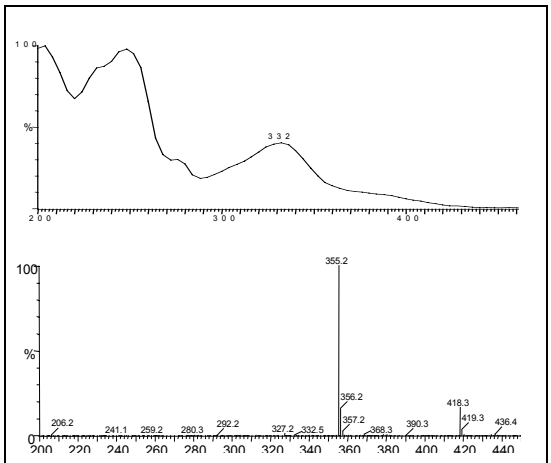

Figure 20. UV spectrum and positive ESI spectrum of 5-methoxysterigmatocystin.

In the study on naturally infested materials (paper 3) it was observed that red coloured areas infested with non- or poorly sporulating isolates contained the largest quantities of ST, whereas areas with many conidia contained very small quantities of ST. This is important for exposure assesment, as the spores are considered the source of exposure to ST, although new studies have shown than smaller fragments than the spores are liberated from its mycelium[84].

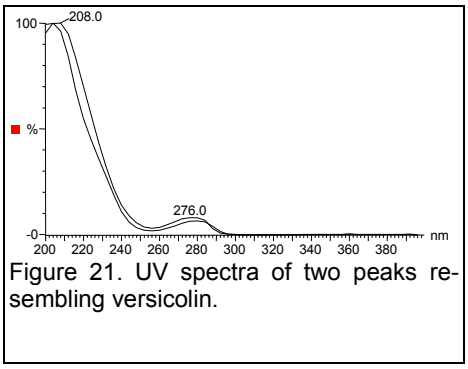

Figure 21. UV spectra of two peaks resembling versicolin.

In both paper 2 and 3, the investigated materials were soakingley wet (a_w > 0.99) and compared with paper 10 and 13 where different humidities were applied, it was apparent that ST production was correlated with RH, and that ST production was not detectable at a_w < 0.90. This complies with findings on cereals[245], where sterigmatocystin production started at a_w 0.89 with a maximum production and biomass at a_w 0.93.

In paper 2 and 3, 5ST was tentative detected based on its UV spectrum, especially the shoulder at 270-280 nm (Figure 20) not seen in the UC-spectra of other sterigmatocystins. Later it was shown by positive electrospray LC-MS, that the molecular weight was 354 Da. This is seen as the $[M+H]^+$ ion in Figure 20. The M+64 adduct could not be accounted for but it was also observed for ST.

A number of *A. versicolor* isolates produced one to five components resembling the known component versicolin[421-423] (J.C. Frisvad, personal communication). Two of the UV spectra are shown in Figure 21. Al least one of these was produced in substantial quantities on wallpapered gypsum boards (paper 2).

It was tried to clean up 5 of these components by growing a particular good producer on YES agar, where they often are produced in very high quantities. But as the components seem to be unstable when cleaned-up, and as time was short the project (2 weeks) it was abandoned. Later it was tried to tentative identify the analogues by LC-MS as a literature review showed that it might be 2,3,6-trihydroxytoluene[423] and esters hereof. However this analogues was not commercially available, but the two analogues to isomers 3,4,5-trihydroxytoluene, and 2,4,6-trihydroxy toluene of were purchased. Especially the 3,5,6 analogue, had a similar UV-spectrum (Figure 22) and a retention time similar to several of the "versicolins".

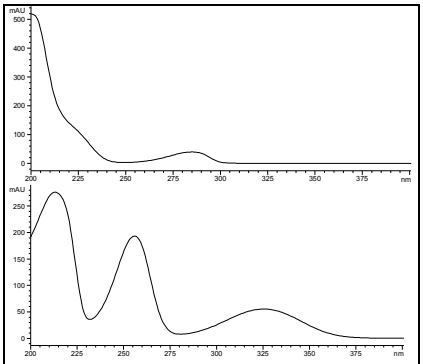

Figure 22. UV spectra 3,4,5-trihydroxytoluene and 2,4,6-trihydroxy toluene.

LC-MS of extracts containing the "versicolins" indicated MW of 260 and 262 Da, and several with 242 Da. However other, less abounded, unexplained ions were also present, meaning that these MW may not be correct. This was further complicated, as LC-MS of the two commercial analogues indicated the 2,4,6-analogue was not ionised at all, and that the 3,4,5 analogue showed 6 major ions at m/z 253, 294, 311 and 481, with no apparent ionization mechanism. Thus the ionisation conditions, including ion-polarity, have to be optimized for this type of components before any definite MW could be assigned.

In paper 10 and 13, where the sterigmatocystins and their analogues were almost never detected, and number of other metabolites were detected. These have previously been detected in extracts of *A. ochraceus* (J.C. Frisvad, personal communication), and are named ROQ, PE1 and XXO until their structure is known, their UV spectra can be seen in Fig. 11. Especially the latter component was often detected in material extracts. Occasional was the known component penigequinolone detected. Looking at some of the very small peaks in the chromatograms from both agar and material extracts (paper 2 and 3) revealed that these metabolites were present in many *A. versicolor* extracts.

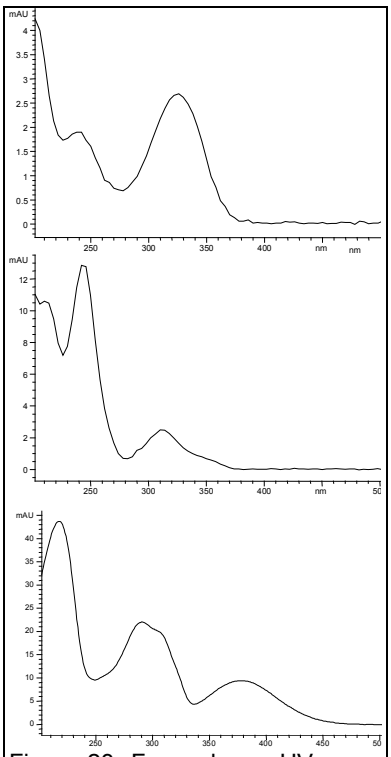

Figure 23. From above, UV spectra of the structurally unknown ROQ, XXO, and PE1.

LC-MS analysis indicated that XXO had a MW of 431 Da, and an analogue eluting at 1-2 min. before a MW of 447 Da. Three analogues of ROQ were detected, however the MW as only determined for on of them as 393 Da. It is interesting that these presumable nitrogen-containing metabolites (nitrogen rule) are still biosynthesised at RH < 90% while the polyketide pathway that produced ST, is shut down. However at 86% RH they were not biosynthesised by the still growing *A. versicolor.*

Four other types of metabolites, eluting between 3 and 10 min, seemed to be strongly associated with growth of this species under low RH, and their UV spectra can be seen in Figure 23, all has several analogues often also seen. A few of the metabolites have been seen in agar culture extracts.

The HPLC-DAD analyses of the samples of paper 10 and 13, also revealed a ERG analogue eluting approx. 2 min after having identical UV spectra, it was only detected in samples infested with *A. versicolor*. Inspection of the full scan segments of the GC-MS analyses indicated no other sterols, which together with the retention time and same UV spectrum strongly indicates that it was an ester of ergosterol.

It is obvious that the metabolism of this species is very diverse, and needs much more attention, as most of the metabolites produced at a_w < 0.95 are unknown. These metabolites may be important for the adverse health effects associated to growth of *A. versicolor*, especially because they were liberated from the materials by a light vacuum, and hence have the capability of becoming airborne.

Animal tests have also shown that *A. versicolor* induces inflammatory responses in rats and mice[145,151]. These things combined with the small liberated fragments from the spores or hyphae[84], means that the growth of *A. versicolor* poses a health risk even if air measurements does not show elevated concentrations of spores.

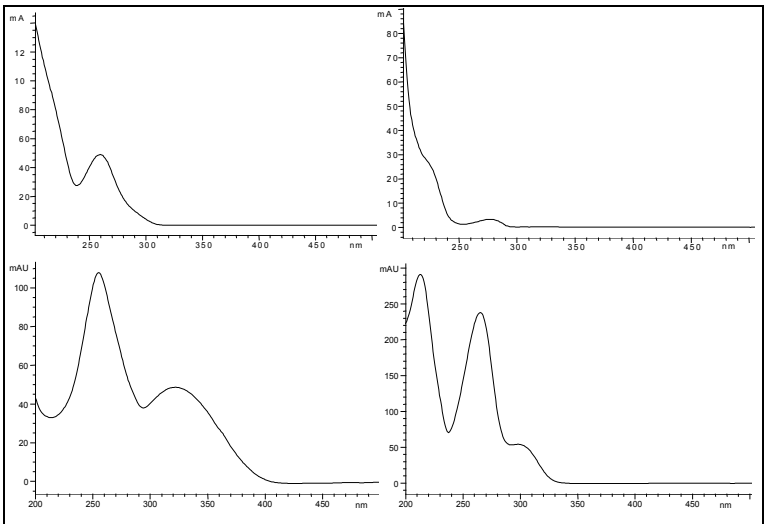

Figure 24. UV spectra of four unknown metabolites presumable produced by *A. versicolor*

4.3.2.2 A. ustus

In paper 3, *A. ustus* were incubated on a number of materials, they grew very slowly on pure gypsum boards and chipboard whereas growth was much faster on the wallpapered ones, which it covered the surface after 2 weeks. On the gypsum boards solid structures, 1-2 mm in diameter, containing up to 100 Hülle cells were observed. The *A. ustus* isolates studied in paper 3, were all isolated from mouldy buildings, and produced no detectable quantities of any known mycotoxins from this species. The highly toxic austamides, austdiols, and the

austocystins (Appendix B, Table 5) who are consistently found in cereal isolates (J.C. Frisvad, personal communication) were not produced in detectable quantities on the materials or in agar cultures. Instead a number of metabolites with UV spectra resembling the ones seen in Figure 25, with varying UV-max, all eluting between from 14 min to 35 min, were observed. The low toxic kotanines, also seen from isolates of *A. niger* was the only known metabolites produced on the materials.

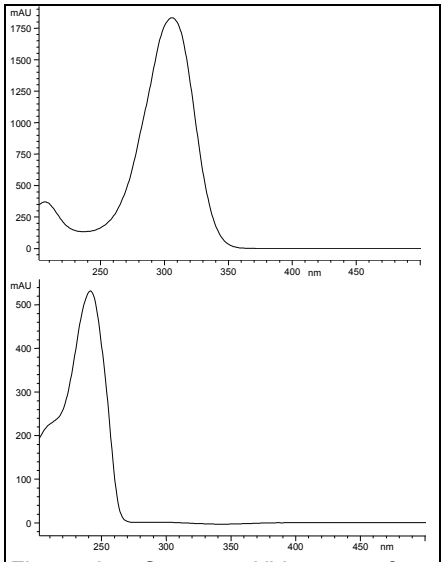

Figure 25. Common UV-spectra from *Aspergillus ustus* var. *pseudodeflectus*.

The indoor isolates appears to be *Aspergillus ustus* var. *pseudodeflectus*, which should be described as a new species, as varieties are not accepted any more[169].

In agar culture extracts of the indoor air type, components resembling the drimane sesquiterpenes, the TMC's, pergillins and ophibolins seem to be present (Appendix B, Table 5). These metabolites are not described as toxic, and have been isolated from *Aspergillus ustus* var. *pseudodeflectus,* but a definitive identification of these metabolites was not possible due to the lack of reference standards and LC-MS analyses.

The general conclusion on the indoor air *A. ustus* isolates, is that studies on their in vitro and in vitro pulmonary toxicity and inflammatory potential is needed (grown on relevant materials), as well as knowledge on what is actually liberated from materials infested by these isolates.

4.3.2.3 *A. niger* complex

Growth of especially *A. niger* was extremely fast on all artificially infested materials except on gypsum board and the wallpapered gypsum boards where almost no biomass were produced (paper 3). The other materials were covered by black *Aspergillus* heads in one to two weeks, and substantial quantities of biomass could be scraped off the material. This indicates that the gypsum boards contains components inhibiting the growth of this species. All isolates (paper 3) produced high quantities (>20 different) naphtho-γ-pyrones and tetracyclic compounds eluting from 6 to 35 min (UV spectra, see Figure 26) and the known compounds orlandin and nigragillin (Appendix B, Table 6). The quantities of these components made detection of the malformins and other end-absorption components impossible, and if the spores are later shown to be highly cytotoxic a more selective method against these small cyclic peptides should be developed. After the study the samples were reanalysed using HPLC-FLD for the presence of ochratoxins, but these analyses were also negative.

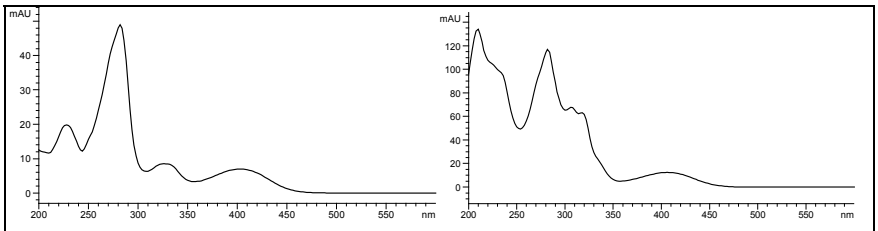

Figure 26. UV spectra of a tetracyclic compound (left) and naphtho-γ-pyrones.

When observing the spores on the media it is clear that they contains a high number of other metabolites, but as for *A. ustus*, studies on their in vitro and in vitro pulmonary toxicity and inflammatory potential is needed.

4.3.2.4 *A. flavus*

In paper 10, *A. flavus* contaminated a number of the wooden materials, presumable due to ineffective X- ray sterilisation (25 kGy), as *A. flavus* growth was seen on a piece of pinewood returned from the sterilisation plant. It should be noted that all boxes were marked with small X-ray indicators to assure that they were x-rayed.

However as *A. flavus* usually produces aflatoxins, extracts from materials where it grew were analysed with HPLC-FLD, where the samples had been derivatised using trifluoroacetic acid to produce the stronger fluorescent hemiacetals[424], which had a 52 times lower detection limit (≈100 pg) for the B_1 analogue than the underivatised. No aflatoxin was detected in of these samples, which complies with the results of Ren et al[262] and by Rao et al[263]. Surprisingly, the isolate recovered from one of the materials did not produce aflatoxins on CYA or YES agar.

However the in vitro and in vivo toxic and inflammatory potential of material cultures should still be investigated as this species produces many other metabolites when growing on materials, and hence may still be a problem.

4.3.3 *Penicillium*

In papers 3 and 10, it was observed that the penicillia produced significant less biomass than the aspergilli, based on visual observations, what could be scraped off the materials and the size ergosterol peak in the HPLC chromatograms.

It has been a problem to obtain materials with other penicillia than *P. chrysogenum*, as identification to the species level is not done by the consultant engineers we collaborates with, and who have a good source of naturally infested materials.

4.3.3.1 *P. chrysogenum*

In paper 3 it was observed that this species grew very fast on the wallpapered gypsum boards and chipboard, seen as grey to light green discolouring patches. The materials were overgrown in two to three weeks.

On the naturally infested materials investigated it was present in almost all samples, with more substantial amount of biomass than on the artificially infested materials. Isolation often also revealed an additional but limited number of *A. versicolor* colonies, indicating that it often grows in mixed cultures, which was also observed in paper 10. The mixed cultures may be due to a lower quantities of antifungal metabolites, or perhaps that the metabolites does not diffuse in these solid materials.

