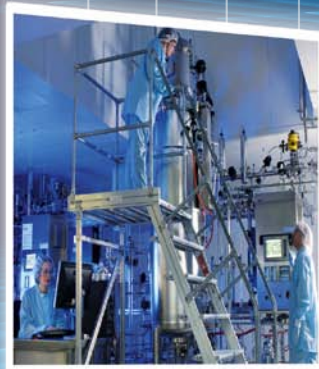


Fraunhofer ITEM



ANNUAL REPORT
2012



The development process for a new pharmaceutical normally starts in the laboratory (first photo from the left, also on the front cover). If pre-clinical tests of the candidate drug were successful, a GMP-grade investigational medicinal product has to be manufactured in compliance with the German Drug Act (second photo) for use in clinical trials with volunteers (third photo). Once clinical testing has been successfully completed, the pharmaceutical will eventually be made available on the market and thus for treatment of patients (fourth photo).

The whole process of translating knowledge gained in basic research into pharmaceutical agents, therapies, or diagnostic methods for use in patients is referred to as translational research.

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PERFORMANCE AND RESULTS

ANNUAL REPORT
2012

CONTENT

Foreword	4		

Profile of the institute	6		
Focuses of our work	6		
Pharmaceutical Biotechnology – from cell line and process development to API and IMP manufacture	8		
The new study center for early-phase clinical trials – Clinical Research Center Hannover	10		
Personalized tumor therapy – ITEM Project Group is exploring novel approaches in the fight against cancer	12		
Future areas of work	14		
Advisory board	16		
Staff and institute budget performance	17		
Fraunhofer ITEM organizational chart	18		
News in 2012	20		

		BUSINESS UNIT 1	
		Drug Research, Drug Development and Medical Biotechnology	22

		Project reports	
		Interactions of nerves and immune cells in the lung	26
		Effect of tiotropium on bronchoconstriction in vivo and ex vivo	29
		Non-human primates as a translational model of human inflammatory pulmonary diseases	31
		Molecular diagnosis of single disseminated cancer cells: from experimental use to clinical routine	34

		Preliminary research	
		Expression of cytochrome P450 monooxygenases in human lung epithelial cell lines	36
		Fast process development for plasmid DNA production with a model-based approach	38

		Project overview	40

		BUSINESS UNIT 2	
		Clinical Airway Research	42

		Project reports	
		Fraunhofer researchers participating in German Center for Lung Research	46
		Low-dose inhalation challenge with endotoxin – a model for proof-of-concept studies	48

		Preliminary research	
		Prognostic value of markers from serum and lung in smokers with and without COPD	52
		Manufacturing license for ozone as a challenge substance	54

		Project overview	55

BUSINESS UNIT 3

Occupational and Environmental Toxicology and Consumer Protection 56

Project reports

Carbon nanotubes – approaches for adequate in-vitro and in-vivo toxicity testing 60

The “SteriHealth” project – for better hygiene in the medical area 62

Do extremely low-frequency magnetic fields influence juvenile brain development and behavior? 64

Bioavailability investigation of the food contaminant 3-MCPD ester 66

DevTox: Further scientific development of the project now complete 68

Aerosol emission from water-saving showerheads and faucets 70

Project overview 71

BUSINESS UNIT 4

Testing and Registration of Chemicals, Biocides and Pesticides 74

Project reports

New ways of deriving indoor air guideline values 78

PaFtox database facilitates toxicological assessment of nano-objects 82

Project overview 84

Fraunhofer-Gesellschaft

Research of practical utility 86

Fraunhofer Group for Life Sciences

Applied science for man and the environment 88

Names, dates, events 90

Publications 90

Doctorates 96

Master's theses 96

Bachelor's theses 97

Invited lectures at congresses and conferences 98

Contributions to congresses and conferences 101

Active participation in committees 107

Research projects 110

Cooperation with institutions and universities 112

Visiting scientists 115

Exhibitions, congresses, and workshops 116

Editorial notes 117

FOREWORD

Dear Reader,

The term “translation” is used with a variety of meanings in the biomedical field. In molecular biology, translation usually means the interpretation of an organism’s blueprint information (mRNA) to build highly effective molecules (proteins). In the medical domain, translation aims to transform basic information about the pathogenesis of diseases into novel, highly effective medications.

The medical translation process from the findings of basic, pre-clinical and clinical research to highly effective and marketable therapeutics comprises several development phases. The results of pre-clinical tests are key to the decision to take a candidate drug into clinical trials or abandon its development. The step from pre-clinical to clinical development, that is, the interface between studies in models and the first use in man, is of particular importance. The first successful proof of efficacy in patients, provided by what is referred to as clinical proof-of-concept studies, in most cases marks the beginning of a clinical development program worth several 100 million euros. At this interface between pre-clinical and clinical development, a decisive factor for a successful outcome is the close dovetailing

of laboratory research and clinical investigations – the optimal situation is to have scientists and clinicians working under the same roof. At the Fraunhofer ITEM, they have successfully done so in the field of airway research for over ten years now.

In Lower Saxony, this concept of medical translational research is being placed on a broad basis with the initiative TRAIN (Translational Alliance in Lower Saxony), in which the Hannover Medical School and a number of university and non-university institutes are involved. Major constituents of TRAIN include the Clinical Research Center (CRC) Hannover for the conduct of early-phase clinical studies and the Fraunhofer ITEM Division of Pharmaceutical Biotechnology with its GMP facility for the manufacture of biopharmaceutical investigational products in compliance with the German Drug Act, for use in clinical trials. Public research institutions and smaller biotech startup companies thus also have easy access to clinical research competence, knowhow in cell line and process development, and to technical facilities for GMP-grade manufacture of biopharmaceutical active ingredients.

The aim of the TRAIN initiative is to promote development of novel medications and diagnostics from publicly funded laboratories in Lower Saxony and also from other industrial or public research institutions and bring these from bench to bedside as quickly and cost-effectively as possible. New buildings and equipment required under TRAIN are being funded for the most part by the *Land* Government of Lower Saxony and the German Federal Ministry of Education and Research.



This Annual Report will give you an insight into the institute's Division of Pharmaceutical Biotechnology, the CRC Hannover, and into several projects concerned, among other things, with translational research.

Translational research, that is, the translation of laboratory findings into practical applications, is a process nanomaterials also have to go through, if they are to persevere in the market. In the translation process, obstacles such as a product-specific health hazard have to be identified as early as possible, and ways of reducing or eliminating potential health hazards that have been recognized have to be found. At the Fraunhofer ITEM, several teams are working on over 20 projects in the field of nanotoxicology. A few examples are presented in this Annual Report.

Let me take this opportunity to thank the institute's staff for their commitment and hard work. I also wish to thank our clients and funders for their confidence in our work, and I look forward to continued successful cooperation.

A handwritten signature in black ink, which appears to read "U. Heinrich". The signature is written in a cursive, flowing style.

Prof. Dr. Dr. Uwe Heinrich
Executive Director

PROFILE OF THE INSTITUTE

FOCUSES OF OUR WORK

Protecting man from health hazards in our industrialized world and contributing to the development of novel therapeutic approaches – these are the aims of the Fraunhofer ITEM.

A focus is on airway research: a wide range of airborne substances – pollutants but also pharmaceuticals – are taken up via the lungs. The scientists of the Fraunhofer ITEM determine the risks of potentially harmful substances, develop and test novel medications against respiratory diseases – in particular asthma, allergic rhinitis, and chronic bronchitis (COPD) –, and study mechanisms of action. Due to a wide spectrum of expertise, the institute is able to offer complete solutions – from the idea to the product – to clients from industry, industry associations, occupational safety and health organizations, and public authorities.

The institute has pooled its competences to form four business units:

- 1. Drug Research, Drug Development and Medical Biotechnology
- 2. Clinical Airway Research
- 3. Occupational and Environmental Toxicology and Consumer Protection
- 4. Testing and Registration of Chemicals, Biocides and Pesticides

Grouped by these business units, the present report presents selected projects and preliminary research conducted by Fraunhofer ITEM scientists in 2012.

Our focus: lungs and airways

The respiratory tract is the focus of research at the Fraunhofer ITEM. In in-vitro and in-vivo models, primarily substances that are taken up via the airways are being studied. These include single components, such as fibrous dusts or ultrafine particles and nanoparticles, but also complex mixtures that are encountered at the workplace or in the environment, as for instance exhaust gases from automobiles and coking plants, or bitumen fumes.

Testing and development of pharmaceuticals

With regard to inflammatory and allergic diseases of the respiratory tract the Fraunhofer ITEM offers research and development services from the molecular level to clinical trials. Methods of cell biology and molecular biology are used to validate novel target structures for diagnosis and therapy and optimize these during early development stages. Once possible drug candidates have been identified, efficacy and safety tests are performed. For drug registration in compliance with GLP (Good Laboratory Practice) regulations the Fraunhofer ITEM performs toxicological and safety pharmacological testing. The institute's Division of Pharmaceutical Biotechnology develops manufacturing processes for biopharmaceutical active ingredients. For clinical trials with biopharmaceuticals investigational medicinal products are manufactured in compliance with GMP (Good Manufacturing Practice) guidelines. A GMP unit for the aseptic filling of infusion solutions is also available.

Clinical studies

For the registration of pharmaceuticals for the indications allergy, asthma, and COPD, the Fraunhofer ITEM conducts clinical studies, mainly of phases I-II, in compliance with GCP (Good Clinical Practice) guidelines, managed by highly qualified physicians. The special equipment the institute has at its



disposal for these studies includes different environmental exposure units. In the "Fraunhofer Environmental Challenge Chamber", which so far has been used to expose test subjects to grass pollen and house dust mite allergens, tests with other allergens will also be possible in the future.

Personalized tumor therapy

Personalized tumor therapy is the research topic of the Fraunhofer project group with exactly this name that took up work at the University of Regensburg in 2011. Its focus is on application-oriented basic research into the formation of metastases and the translation of the results obtained into novel diagnostic methods and therapeutic products.

Assessment of potentially harmful substances

Be it at workplaces, in the environment, or in consumer products – scientists at the Fraunhofer ITEM can detect toxic substances and evaluate the human exposure situation. For toxicological investigations and inhalation toxicity testing in particular – both in vivo and in vitro – complex atmospheres can be reproduced on a laboratory scale.

Risk assessment and registration of chemicals

Based on their own experimental results, literature searches, and data provided by clients, Fraunhofer ITEM scientists prepare reports on test substances and, if required, perform human exposure and risk assessments. In addition, the institute supports its clients in the registration of chemicals and complex mixtures and in the assessment of substances falling under the European chemicals regulation REACH.

Top-level quality

The responsibility of the Quality Assurance Unit (QAU) is to ensure that the studies conducted at the institute are performed at a consistently high level in compliance with GXP guidelines. As one of the institute's central service units, it supervises compliance with the legally required quality assurance systems GLP,

GMP, and GCP, which ensure that the procedures of drug development and manufacture and of chemical safety testing are performed reliably and reproducibly and that the generated data are valid.

Expertise in measurement technology and process engineering: inhalable aerosols for effects research

For inhalation studies, the comprehensive expertise and many years of experience of the aerosol technologists at the Fraunhofer ITEM are an essential prerequisite. Their know-how on the aerosolization of substances and on the deposition and kinetics of inhaled substances is also used to develop pharmaceutical aerosols.

Pooling together expertise

The Fraunhofer ITEM cooperates with partner institutes within the Fraunhofer-Gesellschaft and also pools together its own expertise with that of external cooperating partners. This puts the institute in a position to offer an even broader range of research services. Important partners nearby the institute are, for example, the Hannover Medical School (MHH), the Braunschweig-based Helmholtz Center for Infection Research (HZI), and TWINCORE.

It is in cooperation with the MHH and the HZI that the Fraunhofer ITEM is setting up a new translational research center, the "Clinical Research Center Hannover" (CRC Hannover). The CRC Hannover will offer an optimal infrastructure for early-phase clinical trials (phases I and II) and will provide the basis for a stronger dovetailing of basic research and clinical research. First clinical trials at the new study center are planned to begin in early 2014.



PHARMACEUTICAL BIOTECHNOLOGY – FROM CELL LINE AND PROCESS DEVELOPMENT TO API AND IMP MANUFACTURE

About half of all recently approved pharmaceutical substances are biologics. Most of them are recombinant proteins manufactured by cell lines, which compared to classical pharmaceuticals require far more complex manufacturing processes. There is a still increasing demand for novel pharmaceutical

proteins, but their successful development always strongly depends on the adherence to prefixed cost and time lines. To reduce the risk of failing to meet these is one of the aims of the Fraunhofer ITEM Pharmaceutical Biotechnology.

Based in Braunschweig, the Division of Pharmaceutical Biotechnology recently moved into a new building – allowing the scope of its technological services to be further expanded. Besides a 700-m² floor providing office and meeting rooms, the division now has at its disposal two and a half floors with a total of about 2000 m² of laboratories and pilot plants for process development and scale-up. A clean-room area of over 600 m² allows the biotechnologists to manufacture pilot batches of biopharmaceutical active ingredients (APIs) by micro-organisms and animal cells in compliance with GMP standards.



In direct proximity to their light-flooded offices, the staff members of the institute's Braunschweig branch can find spaces for informative conversations during a cup of coffee and for fruitful meetings.

The bioreactors in the GMP facility (clean room class D), where mammalian cell lines such as CHO cells or microbial production strains such as *E. coli* are cultured, have a capacity of 500 liters.

The Division of Pharmaceutical Biotechnology has its facilities in the so-called "Y-Building" 1 on the HZI research campus in Braunschweig.



Closing the last gap in the development chain for novel pharmaceuticals, a class-B clean room now enables sterile filling of investigational medicinal products (IMPs) in the form of vials and ampoules, which can subsequently be released for use in clinical trials.

With its capabilities to develop clinical IMPs to GMP standards, to do pre-clinical development in compliance with GLP, and to conduct early-phase clinical trials according to GCP, the Fraunhofer ITEM is the only publicly funded research institution in Germany that covers the complete development chain for novel biopharmaceuticals under one roof and offers these services to clients in the context of translational medicine. The Fraunhofer ITEM is thus in a position to offer to public research institutions, the biotech and pharmaceutical industries a "full-service package" for the manufacture of biopharmaceuticals: from cell line and process development to fill and finish of IMPs and their testing in clinical trials.

To be able to cover all manufacturing process aspects for biopharmaceuticals, the Division of Pharmaceutical Biotechnology combines all the required expertise in molecular biology, cell biology, bioprocess engineering, bioanalysis, pharmaceutical technology, and drug regulatory requirements.

FIELDS OF EXPERTISE

- Development of recombinant production cell lines based on microorganisms and animal cells
- Development and validation of cell culturing processes (e.g. CHO, *E. coli*) and product purification sequences for active biopharmaceutical ingredients: proteins, glycoproteins/antibodies, virus-like particles, phages, and nucleic acids/plasmid DNA
- Development and validation of analytical and bioanalytical test methods
- Non-GMP and GMP manufacture of pilot batches of active biopharmaceutical ingredients
- Sterile manufacture and stability testing of investigational medicinal products
- Release of cell lines, active biopharmaceutical ingredients, and investigational medicinal products in compliance with EU and German drug regulations
- Consultancy in European and German drug regulatory issues



CONTACT

Dr. Holger Ziehr
Phone +49 531 6181-6000
holger.ziehr@item.fraunhofer.de



THE NEW STUDY CENTER FOR EARLY-PHASE CLINICAL TRIALS – CLINICAL RESEARCH CENTER HANNOVER

The Clinical Research Center Hannover (CRC Hannover), which is being set up on the grounds of the Fraunhofer ITEM, will be the only medical research center of its kind in Germany. In close cooperation between the Fraunhofer ITEM, the Hannover Medical School (MHH), and the Helmholtz Center for Infection Research (HZI), the CRC Hannover will allow safety (phase-I trials) and efficacy testing (phase-IIa trials) of new medications that have not yet been approved by the authorities for commercial use. The result will be a closer dovetailing of research

and clinical practice, which will expedite the translation of research results into clinical applications. In addition, epidemiological studies will also be performed at the CRC Hannover.

The new study center is an important constituent of the medical translational alliance in Lower Saxony (TrAiN). TrAiN is a cross-disciplinary alliance of university and non-university institutions in Lower Saxony, funded by the Lower Saxony Ministry of Science and Culture and aimed at developing novel medications and

“We will finally have the necessary infrastructure to conduct also early-phase clinical studies on site. Our well-established cooperation with the Fraunhofer ITEM and the HZI is thus entering a new, forward-looking phase.”

Professor Dr. med. Dieter Bitter-Suermann, MHH President



Photo: MHH/Kaiser



Photo: HZI

“The CRC is an excellent example of the dovetailing of different research institutions based in the area: HZI, MHH, and Fraunhofer ITEM are pooling their competencies here in the service of human health.”

Professor Dr. Dirk Heinz, HZI Scientific Director



Photo: Fraunhofer ITEM/Ralf Mohr



“The CRC Hannover will allow us to help accelerate the costly and time-consuming development of novel medications and diagnostic methods. We are looking forward to a fruitful cooperation with MHH and HZI.”

Professor Dr. Norbert Krug, Fraunhofer ITEM Medical Director

“It was a special challenge to distribute the different research, examination, treatment, and recreation areas between the different floors in a sensible and functional way that promotes scientific communication at the same time. I think that this has been accomplished very successfully.”

Dipl.-Ing. Dirk Nelson, architect at Nickl und Partner until 2012 with a major role in the construction of the CRC Hannover



Photo: Dirk Nelson

vaccines and transferring these from bench to bedside at reduced cost and time wherever possible.

A total of about 50 beds will be available in the CRC Hannover, 28 of which will be equipped for intensive monitoring of study participants. Lavishly appointed facilities including a cinema, gym, relaxation room, and inner courtyard will enable also studies that require study participants to stay at the study center for longer periods. In addition, a wide range of special examinations will be possible at the CRC Hannover, including right-heart catheterization, endoscopy, sonography, hearing tests, lung function diagnosis, and metabolic examinations. Cutting-edge imaging methods such as magnetic resonance imaging will be available for clinical studies.

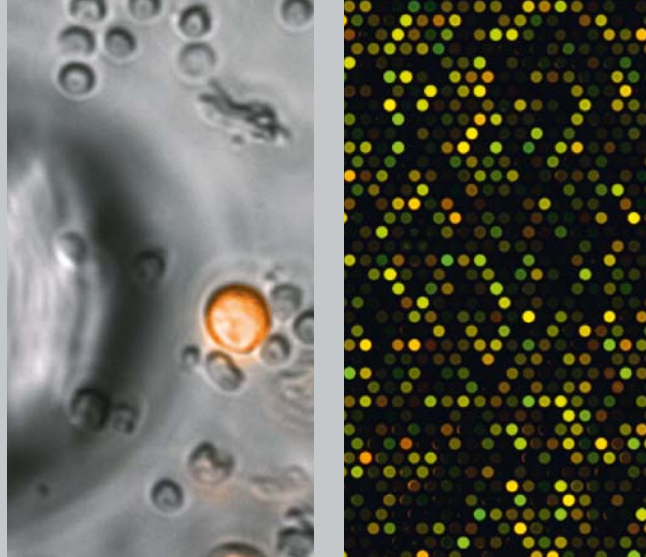
The first sod was turned in 2011. In 2012, the construction work progressed to schedule, and in summer, architects and building contractors celebrated completion of the building's shell with a little topping-off ceremony. First clinical trials in the CRC Hannover are planned to begin in early 2014.

CONTACT

Prof. Dr. med. Norbert Krug
Phone +49 511 5350-602
norbert.krug@item.fraunhofer.de

PROFILE OF THE INSTITUTE

Genome and transcriptome analyses of single circulating tumor cells will help develop novel, more effective, individualized cancer therapies.



PERSONALIZED TUMOR THERAPY – ITEM PROJECT GROUP IS EXPLORING NOVEL APPROACHES IN THE FIGHT AGAINST CANCER



The team of Professor Christoph Klein (eighth from the left) is the Fraunhofer Project Group for Personalized Tumor Therapy.