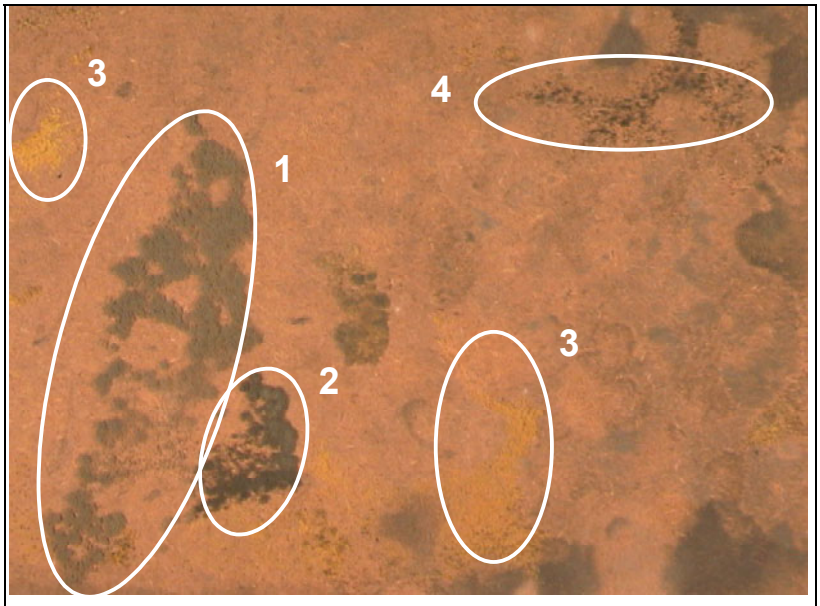

Figure 27. A MDF plate (20×14 cm) from paper 10, after 4 months at 95%RH and 10°C. # 1 and 2 are *P. chrysogenum* growth (2 mm high) and #3 is a *Eurotium* Sp., #4 is Ulocladium sp., and the rest of the material is partly covered with a mixture of *A. versicolor* and *P. chrysogenum*.

In paper 13, *P. chrysogenum* (CBS 401.92) was surprisingly fast on the painted samples, where it grew faster than *A. versicolor*, and was visible after 2 weeks, here it appeared light blue, but changed colour to grey over time.
P. chrysogenum produced (paper 3, 10 and 13) very low quantities of secondary metabolites compared with *Aspergillus* species, e.g. were no *P. chrysogenum* metabolites detected in any of the large areas seen on Figure 27, except for occasional detection of chrysogine, and 2-pyrovoylaminobenzamide no metabolites could be associated to growth of this species under non water damage conditions. A considerable number of the *P. chrysogenum* infested samples in paper 13 were contaminated with an unknown *Aspergillus*, producing totally unknown metabolites perhaps related to *A. ustus* and/or *A. versicolor*.
On water-damaged wallpapered gypsum boards it produced chrysogine (paper 3) whereas this metabolite was not detected on chipboard. The natural samples, meleagrin was detected as the only metabolite, which is interesting as it is a predecessor of the neurotoxic roquefortine C (paper 3). TLC analyses[274] showed that all isolates produced an unknown metabolite appearing as dark blue spots after spraying with anis aldehyde. This metabolite was only detected from *P. chrysogenum* and had approximately 10% higher R_f-value than griseofulvin.
Recently it was shown that double blinded placebo controlled exposure of 8 "sensitive" humans to 6×10^5 spores/m^3 for 6 min of *P. chrysogenum,* grown on wallpapered gypsum boards*,* did not induce any significant changes in self reported symptoms, clinical measurements or blood analyses (Meyer, H.W., Kildesø, J., Nielsen, K.F. et al, to be published).
As for most of the other moulds, no data no the long term toxic potential of this species exists, and hence it may produce toxic metabolites, not detectable with HPLC-DAD. However on the other hand, it may be one of the moulds that obscure detection of more toxic species.

4.3.3.2 P. brevicompactum

All isolates grew well on water-damaged wallpapered chipboard and chipboard (paper 3) whereas the growth was slower on the wallpapered gypsum-boards, and no growth was observed on gypsumboards. This observation suggest that growth it is stimulated by components present in wood, which corresponds well to field observations where it is frequently isolated from wooden materials[124].
On chipboard (paper 3), 1/3 of the isolates produced mycophenolic acid, and 1/2 of the stains also produces asperphenamate, a tanzawaid acid analogue[425](UV in Figure 28), and the structurally unknown metabolite O.
In paper 10, this species was not isolated from any of the materials, indicating that it has difficulties with competing with *P. chrysogenum* and *A. versicolor*. However the dust from one MDF plate (10°C, 95% RH) contained another tanzawaid acid analogue indication the presence of *P. brevicompactum* on the material, and other possible analogue was detected from a beech wood piece (90% RH, 20°C), also indicating the presence of *P. brevicompactum*.

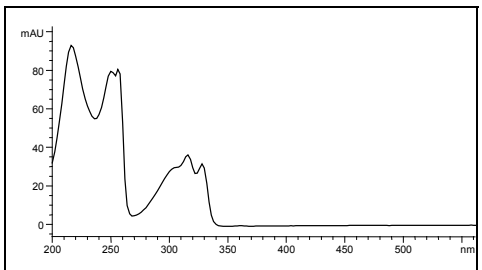

Figure 28. UV spectra of unknown tanzawaid acid analogue.

Especially the presence of the immunosuppressing mycophenolic acid, a number of metabolites with unknown biologically activities, and the anecdotal mycotoxicoses after ingestion of infected food, suggests that may have strong in vitro and in vivo toxic and inflammatory potential, which of needs further investigation, as it is on of the most common penicillia in mouldy buildings.

4.3.3.3 P. polonicum

Only two indoor strains were available, and they grew on all the materials, although usually with not very much biomass (paper 3). They both produced 3-methoxy-viridicatin, verrucofortine, and the tremorgenic verrucosidin.
However as it is not clear how common this species is in the indoor environment, there are other species which need to have their in vitro and in vivo toxic and inflammatory potential determined before this species.

4.3.3.4 Penicillium expansum

Only one isolate of indoor origin was available (paper 3) and it grew very poor on all the four materials, and no metabolites were detected in any of these samples. This is contradictory to Land and Hult[289] who saw production of the patulin, when their strains were inoculated on wood and wood chips.
As this species can produce some of the most toxic components found in this genus, it is necessary to know if its presence in buildings is due to growth on materials or introduced from mouldy fruits.

4.3.4 Trichoderma

In paper 2, where the materials were inoculated at $a_w \approx 1$, growth of *Trichoderma* could be detected after 3-4 days on wooden materials whereas it was much more slow on other materials and did not occur on the new gypsum boards. These observations are fully in accordance with field observations (paper 4) where Trichoderma is generally found on wood products[25,71].
In paper 10, where the humidity was lower, *Trichoderma* was only growing on a very small fraction at the wooden materials and here not even as the dominating mould. This further demonstrates that this genus requires water-damaged materials to grow.
None of the *T. atroviride, T. harzianum, T. longibrachiatum* and *T. viride* infested materials from, paper 2, revealed trichodermol upon hydrolysis, which was also the case for the YES extracts from the 36 isolated investigated by Lübeck et al[71].
In a later paper 8, 150 additional agar extract from U. Thrane's collection were screened for trichodermol, however only one isolate (IBT 9471 = ATCC 90237) was able to produce trichodermol as also found by Corley et al[293]. It was not been possible to obtain other known trichodermol producing isolates, as the isolate used produce the first trichodermin by Godtfredsen & Vangedal[291] at LEO pharmaceuticals, Denmark, is not available.
The literature review on *Trichoderma* showed that the peptides are some of the dominating biologically active metabolites (Appendix B, Table 11), but they were not targeted in this work due to lack of LC-MS facilities.
Recently it was shown that double blinded exposure of 8 "sensitive" humans to 6×10^5 spores/m^3 of *T. harzianum,* grown on wallpapered gypsum boards, during 6 min, did not induce any significant changes in self reported symptoms, clinical measurements or blood analyses (Meyer, H.W., Kildesø, J., Nielsen, K.F. et al, to be published). The set-up was (for economic reasons) partly buildt in plastic, and during characterization of the set-up it was shown that particles smaller than the spores were absorbed to the walls of the set-up.
As T. *harzianum* as *A. versicolor*, also produces smaller particles (Kildesø, J.K., Würtz, H., Nielsen, K.F. et al, to be published) than the spores the people were not exposed to these fine particles.

To conclude on this genus, it is important that their in vitro and in vitro pulmonary toxicity and inflammatory potential is investigated (grown on relevant materials), as well as knowledge on what is actually liberated from materials infested.

4.3.5 *Memnoniella echinata*

No growth tests were performed with this species on materials, but an infested piece of *Memnoniella* infested gypsum board received from Dr. E. Johanning. Dust, sampled by the ALK mouthpiece, from this sample contained griseofulvin and its two dechlorinated derivatives.
Chemical analysis (unpublished) were performed on 11 isolates, grown on ALK, PSA, SYES, CYA and V8 agar: Results showed that the three griseofulvins where consistently produced on all media and in significant in quantities compared to other metabolites, and combined with data from rice cultures[44], it must concluded that these components seems to be produced on all solid substrates. Spiriocyclic drimanes, similar to the ones produced by *S. chartarum*, were also consistent produced, however in significant (ca. 10×) lower quantities than the griseofulvins, based on the UV molecular absorptivities.
The production of trichodermol or esters of it, varied considerable even in the same isolates on the same media (papers 8 and 11).

To conclude on this species, it seems to be isolated the same places as *S. chartarum* although less frequently, which may be due to difficulties of distinguishing it from *S. chartarum*. However studies on its *in vitro* and *in vitro* pulmonary toxicity and inflammatory potential is needed (grown on relevant materials), as well as knowledge on what is actually liberated from infested materials.

4.3.6 *Alternaria*

All the isolates, except of the *A. infectoria* group isolate, inoculated on different materials (paper 3) grew well and produces alternariol, it's mono methyl ether and three to five unknown analogues with identical UV-spectra. However these metabolites very low toxic and should not be considered mycotoxins (see section 2.4.6, p. 22). No altertoxins, tentoxin or tenuazonic acid was detected in any of the extracts, confirming results of Ren et al[308].

It was tried to find naturally infested material with growth of *Alternaria,* but all samples (>15) brought to the department was infested with *Ulocladium* sp. and not *Alternaria*. This may indicate that actual *Alternaria* growth on materials may not be that common, and that the many findings of *Alternaria* in the indoor air environment may originate from out door sources.
However it has still not been shown if the AAL toxins are produced by *Alternaria* in buildings, although this is very unlikely, as this type of strains are only known as endophytes in plants[350,426]. These metabolites are the only really mycotoxins known from this species, but need LC-MS detection or the unspecific OPA derivatisation also used for fumonisins. Thus, the presence of this fungus in buildings only seems to pose a very limited risk, especially as the main source of exposure comes from outdoors, where the air concentrations are magnitudes higher than indoors.

4.3.7 *Chaetomium globosum*

Being an ascomycete this genus has a very characteristic appearance (paper 3) due to its distinct black or dark green, hairy perithecia visible to the naked eye. Field samples were all very wet wallpaper, gypsum board and wood products (paper 3 and 4). On the artificially infested water-damaged material growth was very fast covering the surface with substantial amounts of biomass after two weeks (paper 3).

In paper 10 where mixtures of common moulds were inoculated under controlled humidities *Chaetomium* was only found growing at one material clearly showing that this genus generally requires water-damaged materials to grow.

When growing on building materials (paper 3) *C. globosum* consistently produced high quantities of biomass (up to 10 mg/cm^2). Very high quantities of secondary metabolites, especially chaetoglobosins A, C and analogues were produced in very similar quantities, 28-50 and 5-7 µg/cm^2 respectively, by six isolates incubated on wallpapered gypsum. An unknown metabolite, was detected in all *Chaetomium* extracts except in IBT 7029, which had visible smaller peritricia than the other isolates. Hence this component may be a species-specific marker. Its UV data (see Figure 29) did not seem to match any of the components found in Table 15 in Appendix B.

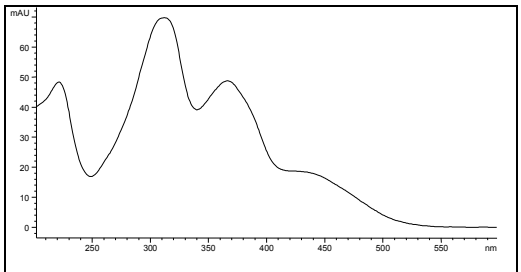

Figure 29. Unknown metabolite from *C. globosum*.

The metabolite profile of naturally infested materials were very similar to the artificially infested materials, chaetoglobosin A and C production in quantities up to 3 µg/cm^2. Besides these, three other chaetoglobosins and approximately 10 unknown metabolites were also detected. Analyses of two old (2-3 years) heavily black-stained materials did not reveal chaetoglobosins A or C, but a number more polar analogues, which are probably hydrolysis or oxidation products of the original metabolites, however these extracts have not yet been subjected to LC-MS analyses.

C. globosum grew very well together with gram negative bacteria on various building materials without it was possible to se this in the stereo microscope. However when determining the inflammatory potential of this mixture in mice macrophages huge quantities of TNFα and NO was liberated due to endotoxin from the bacteria. This observation may point against more studies on the interaction between bacteria and moulds as the bacteria may need the moulds powerful enzyme-systems. However spores from the pure cultures did not induce any inflammatory response in macrophages, but was cytotoxic to the cells (unpublished).

When concerning risk assessment of this fungus in buildings, it is clear the cytotoxic and cytoplasmatic cleavage inhibiting chaetoglobosins is the main concern. However as no data on inhalation of the spores have been found in the literature. As the spores of this fungus is packed in the Peritrecia the exposure to airborne spores may be rather limited and smaller particles released from dry mycelia, as it has been shown for *A. versicolor*, must be studied before any attempt on risk assesment is tried.

4.3.8 Cladosporium

C. sphaerospermum seems to be the most predominant species growing in buildings, and was able to out grow *P. chrysogenum* even in a ratio of 1 to 100 (paper 13). This is a result of their ability to re-attain growth from the hyphal tip much faster than penicillia[119], which is presumable why this and other phylloplanes are so common in bathrooms and on silicon caulkings in the window frame, environments which often have very different humidities during the day.

No secondary metabolites were detected in any of the samples in paper 13, and this genus is known for the very few metabolites it produces, and it ability to grow under these special conditions may account for this.

The high number of spores of *C. cladosporioides* (up to 15000m^{-3}) found out doors during the summer and the apparent lack of metabolite production on materials, and no inflammatory response when in instilled mice lungs[217], suggests that this genus should generally not be considered more than a humidity indicator.

4.3.9 Ulocladium

All four isolates inoculated on materials (paper 3) grew well, but did not produce any detectable quantities of secondary metabolites, which is in accordance with the literature where extremely few metabolites from this genus have been described. Analyses of natural samples with excessive growth have not either revealed any metabolites in the polarity range we look at using present HPLC-DAD method.

In Study 10, it was only isolates at RH ≈ 0.95, indication that is also requires very high RH, and not metabolite seemed to be associated to it.

To conclude on this genus, it seems to be isolated the same places as *S. chartarum* although more frequently, as it is presumable able to grow under the same humidities as *Alternaria*, but the low production of metabolites no known knowledge of mycotoxicoses indicates that it is not a major problem. However this should be confirmed by testing its *in vitro* and *in vitro* pulmonary toxicity and inflammatory potential.

It is a good indicator for wet environments and hence water-damage, but requires significant microscopic training if it should be differentiated from *Alternaria*.

4.3.10 Paecilomyces

P. lilacinus was found to grow poorly on all the artificially infested materials except on gypsum boards, where the characteristic pink cotton-like mycelium was produced, but only in modest amounts, and no metabolites were detected in the extract (paper 3).

P. variotii grew well on the artificially infested chipboards and wallpapered chipboard, but the quantities of biomass were very limited, however at the chipboard did support production of seven components with totally unknown UV-spectra.

These two species, both needs to have their *in vitro* and *in vitro* pulmonary toxicity and inflammatory potential determined (grown on relevant materials) besides determining the size of particles liberated from materials infested with them.