At present, one in four deaths is caused by cancer. Most patients though do not die from their primary tumor, but from metastases that have developed – often not until years later – from single disseminated cancer cells. It is the focus of the Fraunhofer Project Group for Personalized Tumor Therapy, founded in 2011, to enable early detection of such single cancer cells by means of novel diagnostics and bring them to a halt before they form lethal metastases. The team headed by Professor Christoph Klein currently consists of eight scientists and five technical assistants.

Currently available cancer therapies are effective only in a sad estimate of one in four patients. Concomitant systemic treatment after tumor resection – chemotherapy in most cases –, aimed at preventing dissemination of single cells, is far too unspecific. Such treatment is normally based on what is known about the primary tumor. According to research findings, however, primary tumors and disseminated tumor cells clearly differ in both genotype and phenotype. The target cells of therapies thus cannot be inferred directly from the properties of the primary tumor.

This is where the research of the Regensburg project group comes in: Having developed methods for single-cell analysis,

The Fraunhofer Project Group with its research laboratories and office facilities is based in Regensburg's BioPark, where it closely cooperates with the neighboring University of Regensburg.



the scientists for the first time are now in a position to comprehensively characterize disseminated cancer cells, which are extremely rare. And once the properties of these target cells are known, they reckon that systemic therapies directed specifically at hitting the disseminated cells can be developed within less time.

The expertise of the project group is focused on genome and transcriptome analyses of single cells, bioinformatic analyses of high-dimensional single-cell data, development of novel diagnostic and predictive tests, and development of in-vitro and in-vivo models for pre-clinical testing of systemic therapy approaches.

The project group has at its disposal an unrivaled infrastructure. It closely cooperates with the Chair of Experimental Medicine and Therapy Research of the University of Regensburg, which is also held by Christoph Klein and possesses an accredited laboratory for diagnosing minimal residual disease. A constant supply of patient samples is thus guaranteed. Furthermore, a unique tissue bank is being set up in cooperation with the university's Institute of Pathology and the Tumor Center Regensburg, offering new possibilities for translational research.

SERVICES

- Genome and transcriptome analyses of single cells
- Molecular characterization of rare cells (disseminated and circulating tumor cells, stem cells)
- Development of companion diagnostics
- Pre-clinical in-vivo and in-vitro models for adjuvant therapy situations



CONTACT

Prof. Dr. Christoph Klein
Phone +49 941 298480-55
christoph.andreas.klein@item.fraunhofer.de

FUTURE AREAS OF WORK

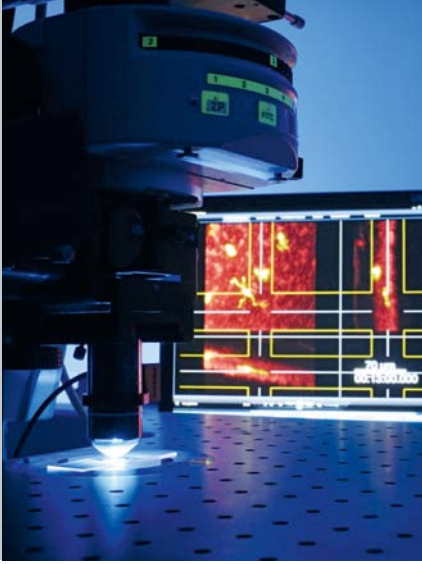
Recognizing technological trends and current market developments and adjusting accordingly the scope of services offered are among the hallmarks of the Fraunhofer ITEM's successful concept. Preliminary research projects and the resulting scientific findings and innovative technologies are just as beneficial to the institute's clients as in-depth studies and downstream projects. This is why the following work areas and competences are being established or further expanded:

Aerosol research

- Development of an aerosol generator for carbon nanotubes for use in inhalation experiments
- Development and validation of a standardized procedure for determination of the risk from inhalation exposure to spray products as part of substance registration
- Generation of exposure atmospheres with different allergens for clinical trials of specific immunotherapy in the Fraunhofer Environmental Challenge Chamber
- Aerosols in medical device technology: development and qualification of innovative inhalation technologies

Airway immunology

- Immunological and histopathological examination of human sample material from the respiratory tract
- Further development of ex-vivo techniques (precision-cut lung slices, PCLS) for investigating the effects of substances on the lungs of different animal species and on human lungs (for example, to determine the allergenic potential of chemicals and pharmaceuticals)
- Development of pulmonary inflammation models in non-human primates (in collaboration with the German Primate Center in Göttingen, Germany)



- Further development of animal models of COPD, asthma, and lung infections for drug development
- Use of nanoparticles for therapeutic purposes, for example as delivery vehicles of therapeutic antibodies

Chemical risk assessment

- Development of intelligent testing strategies in chemical risk assessment
- Setup of toxicological databases
- Investigation of structure-activity relationships in toxicology (QSAR)
- Development of risk assessment strategies for chemical categories to support registration of chemicals under the European chemicals regulation REACH

Clinical airway research

- Use of ozone as challenge substance in clinical trials with novel medications for COPD treatment (ozone manufacturing license, as required by the German Drug Act, has been received)
- Identification of novel biomarkers in exhaled breath for diagnosis and treatment monitoring of respiratory diseases
- Development of novel biomarkers (ncRNA) for chronic obstructive airway diseases
- Imaging techniques (MRI, CT, and PET) for use in clinical effects research

In-vitro toxicology

- Development of in-vitro screening tests to investigate the potential hazards of nanoparticles
- In-vitro testing (screening) of airborne aerosols, including candidate drugs

Pathology

- Development of methods for targeted investigation of pathological changes and of nanoparticles from histological slices by electron microscopy

Pharmaceutical biotechnology

- Development and validation of robust platform technologies for manufacture of biopharmaceutical active ingredients based on recombinant antibodies and nucleic acids

Toxicology

- Development of adequate toxicological and pharmacological test systems for use in the registration of biopharmaceuticals in compliance with EMA (European Medicines Agency) requirements
- Development of test methods for surface-active substances

ADVISORY BOARD

The advisory boards of the individual Fraunhofer institutes act as purely advisory bodies to their institute's management. The members come from academia, industry, and government agencies. In 2012, the Board of the Fraunhofer ITEM was made up of the following members:

Dr. Eckhard von Keutz

Chairman of the Advisory Board
Senior Vice President, Global Head Early Development,
Bayer Pharma AG

Professor Dr. Dieter Bitter-Suermann

Deputy Chairman of the Advisory Board
President and member of the Presidential Council responsible
for the Division of Research and Teaching of the Hannover
Medical School

Professor Dr. Helmut Blome

Director, Institute for Occupational Safety and Health of the
German Institutions for Statutory Accident Insurance and
Prevention

Dr. Ulrich Deschl

Head of Nonclinical Drug Safety,
Boehringer Ingelheim Pharma GmbH & Co. KG

Professor Dr. Paul-Georg Germann

Senior Vice President, Nycomed: a Takeda company

Professor Dr. Thomas Jung

Chief Medical Officer, Delenex Therapeutics AG, Switzerland

Dr. Günther Karmann

Managing Director, Karmann Consulting GmbH

Professor Dr. Hillel S. Koren

Managing Director, Environmental Health, LLC;
former Director Human Studies Division,
United States Environmental Protection Agency;
Research Professor Carolina Environmental Program,
The University of Carolina at Chapel Hill, USA

Dr. Edgar Leibold

Vice President Product Stewardship, BASF SE

Professor Dr. Reinhard Pabst

Lower Saxony Senior Research Professor of Immunomorphology,
Hannover Medical School

Professor Dr. Klaus F. Rabe

Head of Pneumology, Medical Director and Medical Executive
Director, Grosshansdorf Hospital;
Internal Medicine – Pulmonology, Christian Albrechts
University of Kiel

Professor Dr. Gerhard Schlüter

Consultant in Toxicology,
former Global Head Toxicology, Bayer Pharma AG

Ministerialrat Dr. Hans Schroeder

Head of Division for Science and Economy, EU Structural Funds,
Lower Saxony Ministry for Science and Culture

Dr. Thor A. Voigt

Head of Global Clinical Operations, Biometrics &
Data Management,
Boehringer Ingelheim Pharma GmbH & Co. KG

STAFF AND INSTITUTE BUDGET PERFORMANCE

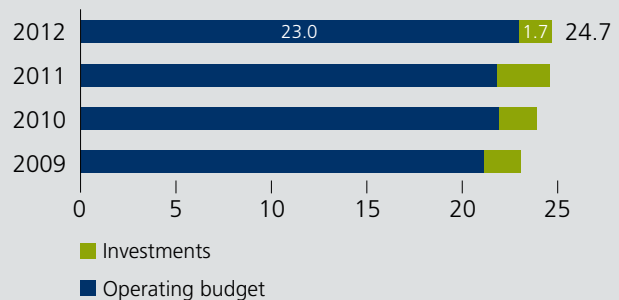
At the end of 2012, 298 people were employed at the Fraunhofer ITEM. The following list gives the numbers of employees by occupational groups:

- 90 scientists
- 72 graduates
- 72 technical staff
- 6 Ph. D. students
- 36 laboratory assistants
- 14 other assistants
- 8 apprentices

In 2012, the institute's budget reached a level of 23.0 million euros*. Financing by acquired funding amounted to 73.8 percent. The share of industrial income in the institute's budget was 34.3 percent – with regard to the Fraunhofer ITEM in Hannover it was 43.3 percent. Investments of the Fraunhofer ITEM amounted to approximately 1.7 million euros.

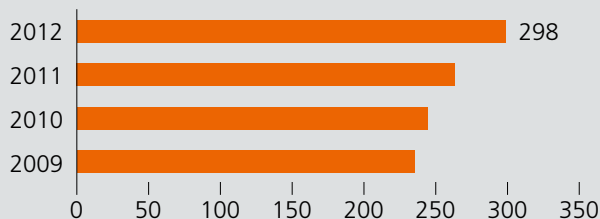
Total budget of the Fraunhofer ITEM

In million euros



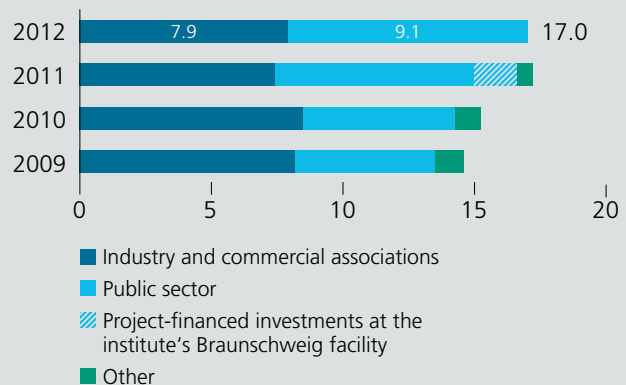
Staff of the Fraunhofer ITEM

No. of employees



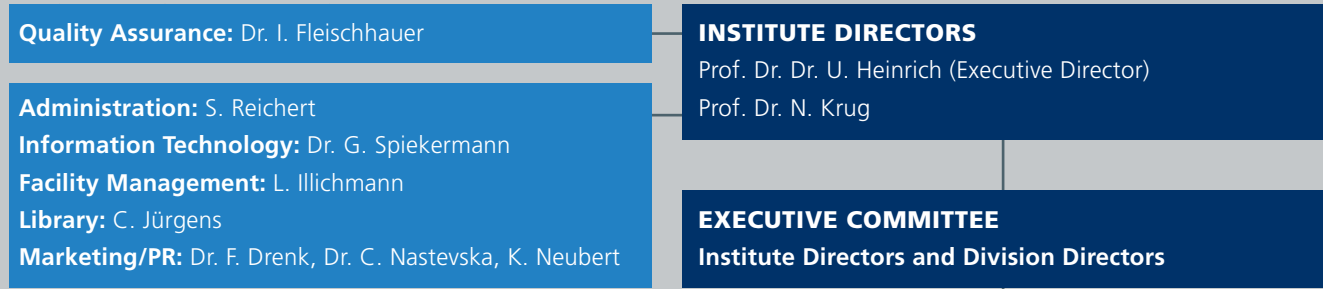
Sponsors and external income of the Fraunhofer ITEM

In million euros



* preliminary figures, valid at the time of printing

FRAUNHOFER ITEM ORGANIZATIONAL CHART





This organizational chart gives you the contact persons for the institute's divisions, departments, and competences at a glance. The Division of Pharmaceutical Biotechnology is based in Braunschweig, but is also responsible for the Fraunhofer ITEM's GMP fill-and-finish facility in Hannover. The Fraunhofer Project Group for Personalized Tumor Therapy is based in Regensburg's BioPark and was set up as a joint initiative of the Fraunhofer ITEM, the Fraunhofer-Gesellschaft, and the University of Regensburg. The institute is currently operating in four business units, which will be presented together with selected projects in the second part of this Annual Report.

NEWS IN 2012

Team spirit at the Fraunhofer ITEM



Running team During this year's corporate challenge B2Run in Hannover, about 20 Fraunhofer ITEM employees demonstrated that "the Fraunhofers" are energetic and perseverant not only in their research. On an approximately six-kilometer course, the whole team circled the lake "Maschsee" and successfully reached the finish line. In addition to receiving certificates and having a lot of fun in the joint activity outside of work, they also served a good cause with this run: The proceeds were donated to the Hannover-based foundation "Eine Chance für Kinder", which is dedicated to preventing child abuse and child neglect.

Quiz team What is rutilism? Which elementary particle name was drawn from a novel by James Joyce? What identifies scientific staff in classical Star Trek episodes? These are only three of over 30 tricky and partly quite weird questions a team of eight Fraunhofer ITEM staff members had to answer during a public table quiz that was part of the series of science-related public events "November der Wissenschaft" (November of science) in Hannover. There was keen rivalry, as teams from almost all Hannover-based research institutions were competing in this quiz. In a total of four rounds, the ITEM team bravely fought its way into the upper third.



Demo team On November 24, the Fraunhofer ITEM opened its doors to the public. Over 200 visitors were attracted by a large variety of lectures and demonstrations, and most people were quite astonished by the wide range of subject matters the institute is engaged in. Kids were offered a hands-on "mini-training". Putting on real-life lab coats, they were allowed to join scientists in their labs and were enthusiastic to learn what can be made of old garbage bags and juice containers with only a few tricks, and what chemists do at work. At the end of the day, everyone agreed that this is definitely worth repeating.



Reception: Fraunhofer Day in Regensburg's BioPark

The Fraunhofer-Gesellschaft and Regensburg's BioPark invited the public to a "Fraunhofer Day" in Regensburg. Two new working groups from different Fraunhofer institutions took up their work in the BioPark and presented their focuses on June 14. The Munich-based Fraunhofer EMFT is exploring the sensor materials of the future, while the team around Professor Christoph Klein is undertaking research in the field of "Personalized Tumor Therapy" as a Fraunhofer ITEM project group. Their findings may provide novel approaches for cancer diagnosis and therapy to the pharmaceutical industry.

Confirmation: Diesel engine exhaust classified as carcinogenic

"Diesel engine exhaust causes lung cancer in humans," was recently ascertained by the IARC, the WHO expert commission responsible for the classification of carcinogens. Based on new epidemiological data, the classification of diesel engine exhaust has now been upgraded from "probably carcinogenic" to "carcinogenic". "This classification, however, is based on studies performed with exhaust from diesel engines as they were state of the art 10 to 30 years ago. With current diesel technology and its integrated soot filters, such evidence could no longer be provided," explains Professor Uwe Heinrich, Fraunhofer ITEM Executive Director and member of the above mentioned WHO expert commission.



Award: Abstract Excellence Award

During this year's international conference of the American Thoracic Society in San Francisco, Vanessa Neuhaus, scientist of the Fraunhofer ITEM Department of Airway Immunology, was awarded a prize: She received the "Respiratory Structure & Function Assembly Abstract Excellence Award" for her abstract about the development of a nano-vaccine and its immunological characterization.

BUSINESS UNIT 1

DRUG RESEARCH, DRUG DEVELOPMENT AND MEDICAL BIOTECHNOLOGY





Project reports

Interactions of nerves and immune cells in the lung

Effect of tiotropium on bronchoconstriction in vivo and ex vivo

Non-human primates as a translational model of human inflammatory pulmonary diseases

Molecular diagnosis of single disseminated cancer cells: from experimental use to clinical routine

Preliminary research

Expression of cytochrome P450 monooxygenases in human lung epithelial cell lines

Fast process development for plasmid DNA production with a model-based approach

Project overview

DRUG RESEARCH, DRUG DEVELOPMENT AND MEDICAL BIOTECHNOLOGY

With the competences pooled in this business unit, we support our clients in all phases of the drug development process: from lead discovery and optimization via pre-clinical selection and testing of candidate drugs to clinical trials (see business unit Clinical Airway Research, page 42). Furthermore, this business unit includes the biotechnological manufacture of biopharmaceuticals.

A broad range of in-vitro test methods can be used both as screening systems in early phases of drug development and for target validation and efficacy testing. The selection of cellular test systems for individual studies is based on a variety of criteria, including relevance of the species, the organ, and the active ingredient, selection of the endpoints to be analyzed, and other requirements. In the context of pre-clinical candidate selection, standard genotoxicity tests and in-vitro ADME studies (e.g. CYP profiling, CYP inhibition, and CYP induction) are performed according to international regulatory guidelines (OECD, EMA, FDA). A broad spectrum of molecular biological and biochemical methods is available to detect unwanted side effects of pharmacological agents already at an early stage of drug development and to find mechanistic explanations for these.

Safety testing of biopharmaceuticals, such as human recombinant antibodies, requires special test systems to allow for unwanted immunological effects to be detected and ruled out with the greatest certainty possible prior to first trials in man. To this end, experimental approaches which reflect possible immunological responses of the human organism as accurately as possible are developed at the Fraunhofer ITEM. The use of viable lung slices, for example, enables species comparisons via monkeys even up to humans.

For pharmaceutical testing and other research issues in-vivo studies continue to be mandatory and required by legislation. The Fraunhofer ITEM offers the following investigations:

- Toxicity studies in rodents and non-rodents
- Toxicity studies in juvenile animals (juvenile toxicology)
- Toxic- and pharmacokinetics studies
- Investigations to detect subchronic and chronic toxic effects
- Identification of carcinogenic, teratogenic, or mutagenic effects
- Safety-pharmacological studies
- Use of imaging techniques, such as micro-computed tomography and optical imaging, to demonstrate target binding and the treatment success of novel pharmaceuticals
- Transgenic mouse models (adenocarcinomata of the lung and liver) and murine infection models for target validation and efficacy studies
- Investigations in asthma, allergy, inflammation, and infection models
- Studies on the measurement of lung function parameters in rodents (invasive and non-invasive)

Both in-vitro and in-vivo studies are conducted in compliance with the applicable GLP guidelines. In addition to experimental studies, the Fraunhofer ITEM offers its clients assistance in meeting the requirements of the pharmaceutical registration process, including the necessary documentation.

In the area of biotechnology, the Fraunhofer ITEM develops and validates manufacturing processes for active biopharmaceutical ingredients. These can be manufactured for pre-clinical and clinical trials according to GMP quality standards, whenever required. The range of active ingredients that can be produced includes proteins, glycoproteins, antibodies, nucleic acids, virus-like particles, and bacteriophages. There is already a great demand for GMP-grade therapeutic antibodies, and a similar situation is foreseeable for nucleic acids. Robust platform technologies that enable GMP manufacture of these compounds are being developed at the Fraunhofer ITEM.

CONTACTS



Dr. med. vet. Rainer Fuhst
Phone +49 511 5350-454
rainer.fuhst@item.fraunhofer.de



Dr. Monika Niehof
Phone +49 511 5350-570
monika.niehof@item.fraunhofer.de



Dr. Holger Ziehr
Phone +49 531 6181-6000
holger.ziehr@item.fraunhofer.de

Project report

INTERACTIONS OF NERVES AND IMMUNE CELLS IN THE LUNG

SUMMARY

Fraunhofer ITEM immunologists are exploring the interaction between nerves and immune cells. They have studied the influence of neuropeptides on airway dendritic cells in particular. What they discovered is that neuropeptides have an impact both on the motility and phagocytotic capacity of these cells and thereby influence the regulation of airway immune mechanisms. Consequently, it could be that they contribute to the pathophysiology of bronchial asthma.