4.3.11 Eurotium

In study 10, *Eurotium* sp. was isolated from several of the wooden materials inoculated at 25, 20 and 10°C (materials were not sterilised prior to inoculation at 10°C).

The HPLC analyses revealed the presence of very high quantities of metabolites compared with *A. versicolor* and *P. chrysogenum.* These metabolites were probably present in the ascoma (see Figure 30) as these structures were very predominant. Echinulin and several derivatives were detected along with a high number of antraquinones, including questin and questinol, several benzoquinones, including flavoglausin, produced by many *Eurotium* species[427]. Also two isochromane toxin analogues[425,428] were detected.

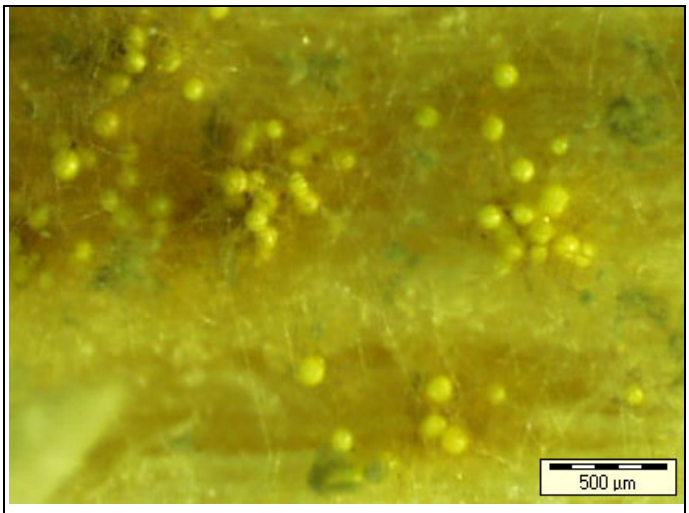

Figure 30. The ascomata from *Eurotium* sp. on a piece of pinewood after 4 months at 10°C and 95% RH.

The high quantities of metabolites sampled on the filters indicates that this genus may be important, and the in vitro and in vitro pulmonary toxicity and inflammatory potential of dust from infested materials is needed.

4.4 Overall discussion

4.4.1 Growth on materials

It has been demonstrated that the tertiary colonisers in practise require almost liquid water to grow on the materials. Hence the name water-damage moulds is very appropriate. To avoid growth of these is theoretically very simple, as it just requires dry constructions. However due to insufficient quality assurance in the building industry and partly also insufficient maintenance, these five problems are observed:

- The climate screen, especially the roof, should be watertight, which should not pose any problem. However this is actually a major problem in Denmark, as seen in paper 4, especially due to leaking flat roofs.
- Leaking pipes, especially when they are hidden in the constructions, constitutes a substantial part of the severe water damages (papers 3 and 4).
- Rising damp from the ground, due to lack of drainage or capillary breaking layer.
- Water build into the construction either from hardening concrete, which had not had the time to dry out. Also materials which have been placed on the ground or out in the rain is becoming an increasing problem and a number of these cases have been reported in the press.
- When parts of the building is exposed to rain during the building process, this an engineering or planning problem which demand that the partly finish construction is shielded during the building process.

Solving these problems is a not a matter of choosing or developing other materials, as almost all materials was able to support fungal growth (paper 4 and 10). Instead it is a matter of creating new quality assurance systems, which can be practically implemented during the building process.

4.4.2 Metabolites

The water-damage moulds produced very high quantities of secondary metabolites, and as secondary metabolites are signal components[169], these metabolites must be very important for the fungi, as they must use significant energy and internal resources on producing them.
Trichoderma spp. produced very low quantities of detected metabolites, which is probably due to the poor extraction and UV-absorption of the peptabols which this genus is so known for.
When comparing the quantities and number of metabolites produced the aspergilli and penicillia on agar substrates with the metabolites produced on building materials, it was clear that the rich agar substrates *short circuits* the metabolism of these genera. It appeared that the aspergilli produced significant higher quantities on moisture saturated materials, whereas the penicillia seemed to need the many nutrients found in the rich agar media.
When comparing the metabolism of aspergilli and penicillia with *Stachybotrys*, it is seems like this *short circuiting* is correlated to the extensively mycelia production, which seemed to be negatively correlated the sporulation. Thus, when trying to predict the production of metabolites on various matrixes such as building materials, by using agar substrates, media enhancing sporulation and decreasing pure mycelia growth should be used.
Especially when working with *A. versicolor,* it was frustrating to see the numbers of unknown metabolites in the extracts. Hopefully accurate-mass LC-MS, will make identification of some metabolites which is probably known in literature possible.
It is essential to investigate the toxicity and inflammatory responses of all appropriate moulds as function of the humidity, as it may only under certain humidities that they are toxic or inflammagenious. Perhaps it is also isolate depended or perhaps loses some of the strains the ability of producing important metabolites when held in the lab, as it observed when working on the membrane-toxin (paper 7).
The total microbial flora still needs to be established, at bacteria presumable means a lot under certain conditions and there may be several types of bacteria present at the materials which have not been determined. The bacteria may need the moulds to degrade the materials, and especially genera as *Stachybotrys*, *Chaetomium* and *Trichoderma* that are very well known producers of cellulases and as they requires almost saturated conditions they will have to compete with bacteria which can also grow at these a_w.

4.4.2.1 Analytical methods

Extraction of the metabolites was the most important step, and it was clear that extracting whole materials in organic solvents is not a suitable technique as: i) very huge quantities of interfering material was also extracted from the material (paper 1-3) which may obscure detection or even react with the target components; ii) mycotoxins as ST and TR, could only be extracted from the material-matrix in very limited quantities, <1% of spiked quantities (paper 2); iii) the detected metabolites may not become airborne, especially if they are excreted into the material. It is important to evade interfering components, as it will require a number of different solid phase extracting (SPE) techniques for each or a group of components. This

makes screening impossible, as it perhaps needed to make 2-6 different SPE clean-up steps per analysis, which is very time and resource consuming.
Scraping off the material using a blade worked better (paper 3) but material is easily lost if it is dry and if the material is very wet then significant quantities of interfering material may still be present from the material. Hence the vacuum sampling technique used in paper 10 and 13, is much better as it only samples metabolites that may become airborne and samples a minimum of matrix.
The used detection methods have unfortunately only worked on medium to apolar substances, which could be detected using HPLC-UV, except for the trichothecenes, which were targeted by GC-MS. However important substances as the nephrotoxic glycopeptides, AAL toxins, malformins, cyclosporin analogues, and many peptides would have evaded detection, this also includes unknown toxins and of course metabolites present below the detection limits.
Appropriate bioassays would cope with these problems as these, but it would still need a lot of assays for the different activities, so it would have been perfect to combine this study with a lot of assay tests, unfortunately this was not possible.

5 CONCLUSION

Moulds growing on water-damaged materials produce a high number of very toxic metabolites. The production of these metabolites is very dependent on the humidity of and for some moulds also the substrate.

Three taxa of *Stachybotrys* are found in buildings of these only one taxon, approx. 35% of the isolates, actually produced satratoxins whereas most other strains stop the trichothecene biosynthesis at trichodermin. All three taxa produced high quantities of the pharmacologically active spiriocyclic drimanes and their precursors. These two groups of metabolites and the atranones, which are produced by the two non-satratoxin producing taxa, are produced on building materials under field conditions. Idiopathic pulmonary hemasiderosis in infants did not seem to be associated with satratoxin production. *Stachybotrys* biomass collected on filters from naturally infested materials samples, contained significant higher quantities of metabolites than any other fungal species investigated during the study.

This study has shown that spiriocyclic drimanes and satratoxins were present on filters from air-samplings in a building with severe health problems due to growth of *S. chartarum*.

Aspergillus versicolor, which is perhaps the most common species found in mouldy buildings, had a very diverse metabolism, where many of its biosynthetic pathways were only occasionally expressed. When growing on materials under high water activity (>0.95%) most isolates produced high quantities of the carcinogenic mycotoxin, sterigmatocystin, whereas a_w<0.90 a number of structurally unknown metabolites, presumably alkaloids, also known from *A. ochraceus* were produced. *A. versicolor* grew often in mixed cultures with other moulds where it sporulated poorly, meaning that it may evade detection by cultivation based methods.

Penicillium chrysogenum is the most frequently detected species, but it produces surprisingly few detectable metabolites and often none. Combined with the lack of observed effects in patients experimentally exposed to high quantities of the spores it indicates that it may not be important from a heath point of view and is actually obscuring the detection of more toxic genera and species.

On water-damaged materials *Chaetomium globosum* produces high quantities of chaetoglobosins, whereas *P. brevicompactum* produces mycophenolic acid and *P. polonicum* the tremorgenic verrucosidin. The *A. ustus* isolates from buildings are macro-morphologically and chemically very different from cereal isolates, and should be described as a new species.

Trichoderma longibrachiatum, T. harzianum, T. citrinoviride, T. atroviride and *T. viride* does not produce detectable quantities of trichothecenes when growing on materials, and even on laboratory media <1% of the isolates produce trichodermol or esters of it.

When mouldy material are investigated for mycotoxins they should be vacuum sampled onto filters, as it dramatically decreases the number of interfering substances from the materials and gives a more precise description of peoples exposure.

Except from *Stachybotrys*, almost no data on the pulmonary toxicity and inflammatory potential of the spores and fragments exist from indoor moulds grown on appropriate materials, and not on agar media where the secondary metabolism is often *short circuited*.

The minimal RH for growth on wood-based materials and material containing starch is just below 80% at room temperature, and increases to about 90% at 5°C. On paper-mineral composites such as gypsumboard the min RH is approx. 90% RH from room temperature to

5°C. Pure mineral based materials with few organic additives seems to be able to support growth at RH ≥ 0.90, although 95% RH was needed to generate chemical detectable quantities of biomass. *S. chartarum* requires RH ≥ 95% to grow on gypsum boards.
When applying transient humidities to material samples during a day, the phylloplane *Cladosporium* was able to outgrow *P. chrysogenum*, even though it can grow under lower RH than *Cladosporium* under constant humidity. This is presumably why phylloplanes like *Cladosporium, Ulocladium, Phoma* and *Aureobasidium* are very common i bathrooms and other places with instationary humidity conditions.
Ergosterol content of building materials could be very precisely be quantified and quickly analysed (60-100 samples per day) by isotope dilution GC-MS/MS, although not being as sensitive as other GC-MS based methods due to interference from the isotope marked standard and instrumental problems on the ion-trap used. Visual assessment, especially supported by dissection microscopy, was however just a sensitive and is able to cope with the high variation in mould biomass on materials, but should occasionally be supplemented with chemical markers for comparison with other studies.

6 PERSPECTIVES AND FUTURE RESEARCH

Although excellent research is being done in this field especially in Scandinavia, The Netherlands and North America, we are far away from a major breakthrough, and hence much more research is needed.

Smaller projects

Studies on the inhalative toxicity of the spiriocyclic drimanes found in the spores of *Stachybotrys* are needed. This should be followed by development of specialised methods for detecting these metabolites as they are present in substantial quantity and have shown to be good biomarkers in this study.

Studies on the three different *Stachybotrys* taxa are needed, to se if atranone and satratoxin producing isolates coexists, and/or also to see if the atranone producing taxa over long time also can produce low quantities of satratoxins.

An immunochemical assay for detection of sterigmatocystin-guanine and other adducts of this toxin could be used to determine if people are exposed to the toxin through the air or only through the food.

The unknown *A. versicolor* metabolites needs to be structure elucidated and produced in sufficient quantities for a toxicological evaluation.

As exposure to mycotoxins may originate from particles significant smaller than the spores it should be determined if filters or adsorption materials, like activated carbon, should be used for sampling of the mycotoxins. These studies should also face clean-up problems due to interfering substances collected from the air.

Major projects

General microbiological work is needed so the total indoor funga can be established precisely and to the species level, as a lot of confusion exists, especially in *Penicillium*.

A lot of work is needed on the ecology of the moulds on the materials and the performance of different materials, especially under dynamic conditions. It is also very important to know the response of the moulds to both short and long periods of increased humidity still close to their critical RH.

Co-ordinated and comparable tests of the inflammatory potential and the toxicity of particles released from infested materials, including materials from problem buildings and materials incubated at realistic conditions, should be performed. These tests should be performed from a representative number of isolates from all relevant species. Such results can be used to rate the health impact of the moulds in epidemiological studies and for risk handling in mouldy buildings.

Inhalation experiments where the cognitive performance on mice or rats and their off-spring are measured should also be tried. This was very successful for low concentration exposure to xylene[429], and if combined with exposures to known areas of naturally infested and artificially infested materials kept under well characterised ventilation conditions, this may be the way to a major breakthrough.

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APPENDIX A

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APPENDIX B

Here are listed chemical and biological data from the components the different mould genera and species covered in section 2.4. When the mono isotopic mass was not listed in the paper it was calculated[1]. This appendix has its own reference list.

Table 1

Trichothecenes from *Stachybotrys* species from *Stachybotrys* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da) [1]
Satratoxin H [2]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{36}O_9$	225(14700), 255(10400)	528.24
Iso-Satratoxin H [3]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{36}O_9$		528.24
Satratoxin G[4]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{36}O_{10}$	256(6500)	544.23
Iso- satratoxin G [3]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{36}O_{10}$	260	544.23
Satratoxin F [4]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{34}O_{10}$	250 (5900)	542.33
Iso- satratoxin F [3]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{34}O_{10}$	251(17700)	542.33
Roridin E [5]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{38}O_8$	195(15800), 223(25100), 263(19900)	514.26
Iso-roridin E[6]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{38}O_8$	223(24000), 262(16000)	514.26
Epi-roridin E[6]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{38}O_8$	223(24000), 262(16000)	514.26
Verrucarin J[7,8]	*S. chartarum*	Highly cytotoxic	$C_{27}H_{32}O_8$	196(15500), 219(19900), 262(14500)	484.21
Verrucarin B[7,8]	*S. chartarum*	Highly cytotoxic	$C_{27}H_{32}O_9$	258.5(23400)	500.20
Roridin L-2[3,9]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{38}O_9$	259(24650)	530.25
Trichoverrol A[7,8]	*S. chartarum*	Highly cytotoxic	$C_{23}H_{32}O_7$	260(36300)	420.21
Trichoverrol B[7,8]	*S. chartarum*	Highly cytotoxic	$C_{23}H_{32}O_7$	260(33900)	420.21
Trichoverrin A [7,8]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{40}O_9$	260(39800)	532.27
Trichoverrin B[7,8]	*S. chartarum*	Highly cytotoxic	$C_{29}H_{40}O_9$	260(33800)	532.27
Trichodermin[10]	*S. chartarum*, *S. cylindrospora*		$C_{17}H_{24}O_4$	End abs.	292.38
Trichodermol[10]	*S. chartarum*, *S. cylindrospora*		$C_{15}H_{22}O_3$	End abs.	250.34