The airway mucosal epithelium is permanently exposed to airborne particles. The airways are also permanently exposed to environmental stimuli such as temperature and humidity shifts, airborne pathogens, pollen and smoke particles, or ozone. To enable homeostasis of lung physiology several mechanisms exist to compensate this blast of influences. A network of immune cells patrols at this interface to the environment. Down the cascade of defense mechanisms, a multitude of immune cells patrols below the epithelial layer to intercept foreign particles and antigens. Mostly macrophages and dendritic cells (DC) capture, process, and present incoming antigens and initiate appropriate immune responses. Nerves co-localizing with DC below the epithelial layer respond to chemical, mechanical, and inflammatory stimuli and in turn interact with the surrounding cells via neurotransmitters and neuropeptides (Fig. 1). DC and other immune cells can receive these neurogenic signals by expressing neuropeptide receptors.

Dysfunction in the interplay between nerves and immune cells in asthma

Neuropeptides that do not belong to the classical transmitters of the parasympathetic or sympathetic nervous systems are classified under the term non-adrenergic non-cholinergic peptides (NANC). Examples of such mediators are calcitonin gene-related peptide (CGRP), substance P (SP), and vasoactive intes-

tinal peptide (VIP). These neuropeptides in general act on bronchus and capillary muscle tone, secretion, and immune cells. Activation of sensory neurons upon a stimulus via axon reflex mechanisms leads to release of SP and CGRP in the airways.

In respiratory diseases like asthma, there is a dysfunction in the interplay between nerves and immune cells. These alterations are encompassed under the term “neurogenic inflammation”. They include, for example, elevated SP concentrations in bronchoalveolar lavage fluid (BALF) of asthma patients that further increase with allergen challenge. Moreover, three to four times higher CGRP and SP expression could be observed 24 hours after allergen challenge in guinea pig airway tissue.

Neuropeptides can influence dendritic cells

Fraunhofer ITEM scientists have investigated the interaction between nerves and immune cells in mouse airways. They addressed the question whether neuropeptides can influence the behavior of a defined immune cell population in the airways. Based on various specific markers in addition to their anatomical localization and morphology, the scientists identified CD11c⁺ cells as airway mucosal DC (Fig. 2). In living tissue, they revealed the dynamics of this DC population under the influence of neuropeptides. As readout parameters, the motility and phagocytotic capacity of airway mucosal DC after different neuropeptide stimuli were determined. The data thus obtained show that neuropeptides can modulate these key features of DC. By linking these findings with two different OVA-induced asthma models in mice, the scientists were able to demonstrate that neuropeptides are involved in adjusting DC behavior during allergic airway inflammation.

Fig. 1: The dense network of nerves in a mouse airway has been stained blue with a pan-neuronal marker. Neuropeptide-containing fibers are displayed in yellow.

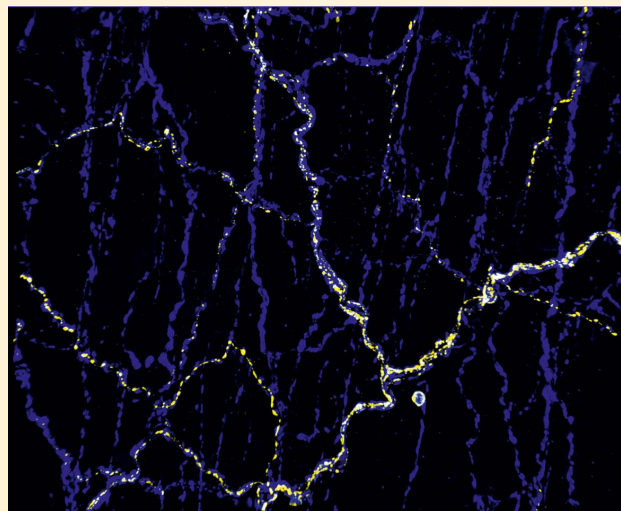
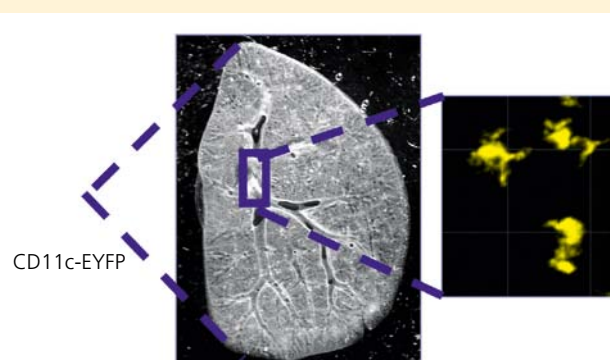


Fig. 2: Longitudinal slice of the lung of a CD11c-EYFP-transgenic mouse with airways cut in longitudinal direction. CD11c-positive dendritic cells are yellow fluorescent here (right image).



Altered motility of dendritic cells demonstrated in living lung slices

Using two-photon microscopic time-lapse analysis of living lung slices from CD11c-EYFP-transgenic mice, the scientists studied the influence of neuropeptides on airway DC motility. Additionally, the phagocytotic capacity of CD11c⁺ cells after neuropeptide stimulation was determined. Electrical field stimulation (EFS) leads to an unspecific release of neuropeptides from nerves. After EFS and treatment with the neuropeptides VIP or CGRP, airway DC in living lung slices showed altered motility. Furthermore, the EFS-mediated effect could partially be blocked by pre-treatment with the receptor antagonist CGRP₈₋₃₇. Additionally, the phagocytotic capacity of bone marrow-derived and whole-lung CD11c⁺ cells could be inhibited by the neuropeptides CGRP, VIP, and substance P. These data were then cross-linked with the in-vivo situation by analyzing DC motility in two different OVA asthma models. Both in the acute and prolonged OVA asthma models, neuropeptide levels and DC motility in the airways were found to be altered.

Neuropeptides might contribute to the pathophysiology of asthma

In summary, the data obtained in this study suggest that neuropeptides modulate the key features motility and phagocytosis of mouse airway DC. Altered neuropeptide levels in the airways during allergic inflammation thus have an impact on regulation of airway immune mechanisms and therefore might contribute to the pathophysiology of bronchial asthma.

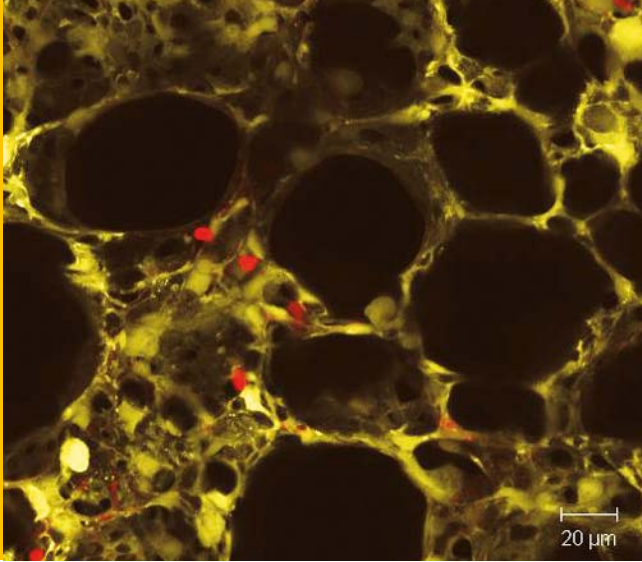
Reference

Voedisch, S.; Rochlitzer, S.; Veres, T. Z.; Spies, E.; Braun, A. (2012) Neuropeptides control the dynamic behavior of airway mucosal dendritic cells. PLoS One, 7 (9): e45951. doi: 10.1371/journal.pone.0045951



CONTACT

Prof. Dr. Armin Braun
Phone +49 511 5350-263
armin.braun@item.fraunhofer.de



Precision-cut lung slices (PCLS), viewed with a confocal laser scanning microscope: Live cells are displayed in yellow, dead cells in red.

Project report

EFFECT OF TIOTROPIUM ON BRONCHOCONSTRICTION IN VIVO AND EX VIVO

SUMMARY

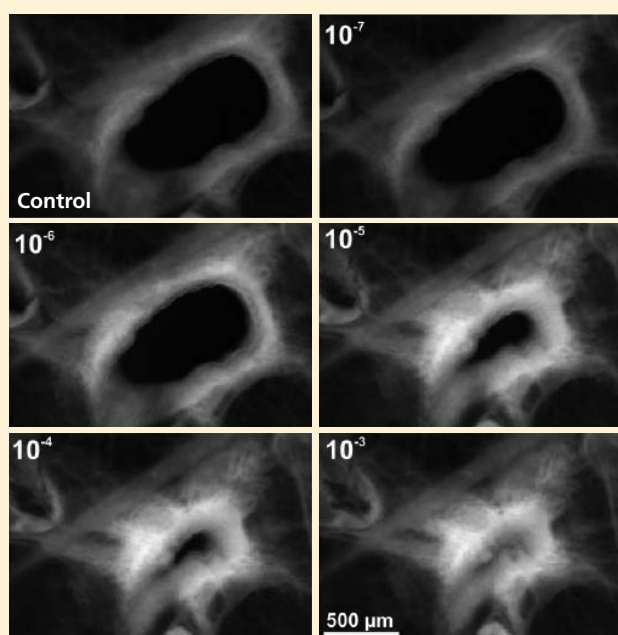
The anticholinergic drug tiotropium can inhibit acetylcholine-induced bronchoconstriction in rats. Fraunhofer ITEM scientists were able to show the bronchodilating effect of tiotropium both in an ex-vivo model of vital lung slices and in an in-vivo model. They thereby demonstrated that precision-cut lung slices (PCLS) are a promising model to study airway narrowing and corresponding therapeutic interventions.

Inhaled anticholinergic drugs are effective in the treatment of chronic obstructive pulmonary disease (COPD) and bronchial asthma. Tiotropium is an anticholinergic agent which selectively acts on the M1- and M3-subtypes of muscarinic receptors. In the present study, Fraunhofer ITEM scientists investigated the effect of tiotropium on acetylcholine-induced bronchoconstriction in rats: either in vivo by invasive lung function measurement or ex vivo in precision-cut lung slices (PCLS; Fig. 1) by videomicroscopy. PCLS are a model that closely mimics morphology and functionality of the respiratory tract and allows investigation of airway narrowing under nearly identical experimental conditions with only a small number of animals required.

The technique of preparation of lung tissue sections has been well described in many publications. In the present study, rat lungs were extracted directly post mortem and filled with a medium/agarose mixture, cooled on ice, and cut into 250- μ m-thick slices. After several very intensive washing steps, these precision-cut slices were taken into culture and maintained under normal cell culture conditions for several days. Bronchoconstriction was induced by acetylcholine and imaged by videomicroscopy. The effect of tiotropium on bronchoconstriction was investigated in the PCLS. Acetylcholine induced strong bronchoconstriction of airway smooth muscles in rat PCLS (Fig. 2). The effective concentration of acetylcholine in the PCLS was about 9.0 μ M. Pre-incubation of lung tissue with tiotropium inhibited acetylcholine-induced bronchoconstriction completely.

Fig. 2: Transmitted light images of acetylcholine-induced bronchoconstriction in rat PCLS.

Acetylcholine was applied to the tissue at molar concentrations as indicated in the upper left corner of the images, inducing strong bronchoconstriction of the airways in rat PCLS.



For the in-vivo measurements, rats were anesthetized and orotracheally intubated. Lung resistance and dynamic compliance were measured before, during, and after inhalation challenge with acetylcholine in control animals versus animals pre-treated with 1 µg per kilogram body weight tiotropium 45 minutes before provocation. Inhaled acetylcholine induced strong bronchoconstriction in the rats. This was characterized by a marked increase in lung resistance and a strong decrease in dynamic compliance in untreated rats. Maximum lung resis-

tance was up to 279 percent above baseline, minimum dynamic compliance was down to -81 percent. A single dose of inhaled tiotropium inhibited the acetylcholine-induced bronchoconstriction in terms of maximum increase in lung resistance nearly completely (97 percent), whereas the decrease in dynamic compliance was inhibited after all by 51 percent.

In the study presented here, Fraunhofer ITEM scientists showed that tiotropium has a strong protective, antibronchospastic effect in in-vivo and ex-vivo models of bronchoconstriction and that tiotropium is useful in the treatment of COPD and asthma. Furthermore, they demonstrated that PCLS are a promising model to study airway narrowing and corresponding therapeutic interventions.



CONTACTS

Dr. Katherina Sewald (PCLS)
Phone +49 511 5350-323
katherina.sewald@item.fraunhofer.de



Dr. Heinz-Gerd Hoymann
(in-vivo lung function)
Phone +49 511 5350-404
heinz-gerd.hoymann@item.fraunhofer.de

1 Common marmoset monkeys are the preferred non-human primate species of the new Fraunhofer working group at the German Primate Center. With an average body weight of 400 grams their size corresponds to that of a rat.



Project report

NON-HUMAN PRIMATES AS A TRANSLATIONAL MODEL OF HUMAN INFLAMMATORY PULMONARY DISEASES

SUMMARY

Biopharmaceuticals developed specifically for human target structures also require pre-clinical and clinical testing. Human-specific target structures, however, may not be present in the classical rodent models, which could lead to less predictable test results. Due to the close homology of non-human primates and humans, pre-clinical disease models in non-human primates are often the only possibility to test such novel biopharmaceuticals. In cooperation with the German Primate Center, Fraunhofer scientists have developed a common marmoset model – a translational model – that enables pre-clinical testing of human-specific biopharmaceuticals for treatment of inflammatory airway diseases such as COPD and asthma.

An increasing share of cases of chronic obstructive pulmonary disease (COPD) are resistant to therapy. New therapeutic options are therefore needed. Numerous new developments are human-specific biopharmaceuticals whose efficacy and safety cannot be sufficiently tested in the classical rodent model. Thus, pre-clinical disease models in non-human primates are often the only possibility to test such novel biopharmaceuticals. Non-human primates display greater homology to humans with regard to anatomy and immunology.

In cooperation with the German Primate Center in Göttingen, the Fraunhofer ITEM Department of Airway Immunology has set up a working group for the development of novel translational animal models in common marmoset monkeys (*Callitrix jacchus*; Fig. 1). The aim is to offer translational non-human primate models for pre-clinical testing of human-specific biopharmaceuticals for COPD and asthma treatment. For the developed animal models a tiered approach is used to keep animal numbers to a minimum. In-vitro and ex-vivo experiments must first be successfully completed, before in-vivo experiments are designed and performed based on the obtained data.

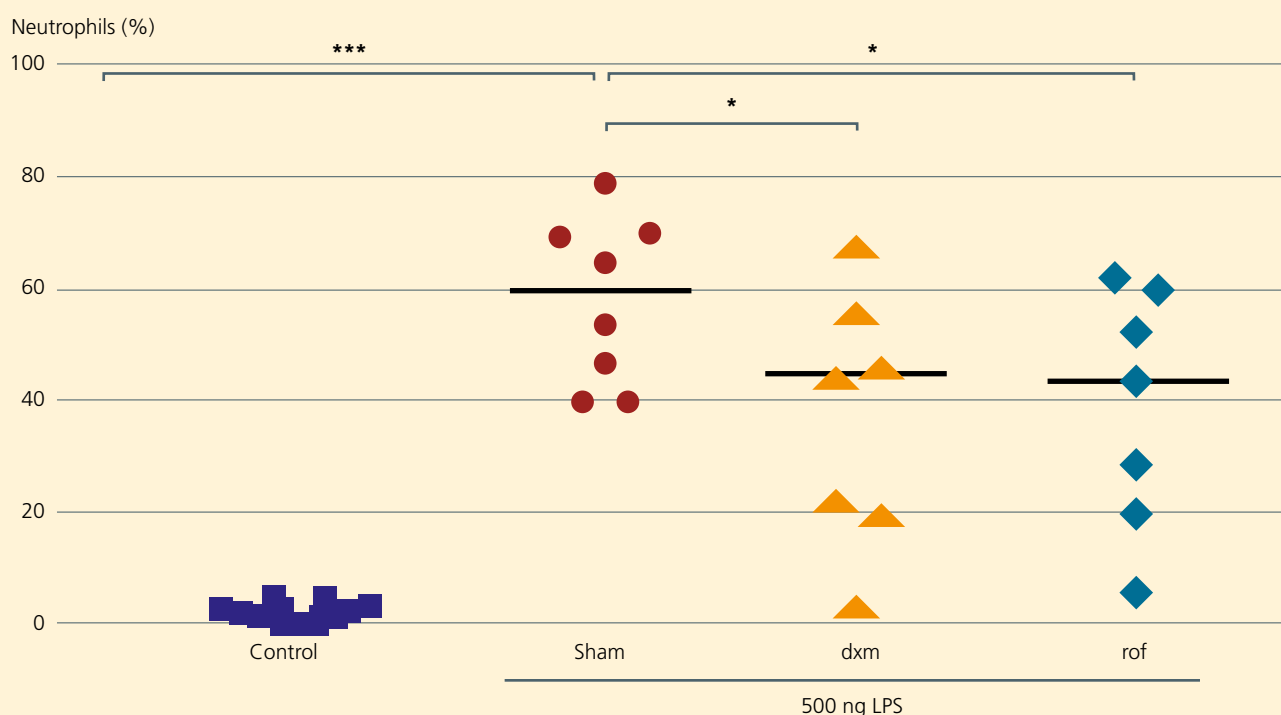
Model of LPS-induced acute inflammation of the lung

Similar to segmental LPS challenge in humans, a model of LPS-induced acute lung inflammation has been established in the common marmoset. LPS-induced inflammation reflects pro-inflammatory aspects of human neutrophil-associated chronic airway diseases. Animals were treated orally with roflumilast, an approved PDE-4 inhibitor, or dexamethasone as treatment control, on five consecutive days. Sham-treated animals served

as controls. After LPS instillation into the lungs, there was a significant influx of cells, mainly neutrophils, into the airways ($p < 0.001$). Roflumilast treatment significantly reduced the neutrophil count in bronchoalveolar lavage fluid ($p = 0.047$; Fig. 2). The cytokine TNF- α was significantly reduced after LPS instillation in the animals that had been pretreated with roflumilast ($p = 0.048$) or dexamethasone ($p = 0.036$). The results show that the common marmoset can be used as a reliable model of human airway inflammation (Seehase et al., 2012).

Fig. 2: Changes in neutrophil count in bronchoalveolar lavage after intratracheal instillation of LPS.

Sham-, dexamethasone- (dxm), and roflumilast-pretreated (rof) common marmoset monkeys were challenged with 500 ng LPS instilled into the lungs. Ipsilateral bronchoalveolar lavage was performed after 18 hours. The figure shows neutrophil percentages in relation to total cell count in the lavage fluid (* $p < 0.05$, *** $p < 0.001$, one-tailed Mann-Whitney test in relation to sham-exposed animals).



Model of allergic asthma

The scientists are currently developing a novel animal model for pre-clinical testing of biopharmaceuticals for asthma treatment. In a first step, common marmosets were sensitized against house dust mite allergen (HDM), followed by HDM aerosol challenge. Cells and cytokines were analyzed in bronchoalveolar lavage fluid. In addition, lung function measurements were performed using the first lung function measurement station for marmoset monkeys worldwide, developed at the Fraunhofer ITEM. The increase in lung resistance upon methacholine challenge was significantly higher in the HDM-sensitized animals compared with untreated animals and was also increased compared with non-sensitized animals that had merely been challenged with HDM extract. First results show that it is possible to induce an asthmatic phenotype with eosinophilia and hyperreactivity in the common marmoset.

Reference

Seehase, S.; Lauenstein, H.-D.; Schlumbohm, C.; Switalla, S.; Neuhaus, V.; Förster, C.; Fieguth, H.-G.; Pfennig, O.; Fuchs, E.; Kaup, F.-J. et al. (2012)
LPS-induced lung inflammation in marmoset monkeys – an acute model for anti-inflammatory drug testing.
PLoS One 7 (8): e43709.