[1]Molecular ion according to

Table 2

Non-trichothecene secondary metabolites and mycotoxins from *Stachybotrys* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Atranone A[11]	*S. chartarum*		$C_{24}H_{32}O_6$	224(10500)	416.22
Atranone B[11]	*S. chartarum*		$C_{25}H_{34}O_7$	231(10800)	446.23
Atranone C[11]	*S. chartarum*		$C_{24}H_{32}O_6$	End abs	416.22
Atranone D[11]	*S. chartarum*		$C_{24}H_{34}O_4$	231(14800)	386.25
Atranone E[11]	*S. chartarum*		$C_{24}H_{34}O_4$	226(12500)	386.2457
Atranone F[12]	*S. chartarum*		$C_{24}H_{32}O_7$	237(4169)	432.2148
Atranone G[12]	*S. chartarum*		$C_{25}H_{34}O_8$		462.2254
Epoxydolabellane A[6,12]	*S. chartarum*		$C_{20}H_{30}O_3$	235(8870)	318.2206
6β-hydroxydolabella-3E,8E,12-trien-14-one [13]	*S. chartarum*		$C_{20}H_{30}O_2$	236(8710)	302.2246
Mellin[5]	*S. chartarum*		$C_{10}H_{10}O_3$	246, 314	178.063
K-76 COOH [14-16]		Anti diabetics, necrosis factor-liberation inhibitors	$C_{23}H_{30}O_7$		418.1992
6,8-dihydroxy-3,5,7-trimethylisochroman[10]	*S. cylindrospora*		$C_{11}H_{13}O_3$	202(38000), 25(8000), 275(41007), 281(1400)	208.1091
Bisbynin[17]	*S. bisbyi*	Enhances fibrinolytical activity	$C_{15}H_{22}O_5$	End abs.	282.1467
Epi-cochlioquinone[18,19]	*S. bisbyi*	Inhibitor of cholesterol acetyltrans-ferece	$C_{30}H_{44}O_8$	270(10200), 386(1100)	523.3004
F1839-A[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{23}H_{31}NO_5$	218(37424), 262(6553), 301(3182)	401.2202
F1839-B[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{24}H_{33}NO_6$	218(41271), 271(6230), 308(2910)	431.2308
F1839-C[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{24}H_{33}NO_6$	217(33069), 267(5293), 302(2525)	431.2308
F1839-D[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{23}H_{31}NO_5$	225(31615), 255(10385), 298(4924)	401.2202
F1839-E[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{25}H_{35}NO_6$	217(31462), 262(6408), 302(2314)	445.2464
F1839-F[20,21]		Inhibitor of Pancreatic cholesterol	$C_{28}H_{39}NO_7$	217(33069), 267(5293),	501.2727

Table 2

Non-trichothecene secondary metabolites and mycotoxins from *Stachybotrys* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
		esterase		300(2525)	
F1839-I[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{23}H_{32}NO_4$	229(11384), 282(9412), 325(3683)	386.2331
F1839-J[20,21]		Inhibitor of Pancreatic cholesterol esterase	$C_{29}H_{41}NO_6$	218(32041), 261(7357), 301(2323)	499.2934
FR901459[22 23]	*S. chartarum*	Immunosuppressant, cyclosporin analogue	$C_{62}H_{111}N_{11}O_{13}$	End abs	1217.8363
K-76[24,25]	*S. complementi*	Complement inhibitor Inhibitor of Pancreatic cholesterol esterase	$C_{23}H_{30}O_6$	246(16500), 307(6700), 359(5400)	402.2043
Kampanol A[26]	*S. kampalensis*	RAS farnasyl-potein transferase inhibitor	$C_{25}H_{32}O_6$	223(13330), 262(5118), 308(2408)	428.2199
Kampanol B [26]	*S. kampalensis*	RAS farnasyl-potein transferase inhibitor	$C_{27}H_{38}O_7$		474.2617
Kampanol C [26]	*S. kampalensis*		$C_{25}H_{25}O_6$	208(23369), 230(sh), 282(7480), 314(3360)	428.2199
L-671 776[27-29]	*S. chartarum, S. cylindrospora*	Complement inhibitor, antimanic depressive drug	$C_{23}H_{32}O_5$	230 (230%), 286(187%), 330(118%)	388.2250
Mer-NF5003 B[28,30]		Cytotoxic, antiviral	$C_{23}H_{32}O_6$	229(12200), 281(9410), 328(4700), PP*	404.2199
Mer-NF5003 E[28,30]		Cytotoxic, antiviral	$C_{23}H_{32}O_5$	225(15100), 286(10800), 328(5430), PP	388.2250
Mer-NF5003 F, [28,30,31]		Cytotoxic, antiviral, cholesterol lowering	$C_{23}H_{30}O_5$	245(14900), 301(5610), 352(4090), PP	386.2093
NG-242[32,33]	*S. parvispora*	Activator of nerve growth	$C_{27}H_{37}NO_6$	214(41800), 258(9600), 306(3300)	471.2622
NG-243[32,33]	*S. parvispora*	Activator of nerve growth	$C_{25}H_{35}NO_5$	214(40800), 257(8900), 302(3300)	429.2515
NG-245[34]	*S. parvispora*	Activator of nerve growth	$C_{31}H_{39}NO_5$	222(27800), 261(10500), 285(4900), 296(4700)	505.2828
Parvisporin[35]	*S. parvispora*	Neurotoxic	$C_{23}H_{34}O_5$	206(16700), 295(5800)	390.2406
SMTP-1 [36]	*S. microspora*	Enhances plasminogen activity	$C_{25}H_{35}NO_5$	214(39700), 254(7200), 299(2800)	429.2515
SMTP-2 [36]	*S. microspora*	Enhances plasminogen activity	$C_{25}H_{37}NO_7$	212(34000), 252(8000), 294(3000)	463.2570
SMTP-3[37]	*S. microspora*	Enhances plasminogen activity	$C_{26}H_{35}NO_7$	214(43000), 256(9500), 298(3400)	473.2414
SMTP-4[37]	*S. microspora*	Enhances plasminogen activity	$C_{32}H_{39}NO_6$	214(40700), 259(8400), 302(2500)	533.2777
SMTP-5[37]	*S. microspora*	Enhances plasminogen activity	$C_{29}H_{41}NO_6$	215(36700), 259(7600), 300(2300)	499.2934
SMTP-6[37]	*S. microspora*	Enhances plasminogen activity	$C_{34}H_{40}N_2O_6$	216(50300), 260(10100), 282(6200), 290(5400), 308(2500)	572.2886
SMTP-7[38]	*S. microspora*	Enhances plasminogen activity	$C_{51}H_{68}N_2O_{10}$	213(82500), 257(18800), 302(5820)	868.4876
SMTP-8[38]	*S. microspora*	Enhances plasminogen activity	$C_{52}H_{70}N_2O_{10}$	213(79500), 257(18200), 302(5600)	882.5033
Spirodihydrobenzofuran-lactam 1 [39,40]	*S. chartarum*	HIV protease inhibitor Anti-manic depression drug	$C_{23}H_{31}NO_4$		385.2253
Spirodihydrobenzofuran-lactam 2 [39,40]	*S. chartarum*	HIV protease inhibitor	$C_{25}H_{35}NO_5$		429.2515
Spirodihydrobenzofuran-lactam 3 [39,40]	*S. chartarum*	HIV protease inhibitor	$C_{28}H_{39}NO_6$		485.2777
Spirodihydrobenzofuran-lactam 4 [39,40]	*S. chartarum*	HIV protease inhibitor	$C_{28}H_{37}NO_8$		515.2519
Spirodihydrobenzofuran-lactam 5 [39]	*S. chartarum*	HIV protease inhibitor	$C_{23}H_{29}NO_5$		399.2046
Spirodihydrobenzofuran-lactam 6 [39,40]	*S. chartarum*	HIV protease inhibitor	$C_{52}H_{70}N_2O_{10}$		882.5030
Stachybocin A[41-43]	*S. chartarum*	Endothelium receptor antagonister	$C_{52}H_{70}N_2O_{10}$	218(70500), 266(15400), 300-310(5300) PP	882.5030
Stachybocin B[41-43]	*S. chartarum*	Endothelium receptor antagonister	$C_{52}H_{70}N_2O_{11}$	218(70500), 265(15700), 300-310(5400) PP	898.4980
Stachybocin C[41-43]	*S. chartarum*	Endothelium receptor antagonister	$C_{52}H_{70}N_2O_{11}$	218(69100), 265(15300), 300-310(5400) PP	898.4980
Stachybocin D[44]	*S. chartarum*		$C_{52}H_{70}O_{12}N_2$	218(77100), 265(17100), 295-315(5800)	914.4929

Table 2

Non-trichothecene secondary metabolites and mycotoxins from *Stachybotrys* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Stachybotramide[6,10]	*S. chartarum, S. cylindrospora*		$C_{25}H_{37}O_5N$		431.2672
Stachybotrin [45]	*S. alternans*		$C_{25}H_{35}NO_5$		429.2383
Stachybotrin A[46]	*S. alternans*		$C_{26}H_{37}NO_5$		443.2673
Stachybotral[46]	*S. alternans*		$C_{23}H_{32}O_4$		372.2302
RF-4667A[47]	*S. elegans*	ACAT inhibitor	$C_{29}H_{44}O_{10}$	End abs.	552.66
RF-4667D[47]	*S. elegans*	ACAT inhibitor	$C_{25}H_{40}O_8$		468.2723
RF-4667F[47]	*S. elegans*	ACAT inhibitor	$C_{25}H_{40}O_8$		468.2723
RF-4667G[47]	*S. elegans*	ACAT inhibitor	$C_{23}H_{38}O_7$		426.2618
RF-4667H[47]	*S. elegans*	ACAT inhibitor	$C_{23}H_{38}O_7$		426.2618
RF-4667I[47]	*S. elegans*	ACAT inhibitor	$C_{23}H_{38}O_7$		426.2618
RF-4667J[47]	*S. elegans*	ACAT inhibitor	$C_{21}H_{36}O_6$		384.2512
Q-11270 A[48]	*S. chartarum*		$C_{28}H_{39}NO_6$	PP	485.2777
Q-11270 B[48]	*S. chartarum*		$C_{28}H_{39}NO_7$	PP	501.2726
BR-011[49]		Bone resorption suppressant	$C_{23}H_{32}O_4$	230(120000), 240(73000), 300(84000), 340(3000)	372.2302
Stachybotrin A[50]		Antibacterial, antifungal	$C_{23}H_{31}NO_5$	220(17000), 254(6400), 302(2900)	401.2202
Stachybotrin B[50]		Antibacterial, antifungal	$C_{23}H_{31}NO_4$		385.2254
Stachybotrin C[35]	*S. parvispora*		$C_{31}H_{39}NO_5$	216(52800), 258(12600), 301(4000)	505.2828
Stachybotrydial[6,10]	*S. chartarum*	Complement inhibitor, Inhibitor of Pancreatic cholesterol esterase	$C_{23}H_{30}O_5$	248, 307, 359,PP	386.21
Stachybotrylactone[6,10] (Stachybotrolide[46])	*S. chartarum*	Complement inhibitor	$C_{23}H_{30}O_5$	218(28000), 268(5300), 309(2600)	386.21
Stachyflin[51]		Antiviral	$C_{23}H_{31}NO_4$		385.229
1[52]	*S. cylindrospora*		$C_{25}H_{26}O_5$	260(10600), 320(3700)	406.1780
2[52]	*S. cylindrospora*		$C_{25}H_{26}O_5$	265(8500), 278(6900)	406.1780
3[52]	*S. cylindrospora*		$C_{25}H_{26}O_5$	330(7700)	406.1780
1[53]		HIV protease inhibitor	$C_{28}H_{37}NO_9$	218, 265, 300	531.2468
1[54], several tautomer	*S. parvispora*	Chymase inhibitor, antifungal	$C_{26}H_{30}O_5$	222(31700), 255(13400), 315(5100)	422.2093
Stachylysin[55]	*S. chartarum*	Haemolytic	Pentamer		11920, monomer
Staplabin[36,56,57]	*S. microspora*	Enhances plasminogen activity	$C_{28}H_{39}NO_6$	216(33500), 258(7300), 300(500)	485.2777

* Printed in paper

Table 3

Secondary metabolites and mycotoxins from *Aspergillus versicolor* related to sterigmatocystin and its biosynthesis

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
5-Methoxysterigmatocystin [58,59]	Cytotoxic	$C_{19}H_{14}O_7$	232(24100), 248(26800), 279(11200), 331(12100)	354.0739
Aversin[59]		$C_{20}H_{16}O_7$	224(36700), 251(13400), 285(33600), 313(8900), 363(4960), 440(7830)	368.0896
Averufin [59-61]		$C_{20}H_{16}O_7$	223(33000), 256(16500), 265(18500), 286(24800), 294(30800), 319(12500), 454(10500)	368.0895
Deoxyaverufinon [62]		$C_{20}H_{16}O_7$	210(21900), 222.7(30150), 254.5(13400), 266(14500), 292.4(23900), 320.5(7050), 454.5(6900)	368.0895
Deoxyaverufin[62]		$C_{20}H_{14}O_7$		366.0739
Demethylsterigmatocystin[63]		$C_{17}H_{10}O_6$		310.0477
Dihydrodemethylsterigmatocystin [59,64]		$C_{17}H_{12}O_6$	233(26800), 250(33100), 259(30300), 335(19400)	312.0633
Dihydrosterigmatocystin [59,64]	Cytotoxic	$C_{18}H_{14}O_6$	208(20400), 232(26300), 247(30900), 325(16300)	326.0790
Norsolorinic acid [59]		$C_{20}H_{18}O_7$	234(23667), 265(16650), 283(17352), 297(19872), 313(23763), 465(7336)	370.1052
Demethyl solorinic acid[65]		$C_{20}H_{18}O_7$	223(30903), 280(33884), 335(4786), 400(4571)	370.1052
O-methylaversin		$C_{21}H_{18}O_7$	222(33800), 285(39200), 348(4700), 407(4200)	382.1052
O-Methylsterigmatocystin [59]		$C_{19}H_{14}O_6$	236(40700), 310(16500)	338.0790
Sterigmatin[66]		$C_{17}H_{10}O_6$		310.0477
Sterigmatocystin [59]	LD_{50} 30-120 mg/kg in animals, carcinogenic	$C_{18}H_{12}O_6$	208(19000), 235(24500), 249(27500), 329(13100)	324.0633
Averufanin[63,67]		$C_{20}H_{18}O_7$		370.1952
Averufin[67,68]		$C_{20}H_{16}O_7$	223(33000), 256(16500), 265(18500), 286(24800),	368.0896

Table 3

Secondary metabolites and mycotoxins from *Aspergillus versicolor* related to sterigmatocystin and its biosynthesis

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
			294(30800), 319(12500), 454(10500)	
Versiconol [59,63]		$C_{18}H_{16}O_8$	224(30100), 266(14100), 294(23900), 315(12300), 455(7499)	360.0845
Versicolorin A [59,69]		$C_{18}H_{10}O_7$	222(28100), 255(13500), 267(18200), 290(25100), 326(6700), 450(7000)	338.0426
Versicolorin B [59,69]		$C_{18}H_{12}O_7$	223(23900), 255(13500), 266(19500), 291(24000), 324(12800), 450(8700)	340.0582
Versicolorin C [59,69-71]	Toxic to ducklings	$C_{18}H_{12}O_7$	223(23800), 255(15800), 267(20400), 292(28800), 326(10000), 450(10700)	340.0582
6-Deoxyversicolorin A[72]		$C_{18}H_{10}O_6$		322.0477
5,6-Dimethoxydihydrosterig-matocystin [73]		$C_{20}H_{18}O_8$	233(25100), 248(33500), 276(7600), 330(18000)	386.1001
5,6-Dimethoxysterigmatocystin [73]	Cytotoxic	$C_{20}H_{16}O_8$	233(27200), 248(34000), 275(7700), 330(19200)	384.0845
6,8-dimethylnidurufin [59,74]		$C_{22}H_{20}O_8$	224(48200), 251(19000), 288(30900), 314(8540), 444(8790)	412.1157
6,8-O-Dimethylversicolorin A[75]		$C_{20}H_{14}O_7$	223(47900), 250(18200), 282(46800), 312(10700), 435(11200)	366.0739
Versicolo<rone [76]		$C_{20}H_{16}O_7$	224(23988), 254(11749), 263(13800), 291(25500), 320(8320), 454(10715)	368.0896