CONTACT

Sascha Knauf, D.V.M, Ph. D.
German Primate Center
Leibniz Institute for Primate Research
Phone +49 551 3851-259
sascha.knauf@item.fraunhofer.de

Project report

MOLECULAR DIAGNOSIS OF SINGLE DISSEMINATED CANCER CELLS: FROM EXPERIMENTAL USE TO CLINICAL ROUTINE

SUMMARY

Scientists of the Fraunhofer Project Group in Regensburg have developed a kit that enables reliable and largely uniform amplification (that is, replication) of the complete genetic information of a single cell. This routine test serves the purpose of investigating single disseminated cancer cells or also tumor cells circulating in the bloodstream on the molecular genetic level – an essential prerequisite for a tumor therapy that is tailored to the individual patient and takes into account that metastatic tumor cells are genetically different from the primary tumor.

Most tumor patients do not die from their primary tumor, but from metastases. If physicians detect disseminated cancer cells (DCC) in bone marrow and lymph nodes or circulating tumor cells (CTC) in the bloodstream, this often means a lower chance of survival for the patient. DCC are commonly looked upon as metastatic precursor cells. Detection of DCC is meanwhile even used by physicians to classify the severity of a breast cancer case. CTC are often detected in patients with metastases. Because they are easy to obtain by simple collection of venous blood specimens, CTC detection is often given preference over DCC detection in clinical practice. In addition, an FDA-approved detection and capturing system is available for CTC: the Cell-Search™ system by Veridex. In the future, this CTC test is planned to enable also monitoring of the therapeutic response via easily available blood specimens instead of invasive biopsies.

Physicians are counting on personalized tumor therapy

For more effective treatment of tumors and their metastases, physicians are counting more and more on personalized tumor therapy – a therapy tailored to the patient and thus to her or his particular tumor cells. The molecular characteristics of these cancer cells, therefore, have to be known. In the future, molecular analysis especially of DCC and CTC could thus play an important role in cancer diagnosis, the more so as many tumor patients



The "Ampli1™ WGA Kit" is a test kit developed by the Fraunhofer Project Group for Personalized Tumor Therapy that enables amplification of the DNA of a single cell.

die from metastases and not from their primary tumor, which can be genetically different. This means that in clinical practice not only detection of DCC and CTC, but also reliable and routine molecular analysis of single such cells must be feasible. This is exactly what the Fraunhofer Project Group is aiming at in its cooperation with the company Silicon Biosystems.



CONTACT

Dr. Bernhard Polzer
Phone +49 941 298480-23
bernhard.michael.polzer@item.fraunhofer.de

Kit for analyzing a single cell has been developed

Scientists of the Project Group for Personalized Tumor Therapy have developed a kit that enables reliable and largely uniform amplification (that is, replication) of the complete genetic information of a single cell. Under the name "Ampli1™ WGA" this kit has been commercially available from Silicon Biosystems since 2011 and can be used for both fresh and fixed cells.

The ITEM scientists in Regensburg have furthermore developed a PCR assay that is based on amplification of three specific regions in the genome and makes it possible to predict whether or not chromosomal changes (resolution 10-20 Mb) in single cells can be determined with a specificity of 94 percent and a sensitivity of 97 percent. They are currently working on specific molecular tests that will enable simple and reliable determination of therapeutically relevant mutations and DNA amplification of single genes in single cells, for example, of HER2 and PI3K. The aim is to bring these to market as diagnostic tests too. To enable short-term integration into numerous clinical studies, the researchers have also developed a semi-automated workflow for the analysis of circulating tumor cells. It consists in detection of CTC with the CellSearch™ system, their isolation with the DEPArray™ by Silicon Biosystems, and subsequent amplification of single-cell DNA using the Ampli1™ WGA kit. This combination of the three technologies is now planned to be tested in clinical trials.

Light microscopic images of untreated A549 cells (left) and Calu-3 cells (right) after 48 hours of culture (10x magnification).

Preliminary research

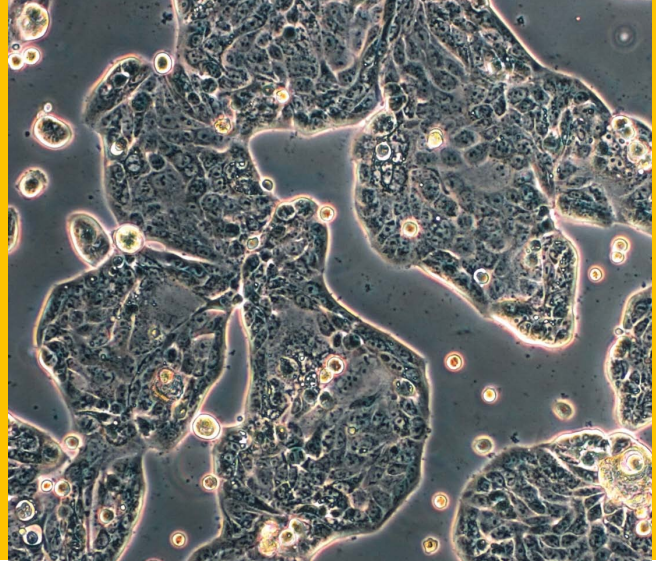
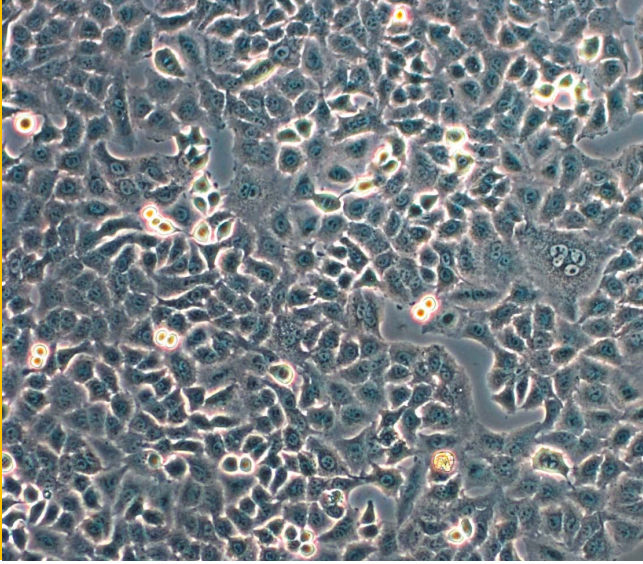
EXPRESSION OF CYTOCHROME P450 MONOOXYGENASES IN HUMAN LUNG EPITHELIAL CELL LINES

SUMMARY

So far, little is known about the metabolic properties of the bronchial epithelial cell line Calu-3. Investigations undertaken by Fraunhofer ITEM scientists have demonstrated that a broad range of cytochrome P450 monooxygenases are basally expressed in this cell line and that different isoforms of these monooxygenases can also be induced.

The pulmonary epithelium is the body's first barrier to airborne xenobiotics and inhaled drugs. Cytochrome P450 monooxygenases (CYP) participate in metabolic inactivation of such xenobiotics and drugs. Beyond this, some compounds require enzymatic activation to exert their toxic effects or their desirable functions. Such enzymes can also be found in the lung. Fraunhofer ITEM scientists have investigated whether lung cell lines that are commonly used by researchers as cell culture models of airway epithelium express CYP isoforms and whether this expression can be induced. The type II-like lung epithelial cell line A549 and the bronchial epithelial cell line Calu-3 are very commonly used in this context. So far, there is little information about their metabolic properties, especially for Calu-3 cells. The aim of this study was to further characterize both these cell lines regarding their basal and inducible expression of CYP isoforms.

CYP expression was determined using real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR). Basal expression of CYP1B1, CYP1A1, CYP2D6, CYP2B6/7, CYP3A5, and CYP2J2, and small amounts of further CYP isoforms were detected in both cell lines, which is consistent with expression in the human lung.



Furthermore, potential CYP inducers were analyzed. Omeprazole acts on aryl hydrocarbon receptor (AhR) activation and induced CYP1A1 and CYP1B1 in both cell lines. Rifampicin acts on pregnane x receptor (PXR) and phenobarbital predominantly on constitutive androstane receptor (CAR), however, both these receptors are not expressed in the lung. Accordingly, both agents did not induce any CYP in these cells. Besides PXR, dexamethasone also acts on glucocorticoid receptors, and induction of members of the CYP3A family was found, mainly of CYP3A7 in Calu-3 cells and of CYP3A5 and CYP3A7 in A549 cells. CITCO is known to act as a CAR agonist and is normally used to induce CYP2B6/7. However, it is also a potent inducer of CYP1B1 in Calu-3 cells and of CYP1A1 and CYP1B1 in A549 cells.

The results have shown that Calu-3 cells and A549 cells express a broad range of CYP and that CYP inducibility is preserved. These cell lines thus provide valuable models of the airway epithelial barrier for metabolic in-vitro experiments.



CONTACT

Dr. Monika Niehof
Phone +49 511 5350-570
monika.niehof@item.fraunhofer.de

Preliminary research

FAST PROCESS DEVELOPMENT FOR PLASMID DNA PRODUCTION WITH A MODEL-BASED APPROACH

SUMMARY

In the future, plasmid DNA will be used increasingly in the form of biopharmaceuticals – as can be seen from the numerous clinical trials that are currently being conducted with therapeutic agents of this kind. Their special feature is the fact that the active protein is produced directly by cells at the site of action. To enable manufacture of sufficient quantities of plasmid DNA for clinical trials – and, above all, in the required quality – scientists of the Fraunhofer ITEM Department of Pharmaceutical Biotechnology have developed a platform technology that allows the time required to develop a manufacturing process for plasmid DNA to be substantially reduced.

Plasmid DNA is gaining increasing importance in the form of vaccines, immune or gene therapeutic agents. With this kind of biopharmaceutical the active protein is produced in vivo directly at the site of action. Already today, numerous clinical trials with human therapeutic agents are being conducted and four veterinary medications have already been approved for commercial use. Appropriate manufacturing processes now have to be developed to enable manufacture of sufficient quantities of plasmid DNA for clinical trials – and, above all, in the required quality.

Scientists of the Fraunhofer ITEM Department of Pharmaceutical Biotechnology are currently developing a platform technology for plasmid DNA production in pharmaceutical quality based on largely generic methods. The development is being realized for the example of an expression system aimed at enabling vaccination against human papilloma virus (HPV). Although such a manufacturing platform can be composed largely of known constituents, the researchers have had to face a number of scientific challenges. For example, the relationship between growth rate and plasmid content of the *E. coli* cells used, which in the literature has been described only qualitatively, could be explained via a model and described quantitatively. This was a precondition for the development of a rationally founded culturing strategy which in addition



The 300-liter bioreactor plant is used for microbial cultivation.

allows the necessary cultivation parameters for new plasmid DNA products to be determined within a short time and with only a few targeted experiments. This exactly is an essential goal of platform development: a substantial reduction of development times.

With regard to process design and control in the manufacture of biopharmaceuticals, the regulatory authorities increasingly demand a thorough understanding of the underlying cellular processes and key parameters of the manufacturing process. The use of well-studied and well-understood generic production methods is a key to meeting this requirement.

With the described model-based approach for plasmid DNA production, clients can benefit not only from fast process development. In addition, current and future regulatory requirements are being met as part of our service.

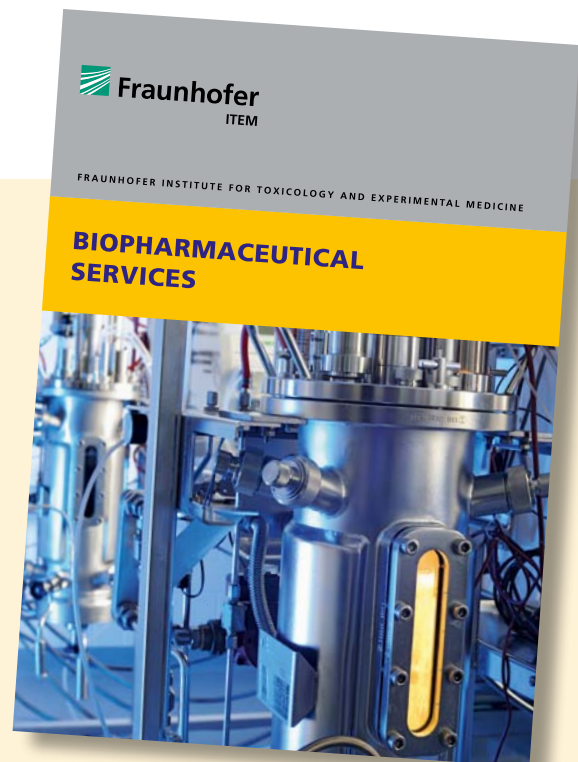
Reference

Bohle, K.; Ross, A. (2011)
Plasmid DNA production for pharmaceutical use: Role of specific growth rate and impact on process design. *Biotechnology and Bioengineering* 108: 2099-2106.



CONTACT

Dr. Anton Roß
Phone +49 531 6181-6300
anton.ross@item.fraunhofer.de



The information folder "Biopharmaceutical Services" presents the wide range of R&D services offered by the Fraunhofer ITEM Division of Pharmaceutical Biotechnology. To order a folder, simply send an e-mail to: biopharmaceutical-services@item.fraunhofer.de.

Business unit 1

PROJECT OVERVIEW

Drug testing

Efficacy of biopharmaceutical drugs in primates

Drug testing in mouse and rat asthma models including lung function measurements

Drug testing in infection models

Drug testing in mouse, rat, and non-human primate models of LPS-induced inflammation

Testing of plant-based drugs in models of inflammation

In-vitro testing of plant-based drugs

Development of a cell culture model to test drugs for COPD treatment

Safety pharmacology of the lung

Testing of bronchodilator drugs for COPD treatment

Determination of concentrations of pharmaceuticals in formulations and exposure atmospheres

Bioanalytics

Determination of concentrations of special pharmaceuticals in blood, urine, and organ samples

Structure elucidation of trace-level and degradation-related impurities in pharmaceuticals by LC-NMR and LC-MS analyses

Immunology

Immunotoxicological evaluation of metals

In-vivo and ex-vivo imaging of the immune response by 2-photon microscopy

Detection of infectious agents in blood samples and on medical equipment

Pharmaceutical biotechnology

Development of a platform for GMP-grade manufacture of recombinant antibodies based on microbial cultures and mammalian cell cultures

Development of a platform for GMP-grade manufacture of nucleic acids/DNA-based agents

GMP-compliant manufacture of investigational provocation substances for use in clinical trials in the Department of Clinical Airway Research

GMP manufacture of a CHO working cell bank

Development of a downstream processing method for a recombinant *E. coli* protein

Consulting and equipment qualification at Braunschweig Clinical Center

Tumor therapy

Workflow for detection, isolation, and molecular analysis of single circulating tumor cells

Detection of HER2 amplifications and PI3K mutations in single circulating tumor cells from breast cancer patients

Development of a quality control process for *Ampli1*TM

Methods for detection of somatic mutations in single cells

Micro drug delivery system for tumor therapy (TUDOS)

BUSINESS UNIT 2

CLINICAL AIRWAY RESEARCH





Project reports

Fraunhofer researchers participating in German Center for Lung Research

Low-dose inhalation challenge with endotoxin – a model for proof-of-concept studies

Preliminary research

Prognostic value of markers from serum and lung in smokers with and without COPD

Manufacturing license for ozone as a challenge substance

Project overview

Clinical studies to test the efficacy of new pharmaceuticals, to develop novel biomarkers, and to assess the potential hazards of pollutants in the air are conducted in the business unit Clinical Airway Research. In this field, the Fraunhofer ITEM closely cooperates with the Hannover Medical School as well as with industry and different research institutions.

Clinical studies are a major focus of work in this business unit. According to the guidelines of Good Clinical Practice (GCP), clinical trials with volunteers and patients to evaluate the efficacy and safety of new anti-obstructive and anti-allergic drugs are carried out, with the main emphasis being placed on the design and conduct of early-phase clinical trials (phases I and II). The efficacy of new anti-allergic drugs in patients with hay fever can be tested in the Fraunhofer Environmental Challenge Chamber (Fraunhofer ECC), a grass pollen exposure room that provides controlled allergen challenge conditions and is operated in cooperation with the Department of Aerosol Technology. To test the efficacy of a specific immunotherapy, test subjects are also exposed to house dust mite allergens in the Fraunhofer ECC. Due to the universal patented aerosol generation

technology, it will also be possible in the future to conduct tests with other allergens, such as cat dander or birch pollen. Another focus of the clinical research activities is on bronchoscopic examinations after inhalation or instillation of allergens, endotoxin, or pharmaceuticals. Only few institutions worldwide have at their disposal comparable expertise and technical facilities.

Under a special research program (SFB 587: "Immune Reactions of the Lung in Infection and Allergy") sponsored by the German Research Foundation (DFG) and within the German Center for Lung Research, clinical research projects are conducted in this business unit to investigate the pathomechanisms of the allergic inflammation in the lung and to develop novel biomarkers.

Cutting-edge technology and high professional expertise are the outstanding features of this business unit. Its current core competencies include research methods of respiratory medicine and allergology, clinical drug trials for the indications allergy, asthma, and COPD, biomarker research and analysis as well as aerosol process technology and aerosol analytics.

CONTACTS



Prof. Dr. med. Norbert Krug
Phone +49 511 5350-602
norbert.krug@item.fraunhofer.de



Prof. Dr. med. Jens Hohlfeld
Phone +49 511 5350-604
jens.hohlfeld@item.fraunhofer.de

Project report

FRAUNHOFER RESEARCHERS PARTICIPATING IN GERMAN CENTER FOR LUNG RESEARCH

SUMMARY

Respiratory diseases are among the most common causes of death worldwide. In order to accelerate development of more effective therapies for chronic diseases in particular, the German Center for Lung Research – a cross-disciplinary research association of leading university and non-university institutions – was set up in 2011, funded by the German Federal Ministry of Education and Research. The Fraunhofer ITEM is also participating: Scientists here are searching for biomarkers to improve the diagnosis of inflammatory diseases such as asthma and COPD and to enable better prediction of the course of a disease and of its response to therapy.

Among the top ten causes of death worldwide, the World Health Organization WHO has listed four respiratory diseases. Today, every fifth death is due to an airway disorder or a related secondary disease. Experts have predicted a further substantial increase in prevalences until 2030. The majority of severe lung conditions are still incurable, medications can only help relieve symptoms, and the economic costs resulting from these diseases are high.

This is why the German Federal Ministry of Education and Research has initiated the establishment of a German Center for Lung Research (DZL), similar to the National Institutes of Health in the United States. The aim is to accelerate the development of new options for diagnosis, treatment, and prevention of respiratory diseases. The research activities are focused on the disease areas asthma and allergy, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acute lung injury and pneumonia, interstitial lung diseases, pulmonary hypertension, end-stage lung diseases, and lung cancer.

The DZL is intended to become a permanent institution, funded by the German Federal Government and the *Länder*. It was founded in November 2011. Members of the DZL are selected university hospitals, clinics, and non-university research institutions performing cutting-edge lung research of international reputation. The DZL members are based at five different locations, one being Hannover with the research network BREATH (Biomedical Research in Endstage and Obstructive Lung Disease). More than 20 physicians and scientists of the Hannover Medical



The scientists are searching for novel biomarkers in exhaled breath to improve diagnosis, prediction of the course of disease and of its response to therapy.

School (MHH), the Fraunhofer ITEM, and the Center for Health Economics Research Hannover of the Leibniz University have joined forces and are working on BREATH projects together with over 80 staff members.

Fraunhofer ITEM scientists are working on projects addressing asthma and COPD. The institute's Division of Clinical Airway Research has placed its focus on the search for novel biomarkers to improve diagnosis, prediction of the course of disease and of its response to therapy – with an emphasis on the response to therapy at an early stage of clinical research.

A key interest is in non-invasive measurement techniques for exhaled breath analysis. Such techniques are suitable not only for use in clinical trials, but could also become everyday tools in respiratory medical practice. The current investigations, performed in close cooperation with the Department of Bio- and Environmental Analytics, are focused on measurement of volatile compounds in exhaled breath of patients by means of gas chromatography and mass spectroscopy. Because of the multitude of measurable substances, a key challenge is the search for substance patterns that could provide early signs of disease progression or clues to appropriate treatment options. These investigations are performed in cooperation with researchers at the DZL sites in Marburg and Munich.