Table 4

Secondary metabolites not related to the sterigmatocystin biosynthesis from *A. versicolor*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
A [77]	Cholesterol lowering	$C_{31}H_{40}O_8$	240, 340	540.2724
B [77]	Cholesterol lowering	$C_{31}H_{40}O_8$		554.2881
SIPI-1-2[78]	Cholesterol lowering	$C_{21}H_{22}O_7$	223, 263, 292, 451	386.1366
SIPI-1-3[78]	Cholesterol lowering	$C_{22}H_{24}O_7$	223, 263, 292, 449	400.1522
SIPI-1-4[78]	Cholesterol lowering	$C_{24}H_{28}O_7$	223, 263, 293	428.1835
Aspercolorin[71]	Toxic to ducklings	$C_{25}H_{28}N_4O_5$	210(28080), 226(18920), 260(13620), 315(4170)	464.206
Versiol [79]		$C_{16}H_{22}O_3$		262.157
Ferricrocin [80]	Iron III binding peptide	$C_{29}H_{44}FeN_9O_{13}$		782.2408
Ferrirhodin [81]	Iron III binding peptide	$C_{41}H_{64}FeN_9O_{17}$		1010.377
MM 4084 [82]				
Versimide (MM4086)[83-85]	Insecticide	$C_9H_{11}NO_4$	204.5(10260)	197.0688
Nidulotoxin[86,87]				
Nitrobenzoyl ester 2[88]		$C_{22}H_{25}NO_8$	257(21100)	431.1581
Nitrobenzoyl ester 3[88]		$C_{22}H_{25}NO_7$	256(8200)	415.1631
Nitrobenzoyl ester 4[88]		$C_{22}H_{25}NO_8$	258(7600)	431.1581
FK17-P2a[89]		$C_{13}H_{16}O_5$		252.0998
FK17-P2b1[89]		$C_{13}H_{16}O_4$		236.1049
FK17-P2b2[89]		$C_{13}H_{16}O_4$		236.1049
FK17-P3[89]		$C_{13}H_{15}ClO_4$		270.066
Insulicolide A[88,90]	Cytotoxic to cancer cells in NCI assay (0.3-1µg/ml)	$C_{22}H_{25}NO_8$	255(16900)	431.1581
Lactone 1[91]		$C_{16}H_{12}O_6$		300.0643
Lactone 2[91]		$C_{16}H_{12}O_7$		316.0583
Versicolin = 2,3,6-trihydroxy toluene [92-95]	Antifungal	$C_7H_80_3$	222(25120), 256(7943), 390(400), 520(150)	140.0473
Versilin[96]	Antifungal	$C_7H_6O_4$	212, 257, 387	154.0266
Mycoversilin [97-99]	Antifungal	$C_{18}H_{16}O_8$	End, 269(1290), PP	360.0845

Table 5

Secondary metabolites and mycotoxins from *Aspergillus ustus*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
10,20-dehydro[12,13-dehydroproly]-2-(1',1'-dimethylallyltrytophyl) dike-topiperazine[100]		$C_{21}H_{21}O_2N_3$	224(27540), 272(8510), 284(6920), 292(5130)	347.1635
12,13-dehydroproprolyl-2-(1',1'-dimethylallyltrytophyl) diketopiper-azine[100]		$C_{21}H_{23}N_3O_2$	223(34674), 268(10715), 283(10000), 292(7760)	349.1792
12,13-dihydro-12-		$C_{21}H_{23}N_3O_4$	231(30200), 255(10965), 390(2950)	381.169

Table 5

Secondary metabolites and mycotoxins from *Aspergillus ustus*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
hydroxyaustamide[101]				
12,13-dihydro-austamide [100]		$C_{21}H_{23}O_3N_3$	238(30900), 256(13490), 390(3310)	365.1741
4,6-bisdemethylautocystin A[67]		$C_{17}H_9ClO_6$	231(31623), 241(32359), 254(37154), 261(35481), 270(32359), 325(25119), 360(12300)	224.0088
4-O-demethylautocystin A[67]		$C_{18}H_{11}ClO_6$	225(26300), 249(26915), 257(25120), 269(15488), 314(12023), 361(4075)	344.0088
6-demethylautocystin A[67]		$C_{18}H_{11}ClO_6$	239(35480), 254(32359), 261(31625), 270(24547), 312(16980), 362(5888)	358.0244
6-epi-Ophiobolin K[102]	Antibiotic	$C_{25}H_{36}O_3$	239(21395)	384.2631
7-chloro-2-(3-furyl)-1,3,8-trimethoxyxanhone[67]		$C_{20}H_{15}ClO_6$		386.0558
8-deoxy-6-O-methylversicolorin A[67]		$C_{19}H_{12}O_6$	221(22387), 240(14125), 274(20893), 412(7080), 436(2344)	336.0634
Austalide A[102,103]		$C_{28}H_{36}O_9$	222(35400), 267(17140)	516.236
Austalide B[102,103]		$C_{26}H_{34}O_9$	223(28700), 269(16800)	490.2203
Austalide C[102,103]		$C_{30}H_{38}O_{11}$	221(26900), 265(13800)	574.242
Austalide D[102,103]		$C_{28}H_{36}O_{10}$	222(32700), 268(17700)	532.2308
Austalide E[102,103]		$C_{28}H_{36}O_{10}$	222(34600), 266(19600)	532.2308
Austalide F[102]		$C_{26}H_{34}O_9$	220(30900), 264(16800)	490.2203
Austalide G[104]		$C_{28}H_{38}O_9$	221(26500), 267(14100)	518.251
Austalide H[104]		$C_{26}H_{36}O_8$	221, 267	476.240
Austalide I[104,105]		$C_{27}H_{34}O_8$	221(35600), 266(17000)	486.225
Austalide J[105]		$C_{25}H_{32}O_7$	221(31900), 267(16200)	444.214
Austalide K[104,105]		$C_{25}H_{32}O_5$	222(18900), 267(11000)	412.224
Austalide L[104,105]		$C_{25}H_{32}O_6$	223(31200), 269(16600)	428.219
Austamide[100]	Acute toxic to ducklings	$C_{21}H_{21}O_3N_3$	234(26300), 256(117), 256(1100), 282(8709), 392(2691)	363.1584
Austdiol[106,107]	Acute toxic to ducklings	$C_{12}H_{12}O_5$	256(15100), 376(24000)	236.0685
Austin[108]		$C_{27}H_{32}O_9$	243(11900)	500.2047
Austinol[107]		$C_{25}H_{30}O_8$	246(8080)	458.1941
Austocystin A[68]	Mutagenic, cytotoxic	$C_{19}H_{13}ClO_6$	229(25120), 239(33110), 247(34675), 258(10715), 303(12300), 335(5623)	372.0401
Austocystin B[68]	Mutagenic, cytotoxic	$C_{22}H_{20}O_7$	227(24550), 240(25120), 254(33113), 263(21878), 274(23442), 328(16218), 372(7244)	396.1209
Austocystin C[68]	Mutagenic, cytotoxic	$C_{23}H_{22}O_7$	229(20417), 238(24000), 255(20895), 277(18200), 304(12590), 368(4570)	398.1366
Austocystin D[68]	Mutagenic, cytotoxic	$C_{22}H_{20}O_8$	227(19500), 254(31625), 263(22910), 273(23440), 329(12883), 370(4365)	412.1158
Austocystin E[68]	Mutagenic, cytotoxic	$C_{22}H_{22}O_8$	228(19500), 236(23442), 257(22910), 262(22390), 273(21380), 304(10233), 368(4365)	414.1315
Austocystin F[68]	Mutagenic, cytotoxic	$C_{17}H_{10}O_7$	224(27542), 252(34675), 259(30200), 268(25120), 325(14791), 368(4266)	326.0426
Austocystin G[109]	Mutagenic, cytotoxic	$C_{18}H_{11}ClO_7$	225(18620), 249(23442), 309(9772), 340(3236)	374.0193
Austocystin H[109]	Mutagenic, cytotoxic	$C_{22}H_{18}O_7$	226(11482), 253(14791), 272(10233), 328(6166), 360(2455)	394.1053
Austocystin I[109]	Mutagenic, cytotoxic	$C_{18}H_{12}O_7$	229(21878), 238(27542), 252(29302), 264(19953), 300(13800), 355(5129)	340.0583
Aversin [59]		$C_{20}H_{16}O_7$	224(36700), 251(13400), 285(33600), 313(8900), 363(4960), 440(7830)	368.0896
Averufanin[63,67]		$C_{20}H_{18}O_7$		370.1952
Averufin[67,68]		$C_{20}H_{16}O_7$	223(33000), 256(16500), 265(18500), 286(24800), 294(30800), 319(12500), 454(10500)	368.0896
Dehydroaustin[107]		$C_{27}H_{30}O_9$	End, 239(3800)	498.189
Deoxybrevianamide E				
Dihydropergilin[110]		$C_{15}H_{18}O_4$	218(21400), 260(12000)	262.1204
Dihydroxy-8-epi-austdiol[106]		$C_{12}H_{14}O_4$	231(6920), 352(20000)	222.0892
Drimane sesquitepene 1[111]	Binds to endo-thelium receptor	$C_{23}H_{30}O_5$	304(36600)	386.2094
Drimane sesquitepene 2[111]	Binds to endo-thelium receptor	$C_{23}H_{32}O_4$	303(37000)	372.2302
Drimane sesquitepene 3[111]	Binds to endo-thelium receptor	$C_{23}H_{32}O_5$	205(6000), 303(32000)	388.2251
Drimane sesquitepene 4[111]	Binds to endo-thelium receptor	$C_{23}H_{32}O_4$	202(8400), 294(34500)	372.2302
Drimane sesquitepene 5[111]	Binds to endo-	$C_{21}H_{28}O_5$	255(24100)	360.1937

Table 5

Secondary metabolites and mycotoxins from *Aspergillus ustus*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
	thelium receptor			
Drimane sesquitepene 6[111]	Binds to endo-thelium receptor	$C_{23}H_{30}O_5$	300(36200)	386.2094
Drimane sesquitepene 7[111]	Binds to endo-thelium receptor	$C_{15}H_{24}O_3$	232(1800	252.1726
Iso-austin[107]		$C_{27}H_{32}O_9$	240(7300)	500.2047
Mer-NF8054X[112]		$C_{38}H_{42}O_5$	242(20400)	458.3032
Ophibolin G[113]	Inhibiting wheat and bacteria	$C_{25}H_{34}O_2$	235(36300)	366.2559
Ophibolin H[113]	Antibiotic	$C_{25}H_{38}O_3$	243(19500)	386.2821
Ophiobolin K[102]	Antibiotic	$C_{25}H_{36}O_3$	240(23470)	384.2631
Pergillin[114]	Plant growth inhibitor	$C_{15}H_{16}O_4$	225(9550), 287(10700)	260.105
Phenylahistin[115,116]	Mammalian cell cycle inhibitor, anti-tumor activity	$C_{20}H_{22}N_4O_2$	202(24000), 233(11220), 320(26900)	350.1743
Prolyl-2-(1',1'-dimethylallyl) trypto-phyldiketopiperazine[100]		$C_{21}H_{25}N_3O_2$	225(32359), 275(7079), 283(8128), 291(7079)	351.1949
TMC-120A[117,118]	Inhibitor of IL-5 mediated pro-longed eosiophil survival	$C_{15}H_{14}NO_2$	210(31520), 250(33880), 323(7080), 340(11220), 354(12880)	241.1103
TMC-120B[117,118]	Inhibitor of IL-5 mediated pro-longed eosiophil survival	$C_{15}H_{12}NO_2$	212(34670), 233(12880), 239(12880), 271(23440), 295(21380), 302(21380), 365(7760)	239.0946
TMC-120C[117,118]	Inhibitor of IL-5 mediated pro-longed eosiophil survival	$C_{15}H_{14}NO_3$	211(32360), 253(31620), 354(10230), 413(1120)	257.1052
Ustic acid[119,120]		$C_{21}H_{18}O_6Cl_2$		436.0481
Nornidulin (Ustin) [119]		$C_{19}H_{15}O_5Cl_3$		427.9987
Versicolorin C [59,102]		$C_{18}H_{12}O_7$	223(23800), 255(15800), 267(20400), 292(28800), 326(10000), 450(10700)	340.0582
PR-1636[86]				

Table 6

Secondary metabolites and mycotoxins from *Aspergillus niger*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
10, 23-Dihydro-24,25,dehydro-21-oxo-aflavinine[121]	Antiinsectan	$C_{28}H_{37}NO_2$	224(18200), 267(4200), 273(1400), 283(2100), 291(1750)	419.2824
10, 23-Dihydro-24,25,dehydro-aflavinine[121]		$C_{28}H_{39}NO$	226(31600), 284(4400), 291(4100)	405.3032
14-Epi-14-hydroxy-10, 23,dihydro-24,25,dehydro-aflavinine[121]		$C_{28}H_{39}NO_2$	226(16400), 284(2290), 292(2100)	421.2980
16-Keto-aspergillimide [122]	Anthelmintic	$C_{20}H_{27}N_3O_4$		373.2003
1-Hydroxyyanuthone A[123]	Antifungal, antibacterial	$C_{24}H_{32}O_5$	234(8510), 290(220)	400.2251
1-Hydroxyyanuthone C[123]	Antibacterial	$C_{24}H_{32}O_5$	232(4680), 282(468)	400.2251
22-Deacetylyanuthone A[123]	Antibacterial	$C_{22}H_{32}O_4$	238(16220), 302(480)	360.2302
2-Methylene-3-(6-hydroxyhexyl)-butanedioic acid [124,125]	Plant growth regulator	$C_{11}H_{18}O_4$		214.1225
2-Methylene-3-hexyl-bubutanedioic acid [124]		$C_{11}H_{18}O_5$		230.1154
2-Methylene-3-hexyl-maleic acid anhy-dride [124,126]	Plant growth regulator	$C_{12}H_{16}O_5$	253	240.0998
4-hyroxymandelic acid*		$C_8H_8O_4$		168.0423
Orbole*				
Antifumicin A*				
Antifumicin B*				
Aspereyellone*				
6'-O-demethylnigerone[127]		$C_{31}H_{24}O_{10}$	226(39810), 278(63095), 408(10000)	556.139
Aflavinine[121]		$C_{28}H_{39}NO$	225(18700), 283(3010), 291(2710)	405.3032
Antafumicin A[128]	Antifungal	$C_{13}H_{14}O_6$	217(21000), 279(15500), 317(8720)	266.0786