The goal of another project is to enhance the diagnostic possibilities of sputum analysis. In this context, the scientists are investigating, among other things, how individual cell populations from sputum can be selected and how novel techniques for measuring the activity of single cells can be applied also to human cells. To this end, highly sensitive FRET (Förster resonance energy transfer)-based sensors for quantitative determination of pulmonary inflammation have been developed at the DZL site in Heidelberg.

In a further research project, the scientists are exploring whether magnetic resonance tomography (MRT) is generally a suitable technique for quantitative determination of airway inflammation in patients with asthma or COPD. To this end, segmental allergen challenges were at first performed in patients with allergic asthma and in healthy volunteers as controls. Thereafter, the sensitivity and specificity of different MRT protocols was analyzed. In the next step, investigations in the experimental model of segmental endotoxin challenge will be performed to find out whether this way of detecting inflammation can basically also be used for non-allergic inflammatory processes. Imaging is performed in cooperation with the MHH Institute of Diagnostic and Interventional Radiology. Within the scope of the DZL platform Imaging, MRT protocols are being standardized and further developed. This is done in close cooperation with scientists at the DZL site in Heidelberg.

The cooperation across disciplines and between different sites offers excellent chances for the development of novel biomarkers, which in a subsequent step can then be validated in shared patient cohorts within the DZL.



CONTACT

Prof. Dr. med. Jens Hohlfeld
Phone +49 511 5350-604
jens.hohlfeld@item.fraunhofer.de

Project report

LOW-DOSE INHALATION CHALLENGE WITH ENDOTOXIN – A MODEL FOR PROOF-OF-CONCEPT STUDIES

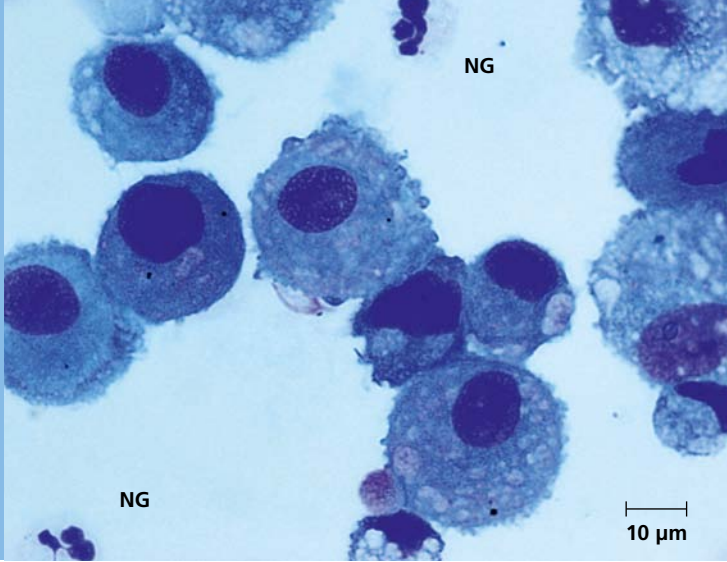
SUMMARY

Scientists of the Department of Clinical Airway Research have established a novel challenge method with little invasive intervention that can be used for proof-of-concept studies in early-phase clinical development of anti-inflammatory drugs for COPD treatment. The improved inhalation method is suitable for use with GMP-grade endotoxin (LPS) and despite a very low LPS dose induces a reproducible influx of inflammatory cells into the airways.

A helpful tool for proof-of-concept studies in early-phase development of novel anti-inflammatory drugs is provided by challenge models that allow precisely defined, temporary inflammatory processes to be induced in the airways of healthy volunteers. Already in 2011, scientists of the Department of Clinical Airway Research were able to demonstrate that this can be achieved non-invasively by inhalation challenge with a very low dose of GMP-grade endotoxin, if the lung deposition rate is substantially increased by applying a newly developed inhalation method.

In the second part of this research project, the new method proved to be reproducible and thus suitable for use as a model in drug development. In the last project part, the scientists explored whether roflumilast, an agent recently approved for COPD treatment, can diminish the endotoxin-induced inflammation (5-day treatment) and could thus be used as positive control in future studies. Although this relatively short treatment duration did lead to an alteration in certain surface markers on inflammatory cells, it did not quantitatively inhibit the influx of these cells into the airways.

In summary, another specific challenge method for proof-of-concept studies has been established in this research project. Since both the challenge and analysis of the airway inflammation are performed without bronchoscopy, this novel method



Microscopic image of sputum cells: The displayed cells are mostly large and small macrophages, besides two neutrophils (NG).

reduces invasive intervention for study subjects. In addition, this study has shown that short-term treatment with roflumilast, in contrast to the effects observed in studies with experimental animals, is not suitable for use as positive control in endotoxin challenge studies.

Methods

Twelve healthy volunteers (non-smokers, mean age 38 ± 11 years, FEV_1 : 104.2 ± 7.3 percent pred.) each inhaled a very low dose of $2 \mu\text{g}$ endotoxin (LPS). A novel inhalation method

was used for this, precisely controlling the flow rate during the inhalation and the inhaled volume, so as to increase the deposition rate. Six hours after LPS challenge, sputum was induced and the cellular composition was compared with baseline values (measured during a screening visit 2 to 4 weeks prior to the first LPS challenge). Blood specimens were taken before and after the challenge and lung function was monitored for a 24-hour period. Sputum was processed and analyzed according to standard protocols. In addition, specific immunological parameters were evaluated by flow cytometry.

Fig. 1: Left: Increase in the percentage of sputum neutrophils, monocytes, and small macrophages (cumulative inflammatory response) 6 hours after LPS challenge compared with baseline (BL). Right: Concentration of the inflammatory mediator myeloperoxidase (MPO) in sputum supernatant.

Data is displayed as mean, SEM (boxes), and SD (whiskers), for MPO of log-transformed values. Statistical analysis: repeated measures ANOVA, Newman-Keuls post-hoc test. *** $p < 0.001$ compared with BL (LPS1: first LPS challenge; LPS2: second LPS challenge 4 weeks after LPS1; LPSTx: third LPS challenge 4 weeks after LPS2 and after 5 days of treatment with roflumilast at $500 \mu\text{g}/\text{day}$).

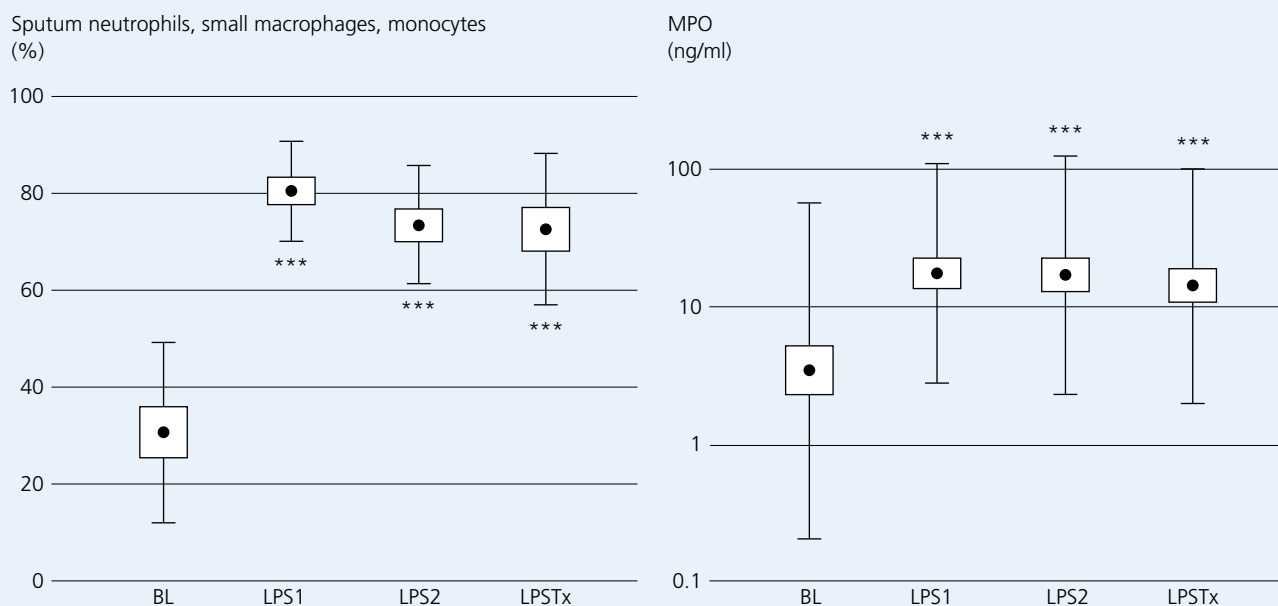
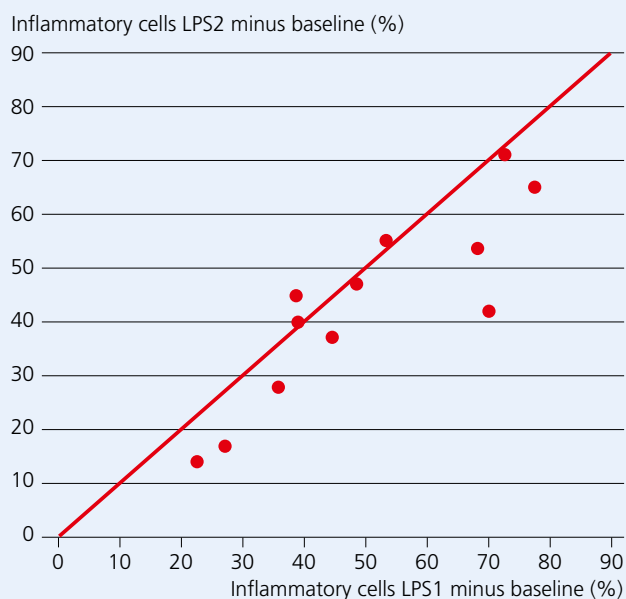


Fig. 2: Reproducibility of the cumulative inflammatory response to LPS.

The figure shows the correlation between the increase (= values after LPS challenge minus baseline value) after the first and the second LPS challenges and the "line of identity", on which the dots should lie ideally.



Results

The low-dose LPS challenge was well tolerated by the test subjects. A slight impairment of lung function was observed only within the first hour after the LPS challenge (on average by less than 5 percent). Compared with baseline values, the leucocyte count increased on average from 4.4 to $9.5 \times 10^9/\text{ml}$ blood. The proportion of specific inflammatory cells (neutrophils) in blood rose from 54.1 percent to 74.1 percent after inhalation of LPS. The effects were temporary and blood test results on the mornings before the LPS challenges did not differ from the baseline values measured at the beginning of the study.

With the optimized inhalation method, even the very low LPS dose was able to induce a substantial increase in the percentage of inflammatory cells and of specific mediators in induced sputum (Fig. 1). The increase in the cell count was slightly less pronounced after the second LPS challenge and furthermore showed a minor shift in the ratio of monocytes to small macrophages and neutrophils. Reproducibility was good for the increase in neutrophils alone and for the cumulative increase in inflammatory cells after LPS inhalation compared with baseline values (Fig. 2).

Five-day treatment with roflumilast, which had led to a reduction of the inflammatory response in previous animal experiments under comparable conditions and in man after longer-term treatment, did not diminish the influx of inflammatory cells into the airways. Only expression of certain surface markers on sputum macrophages was upregulated. This unexpected finding requires further investigation, but homogeneity of this response in all study subjects at least is a good indicator that the medication was actually taken as planned.

In a follow-up examination 57 to 156 days after the last LPS challenge, the percentage of neutrophils in sputum was still slightly increased compared with the baseline value. The most likely cause of this finding is a seasonal effect, since the first baseline measurement was performed in summer and the second one in winter.

Conclusions

A novel challenge method with little invasive intervention that can be used in proof-of-concept studies in early-phase clinical development of anti-inflammatory drugs for COPD treatment was established in this study. The improved inhalation method is suitable for use with GMP-grade LPS and in spite of a very low LPS dose induces a reproducible influx of inflammatory cells into the airways.

Reference

Janssen, O.; Schaumann, F.; Holz, O.; Lavae-Mokhtari, B.; Welker, L.; Winkler, C.; Biller, H.; Krug, N.; Hohlfeld, J. M. (submitted in 2012)

Low-dose endotoxin inhalation in healthy volunteers – a challenge model for early clinical drug development.



CONTACT

Dr. Olaf Holz
Phone +49 511 5350-245
olaf.holz@item.fraunhofer.de

Preliminary research

PROGNOSTIC VALUE OF MARKERS FROM SERUM AND LUNG IN SMOKERS WITH AND WITHOUT COPD

SUMMARY

Biomarkers can be helpful in diagnosing diseases and also in monitoring treatment response. In clinical trials, biomarkers can provide early indication of the efficacy of a novel medication. Fraunhofer ITEM scientists were interested to see whether different markers they had investigated in participants of a COPD study in 2006 and 2007 could have a prognostic value with respect to the type and degree of clinical alterations. They were able to recruit a part of the former study participants for a comprehensive clinical follow-up examination in 2012. For some markers they found quite a close correlation with the clinical course of the disease over the past five years. To determine the validity of the obtained data, however, these results will have to be verified in a larger, independent patient cohort.

In the years 2006 and 2007, scientists of the Fraunhofer ITEM Department of Clinical Airway Research conducted a study in 24 smokers with and 23 smokers without COPD (grade GOLD II), involving repeated collection of serum, sputum, and bronchoalveolar lavage (BAL) fluid and analysis of over 100 different markers in these different lung compartments. In 2012, they were able to recruit 14 of the smokers with COPD (= 58 percent) and 11 of the previously healthy smokers (= 48 percent) for a clinical follow-up examination. The aim was to find out whether the investigated markers have a prognostic value with respect to the type and degree of clinical alterations.

The study participants underwent thorough clinical examination and lung function testing prior to and after broncholysis, that is, the opening of constricted airways by administration of appropriate bronchodilators. The scientists collected blood samples and determined urine cotinine levels. Given that cotinine is the main metabolite of nicotine and thus a specific marker of nicotine uptake, this measurement objectively reflects the recent smoking behavior. In addition, study participants were asked to complete a specifically designed questionnaire to evaluate changes in their clinical status. The scientists included only those markers in the subsequent data analysis that had proven reproducible in repeated samples in the studies performed in 2006 und 2007: 10 BAL, 10 sputum, 24 serum,



and 23 whole-blood markers (Röpcke et al., 2012). Correlation analyses were performed for all test subjects together and for both groups separately. Multiple testing was taken into account and only correlations with $p < 0.01$ were considered significant.

The mean smoking behavior (that is, the number of cigarettes smoked per day) did not significantly differ from the data recorded in the years 2006 and 2007; cotinine levels at both measurement time points were highly correlated ($r = 0.79$; $p < 0.001$). In the smokers with COPD, lung function (FEV₁ percent of normal) had deteriorated on average by 16.1 percent, in the formerly healthy smokers this decrease was only 5.4 percent.

The results of the questionnaire were in agreement with these findings. Five of the smokers with COPD had progressed to COPD grade GOLD III and one patient even to GOLD IV. Two formerly healthy smokers displayed initial signs of COPD during the 2012 examination, with an FEV₁/FVC ratio of less than 70 percent. When analyzing both groups together, correlations between the clinical deterioration (changes in the FEV₁/FVC ratio) and some inflammatory markers in serum and sputum were observed. The blood monocyte count had been elevated in both groups already in 2006 and 2007, and the clinical deterioration over the past five years was more severe in those smokers where the blood monocyte count had been high during the first examinations (2006/2007).

Despite the relatively small number of study participants, the scientists were able to identify in this follow-up study certain correlations between the degree of clinical alterations and markers that had been investigated in different COPD-relevant lung compartments in the years 2006 and 2007. These data provide first indications of a potential prognostic value of

these markers. In the future, the Fraunhofer scientists will try to verify their findings in larger patient cohorts – an undertaking that could be managed in cooperation with one of the partner sites of the German Center for Lung Research (DZL).

Reference

Röpcke, S.; Holz, O.; Lauer, G.; Müller, M.; Rittinghausen, S.; Ernst, P.; Lahu, G.; Elmlinger, N.; Krug, N.; Hohlfeld, J. M. (2012)

Repeatability of and relationship between potential COPD biomarkers in bronchoalveolar lavage, bronchial biopsies, serum, and induced sputum.

In: PLoS One 7 (10): e46207, 11 p.

doi: 10.1371/journal.pone.0046207



CONTACT

Dr. Olaf Holz

Phone +49 511 5350-245

olaf.holz@item.fraunhofer.de



Preliminary research

MANUFACTURING LICENSE FOR OZONE AS A CHALLENGE SUBSTANCE

SUMMARY

For clinical trials with new drugs against chronic obstructive pulmonary disease (COPD) Fraunhofer ITEM scientists have developed a model that uses ozone as challenge substance. In summer 2012, they received a manufacturing license for ozone, as required by the German Drug Act. A clinical trial to test a novel anti-inflammatory drug against COPD was started already in summer 2012.

Ozone inhalation can be used to induce temporary inflammation of the airways in healthy study participants. The ozone-induced inflammation resembles the one seen in chronic obstructive pulmonary disease (COPD), with similar inflammatory cells and mediators of inflammation. Investigators in the institute's Department of Clinical Airway Research are using this disease model for efficacy testing of novel medications in clinical trials. Utilization of this model has the advantage that it

allows the efficacy of a new drug to be verified under controlled conditions already in the early stages of clinical development.

Since the last amendment of the German Drug Act, a manufacturing license must be applied for, if ozone is to be produced as a challenge substance. This application requires comprehensive validation processes and seamless definition of all manufacturing steps to prove beyond doubt that the ozone generation process complies with all technical standards and is safe for study participants at any time. Thanks to close cooperation with Fraunhofer ITEM aerosol physicists and quality assurance staff, this manufacturing license could be obtained within a very short time.

As a result, a clinical trial to test a novel anti-inflammatory drug could be started in the ozone challenge chamber already in summer 2012.



CONTACT

Dr. Heike Biller
Phone +49 511 5350-623
heike.biller@item.fraunhofer.de

Smoking is the number one cause of COPD – between five and ten percent of the adult population over 40 in Germany are estimated to suffer from COPD. Despite intense research, COPD still cannot be cured today.

Business unit 2

PROJECT OVERVIEW

Safety and efficacy testing of anti-inflammatory compounds and immunotherapy in patients with allergic rhinitis using the Fraunhofer Environmental Challenge Chamber

Safety and efficacy testing of inhaled bronchodilators in patients with chronic obstructive pulmonary disease

Characterization of exhaled particles in patients with asthma and chronic obstructive pulmonary disease

Bronchoscopic sampling of airway inflammatory cells in patients with asthma

Monitoring of pulmonary inflammation after segmental allergen challenge by using magnetic resonance imaging

Efficacy of an anti-inflammatory compound in patients with asthma

Further development of a system for aerosolization and controlled administration of lung surfactant by inhalation

Development and validation of a universal method for challenging volunteers with inhaled environmental and indoor allergens

Study on the effect of grass pollen to induce skin lesions in patients with atopic dermatitis

Study on non-coding RNA as a biomarker in patients with chronic obstructive pulmonary disease

Establishment of low-dose inhalation challenge with endotoxin as a model for drug testing

Safety and efficacy testing of an anti-inflammatory compound in healthy subjects following ozone challenge

Safety and tolerability of an inhaled anti-inflammatory agent in allergic asthma

Bronchoscopic sampling of airway biopsies to assess the efficacy of an anti-inflammatory compound in patients with chronic obstructive pulmonary disease

BUSINESS UNIT 3

OCCUPATIONAL AND ENVIRONMENTAL TOXICOLOGY AND CONSUMER PROTECTION





Project reports

Carbon nanotubes – approaches for adequate in-vitro and in-vivo toxicity testing

The “SteriHealth” project – for better hygiene in the medical area

Do extremely low-frequency magnetic fields influence juvenile brain development and behavior?

Bioavailability investigation of the food contaminant 3-MCPD ester

DevTox: Further scientific development of the project now complete

Aerosol emission from water-saving showerheads and faucets

Project overview

OCCUPATIONAL AND ENVIRONMENTAL TOXICOLOGY AND CONSUMER PROTECTION

The business unit Occupational and Environmental Toxicology and Consumer Protection is engaged in the investigation of chemicals, particles (including nanoparticles), and complex mixtures as they occur at workplaces, in the environment, and in consumer products. Profound knowledge in inhalation toxicology, aerosol process technology, chemical analysis, and toxicological pathology are the hallmarks distinguishing this business unit. The required studies are undertaken at the Fraunhofer ITEM in accordance with national and international guidelines and complying with the principles of Good Laboratory Practice (GLP).

To register a substance, numerous legal regulations controlling the introduction of new products and re-investigation of existing substances need to be taken into account. In many cases, new products and production technologies have to be subjected to evaluation, and indoor air pollution in general has to be assessed. In this context, the development of new techniques for measuring airborne pollutants and

their source strengths represents another focus of research. Physico-chemical and biological models help determine active substances and their release from building materials, furniture, interior decoration, and from consumer products. In addition, the Fraunhofer ITEM develops mathematical simulation models for exposure assessment.

Immunology studies are conducted to investigate sensitizing and immunomodulating effects. Furthermore, potential irritant effects of chemicals and environmental pollutants on the airways are detected by means of different validated in-vitro and, if need be, animal models. A wide scope of in-vitro testing methods is available for use as screening methods and for assessing the genotoxic potential, allowing the number of necessary animal experiments to be reduced. In the Environmental Challenge Chambers of the institute's clinical unit, studies with volunteers are performed to investigate specific aspects of environmental and occupational toxicology.

CONTACTS



Prof. Dr. Clemens Dasenbrock
Phone +49 511 5350-408
clemens.dasenbrock@
item.fraunhofer.de



Prof. Dr. Wolfgang Koch
Phone +49 511 5350-117
wolfgang.koch@item.fraunhofer.de

Project report

CARBON NANOTUBES – APPROACHES FOR ADEQUATE IN-VITRO AND IN-VIVO TOXICITY TESTING

SUMMARY

Carbon nanotubes (CNT) have become important constituents of materials used in the electronic, automotive, and aircraft industries and are being marketed at still increasing high volumes. Because of their large length-to-diameter aspect ratio, there is concern that CNT may induce fiber-specific toxic effects. Therefore, adequate experimental tools are needed to screen the toxicity of different kinds of new CNT. With many years of experience in studies on fibers and particles, the Fraunhofer ITEM scientists are in good shape to take on this challenge.

To set the stage for the development of adequate test methods for toxicity screening of different types of CNT, Fraunhofer ITEM scientists first performed physico-chemical characterization of the CNT test items, including length/diameter distribution measurements and determination of purity and dissolution behavior of residual metal catalyst.

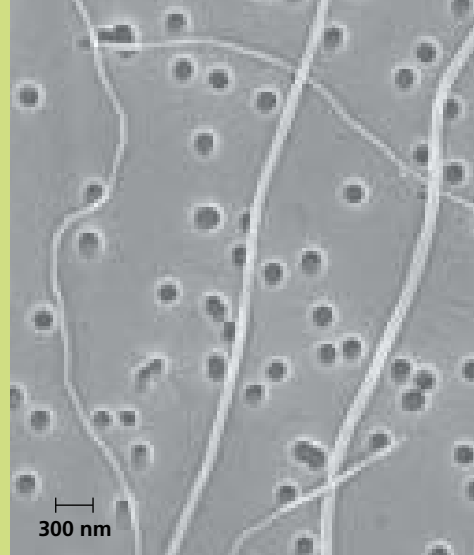
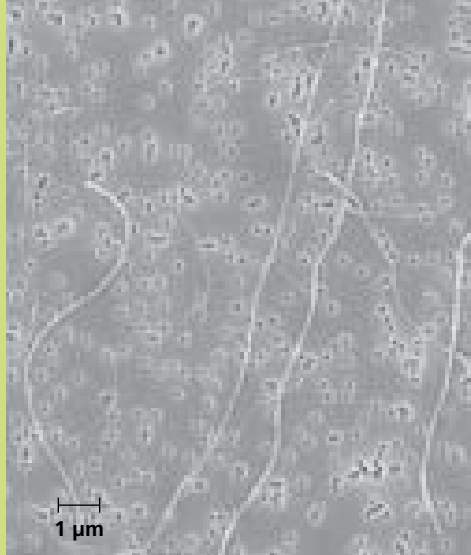
Appropriate CNT suspensions for in-vitro testing

For in vitro testing, a proper suspension of CNT in biocompatible media is crucial. Wide experience in optimization of media composition and in mechanical and ultrasonic suspension techniques allows the ITEM scientists to achieve satisfactory results. In addition, selection of cell lines representative for the respiratory tract (epithelial, mesothelial cell lines) is important to obtain results with predictive value for the in-vivo situation. Endpoints of assays include cytotoxicity and genotoxicity (Comet assay, micronucleus test).

CNT aerosolization with strongly reduced agglomeration in in-vivo tests

In-vivo testing requires effective aerosolization of CNT, which typically tend to build strong agglomerates. To assure respirability of CNT in inhalation tests with rats, two different approaches are the preferred methods for acute and subacute/subchronic testing.

There is concern that carbon nanotubes, visualized by electron microscopy here, may induce fiber-specific toxic effects.



For acute inhalation tests (single 4-hour nose-only exposure), CNT are suspended homogeneously in liquid formulations that can subsequently be nebulized to result in respirable aerosols. Maximum aerosol concentrations in the range of 40 mg/m³ can be achieved with this technique. This method was also used in a biokinetics study with radioactively tagged CNT (⁶⁰Co gamma-tag of the catalyst cobalt). For this type of study it is important to achieve a deposited dose that is as high as possible.

For subacute and subchronic inhalation tests (28-day and 3-month nose-only exposure, respectively), an effective dry aerosolization of CNT with an acoustic feeder system (adaptation and optimization of a system developed by NIOSH, USA) has been established at the Fraunhofer ITEM. A membrane vibrating with high frequency generates atmospheres with highly deagglomerated CNT directly from the bulk material. Depending on the CNT type, deagglomeration can be supported by beads in the aerosol generator. Functionality of this system has been well confirmed in a 3-month inhalation study with various specially designed experimental CNT (exposure completed, endpoint evaluation still ongoing).

Currently, a chronic study with these CNT is also being performed. In this study, the carcinogenic potential of the experimental CNT is being investigated using the lifetime intraperitoneal injection test in rats.

Taking into account CNT-specific characteristics

For CNT registration, OECD guidelines 412 and 413 for toxicological testing can be slightly modified to take into account CNT-specific characteristics. More sophisticated study protocols addressing the potential fiber-specific toxicity of CNT should include the following endpoints:

- Persistence of CNT in lungs; analysis of CNT translocation from lungs to pleura.
- Investigation of the proliferative, genotoxic, and carcinogenic potentials of CNT.
- Establishment of in-vitro assays that can reliably predict a biological effect in vivo.

At the Fraunhofer ITEM, all these methods are available and have been successfully applied in studies performed for industrial and public sponsors.



CONTACTS

Dr. Bernd Bellmann
Phone +49 511 5350-452
bernd.bellmann@item.fraunhofer.de



Dr. Otto Creutzenberg
Phone +49 511 5350-461
otto.creutzenberg@item.fraunhofer.de

Project report

THE “STERIHEALTH” PROJECT – FOR BETTER HYGIENE IN THE MEDICAL AREA

SUMMARY

Poor hygiene, dirty surgical instruments, hospital germs – there are more and more reports on infections acquired in medical environments, and the consequences for patients are in some cases severe. The demands on new sterilization technologies are that they should be affordable and allow on-site use, and that they should lower the risk of infection in hospitals, doctor's offices, and rest homes. Fraunhofer researchers in six institutes are working together on solutions in the “SteriHealth” project. At present, a mini-sterilizer for gentle yet highly effective sterilization of medical products is being developed. The Fraunhofer ITEM is contributing above all by developing a monitoring process to verify the sterilization efficacy of this novel device.

According to the German Society for Hospital Hygiene, more than 800,000 people get infected with germs in German hospitals each year, and up to 40,000 of these patients die from the consequences of sepsis. Related secondary infections are causing annual costs of up to 7 billion euros. This shows that the existing hygiene measures have to be optimized.

New sterilization technologies would be of great value in particular for use immediately before surgery. Surgeons use complex instruments and equipment that are difficult to sterilize with the methods commonly used today, that is, sterilization by superheated steam, ethylene oxide, or gamma radiation. This is due to the complex geometry of such equipment – disinfectants do not penetrate into the openings, slits, and corners – and to the use of sensitive materials, integrated electronics and sensors. In addition, even the state-of-the-art sterilization methods established in today's clinical practice do not offer the possibility to perform sterilization directly in the patient's environment. This would be an important measure though, for example, to minimize the risk of infection in the operating room whenever an implant first has to be customized and then directly inserted into the body – given the fact that complications in most cases result from bacterial infections.

Scientists of the Fraunhofer institutes IBMT, ITEM, IZI, FEP, IVV, and IZFP have now joined forces to develop an effective hygiene assurance process aimed at allowing sterile packaged medical products to be made available in hospitals, doctor's offices,



The mini-sterilizer could be used in operating rooms: The new technology is aimed at enabling fast and effective sterilization of medical products on site, for example, immediately before inserting an implant.

and in geriatric care. Sterilization – inexpensive and on site – should be possible for all medical materials, including packaging, transport, storage, and ultimate use.

With their pooled competencies, the cooperating scientists are now developing a mini-sterilizer and are testing novel gentle yet highly effective technologies (such as electron beam) for sterilizing different materials. In addition, they are developing intelligent packaging concepts and verify product safety after completion of the sterilization treatment.

In the “SteriHealth” project, the Fraunhofer ITEM is working primarily on the development of a monitoring process to verify sterilization efficacy. To this end, different materials are first covered with a broad spectrum of test germs. The sterilization efficacy is then tested to evaluate the sterilization parameters and influencing factors to be monitored. The aim is to verify whether the sterilization method effectively reduces the germ load, as this is decisive for the acceptance of the novel sterilization method. The next steps in the project will be to systematically use the sterilization method for relevant medical products and verify the sterilization efficacy achieved with the mini-sterilizer.

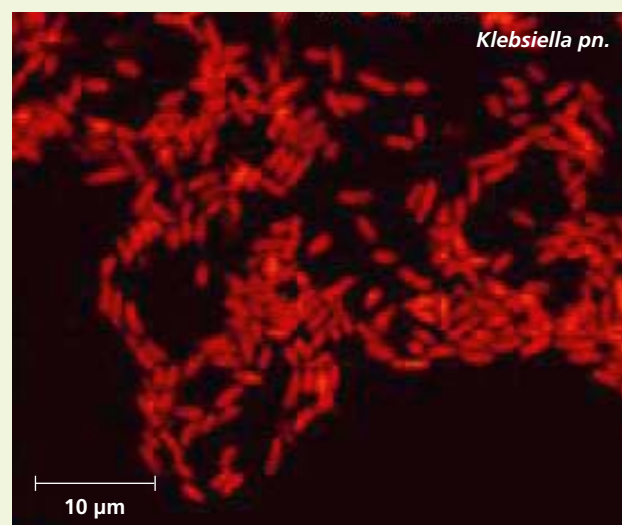
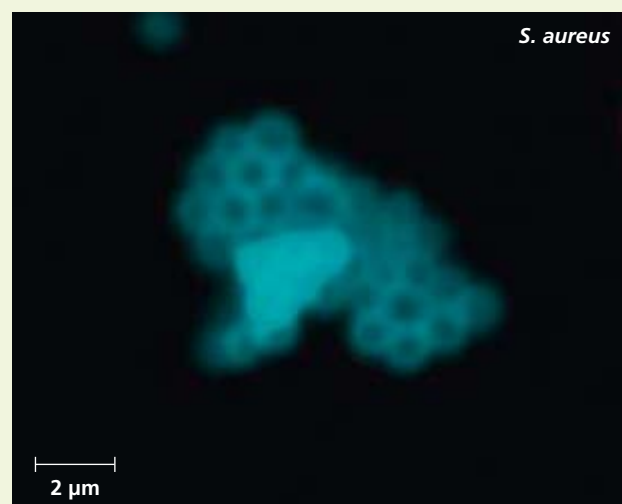
The “SteriHealth” project is part of the Fraunhofer research program “Markets beyond tomorrow” and will be funded by the Fraunhofer-Gesellschaft for three years with a budget of 4.5 million euros.



CONTACT

Dr. Meike Müller
Phone +49 511 5350-262
meike.mueller@item.fraunhofer.de

Fluorescent staining of test germs: The sterilization efficacy of the new technology is being tested with a large variety of test germs, including reference germs and highly relevant pathogens such as *Staphylococcus aureus* (top) and *Klebsiella pneumoniae* (bottom).



Project report

DO EXTREMELY LOW-FREQUENCY MAGNETIC FIELDS INFLUENCE JUVENILE BRAIN DEVELOPMENT AND BEHAVIOR?

SUMMARY

Low-frequency electromagnetic fields are ubiquitous in modern society – they are generated by electrical appliances, electric conductors, and high-voltage power lines. Results from epidemiological studies suggest that such fields might have an impact on the development of different organ systems. It could also be that they increase susceptibility to childhood leukemia. No animal experimental studies have so far been available to support these suggestions. On behalf of the German Federal Office for Radiation Protection, the Fraunhofer ITEM has therefore investigated the influence of low-frequency electromagnetic fields on the developing hematopoietic system, immune system, and central nervous system in a study with juvenile animals. This report presents first results from the study part investigating the effects on the central nervous system.

Modern society's constant exposure to low-frequency electromagnetic fields, generated for example by electric conductors and appliances in household surroundings and also by high-voltage power lines, has been a matter of constant debate, as epidemiological and animal experimental data on exposure risks are not consistent. It was the aim of the animal experimental study "Influence of low frequency electromagnetic fields on the developing hematopoietic system, immune system and CNS in vivo", performed on behalf of the German Federal Office for Radiation Protection, to elucidate whether such fields can affect healthy childhood development.

To allow the results of this study to be eventually extrapolated to the developing human organism, Fraunhofer ITEM scientists developed a special animal model with juvenile animals and a novel exposure setup.

Study design

Time-mated CD-1 mice were continuously exposed to 50-Hz sinusoidal magnetic fields for 20 hours per day, starting prenatally on gestational day 10. The field strengths for the exposure – 10 microtesla (μT), 1 mT, and 10 mT – were chosen such that the current densities in the animal bodies resembled those induced in humans exposed to magnetic flux densities of 1, 100, and 1000 μT .



Two additional control groups were included in the experiments: a cage control group and a sham-exposure group. Temperature, relative humidity, vibration and noise levels – typical stress factors in technical surroundings and possibly influencing the test results – were controlled and did not differ between the experimental groups. Litters were raised by their mothers and weaned on day 21 after birth, and the young animals were group-housed afterwards.

Clinical observations were performed daily and bodyweight was measured on days 4, 7, 10, 14, 17, and 21 after birth and weekly afterwards up to day 90 – an age corresponding to that of young adults in humans. To assess the animals' ability to coordinate body movement and muscle function, the development of reflexes was tested on days 1-3 after birth for surface righting and on days 10-12 for negative geotaxis. The spontaneous locomotor activity and functional observational battery (FOB) were tested on days 20, 30, and 60. The FOB is used to assess a multitude of physiological parameters, including body temperature, muscle strength, muscle coordination, and spatial orientation. For testing auditory function and the ability to process sensory data and to test certain aspects of memory, the auditory startle reflex with habituation and pre-pulse inhibition was assessed on days 20 and 60. Vaginal opening and the corresponding bodyweight as indicators of sexual maturation were examined on days 22-30. All data were tested for statistical significance ($p < 0.05$), and ANOVA and Dunnett's test or Chi-square testing were performed depending on data type.

Results

The exposure did not affect maternal clinical findings during pregnancy and lactation, bodyweight, or delivery data. Pre- and postnatal mortality in the offspring was low and did not

differ between exposure and control groups. Pup bodyweight development did not differ between the animals of the sham and field exposure groups. No differences were observed in the development of reflexes and in the behavioral tests. Neither was the activity of the young animals changed, nor any other physiological parameter or their cerebral handling of sensory data. There were also no dose-related differences in animal age at sexual maturation.

The presented data do not imply any detrimental effect of extremely low-frequency magnetic fields on reproductive performance, postnatal survival, reflex and behavioral development, or any teratogenic effects. The results of the study part investigating potential effects on the immune system and the development of other organ systems are still under analysis.



CONTACT

Dr. Geertje Lewin
Phone +49 511 5350-453
geertje.lewin@item.fraunhofer.de

Project report

BIOAVAILABILITY INVESTIGATION OF THE FOOD CONTAMINANT 3-MCPD ESTER

SUMMARY

Ester-bound 3-monochloropropanediol (3-MCPD) has long been known to be a potentially hazardous contaminant in a variety of foods, in refined vegetable oil and fat in particular. To improve assessment of the risks of this compound to human health, the Fraunhofer ITEM conducted an animal study on behalf of consumer protection agencies. The aims were to determine to what extent 3-MCPD fatty acid esters are hydrolysed to 3-MCPD in the gastrointestinal tract after oral ingestion and to obtain data on absorption and distribution in organs.

The Annual Report 2011 already included a project report on the development and validation of chemical analytical methods that allow both free and bound 3-monochloropropanediol (3-MCPD) to be determined in different biological matrices by the institute's Working Group on Bio- and Environmental Analytics. The aim of the study described here was to obtain hitherto missing data on the hydrolysis of 3-MCPD fatty acid esters in the gastrointestinal tract and on their absorption and distribution in the organism. In scientific consultation with the Federal Institute for Risk Assessment, the German Federal Ministry of Food, Agriculture and Consumer Protection commissioned this study to the Fraunhofer ITEM.

The study was performed in Wistar rats that received single oral doses of 3-MCPD diester (1,2-dipalmitoyl-3-chloro-1,2-propanediol; 53.2 mg/kg body weight) or 3-MCPD (10 mg/kg body weight, equimolar dosage). At predefined time points, concentrations of free 3-MCPD and 3-MCPD ester in blood, urine, organs, and intestinal contents were determined by chemical analyses.

Fast absorption of 3-MCPD

Bioavailability of 3-MCPD in blood was similar after oral ingestion of 3-MCPD ester and of free 3-MCPD. The ITEM scientists found comparable AUC_{24} values – as a measure of bioavailability – of 7760 and 9030 ng × h/ml, respectively. Administration of 3-MCPD ester resulted in a value that was 86 percent of the value measured after administration of the free compound. However, maximal concentrations of 3-MCPD in blood



and the corresponding time points differed considerably (C_{max} 949 ng/ml, t_{max} 3.01 hours after administration of 3-MCPD ester, and C_{max} 4850 ng/ml, t_{max} 0.37 hours after administration of 3-MCPD). These results suggest fast absorption of 3-MCPD into the bloodstream after oral ingestion of free 3-MCPD. In contrast, after administration of 3-MCPD ester, absorption is delayed due to intestinal ester hydrolysis, resulting in a later and smaller increase in the 3-MCPD blood level.

Further measurements showed that during the time period 3-6 hours after administration of 3-MCPD ester, there were maximally between 8 and 10 percent of free 3-MCPD in intestinal

contents (in relation to the administered dose) and 33-72 percent of the administered 3-MCPD ester itself. Figure 1 gives a graphical representation of the time course of intestinal ester hydrolysis. No ester was detected in liver and kidneys, but free 3-MCPD was found there. In relation to the administered dose, however, the measured values were very low (below 0.25 percent).