Table 6

Secondary metabolites and mycotoxins from *Aspergillus niger*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Antafumicin B[128]	Antifungal	$C_{13}H_{14}O_6$	217(21000), 279(15500), 317(8720)	266.0786
Asnipyrone A[129]		$C_{21}H_{22}O_3$	240(18600), 290(19055), 378(31625)	322.1570
Asnipyrone B[129]		$C_{20}H_{20}O_3$	235(16600), 265(15490), 376(33885)	308.1413
Asperazine[130,131]	Cytotoxic, anti leukemic	$C_{40}H_{36}N_6O_4$	225, 275, 300	
Asperenone[132]		$C_{22}H_{24}O_3$	242(13800), 300(9200), 414-416(94200)	312.1726
Asperic acid[130]		$C_{16}H_{28}O_4$	225, 280	
Asperparaline A (Aspergillimide)[122,133,134]	Paralyses silkworms, Anthelmintic	$C_{20}H_{29}N_3O_3$	206	359.2209
Asperparaline B[133]	Paralyses silkworms	$C_{19}H_{27}N_3O_3$		345.2053
Asperparaline C[133]	Antiins Paralyses silkworms ectan	$C_{19}H_{27}N_3O_3$		345.2053
Asperrubrol[132,135]		$C_{20}H_{22}O$	242(9800), 293(11200), 400(63200)	278.1672
Aurasperone A[136-138]	Acute toxic	$C_{32}H_{26}O_{10}$	225(51300), 258(53700), 280(100000), 325(8710), 406(12880) , PP	570.1526
Aurasperone B[136,138]	Acute toxic	$C_{32}H_{30}O_{12}$	235(51000), 282(87700), 321(20100), 334(20000), 410(13600) , PP	606.1737
Aurasperone C[136,138]	Acute toxic	$C_{31}H_{28}O_{12}$	236, 283.5, 323, 336, 412 , PP	592.1581
Aurasperone D[137,138]	Depress central nervous system	$C_{31}H_{24}O_{10}$	235-240(50119), 280(51286), 320-325(15136), 380(7080)	556.139
Aurasperone E[137]	Depress central nervous system	$C_{32}H_{28}O_{11}$	230(72444), 282(147910), 322(22387), 330(20418), 400(19500)	588.1631
BMS-192548[139]				
BMS-192548[140]	Neuropeptide Y receptor inhibitor	$C_{21}H_{18}O_9$	280(4440), 320(35548), 414(38822) , PP	414.0950
Dianhydro-aurasperone C[141]	Acute toxic, *Anti-cancer cell drug*	$C_{31}H_{24}O_{10}$	225(22908), 255(26915), 280(85113), 325(3715), 405(5754)	556.1369
Flavasperone[136-138]		$C_{16}H_{14}O_5$	225(28184), 254(47863), 406(5495) , PP	286.0841
Fonsecin monomethylether[138,142]		$C_{16}H_{16}O_6$	232(28500), 277(40500), 317(9100), 330(10000), 395(8400)	304.0947
Fonsecinone A[143]		$C_{32}H_{26}O_{10}$	228(45700), 256(44670), 278(67600), 325(11480), 398(7080)	570.1526
Fonsecinone B[143]		$C_{32}H_{28}O_{11}$	229(38900), 255(41700), 280(70800), 320(14125), 328(14125), 403(9120)	588.1631
Fonsecinone C[143]		$C_{32}H_{28}O_{11}$	234(51285), 254(38000), 279(60255), 315(19500), 327(14800), 398(7080)	588.1631
Fonsecinone D[143]		$C_{32}H_{26}O_{10}$	227(26900), 279(48975), 316(8128), 328(6920), 403(6310)	570.1526
Heminigerone[127]		$C_{16}H_{14}O_5$	225(25119), 242(32360), 247(31623), 277(33884), 378(4467)	286.0841
Hexylitaconic acid[125,130]	Plant growth inhibitor			
Hydroxyhexyl-butanedioic acid[125]				
Iso-aurasperone A[137,138]	Depress central nervous system	$C_{32}H_{26}O_{10}$	255(33884), 275(38905), 385-390(3467)	570.1626
Iso-nigerone[127]		$C_{32}H_{26}O_{10}$	228(50119), 248(56234), 279(66069), 390(9550)	570.1626
Kotanin[86,144]		$C_{23}H_{20}O_8$	203(92%), 208(100), 237(35), 259(15%), 296(36%), 306(41%), 317(35%)	424.1158
Malformin A_1[59,145]	Cytotoxic	$C_{23}H_{39}O_5N_5S_2$	End abs.	529.2396
Malformin A_2[59,145]	Cytotoxic	$C_{22}H_{37}O_5N_5S_2$	End abs.	515.2239
Malformin B_{1a}, B_{1b}, B_3, B_5[59,145,146]	Cytotoxic	$C_{23}H_{39}O_5N_5S_2$	End abs.	529.2396
Malformin B_2, B_5[59,145,146]	Cytotoxic	$C_{22}H_{37}O_5N_5S_2$	End abs.	515.2239
Malformin C[59,147]	Cytotoxic	$C_{23}H_{39}O_5N_5S_2$	End abs.	529.2396
Nigerazine A[148]	Plant growth inhibitor			
Nigerazine B[148]	Plant growth inhibitor	$C_{16}H_{22}N_2O$	280(22400)	258.1732
Nigerone[127]		$C_{32}H_{26}O_{10}$	226(51286), 278(83186), 407(14125)	570.1626
Nigragillin[59]	Toxic to silkworms	$C_{13}H_{22}ON_2$	262(26200)	222.1739
Ochratoxin A[86,149]	Cytotoxic, nephrotoxic	$C_{20}H_{18}ClNO_6$	205(94%), 215(98%), 218(21%), 283(2%), 332(17%)	403.0823
Orlandin[144]	Plant growth inhibitor	$C_{22}H_{18}O_8$	311(29500), 321(25120)	410.1002
Oxalic acid[86,150]	Toxic			
Pyrophen[130,151]		$C_{16}H_{17}NO_4$		287.1158
Rubrofusarin B[137,141]	Anti-cancer cell drug	$C_{16}H_{14}O_5$	225(39810), 250(37153), 375(79433), 320(5248), 395(9120)	286.0841
Rubrofusarin[127]				
SB200437[122,122,152]	Anthelmintic			
SB203105[122,122,152]	Anthelmintic			
Tubingensin A[153]	Antiviral			
Tubingensin B[153]	Cytotoxic	$C_{28}H_{35}NO$	218(17200), 237(25500), 260(10100),	401.2720

Table 6

Secondary metabolites and mycotoxins from *Aspergillus niger*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
			299(10100), 325(2200), 338(6700)	
VM54159[122 122,152]	Anthelmintic			
Yanuthone A[123]	Antibacterial	$C_{24}H_{34}O_5$	232(7950), 310(500)	402.2407
Yanuthone B[123]	Antifungal, antibacterial	$C_{24}H_{32}O_5$	244(4470), 290(1950), 338(830)	400.2251
Yanuthone C[123]	Antibacterial	$C_{24}H_{34}O_5$	232(13180), 280(2040), 322(1070)	402.2407
Yanuthone D[123]	Antifungal, antibacterial	$C_{28}H_{38}O_8$	226(7940), 254(3715), 298(1150)	502.2567
Yanuthone E[123]	Antibacterial	$C_{29}H_{42}O_8$	234(9120), 280(1000), 340(450)	518.2881

* J.C. Frisvad, personal communication.

Table 7

Secondary metabolites and mycotoxins from *Penicillium chrysogenum*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
ω-hydroxyemodine [154]		$C_{15}H_{10}O_6$		286.0477
2-Acetyl-4(3H)-quinazolinone [155,156]		$C_{10}H_8N_2O_2$		188.0586
2-pyrovoylaminobenzamide [154,157,158]		$C_{10}H_{10}N_2O_3$	211(16500), 242(9700), 305(6930)	206.0690
2-[(2-hydroxypropionyl)amino] benzamide [159,160]		$C_{10}H_{12}O_3N_2$	249(23440), 293(5838)	208.0849
Chrysogine [154,155,161]		$C_{10}H_{10}N_2O_2$	226(21877), 230(20892), 238(12882), 265(7244), 273(6606), 292(2884), 305(3890), 316(3235)	190.0743
Emodic acid [154]		$C_{15}H_8O_6$		284.032
Meleagrin [154]			218(60%), 229(67%), 259(20%), 283(25%), 329(66%)	
N-acetyl-amino-3H-phenoxazine-3-one [154]				
N-formyl-O-aminophenol [154]				
Questiomycin A [154,162,163]		$C_{12}H_8N_2O_2$	425(23200)	212.0586
Questiomycin B [154]				
Roquefortine C [59,154]		$C_{22}H_{23}O_2N_5$	209(29500), 240(16200), 328(27000)	389.1854
Roquefortine D [59,154]			203(67%), 218(100%), 283(43%), 288(45%), 294(44%), 302(45%)	
Sorbicillin [164-167]	Antioxidant	$C_{14}H_{16}O_3$	320(22900), 380(8000)	232.1100
Xanthocillin X (Brevicid®) [154,168,169]	Antibiotic	$C_{18}H_{12}O_2N_2$	221(18%), 239(21%), 265(5%), 294(12%), 362(100%)	288.0900
Xanthocillin X monomethylether [170]	Antibiotic	$C_{19}H_{14}O_2N_2$	243, 303, 368, 385[170] 236(14200), 295(17200), 360(30000)[171]	302.1056
Xanthocillin X dimethylether [170]	Antibiotic	$C_{20}H_{16}O_2N_2$	230, 296, 363, 380	316.1212
Methoxy xanthocillin X dimethylether [170]	Antibiotic		243, 303, 368, 385	346
α-Penitrin[172]		$C_{14}H_{17}NO_3$	PP	247.1208
β-Penitrin[164,172]		$C_{14}H_{17}NO_3$	PP	247.1208
Penitrinic acid[164,172]		$C_{15}H_{17}NO_5$	PP	291.1107
Tiglic acid[164]		$C_5H_8O_2$		100.0524
d-α-methylbutyric acid[164]				
Furoic acid[164]				
β-Indoleacetic acid[164]				
Phenylacetic acid[164]				
2-Decenedioic acid[164]		$C_{10}H_{10}O_4$		194.0579
Xanthocillin Y_1 (Brevicid®) [168,173]		$C_{18}H_{12}N_2O_3$		304.0849
Xanthocillin Y_2 (Brevicid®) [168,173]		$C_{18}H_{12}N_2O_4$		320.0798
1,4-Di-4-hydroxyphenyl-2,3-diformamid-(1,3)-butandien[168]				
2-Aminophenol[163,168]		C_6H_7NO		109.0528
N-formyl-2-amino-phenol[168]		$C_{12}H_8N_2O_2$	237(27990), 422(21827)	212.0586
2-Amino-3H-phemoxazon-(3) [168]				
N-Acetyl-2-amino-3H-phenoxazon-(3)[168]				
A[168]		$C_{12}H_{18}N_2O_2$	237(28184), 422(21827), 434(22029)	222.1368
e[168]		$C_{14}H_{10}N_2O_3$	243(20417), 406(15136)	254.0691
B[168]			218(10233), 245(12023), 286(6310)	
d[168]		$C_{18}H_{16}N_2O_4$		324.1111
C[168]				
Penicillin G[174 154]			208(100%), 244(4%), 259(4%)	
Penicillin F[154]		$C_{14}H_{20}N_2O_4S$		312.1145
Chrysogenin[175]		$C_{18}H_{22}O_6$		334.1417
Sorrentanone[167]		$C_{14}H_{14}O_4$	194(5300), 272(8700)	246.0892
Secalonic acid D[176-179]**	Toxic, teratogenic, toxic to mitochon-	$C_{32}H_{30}O_{14}$	239(18200), 267(16200), 338(33885)	638.1635

Table 7

Secondary metabolites and mycotoxins from *Penicillium chrysogenum*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
	dria			
Bisvertinolone[167,180]	Antibacterial			512
Lumdidin = met Ø				

Produced by the closely related *P. oxalicum,* making it very likely that it is also produced by *P. chrysogenum* (J. C. Frisvad, personal communication).

Table 8

Secondary metabolites and mycotoxins from *Penicillium brevicompactum*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
1,4-Dimethyl-hydroxy-3-[4'-methoxyphenylmethyl]-2-5piperazinedione 5 [181]		$C_{14}H_{18}N_2O_4$	213(6600), 228(8700), 276(1200)	278.1267
11-(5'-epoxy-4'-hydroxy-3'-hydroxymethylcyclo-2'-hexenone)-Δ-drimene [181]	Antifungal	$C_{22}H_{32}O_4$	221(4650), 239(8250)	360.2301
1-Deoxypebrolide [182]		$C_{24}H_{30}O_6$		414.2042
2,4-Dihydroxy-6-(1,2-dioxopropyl)benzoic acid [120,183-187**]		$C_{10}H_8O_6$	214(100%), 239(18%), 261(46%), 279(15%), 296 (23%)	224.0320
2,4-Dihydroxy-6-(1-hydroxy-oxopropyl)benzoic acid [120,183-186**187]		$C_{10}H_{10}O_6$	212(100%), 240(22%), 261(33%), 287(18%), 3098(20%)	226.0477
2,4-Dihydroxy-6-(2-oxopropyl)benzoic acid [183,184,188**]		$C_{10}H_{10}O_5$	214(100%), 239(18%), 263(37%), 287(18%), 298(21%)	210.0528
2,4-Dihydroxy-6-propylbenzoic acid [154]				
2-Carboxy-3,5-dihydoxybenzylmethylketone [154]				
2-Carboxy-3,5-dihydoxyphenylethyl carbinol [154]				
3,5-Dihydroxyphthalic acid [154,184,188]		$C_8H_6O_6$		198.0164
3-Thiomethyl-3-[4'-(3''-methyl-2''-butenoyl)phenylmethyl]-2-5-piperazinedione [181]		$C_{17}H_{22}O_3S$	207(14125), 229(15136), 277(4000)	334.1352
6-Hydroxy-3-methylthio-3-[4'-(3''-methyl-2''-butenoyl)phenylmethyl]-2-5-piperazinedione 4 [181]		$C_{17}H_{22}N_2O_4S$		350.1301
Adenophostin A [189-191]	Ca^{2+} release in muscle[189]	$C_{14}H_{26}N_5O_{18}P_3$	256	645.0486
Adenophostin B [189-191]	Ca^{2+} release in muscle[189]	$C_{18}H_{28}N_5O_{19}P_3$	256	711.0591
Asperphenamate [192,193]		$C_{30}H_{26}N_2O_4$		478.1894
Botryodiploidin [154,194-196]	Genotoxic	$C_7H_{12}O_3$	278	144.0787
Brevianamide A[154,197-199]		$C_{21}H_{23}N_3O_3$	235(28600), 256(7100), 404(3260)	365.1739
Brevianamide B[154,197,200]		$C_{21}H_{23}N_3O_3$	As Brevianamide A	365.1745
Brevianamide C*[197,200]		$C_{21}H_{23}N_3O_3$	234, 259, 450	365.1741
Brevianamide D*[197,200]		$C_{21}H_{23}N_3O_3$	235, 264, 306, 479	365.1741
Brevianamide E [198,199]		$C_{21}H_{15}N_3O_3$	239(7500), 296(2050)	357.1113
Brevianamide F[197,200]		$C_{16}H_{17}N_3O_2$	223, 275, 280, 288	283.1321
Brevicompanine A [201]	Inhibit plant growth	$C_{22}H_{29}N_3O_2$	210, 245, 303	367.2236
Brevicompanine B [201]	Inhibit plant growth	$C_{22}H_{29}N_3O_2$	208, 245, 300	367.2246
Brevigellide [154]				
Brevigellin A [202]		$C_{31}H_{41}N_5O_7$	230(10000)	595.3019
Brevione A [203]	Inhibit plant growth	$C_{27}H_{34}O_4$		422.2457
Brevioxime[204,205]	Plant hormone activity	$C_{15}H_{22}N_2O_3$		278.1630
Cis-bis(methylthio)silvatins[181,206]	[207]			
Cis-bis(methylthio)silvatins[181,206] parent alcohol	[207]			
Compactin [208]		$C_{23}H_{34}O_5$	230(19050), 237(19950), 246(12882)	390.2403
Deoxybrevianamide E [197]		$C_{21}H_{25}N_3O_2$	227, 279, 291.5	351.1947
Desacetylpebrolide[182]		$C_{22}H_{28}O_6$	230(11900)	388.1886
Erthryo mycophenolic acid [209]		$C_{17}H_{20}O_7$		336.1209
Ethyl mycophenolat [209]		$C_{19}H_{24}O_6$	303(4700)	348.1573
Iso Brevianamide A [154]				
Metabolites O				
Mycochromenic acid [154,209]		$C_{17}H_{18}O_6$	246(20500), 280(3200), 321.5(3500), 332.5(300)	318.1103
Mycophenolic acid [154,184,210]	Anti-cancer[211]	$C_{17}H_{20}O_6$	214(100%), 235(14%), 249(22%), 273(2%), 303(11%)	320.1260
Mycophenolic acid diol lactone [154,209]				
N-(2-methyl-3-oxodec-8-enoyl)-pyrrole[212]	Plant hormone activity	$C_{15}H_{21}NO_2$		247.1572
N-(2-methyl-3-oxodecanoyl)-2-pyrroline[213]	Plant hormone activity	$C_{15}H_{25}NO_2$		251.1885
N-(2-methyl-3-oxodecanoyl)-pyrrole[212]	Plant hormone activity	$C_{15}H_{23}NO_2$		249.1729
N-Benzoylphenylalanine[193,214,215]		$C_{17}H_{17}NO_3$		283.1209

Table 8

Secondary metabolites and mycotoxins from *Penicillium brevicompactum*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
N-benzoylphenylalaninol[193,214,215]		$C_{16}H_{17}NO_2$		255.126
Pebrolide[182,216]		$C_{24}H_{30}O_7$	230(9700)	430.1992

** Only produced when extract of culture are irradiated with light. **Has a tautomer.*

Table 9

Secondary metabolites and mycotoxins from *Penicillium polonicum*

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
3-methoxyviridicatin[217]			203(100%), 212(88%), 221(98%), 263(16%), 281(21%), 300(14%), 315(19%), 323(23%), 335(17%)	
Anacine[217]				
Cyclopenin [154]			203(93%), 210(100%), 231(59%), 251(25), 275(5), 288(7%)	
Cyclopenol [154]			201(100%), 214(67%), 233(35%), 269(5%), 285(7%)	
Cyclopetin[217]				
Dehydrocyclopeptin[217]				
Leucyltryptophanyldiketopiperazine[217]				
Met AA4				
Met B[217]				
Met C[217]				
Met DO[217]				
met FO[217]				
Nephrotoxic glycopeptides,	Nephrotoxic			
Normeyhylverrucosidin [154]				
Orsellinic acid [154]				
Aspterric acid				
Anasine				
Pseurotins				
4-methyl-4-[2-(2R)-hydroxyl-3-butynyloxy]				
Ruglosuvine				
Penicillic acid [154]	Cytotoxic			
Met POLX[217]				
Puberuline[217]				
Verrucofortine [154]				
Verrucosidin [154,218]	Tremorgenic	$C_{24}H_{32}O_6$	241(21000), 294(13000)	416.22
Viridicatin [154]			205(83%), 219(81%), 223(100%), 239(55%), 265(14%), 288(21%), 297(20%), 308(24%), 318(29%), 329(22%)	
Viridicatol [154]				

Table 10

Secondary metabolites and mycotoxins from *Trichoderma* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
(2S,3S,4R)-2-[(2R)-2-hydroxytetracosanoylamino]-1,3,4-octadecatriol [219]	*T. koningii*		$C_{42}H_{85}O_5N$		683.6428
24,25-Dihydro trichotetronine [220]			$C_{28}H_{34}O_8$	257(35500), 368(39800)	498.2254
3-(2-hydroxypropenyl)-4-(hexa-2E,4E-dien-6-yl)furan-2(5H)-one[221]	*T. harzianum*		$C_{13}H_{18}O_3$		222.1256
3-(propenyl)-4-(hexa-2E,4E-dien-6-yl)furan-2(5H)-one[221]	*T. harzianum*		$C_{13}H_{20}O_4$		240.1362
3-3'-isocyanocyclopent-2-enylidene)propionic acid[222]					
3-Dimethylamino-5-hydroxy-5-vinyl-2-cyclopenten-1-one[223]	T. koningii	Antifungal	$C_9H_{13}NO_2$	Unstable	167.0952
4-Hydroxyphenetyl alcohol [219]	*T. koningii*		$C_8H_{10}O_2$		138.0681
4β-Epi- exahydrobenzopyran-5-one [221,224]	*T. harzianum*	Antifungal	$C_{16}H_{26}O_5$		298.1780
4β-Epi-dihydropyran [221,224]	*T. harzianum*		$C_{16}H_{26}O_4$		282.1831
6-n-pentenyl-2H-pyran-2-one[225,226]		Antifungal	$C_{10}H_{12}O_2$	302	166.0994
6-n-pentyl-2H-pyran-2-one[225,226]		Antifungal	$C_{10}H_{14}O_2$	302	164.0845
Bisorbibutenolide[227]		Antioxidant	$C_{28}H_{32}O_8$	263(14700), 293(16300), 369(14500)	496.2097
Bisorbicillinolide[227]		Antioxidant	$C_{28}H_{32}O_8$	293(20900), 374(17900),	496.2097

Table 10

Secondary metabolites and mycotoxins from *Trichoderma* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Bisvertinol[180,228]	*T. longibrachiatum*			227(9900), 274(15400), 300(15000), 313sh, 400(24000)	
Bisvertinolone[180,228]	*T. longibrachiatum*			272(23000), 294(23000), 366(24000)	
Chrysophanol[86,229]	*T. viride*		$C_{15}H_{10}O_4$	208(51%), 225(100%), 237(33%), 259(65%), 275(30%), 279(31%), 283(30), 287(31%), 308(30%), 428(30%)	254.0579
Cyclo-(L-Pro-L-Leu)[219,230,231]	*T. koningii*		$C_{11}H_{18}O_2N_2$		210.1368
Cyclonerodiol [219,230,231]	*T. harzianum , T. koningii*	Plant growth regulator	$C_{18}H_{28}O_2$		276.2089
Cyclonerodiol-keto-diol[224]	*T. harzianum , T. koningii*		$C_{16}H_{26}O_4$		282.1831
Demethylsorbicillin[232]		Antioxidant	$C_{13}H_{14}O_3$	206(16300), 325(13800)	218.0946
Diene isocyanide[222,233]	*T. harmatum*				
Dihydropyran [221,224]	*T. harzianum*		$C_{16}H_{26}O_4$	260(79400)	282.1831
Diterpenoid diketone 4 [234]	*T. harzianum*				
Emodin[86,229]	*T. viride*		$C_{15}H_{10}O_5$	207(58%), 223(100%), 237(37%), 255(51%), 267(56%), 275(52%), 288(60%), 331(6%), 441(33%)	270.0528
Ergokonin A[235]	*T. koningii*	Antifungal	$C_{34}H_{53}NO_{10}S$		667.3390
Ergokonin B[235]	*T. koningii*	Antifungal	$C_{28}H_{42}O_5$		458.3032
Harziandione [224,231]	*T. harzianum*				
Harzianolide[236]	*T. harzianum*		$C_{13}H_{18}O_3$		222.125
Harzianum A [237]	*T. harzianum*	Antifungal	$C_{23}H_{28}O_6$	204(9200), 303(21600)	400.1886
Hexahydrobenzopyran-5-one [221]	*T. harzianum*	Antifungal	$C_{16}H_{26}O_5$		298.1780
Homothallin II[233]	*T. koningii*	Antibacterial, antifungal	$C_8H_7NO_2$	257	149.0527
Iso nitril acid 1[238]	*T. harmatum*		$C_9H_7NO_3$		177.0426
Iso nitril acid 2[238]	*T. harmatum*		$C_9H_9NO_2$		163.0634
4,4-Dihydroxy-2-(1-hydroxyheptyl)-3,4,5,6,7,8-hexahydro-2H-1-benzopyran-5-one[239]	*T. koningii*	Antifungal	$C_{16}H_{26}O_5$	260(7943)	298.1780
Isoharzandione[240]	*T. viride*	Antifungal	$C_{20}H_{28}O_2$	255.5(1760)	300.2089
Isonitrin D[233]	*T. koningii*		$C_8H_7NO_2$	236	149.0527
Koninginin A [241,242]	*T. koningii*	Inhibiting wheat growth	$C_{16}H_{28}O_4$	End abs.	284.1988
Koninginin B[243,244]	*T. koningii*	Inhibiting wheat growth	$C_{16}H_{26}O_4$	262(17400)	282.1831
Koninginin D[243]	*T. koningii*		$C_{16}H_{26}O_5$		298.1780
Koninginin E[243]	*T. koningii*	Inhibiting wheat growth	$C_{16}H_{26}O_4$	262	282.1831
Koninginin G[245]	*T. aureoviride*	Inhibiting wheat growth	$C_{16}H_{30}O_5$	212(8510), 260(7590)	302.2069
Methyl Benzoate[219]	*T. koningii*		$C_8H_8O_2$		136.25
MR-304A [246]	*T. harzianum*	Melanin synthe-sis inhibitor	$C_8H_{11}NO_4$	209(4204), 268(726)	174.9906
MR-93A [247]	*T. harzianum*		$C_8H_{11}NO_3$	226(8991)	169.0751
Octaketide-acetat diol 3 [221]	*T. harzianum*	Antifungal	$C_{16}H_{28}O_4$		284.1988
Octaketide-triol 10 [224]	*T. harzianum*	Antifungal	$C_{16}H_{26}O_5$		298.1780
Oxosorbicillinol[232]		Antioxidant	$C_{14}H_{16}O_5$	231(11000), 301(9000), 377.5(17600)	264.0996
Pachybasin[229]	*T. viride*		$C_{15}H_{10}O_3$	327(3.47), 403(3.78)	238.0630
Sorbicillin[165,227,228]	*T. longibrachiatum*	Antioxidant	$C_{14}H_{16}O_3$	318(27000)	232.1099
Sorbiquinol [248]	*T. longibrachiatum*			292(23000), 359(22500), 374(19500)	480.2132
Tricho-acorenol[219]	*T. koningii*		$C_{15}H_{26}O$		222.1984
Trichodermin [249]	*T. longibrachiatum, T. harzianum, T. viride*	Cytotoxic	$C_{17}H_{24}O_4$	End abs.	292.1675
Trichodermol [249]	*T. longibrachiatum, T. harzianum, T. viride*	Cytotoxic	$C_{15}H_{22}O_3$	End abs.	250.1569
Trichodermolide [248]	*T. longibrachiatum*		$C_{24}H_{28}O_5$	280(52480), 217(14125)	396.1937
Trichodimerol[220,228]	*T. longibrachiatum*		$C_{28}H_{32}O_8$	362(4.48), 307(4.20), 295(4.17), 240(4.0)	496.2090
Trichotetronine[220]			$C_{28}H_{32}O_8$	271(38000), 291(42660), 384(19500)	496.2098
Trichoviridin[233,250]			$C_8H_9NO_4$	220(2500)	183.0532
U-21963[251]	*T. viride*	Antibiotic	$C_9H_7NO_3$	223(15115)	177.0426

Table 10

Secondary metabolites and mycotoxins from *Trichoderma* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Harzianic acid[252]	*T. harzianum*	Antibiotic	$C_{19}H_{27}NO_6$	244(10964), 299(10471), 343(23422), 359(25120), 376(23422), 398(10471)	365.1838

Table 11

Peptides and peptabols from *Trichoderma* species

Component	Producing species	Biologically effect	Amino acids	M (Da)
Atroviridin A, B, C [253]	*T. atroviride*		20 aa	1863
Harzianin HB I[254]	*T. harzianum*	Antibacterial, membrane modifying	11aa	1160
Harzianin HC: I, III, IX, VI, VIII, X, XI, XII, XIII, XIV, XV [255]	*T. harzianum*	Antibacterial, membrane modifying	14aa	1401, 1415, 1413, 1385, 1399, 1413, 1415, 1429, 1443, 1399, 1427
Harzianin HK VI [256]	*T. psedokoningii*	Membrane modifying	11aa	1174
Hypomurocin A-1, A-2, A-3, A-4, A-5 [257]	*Hypocrea muroiana*	Antibacterial	11aa	1160, 1174, 1174, 1174, 1188
Hypomurocin B-1, B-2, B-3a, B-3b, B-5, B-5 [257]	*Hypocrea muroiana*	Antibacterial	18 aa	1718, 1722, 1702, 1732, 1732, 1746
Trichocellin A , A-I, A-II, A-III, A-IV, A-V, A-VI, A-VII, A-VIII [258]	*T. viride*	Membrane modifying	20aa	1921, 1935, 1921, 1935, 1949, 1963, 1949, 1963
Trichocellin B-I, B-II [258]	*T. viride*	Membrane modifying	20aa	1922, 1936
Trichokindin TK-Ia, Ib, IIa, IIb, IIIa, IIIb, IV, Va, Vb, VI, VII [259]	*T. harzianum*	Membrane modifying	18aa	1748, 1748, 1762, , 1762, 1762, 1762, 1776, 1776
Tricholin[260,261]	*T. viride*	Fungicide	Protein (14200 Da)	
Trichorozin I, II, III, IV [262]	*T. harzianum*	Membrane modifiyng	11aa	1161, 1175, 1175, 1189
Trichorzianin B, IIa, IIIc, IVb, Vb, VIa, VIb, VII [263]	*T. harzianum*	Antifungal	19aa (UV data[86])	
Trichorzianin A IIA, IIIA, IIIB, IIIC, IVB, VB, VIA, VIB VII [263]	*T. harzianum*	Antifungal	19aa (UV data[86])	
Trichorzin HA I ,II, III, V, VII [264,265]	*T. harzianum*	Antibacterial, membrane modifying	18aa	
Trichorzin HC VIII, XV [264]	*T. harzianum*	Antibacterial, membrane modifying	14aa	
Trichorzin KA V [264]	*T. harzianum*	Antibacterial, membrane modifying	19aa	
Trichorzin MA I, II, III [264,265]	*T. harzianum*	Antibacterial, membrane modifying	18aa	
Trichorzin PA VI, II, IV, V, VII, VIII, IX [266,267]	*T. harzianum*	Membrane modifying	18aa	
Trichorzin SA II [264]	*T. harzianum*	Antibacterial, membrane modifying	20aa	
Trichorzin TA IIIc [264]	*T. harzianum*	Antibacterial, membrane modifying	19aa	
Trichotoxin A[268]	*T. viride*		191 aa	
Trichotoxin A-40[269]	*T. viride*	Membrane modifiyng	18 aa	
Trichotoxin A-50[269]	*T. viride*	Membrane modifiyng		
Trikoningin KA V[270]	*T. koningii*	Antibacterial, membrane modifying	19aa	1889
Trikoningin KB I, II [270]	*T. koningii*	Antibacterial, membrane modifying	11aa	1037, 1051
Trichokonin TK-IIa, IIb, IIc, V, VI, VII, VIII[271,272]	*T. koningii*		20 aa	1907, 1923, 1921, 1865, 1936, 1950, 1950

Table 12

Secondary metabolites and mycotoxins from *Memnoniella* species

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Dechlorogriseofulvin[3]		$C_{17}H_{18}O_6$	235(21400), 253(15100), 290(24500), 322(4100)	318.1104
Epidechlorogriseofulvin[3]		$C_{17}H_{18}O_6$	248(21880), 288(28840), 320(7244)	318.1104
Griseofulvin[3]		$C_{17}H_{17}O_6Cl$	236(21300), 252(12500), 291(21800), 324(5200)	352.0714
Memnobotrin A[273]	Cytotoxic to breast cells in NCI assays	$C_{25}H_{33}NO_5$	217(26200), 257.5(5600), 300(2300)	427.2359

Table 12

Secondary metabolites and mycotoxins from *Memnoniella* species

Component	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Memnobotrin B[273]	Cytotoxic to cells in NCI assays	$C_{27}H_{37}NO_6$	218.5(37200), 259(10600), 302(3300)	471.2621
Memnoconol[273]	Cytotoxic to cells in NCI assays. Related to mycophenolic acid	$C_{23}H_{32}O_6$	219(28700), 261.5(11100), 290(3000)	404.2199
Memnoconone[273]	Cytotoxic to cells in NCI assays Related to mycophenolic acid	$C_{23}H_{30}O_5$	219(38000), 261(14600), 289(2900)	386.2093
Norlicxanthone[86,274-276]		$C_{14}H_{12}O_5$	205(68%), 218847%), 241(100%), 267(26%), 281(19%), 313(60%), 346(29%)	260.0685
L-671 776[27-29,277]	Complement inhibitor, antimanic depressive drug, inhibitor of myo-inositol monophos-phatase	$C_{23}H_{32}O_5$	230 (230%), 286(187%), 330(118%)	388.2250
Trichodermin[274]	Cytotoxic	$C_{17}H_{24}O_4$	End abs	292.1675
Trichodermol[274]	Cytotoxic	$C_{15}H_{22}O_3$	End abs	250.1569
Factor A [277]	Inhibitor of myo-inositol monophosphatase	$C_{23}H_{30}O_5$	247, 308, 356	386.2093
Factor C [277]	inhibitor of myo-inositol monophosphatase	$C_{23}H_{30}O_6$	247, 308, 356	402.2042