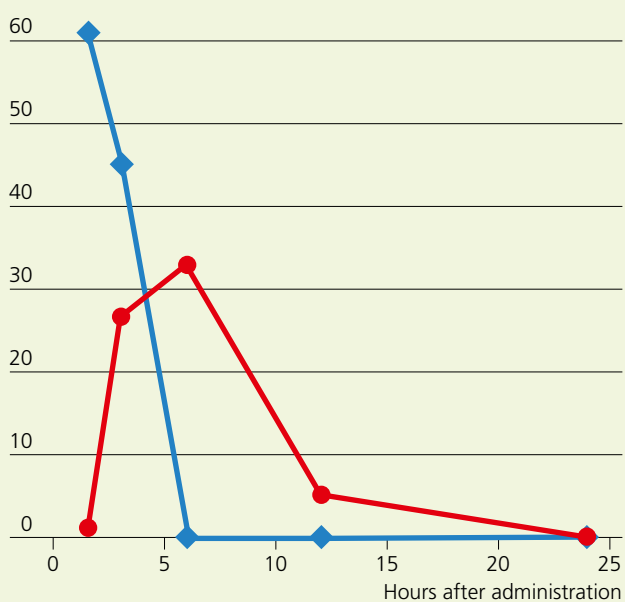
In the animals that had received free 3-MCPD, the highest 3-MCPD levels in intestinal contents and organs were observed already during the first hour after ingestion and thus considerably earlier than after administration of 3-MCPD ester. In total, maximally 8-10 percent of the administered dose were detected as 3-MCPD in the organism.

In addition, urine and feces samples from the experimental animals were analyzed: 3-MCPD levels in urine were 2 percent with both test substances, and about 1 percent in feces.

Fig. 1: Time course of 3-MCPD ester hydrolysis in the rat intestinal tract.

Blue curve: small intestine; red curve: colon.

Percent of administered dose
70



Experimental evidence of 3-MCPD ester hydrolysis in the organism

This study has demonstrated that the administered 3-MCPD ester is subject to hydrolysis in the rat organism and that the resulting free 3-MCPD is quickly absorbed and metabolized. Supported by these new findings, the hazard potential associated with oral ingestion of these contaminants via food can now be better assessed.



CONTACT

Dr. Edith Berger-Preiß
Phone +49 511 5350-213
edith.berger-preiss@item.fraunhofer.de

Project report

DEVTOX: FURTHER SCIENTIFIC DEVELOPMENT OF THE PROJECT NOW COMPLETE

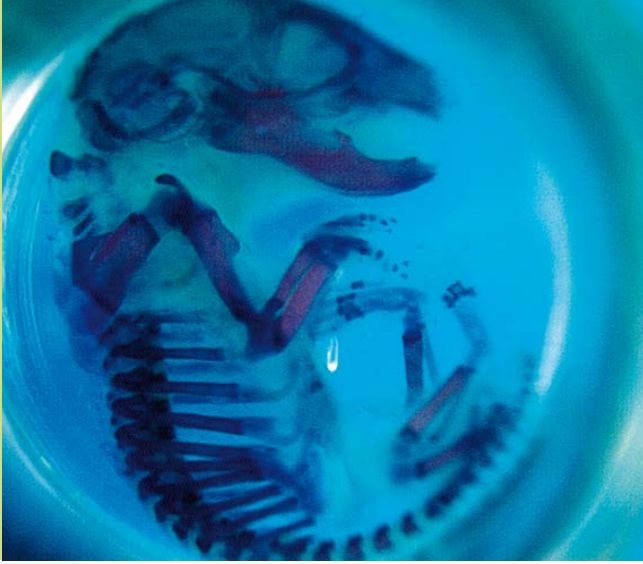
SUMMARY

DevTox is a project initiated 10 years ago by the German Federal Institute for Risk Assessment with the aim to support industry, authorities, and research institutions in the evaluation of developmental toxicological studies. Scientists, some of them from the Fraunhofer ITEM, have set up the DevTox Web site, which provides a lexicon of internationally harmonized definitions and terms for abnormalities found in developmental toxicity studies and a corresponding image database. Further development of the project was completed in 2012. As a result, the database now contains a total of 1742 diagnoses.

Under the name DevTox, the German Federal Institute for Risk Assessment 10 years ago initiated a project aimed at supporting industry, authorities, and research institutions in the evaluation of developmental toxicity studies on pesticides, biocides, and other chemical materials and products. Scientists of the Fraunhofer ITEM and of the Institute for Clinical Pharmacology and Toxicology at Charité Berlin joined forces to set up the DevTox Web site, which provides a lexicon of internationally harmonized definitions and terms for abnormalities found in developmental toxicity studies and a corresponding image database.

In 2012, further scientific development of the project was completed. Most notably, the scientists adjusted the DevTox nomenclature to the Terminology of Developmental Abnormalities in Common Laboratory Mammals published in 2009 (former IFTS terminology) and incorporated the new internationally harmonized definitions and terms for abnormalities found in developmental toxicity studies (Makris et al., 2009) into the computerized database. In addition, they enhanced the existing terminology by introducing a new category of findings, called “maternal-fetal abnormalities”, which includes not only placental findings, but also abnormalities in other structures such as the amnion.

Previously, diagnostic images had been mainly of fetuses. They have been systematically complemented with diagnostic images of juvenile and adult animals. These allow conclusions to be drawn about potential remission or persistence of structural



abnormalities after birth, an important aspect in the assessment of postnatal consequences. Due to this enhancement, the DevTox Web site is now a lot more functional.

Very importantly, the scientists have now also incorporated findings and corresponding images for which previously there was no internationally harmonized terminology available. These include, for example, diagnostic images of abnormalities observed in developmental toxicity studies in common marmoset monkeys (*Callithrix jacchus*). For primate-specific findings, appropriate internationally harmonized terms need to be defined yet. Furthermore, diagnostic images and corresponding terminology of abnormalities observed in studies with Japanese quail (*Coturnix coturnix japonica*) have been included.

The scientists have redesigned and systematically enhanced the structure of the Web site according to the project structure, to enable inclusion of new diagnostic images and to make use of the possibility offered by the Web site to classify novel findings into malformations and variations.

The existing database structures for prenatal anomalies (that is, findings observed pre-partum) have been systematically enhanced so as to further improve the technical possibilities for presenting possible postnatal manifestations of abnormalities (that is, findings observed post-partum). Such postnatal findings thus can now also be entered on the Web site. Furthermore, images reflecting postnatal normogenesis of rats and further images explaining special features of the avian skeleton have been added.

In the course of the Web site redesign, the number of diagnoses could be increased by 912 to a total of 1742. To guarantee that DevTox can continue to provide optimal assistance to scientists and authorities, continual updates are necessary. Important issues that will be discussed by experts in the near

future include the classification of a novel term as variation, malformation, or "grey zone anomaly" (that is, an abnormality that cannot be classified) and the assessment of complex abnormalities. In addition, it is planned to incorporate findings from studies in non-human primates (Solecki et al., 2010).

References

Solecki, R.; Heinrich, V.; Rauch, M.; Chahoud, I.; Grote, K.; Wöffel, B.; Buschmann, J.; Morawietz, G.; Kellner, R.; Lingk, W. (2010)

The DevTox Site: Harmonized Terminology and Database. In: Charlene A. McQueen, Comprehensive Toxicology 12: 339-346, Oxford: Academic Press.

Makris, S. L.; Solomon, H. M.; Clark, R.; Shiota, K.; Barbellion, S.; Buschmann, J.; Ema, M.; Fujiwara, M.; Grote, K.; Hazelden, K. P.; Hew, K. W.; Horimoto, M.; Ooshima, Y.; Parkinson, M. and Wise, L. D. (2009) Terminology of developmental abnormalities in common laboratory mammals (Version 2). Reproductive Toxicology 28: 371-434.



CONTACT

Dr. Jochen Buschmann
Phone +49 511 5350-462
jochen.buschmann@item.fraunhofer.de



Project report

AEROSOL EMISSION FROM WATER-SAVING SHOWERHEADS AND FAUCETS

SUMMARY

Aerosol technologists of the Fraunhofer ITEM have investigated whether or not water-saving showerheads and faucets are associated with an increased risk of inhaling legionellae that can be present in building water systems. The scientists first developed a detection and measurement method that allows them to measure the aerosol emission from showerheads and taps under common operating conditions. Risk assessment will follow.

The development trend for showerheads and faucets is more and more towards water-saving technologies. One method to reduce water consumption without sacrificing water pressure consists in aerating the water stream. It is generally assumed that this technology causes (or increases) release of inhalable droplets. As a result, experts are more and more discussing the role of this technology in the aerogenic spread of legionellae, which tend to colonize biofilms in building water systems, preferably at temperatures between 30 and 50 °C. To enable realistic assessment of the risk of inhaling legionellae via aerosols from showerheads and flow-restricted faucets, quantitative data about the aerosol production rate during operation of different showerheads and taps were collected at the Fraunhofer ITEM by using a specially developed detection and measurement method. The results showed substantial differences in droplet emission rates between different products, both for showerheads and for faucet flow regulators and aerators. The next step will be to perform a risk assessment in cooperation with water hygiene experts.



CONTACT

Prof. Dr. Wolfgang Koch
Phone +49 511 5350-117
wolfgang.koch@item.fraunhofer.de

Business unit 3

PROJECT OVERVIEW

General and reproductive toxicology

Impact of low-frequency electromagnetic fields on the developing hematopoietic system, the immune system, and the CNS in vivo

Inhalation toxicology

Size separation of fibers into respirable fractions

Studies on the in-vivo solubility of glass fiber dusts

Studies to assess lung toxicity of toner powders or toner additives

Study into the toxicokinetics of inhaled, poorly soluble nanoscale particles in rats

Dispersion and retention of dusts containing ultrafine primary particles in the lung

Comparative investigation of three nanoscale titanium dioxides with different surface characteristics in a 28-day inhalation study

Development of screening methods for detection of a possibly carcinogenic potential of carbon nanotubes

Toxicokinetics study in rats after inhalation exposure to carbon nanotubes

Lung toxicity testing of surface-active substances in the isolated perfused rat lung

Development of a rat lung lavage model for efficacy testing of surface-active substances

Genetic toxicology

Genotoxicological guideline studies as part of toxicological testing of chemicals, particles, and fibers

In-vitro and in-vivo investigations to determine potential genotoxic effects of electromagnetic fields in the radio-frequency spectrum

Comet assay-based evaluation of the genotoxic potential of SiO₂-containing high-temperature insulation wools

Studies on the in-vitro and in-vivo genotoxicity of novel pharmaceuticals

Studies on the in-vitro and in-vivo genotoxicity of SiO₂ nanoparticles

Establishment of mesothelial cell models, and establishment and optimization of in-vitro methods to evaluate the toxic and genotoxic potential of multi-walled carbon nanotubes

Establishment of conclusive gene expression markers for detection of quartz-dependent toxicity of ceramic raw materials

In-vitro and mechanistic toxicology

In-situ analysis of the cellular effects of airborne pollutants and active substances in vitro

Extended prevalidation of the Air/Liquid Interface (ALI) technology as a testing method for inhalable substances (gases) in a round-robin study with participation of governmental laboratories

OCCUPATIONAL AND ENVIRONMENTAL TOXICOLOGY AND CONSUMER PROTECTION

Generation of complex cell culture models for use in air/liquid interface-based tests

Studies to investigate the biological effects of inhaled substances in cells from the respiratory tract

Establishment of pathway-specific gene expression analyses in human lung epithelial cells

Studies on the mechanism of action of multi-walled carbon nanotubes in bronchial epithelial cells

Differentiated THP-1 cells as a model for nanoparticle testing

Toxicity screening tests with Carbon Black nanoparticles in human cell lines from different parts of the respiratory tract

Airway immunology

Evaluation of the toxicity of airborne pollutants in mouse, rat, non-human primate, and human precision-cut lung slices

Airway pharmacology

Lung function measurements in toxicological studies

Alarie test to evaluate the irritant potential of chemicals

Clinical chemistry and ADME

Hematological and clinico-chemical analyses in toxicological studies

Investigations on inflammatory parameters and oxidative stress in rat bronchoalveolar lavage fluid

Pathology

Analysis of the translocation of gold nanoparticles to the CNS by electron microscopy

Demonstration of inhaled or instilled nanoparticles in the respiratory tract by electron microscopy

Analysis of the translocation of fine and nanoscale titanium dioxide particles from the nose to the brain by electron microscopy

Impact of low-frequency electromagnetic fields on the developing hematopoietic system, the immune system, and the CNS in the mouse

Genotoxic mechanisms of action and histological effects of fine and ultrafine particulate matter in the lung

Histological, immunohistochemical, and morphometric evaluation of the effects of different types of fibers in peritoneal cells

Pathology database RITA (Registry of Industrial Toxicology Animal-data) in collaboration with the Working Group on Databases and Information Systems

Determination of cell proliferation in the respiratory tract after inhalation of different types of fibers

Cellular and subcellular effects in rat lung epithelial cells after inhalation of fine and nanoscale titanium dioxide particles

Aerosol technology

Development of a continuous procedure for the generation of calibration aerosols in the ultrafine particle size range

Characterization of the exposure resulting from the use of cosmetic sprays and surface treatment sprays

Design and construction of an aerosol generator for carbon nanotubes

Development and validation of a method to screen surface-active substances for lung toxicity

Studies on protective measures for first responders during radiological emergencies: resuspension of deposited radioactive contamination from surfaces

Supply of aerosol technological know-how and equipment for setting up and operating an aerosol chamber for microorganisms

Determination of airborne and respirable particle release during fragmentation of brittle materials

Measurement of respirable droplet release from showerheads and faucets with flow regulators and aerators

Studies on emissions from lithium-ion batteries under accident conditions

Bio- and environmental analytics

Chemical characterization of petroleum products (fuels and lubricants)

Characterization of the composition of biocidal products (substance mixtures)

Studies on formaldehyde release from formaldehyde depot substances

Development and validation of analytical methods for bio-monitoring of selected metabolites

Determination of hemoglobin adducts

Development of methods for non-target analysis of complex mixtures

Collateral analytical investigations in in-vitro exposure studies with gaseous substances

Chemical characterization of gases and aerosols at workplaces and in safety areas

Determination of toxic element concentrations in consumer products

Determination of elements in organs and body fluids in studies investigating the effects of nanoparticles

Databases and information systems

RITA – Registry of Industrial Toxicology Animal-data

CEPA – Cell Proliferation and Apoptosis

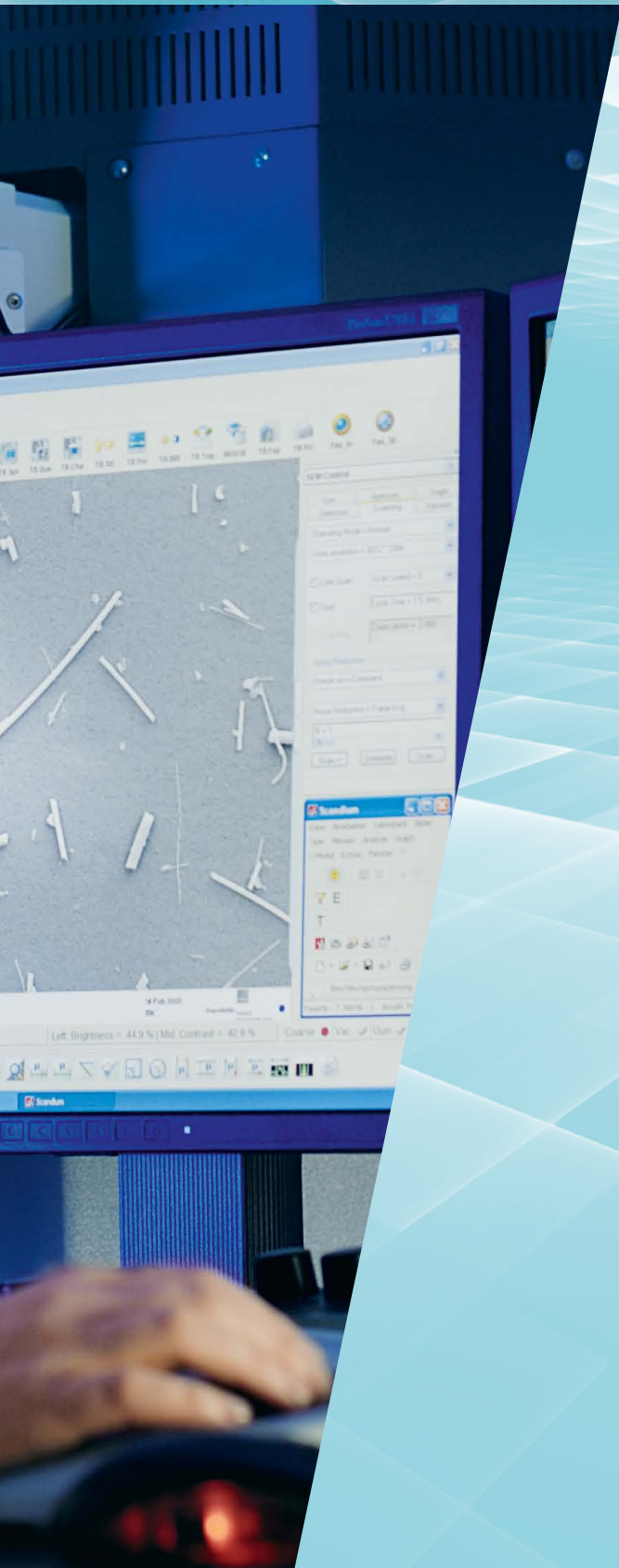
goRENI INHAND – International Harmonization of Nomenclature and Diagnostic criteria

Further scientific development of the project DevTox

BUSINESS UNIT 4

TESTING AND REGISTRATION OF CHEMICALS, BIOCIDES AND PESTICIDES





Project reports

New ways of deriving indoor air guideline values

PaFtox database facilitates toxicological assessment of nano-objects

Project overview

The business unit Testing and Registration of Chemicals, Biocides and Pesticides pools the institute's long-standing experience and comprehensive expertise in risk assessment, covering the fields of toxicology and ecotoxicology as well as assessment of the exposure and behavior in the environment.

Numerous substances for which data are already available require additional evaluations to allow risk assessment. In addition, the European chemicals policy REACH, which came into force in 2007, requires re-investigation of a large number of active substances that are already on the market. The scientists working in this business unit view and evaluate the existing data and will recommend additional tests for a substance whenever this seems necessary. To close existing data gaps, studies addressing the following endpoints are performed at the Fraunhofer ITEM: toxicokinetics, sensitization, immunotoxicity, subchronic and chronic toxicity, reproductive toxicity, teratogenicity, carcinogenicity, and mutagenicity. Investigations into the mechanisms of action of chemicals can also be conducted.

According to requirements, the Fraunhofer ITEM closely cooperates with different Fraunhofer institutes and other contract research institutions. All

data necessary for risk assessments as required by regulations (including physico-chemical properties and ecotoxicity) can thus be provided by a single source, and the overall assessment and registration dossiers can be prepared. All expert reports are created in accordance with high standards.

Legal requirements, in particular the criteria for risk assessments, are subject to constant changes. Through cooperation with national and international committees and authorities as well as participation in round-robin studies, the Fraunhofer ITEM takes part in the development of guidelines and can thus react immediately to changes – a benefit particularly for our clients. It is foreseeable that the demand for risk assessments and additional toxicological studies of chemicals will continue to increase. The assessment of substances falling under REACH is one of the challenges of the years to come. The expertise in this business unit, therefore, will continue to be further expanded.

A rapidly growing field of activity is the assessment of potential effects of nanoparticles. In this field, the Fraunhofer ITEM conducts experimental studies and develops concepts and databases for the assessment of substances in this size range.

CONTACTS



Dr. Inge Mangelsdorf
Phone +49 511 5350-303
inge.mangelsdorf@item.fraunhofer.de



Dr. Jochen Buschmann
Phone +49 511 5350-462
jochen.buschmann@item.fraunhofer.de

Project report

NEW WAYS OF DERIVING INDOOR AIR GUIDELINE VALUES

SUMMARY

Fraunhofer ITEM scientists are venturing on new paths of risk assessment, more precisely, in assessing the toxic effects of glycol ethers. Instead of assessing each glycol ether individually, they evaluated the whole category, derived a default value for insufficiently investigated glycol ethers, and took into account possible additive effects of different glycol ethers. The databases RepDose and FeDTeX, developed by the Fraunhofer scientists during previous years, proved to be useful tools for deriving threshold and guideline values in the context of risk assessment by means of substance categories.