Table 13

Secondary metabolites and mycotoxins from *Alternaria* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Altenuene [278]	*A. alternata, sp.(= A. tenuis)*	Cytotoxic	$C_{15}H_{16}O_6$	319(6600), 278(10000), 240(30000)	292.0946
Altenusin[278]	*A. alternata, sp.(= A. tenuis)*		$C_{15}H_{14}O_6$	217, 247, 290	290.0790
Alterlosin I[278]	*A. alternata*		$C_{20}H_{14}O_7$	256(31500), 285(15700), 366(5100)	366.0752
Alterlosin II[278]	*A. alternata,*		$C_{20}H_{16}O_7$	225(30400), 348(5000)	368.0669
Alternariol [278-280]	*A. alternata, A. tenuissima*	Teratogenic, 100 mg/kg in mice	$C_{14}H_{10}O_5$	218, 258(38000), 302, 330	258.0528
Alternariol mono methyl ether [278,279]	*A. alternata, A. tenuissima*	Cytotoxic	$C_{15}H_{12}O_5$	335-342, 301, 290, 257, 230	272.0684
Altenuisol [278]	*A. alternata, sp.(= A. tenuis)*		$C_{14}H_{19}O_6$	216(9000), 256(11000), 278(3500)	274.0476
Altertoxin I [280,281]	*A. alternata, A. tenuissima*	Mutagenic, LC_{50} 200µg/ml to brine shrimp, toxic to fibroblast >5µg/ml	$C_{20}H_{16}O_6$	215(25500), 256(34600), 285(16300), 296(13300), 356(6000)	352.0946
Altertoxin II [281]	*A. alternata*	Mutagenic, LC_{50} 200µg/ml brine shrimp, toxic to fibroblast >0.02 µg/ml	$C_{20}H_{14}O_6$	215(27000), 258(31700), 286(17000), 297(13500), 358(5300)	350.0790
Altertoxin III [281]	*A. alternata*	Mutagenic, , toxic to fibroblast >0.2 µg/ml	$C_{20}H_{12}O_6$	210(19500), 265(14500), 352(5200)	348.0636
Dehydroaltenusin [278]	*A. alternata, sp.(= A. tenuis)*		$C_{15}H_{12}O_6$	217(33800), 249(12600), 300(7500)	288.0633
Dihydrotentoxin[278]	*A. alternata*	Interferes with chlorophyl formation	$C_{22}H_{32}N_4O_4$	258	416.2392
Helmidiol[282]	*A. alternata*		$C_{16}H_{24}O_6$	207(17850)	312.1573
Iso-altenuene[278]	*A. alternata, sp.*	Phytotoxic.	$C_{15}H_{16}O_6$	243(25800), 281.4(8490), 325.7(4863)	292.0946
Muculosin [283]	*A. alternata*		$C_{14}H_{16}N_2O_3$		260.1161
Stemphyltoxin [278]	*A. alternata*	Mutagenic	$C_{20}H_{12}O_6$	215(29000), 269(24600), 287(20000), 300(16500), 374(4700)	348.0636
Tentoxin[278]	*A. alternata*	Interferes with chlorophyl formation	$C_{22}H_{30}N_4O_4$	285(17500)	414.2270
Tenuazonic acid	*A. alternata, A. tenuissima*	Monkey LD_{50} 50mg/kg	$C_{10}H_{15}NO_3$	218(5000), 277.5(12500)	197.1051

Table 14

Secondary metabolites and mycotoxins from *Chaetomium* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Aureonitol [284]	*C. cochlioides*		$C_{13}H_{18}O_2$		206.1307
Spiroketal 4 [284]	*C. cochlioides*		$C_{13}H_{20}O_4$		240.1362
Chaetochromin A[285,286]	*C. gracile*	Cytotoxic, delayed liver injuries, teratogenic	$C_{30}H_{26}O_{10}$	235(43680), 270(48230), 292(59150), 325(15470), 335(10740), 410(10470)	546.1526
Chaetochromin B[287]	*C. gracile*	Cytotoxic, delayed liver	$C_{30}H_{26}O_{16}$	230(37200), 270(52100), 292(62900),	546.1526

Table 14

Secondary metabolites and mycotoxins from *Chaetomium* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
		injuries, teratogenic		325(10300), 340(6500), 412(9500)	
Chaetochromin C[287]	*C. gracile*	Cytotoxic, delayed liver injuries, teratogenic	$C_{29}H_{24}O_{10}$	233(33700), 270(37700), 293(45200), 325(12000), 338(8100), 414(7900)	532.1369
Chaetochromin D[287]	*C. gracile*	Cytotoxic, delayed liver injuries, teratogenic	$C_{30}H_{24}O_{10}$	234(36300), 270(38800), 293(47500), 325(13000), 338(8200), 416(8700)	544.1323
Chaetocin B.[288]	*C. virescens*	cytotoxic in Hela, IC_{50} 30ng/ml	$C_{30}H_{28}N_6O_6S_5$ Unstabile	Triacetyl-derivat: 209(50100), 237(20000), 299(6300)	760.0575
Chaetocin C[288]	*C. virescens*	cytotoxic in Hela, IC_{50} 20ng/ml	$C_{30}H_{28}N_6O_6S_6$ Unstabile	Triacetyl-derivat: 210(31600), 238(12600), 301(5000)	760.0575
Chaetocin [59]	*C. minutum*	Cytostatic, cytotoxic in Hela, IC_{50} 40ng/ml	$C_{30}H_{28}O_6N_6S_4$	306(6000)	696.0938
Chaetoglobosin A[289]	*C. globosum*	LD_{50} 6-18 mg/kg in mice, multinucleated cells	$C_{32}H_{36}O_5N_2$	223(40700), 274(6600), 282(6600), 291(5300)	528.262
Chaetoglobosin B[289]	*C. globosum*	ED_{50} 3-10 µg/ml in HeLa cells, multinucleated cells, multinucleated cells	$C_{32}H_{36}O_5N_2$	222(43600), 274(7900), 281(7900), 290(6700)	528.262
Chaetoglobosin C[289]	*C. globosum*	ED_{50} 10-32 µg/ml in HeLa cells, multinucleated cells	$C_{32}H_{36}O_5N_2$	222(36300), 273(6700), 281(6700), 291(5700)	528.262
Chaetoglobosin D[289]	*C. globosum*	ED_{50} 3-10 µg/ml in HeLa cells, multinucleated cells	$C_{32}H_{36}O_5N_2$	221(43600), 273(9100), 281(9100), 290(7500)	528.262
Chaetoglobosin E[289]	*C. globosum*	ED_{50} 3-10 µg/ml in HeLa cells, multinucleated cells	$C_{32}H_{38}O_5N_2$	221(56200), 275(7100), 281(7000), 291(6300)	530.278
Chaetoglobosin F[289]	*C. globosum*	ED_{50} 10 µg/ml in HeLa cells, multinucleated cells	$C_{32}H_{38}O_5N_2$	222(47800), 276(6900), 283(6700), 292(6000)	530.278
Chaetoglobosin G[289]	*C. globosum*	ED_{50} 3 µg/ml in HeLa cells, multinucleated cells	$C_{32}H_{36}O_5N_2$	222(32300), 275(6000), 282(6000), 291(5300)	530.278
Chaetoglobosin J[289]	*C. globosum*	ED_{50} 3 µg/ml in HeLa cells	$C_{32}H_{36}O_4N_2$	224(47800), 270(7000), 280(7000), 290(6000)	512.258
20-Dihydrochaetoglobosin A[290]	*C. subaffe*		$C_{32}H_{32}N_2O_5$	212(51286), 221(63100), 266(8510), 272(8320), 291(6600)	530.2728
20-Dihydroprochaeto-globosin II [290]	*C. subaffe*		$C_{32}H_{36}N_2O_2$	221(21880), 291(2400)	480.2779
20-Dihydroprochaeto-globosin III[290]	*C. subaffe*		$C_{32}H_{38}N_2O_4$	222(42660), 291(5250)	514.2833
Chaetohalasin A[291]	*C. brasiliense*	Cytotoxic in NCI's human cell line 8µg/ml, antibacterial	$C_{27}H_{39}NO_2$	212 (6200)	409.2971
Chaetomin [59,292]	*C. globosum, C. cochliodes*	20ng/ml inhibits protein synthesis in HeLA cells	$C_{31}H_{30}O_6N_6S_4$	295(8250), 284(9600), 275(9100)	710.1094
Chaetoviridin A[293]	*C. globosum*		$C_{23}H_{25}ClO_6$	305(26000), 365(19000), 450(4600)	432.1341
Chaetoviridin B[293]	*C. globosum*		$C_{23}H_{29}ClO_7$	290(14000), 385(27000), 405(24000), 430(11200)	452.1604
Chaetoviridin C[293]	*C. globosum*		$C_{23}H_{27}ClO_6$	294(7600), 386(14000), 406(12600), 430(5500)	434.1498
Chaetoviridin D[293]	*C. globosum*		$C_{23}H_{28}ClO_8$	290(8900), 395(16000), 410(13800), 430(6200)	468.1552
Chetracin A [288]	*C. abuense*	cytotoxic in Hela, IC_{50} 70ng/ml	$C_{30}H_{28}N_6O_8S_8$		855.9738
11α,11'α-dihydroxychaetocin [288]	*C. retardatum*	cytotoxic in Hela, IC_{50} 40ng/ml	$C_{30}H_{28}O_8N_6S_4$	242(17400), 302(2400)	728.0854
Cochliodinol[294295]	*C. globosum* and *C. cochliodes*	Antibiotic.	$C_{32}H_{32}N_2O_4$	272(11500), 293(11200), 352(5400), 470(22400)	508.2362
Colletodiol [296,297]	*C. funicola*		$C_{14}H_{20}O_6$	210(20500), 215(17500), 220(13400), 225(9700), 230(6400)	284.126
Differanisole A[298]		Induces cell differentiation in mouse leukemia cells	$C_{11}H_{12}Cl_2O_4$	318(2700), 257(4060), 220(23000)	278.0114
Chrysophanol[86,229]	*C. elatum*		$C_{15}H_{10}O_4$	208(51%), 225(100%), 237(33%), 259(65%), 275(30%), 279(31%), 283(30), 287(31%), 308(30%), 428(30%)	254.24
Flavipin [289]					196.037
Heptelidic acid[299,300]		Antibiotic	$C_{15}H_{20}O_5$	End abs.	280.1311
Isocochliodinol[300,301]			$C_{32}H_{32}N_2O_4$		508.2362
Mollicellin A [302]	*C. mollicellins*		$C_{21}H_{18}O_7$		382.1052
Mollicellin B [302]	*C. mollicellins*		$C_{21}H_{18}O_7$		382.1052
Mollicellin C [302]	*C. mollicellins*	Mutagenic, antibacterial	$C_{22}H_{20}O_8$		412.1158
Mollicellin D [302]	*C. mollicellins*	Antibacterial	$C_{21}H_{21}ClO_6$		404.1027
Mollicellin E [302]	*C. mollicellins*	Mutagenic, antibacterial	$C_{22}H_{19}ClO_8$		446.0769
Mollicellin F [302]	*C. mollicellins*	Antibacterial	$C_{21}H_{17}ClO_8$		432.0612

Table 14

Secondary metabolites and mycotoxins from *Chaetomium* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Mollicellin G[301,302]	*C. amygdalisporum, C mollicellins*	Mutagenic, antibacterial	$C_{21}H_{20}O_6$		368.1285
Mollicellin H [302]	*C. mollicellins*		$C_{21}H_{10}O_6$		368.126
Neococochliodinol[300,301]	*C. amygdalisporum*		$C_{32}H_{32}N_2O_4$		506.0
O-methylsterigmatocystin[301]	*C. thielavioideum*	Carcinogenic	$C_{19}H_{14}O_6$	236(40700), 310(16500)	338.0790
Oosporein[303,304] = Chaetomidin[305]	*C. aureum, C. trilaterale*	LD_{50} 6 mg/mg in cockerels	$C_{14}H_{10}O_8$	208(33500), 291(23000)	306.0375
Prenisatin[295]	*C. globosum*	Antifungal	$C_{13}H_{13}O_2N$	247(19000), 299(3900), 422(1000)	215.0946
Spiroketal [284]	*C. cochlioides*		$C_{13}H_{20}O_2$		208.1464
Sterigmatocystin[301]	*C. udagawae, C. thielavioideum*	Carcinogenic	$C_{18}H_{12}O_6$	208(19000), 235(24500), 249(27500), 329(13100)	324.0633
Chaetoatrosin A[306]	*C. atrobrunneum*	Inhibitor of chitin synthase II	$C_{14}H_{14}O_5$	225(2400), 272(1625), 408(250)	262.0841
Tomichaedin[305]			$C_{12}H_8O_5$		276.9984

Table 15

Secondary metabolites and mycotoxins from Cladosporium species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
Cladosporol[307]	*C. cladosporioides*	β-glucan inhibitor	$C_{20}H_{16}O_6$	214(19500), 260(11200), 338(6000)	352.0947
Cladospolide A[308]	*C. cladosporioides, C. tenuissimun*	Plant growth regulator	$C_{12}H_{20}O_4$	217(10650)	228.1362
Cladospolide B [308]	*C. cladosporioides, C. tenuissimun*	Plant growth regulator	$C_{12}H_{20}O_4$	211(5730)	228.1362
Cladospolide C[309]	*C. tenuissimun*	Plant growth inhibitor	$C_{12}H_{20}O$	214(3.9)	228.1362
Calphostin A[310,311]	*C. cladosporioides*	Inhibitor of protein kinase C	$C_{44}H_{38}O_{12}$	225(56199), 269(25300), 476(20400), 543(10200), 686(9880)	758.2363
Calphostin B[310,311]	*C. cladosporioides*	Inhibitor of protein kinase C	$C_{37}H_{34}O_{11}$	225(49500), 269(26600), 476(21800), 543(11000), 585(10900)	654.2101
Calphostin C[310,311]	*C. cladosporioides*	Inhibitor of protein kinase C	$C_{44}H_{38}O_{14}$	223(58200), 270(29400), 476(22900), 543(11600), 586(11200)	790.2262
Calphostin D[310,311]	*C. cladosporioides*	Inhibitor of protein kinase C	$C_{30}H_{30}O_{10}$	226(44800), 269(29500), 474(23500), 539(11900), 582(12000)	550.1839
Calphostin I[310,311]	*C. cladosporioides*	Inhibitor of protein kinase C	$C_{44}H_{38}O_{15}$	217, 258, 348, 475, 540, 582	806.2211
Indoleacetic acid[86]					
Cladosporide A[312]		Antifunga	$C_{25}H_{40}O_3$	284(162)	388.2977
23,24,25,26,27-Pentanorlanost-8ene-3β-22-diol[312]		Antifunga	$C_{25}H_{42}O_2$		374.3187
Isocladosporin[313]	*C. cladosporioides*	Antifungal, inhibiting growth of wheat	$C_{16}H_{20}O_5$	218(20900), 231(11950), 269(13030), 306(5984)	292.1312
Cladosporin [313,314]	*C. cladosporioides*	Antifungal, inhibiting growth of wheat	$C_{16}H_{20}O_5$	217(20900), 230(11950), 270(13030), 303(5984)	292.1312

Table 16

Secondary metabolites and mycotoxins from *Ulocladium* species

Component	Producing species	Biologically effect	Elementary composition	λ(log ε)	M (Da)
1-hydroxy-6-methyl-8-(hydroxymethyl)xanthone [315,316]	*U. botrytis*	Antibacterial	$C_{15}H_{14}O_4$		258.0892
Ulocladol [317]	*U. botrytis*	Tyrosin kinase inhibitor	$C_{16}H_{14}O_7$	251(12880), 299(3465	318.074

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Mould growth in buildings is associated with adverse health effects among the occupants of the building. However actual growth only occurs in damp and water-damaged materials, and is an increasing problem in Denmark, due to less robust constructions, inadequate maintenance, and too little ventilation. This project was started to determine if mycotoxins are produced in damp and water-damaged buildings as well investigating the influence of environmental conditions (humidity and temperature) on the production of fungal growth and secondary metabolism.

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