Glycol ethers are chemical compounds that are manufactured at large quantities and are used in a large variety of application areas, above all as solvents in water-based paint. Their volatility is rather low, so that they may be detected in indoor air even years after paint has been applied. In the past, the commonly used ethylene glycol monomethyl ether (EGME) had been found to have reproduction toxicity and developmental toxicity potentials. As a result, it has been increasingly replaced by other glycol ethers. Some of these have been detected in indoor air, but whether or not they are associated with a similar range and strength of toxic effects is in many cases unknown.

People in central Europe spend most of their time indoors. To protect their health, the toxic potential of substances that are detectable in indoor air must be assessed. Guideline values are derived to this end. These are developed by the German Ad-hoc Working Group on Indoor Guidelines of the Indoor Air Hygiene Committee and of the Supreme State Health Authorities. Inge Mangelsdorf, head of the Fraunhofer ITEM Division of Chemical Risk Assessment, Databases and Expert Systems, is also a member of this working group. She and her team resolved to analyze and assess not every single glycol ether, but the whole substance category.



Glycol ethers are used as solvents in water-based paint.

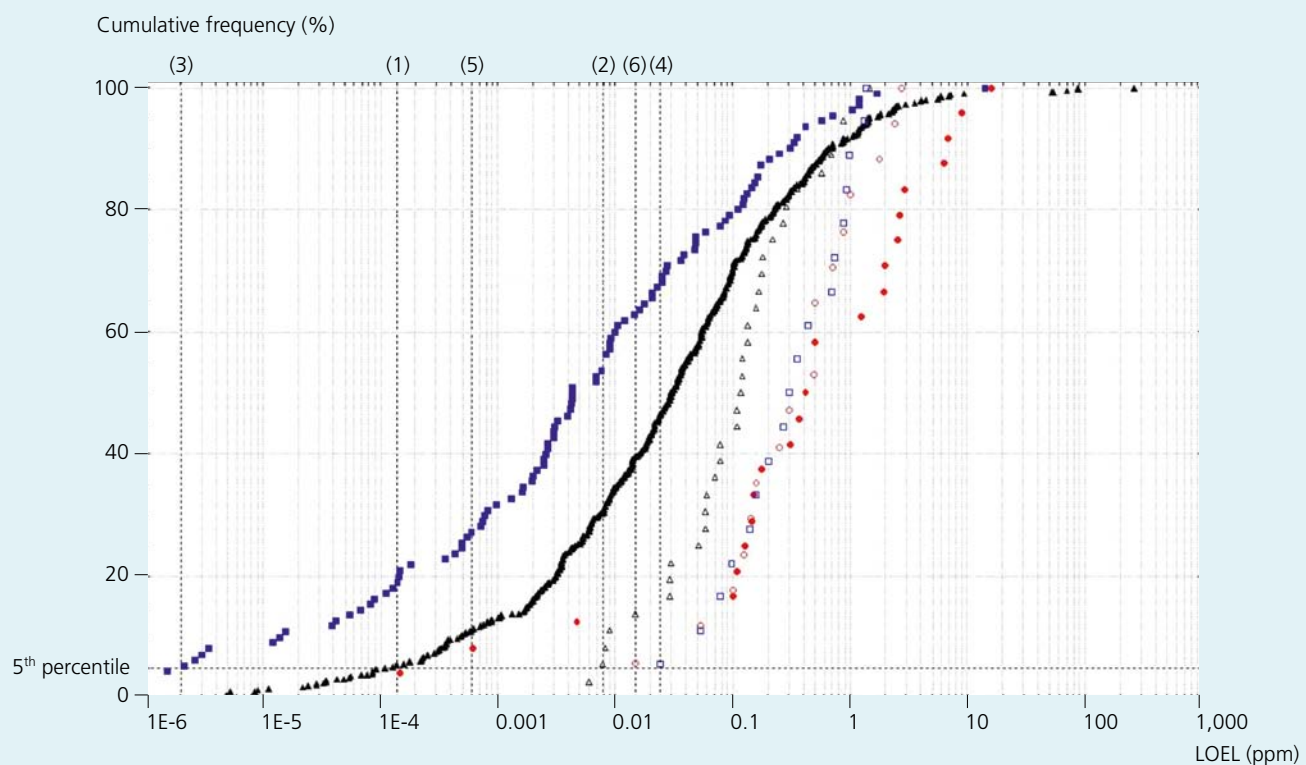
The team started by compiling toxicology data of the different glycol ethers, making use of assessments performed by a variety of institutions, including ECETOC and the German MAK Commission. For 47 glycol ethers, repeated-dose studies were available. The scientists entered the toxicological data into the existing databases RepDose (containing data on repeated-dose toxicity and carcinogenicity of substances) and FeDTex (containing data on reproduction toxicity and teratogenicity) and

compared the toxicity of the glycol ethers with that of all other compounds in these databases.

Compared with the effects of other chemicals, repeated-dose toxicity studies with glycol ethers more frequently revealed effects on the testes, spleen, thymus, and on hematological parameters. Detailed analysis of the data on reproductive and developmental toxicity as endpoints that cause particular

Fig. 1: Cumulative frequencies for the LOELs of glycol ethers in repeated-dose toxicity (black), reproductive toxicity (blue), and developmental toxicity studies (red).

(1) Repeated dose RepDose (symbol: black solid triangle); (2) repeated dose GE (symbol: black open triangle); (3) reproductive toxicity FeDTex (symbol: blue solid square); (4) reproductive toxicity GE (symbol: blue open square); (5) developmental toxicity FeDTex (symbol: red solid circle); (6) developmental toxicity GE (symbol: red open circle).



concern, however, showed that all other glycol ethers are either considerably less toxic than EGME or do not show any such effects at all.

Overall, glycol ethers are of relatively low toxicity, as can be seen in Figure 1. This figure shows the cumulative frequencies for the LOELs regarding repeated-dose toxicity, reproductive toxicity, and developmental toxicity of glycol ethers compared with the other substances recorded in RepDose and FeDTeX. Among each other, glycol ethers differ in toxicity maximally by a factor of about 100. It is true that the differences among glycol ethers are thus not as large as among all chemicals in the databases, but nevertheless glycol ethers differ from each other so markedly that guideline values for every single compound are required. Wherever there were sufficient data available, the scientists derived guideline values. In addition, where the available data were not sufficient to allow a guideline value to be derived, they derived a default guideline value corresponding to the 5th percentile of this value within the distribution of all glycol ethers in Figure 1 – thus assuming high toxicity for insufficiently investigated substances. They furthermore took into consideration that exposure to several glycol ethers at once can occur and that their effects can add up. For the derivation of guideline values, therefore, there is the request to apply the hazard index method to determine to what degree the corresponding guideline value is achieved by the presence of each individual substance. The sum of these quotients must not be larger than 1.

With this project, the ad-hoc working group has ventured on several new paths at once in chemical risk assessment: by assessing a whole category, by deriving a default guideline value for insufficiently investigated substances, and by taking into account possible additive effects. During this project (as already during numerous other applications – see reference list), the databases RepDose and FeDTeX once again proved to be helpful tools for deriving threshold and guideline values for substance categories: The multitude of data they comprise allows easy queries, statistical analyses, and clear presentation of results.

The above described approach for deriving guideline values for the substance category of glycol ethers will be published in the "Bundesgesundheitsblatt" (German Federal Health Gazette).

References

Batke, M.; Aldenberg, T.; Escher, S.; Mangelsdorf, I. (2012)
Relevance of non-guideline studies for risk assessment:
The coverage model based on most frequent targets in
repeated-dose toxicity studies. *Toxicol. Lett.*
doi: 10.1016/j.toxlet.2012.09.002

Batke, M.; Escher, S.; Hoffmann-Doerr, S.; Melber, C.;
Messinger, H.; Mangelsdorf, I. (2011)
Evaluation of time extrapolation factors based on the database
RepDose. *Toxicol. Lett.* 205 (2): 122-129.

Tluczkiwicz, I.; Buist, H. E.; Martin, M. T.; Mangelsdorf, I.;
Escher, S. (2011)
Improvement of Cramer classification for oral exposure
using the database TTC RepDose – a strategy description.
Regul. Toxicol. Pharmacol. 61 (3): 340-350.

Escher, S. E.; Tluczkiwicz, I.; Batke, M.; Bitsch, A.; Melber, C.;
Kroese, E. D.; Buist, H. E.; Mangelsdorf, I. (2010)
Evaluation of inhalation TTC values with the database
RepDose. *Regul. Toxicol. Pharmacol.* 58 (2): 259-274.



CONTACT

Dr. Inge Mangelsdorf
Phone +49 511 5350-303
inge.mangelsdorf@item.fraunhofer.de

Project report

PAFTOX DATABASE FACILITATES TOXICOLOGICAL ASSESSMENT OF NANO-OBJECTS

SUMMARY

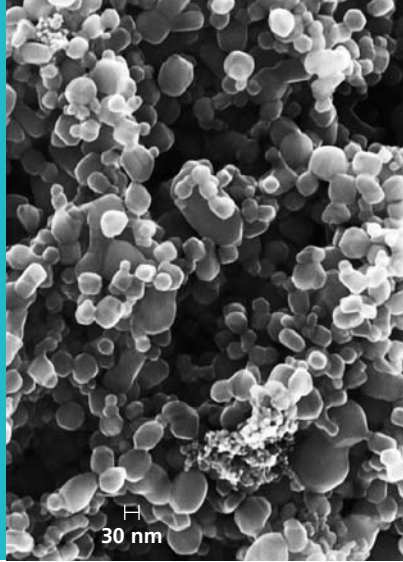
Nano-objects are defined as those objects that have one, two, or three external dimensions in the nanoscale size range, that is, between 1 and 100 nanometers. Although numerous publications about toxicological studies with nanomaterials are available, it is still difficult to get the big picture. The reason for this is the strong heterogeneity of the available data, which is a handicap to toxicological assessment. On behalf of the German Federal Environment Agency, Fraunhofer scientists have developed the database PaFtox, which is aimed at making the assessment of nano-objects easier in the future. First analyses using this database have confirmed individual statements from the literature.

Nano-objects are suspected of being more toxic than fine particles of the same composition at equal mass. Numerous publications on nanotoxicology are available. The published data, however, are very heterogeneous, because there are substantial differences in the investigated objects – regarding composition, shape, and surface area – and study designs – route of administration, study duration, and investigated end-points. Consequently, it is very difficult to get the big picture and draw general conclusions. And even though many review articles on this topic have been published already, a lot of questions are yet to be answered. To enable systematic and overall assessment of the available data, scientists of the institute's Division of Chemical Risk Assessment, Databases and Expert Systems have developed the database "Particle and Fiber toxicity" – PaFtox in short – on behalf of the German Federal Environment Agency.

A database in general offers several advantages over simple literature analysis:

- Due to the database structure, the available data can be entered systematically.
- Weaknesses of a study and of its description are immediately visible and can be taken into account accordingly in analyses.

Titanium dioxide nanoparticles at 300000x magnification. Mostly agglomerates are displayed – titanium dioxide primary particles are visible as small beads at the bottom of the image.



- Different types of queries enable systematic processing of the data from the larger datasets, for example with regard to effect patterns, LOELs, and dose-effect analyses for different (nano-)objects, or identification of sensitive parameters, that is, effects occurring already at low doses.
- Easy visualization of the analyses makes it easier to recognize and understand correlations than when working with large tables.

The PaFtox database documents particle characterization data (both primary and secondary), the study design, target organs, effects, and effect sizes. At present, it includes the data of 131 inhalation and instillation studies with rodents (study duration more than 28 days) that investigated inert particles, different types of silica oxide, metals or metal oxides, and carbon nanotubes.

At this stage already, individual statements from the literature have been found to be confirmed by the larger pool of data from the PaFtox database. One example is the LOELs for nano-objects. The small nanoparticle diameters result in a relatively large specific surface area. For these two properties, categories were defined and the corresponding LOELs determined. Based on the studies currently contained in the database, the LOELs for nano-objects on average are by a factor of 18 lower than for larger-scale objects.



CONTACT

Dr. Katrin Schröder
Phone +49 511 5350-338
katrin.schroeder@item.fraunhofer.de

Business unit 4

PROJECT OVERVIEW

Assessment of chemicals

Activities in connection with the European chemicals policy (REACH):

- Consulting for companies, assistance in preparing registration
- Update and enhancement of existing registrations
- Evaluation of the necessary data
- Preparation and revision of IUCLID data sets and of chemical safety reports
- Development of testing strategies, justification for waiving, and exposure scenarios

Assessment of chemicals using category approaches

International Chemical Safety Cards (ICSC) under the WHO International Programme on Chemical Safety (IPCS)

Substance reports for the German “Noxious Agents Information System” (NIS) on behalf of different German *Länder* ministries

Consulting contracts and notification of new substances on behalf of Japanese companies

Toxicological expert reports on different chemicals

Toxicological expert reports on and risk assessment of impurities or residues in medicinal products

Biocides

Activities in connection with the European Biocidal Products Directive (BPD, Directive 98/8/EC) and the Biocidal Products Regulation (BPR 528/2012) that will become effective in September 2013

Processing of supplementary requests and communication with the registration authorities to include biocidal active substances in Annex I/IA according to guideline 98/8/EC

Assistance in preparing for product authorization

Evaluation of the required data

Development of exposure scenarios and testing strategies, risk assessments

Consulting on issues of biocidal product classification

Foodstuffs

Preparation of pre-evaluation documents for food additives

QSAR, databases

Data collection and analysis to define categories of hydro-carbon mixtures

Threshold of Toxicological Concern (TTC) for inhalation exposure: improvement of the TTC concept for inhalation exposure and derivation of thresholds using the RepDose database on behalf of Cefic

Assessment of substances based on (Q)SAR and read-across

Analysis of extrapolation factors for time, interspecies, and routes, and combination of the distributions on behalf of ERASM

Derivation of guideline values for the category of glycol ethers within the collaboration in the German Ad-hoc Working Group of the Indoor Air Hygiene Committee

Mechanism-based characterization of systemic toxicity for RepDose database substances employing in-vitro toxicogenomics on behalf of TNO for Cefic

Assessment of human and veterinary pharmaceuticals

Environmental assessment activities as required by the European EMA guidelines for drug registration

Preparation of pharmacological and toxicological expert reports

Consulting for companies: analysis of the required data, response to complaints, communication with the authorities, consulting in special cases, study monitoring, preparation of expert reports including risk assessment for registration

Support for industry with project proposals for development of environmentally compatible drugs

Collection of substance properties for GSBL, the joint substance data pool of the German Federal Government and the German Federal *Länder*

Exposure estimates

Preparation of "Environmental Health Criteria Documents" (EHC) on "Dermal exposure" under the WHO International Programme on Chemical Safety (IPCS)

Miscellaneous scientific projects

Development of ontologies for repeated-dose toxicity studies and for developmental and reproductive toxicity studies for implementation in the QSAR Toolbox on behalf of ISS for the ECHA

Project "SteriHealth" – for better hygiene in the medical area, as part of the Fraunhofer research program "Markets beyond tomorrow"

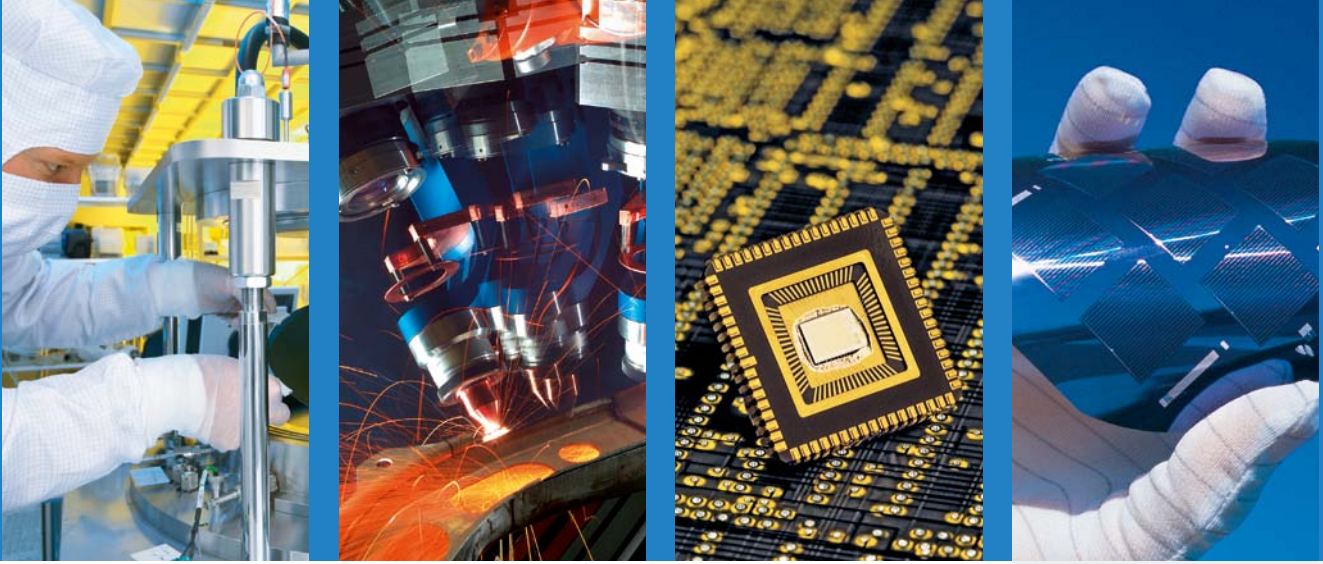
Identification of limitations of the OECD water-sediment test (OECD 308) and development of suitable alternatives to assess persistence on behalf of Cefic

RESEARCH OF PRACTICAL UTILITY

Research of practical utility lies at the heart of all activities pursued by the Fraunhofer-Gesellschaft. Founded in 1949, the research organization undertakes applied research that drives economic development and serves the wider benefit of society. Its services are solicited by customers and contractual partners in industry, the service sector, and public administration.

At present, the Fraunhofer-Gesellschaft maintains 66 institutes and independent research units. The majority of the more than 22,000 staff are qualified scientists and engineers, who work with an annual research budget of 1.9 billion euros. Of this sum, more than 1.6 billion euros is generated through contract research. More than 70 percent of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Almost 30 percent is contributed by the German federal and *Länder* governments in the form of base funding, enabling the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

Affiliated international research centers and representative offices provide contact with the regions of greatest importance to present and future scientific progress and economic development.



With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits perceived by the customer: Through their research and development work, the Fraunhofer institutes help to reinforce the competitive strength of the economy in their local region, and throughout Germany and Europe. They do so by promoting innovation, strengthening the technological base, improving the acceptance of new technologies, and helping to train the urgently needed future generation of scientists and engineers.

As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills that will allow them to take up positions of responsibility within their institute, at universities, in industry and in society. Students who choose to work on projects at the Fraunhofer institutes have excellent prospects of starting and developing a career in industry by virtue of the practical training and experience they have acquired.

The Fraunhofer-Gesellschaft is a recognized non-profit organization that takes its name from Joseph von Fraunhofer (1787–1826), the illustrious Munich researcher, inventor and entrepreneur.

CONTACT

Fraunhofer-Gesellschaft
Press and Public Relations
Franz Miller
Phone +49 89 1205-1300
Fax +49 89 1205-771300

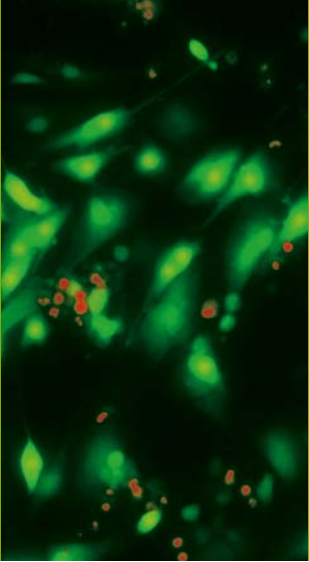
Hansastraße 27c
80686 München (Germany)

FRAUNHOFER GROUP FOR LIFE SCIENCES

APPLIED SCIENCE FOR MAN AND THE ENVIRONMENT

Six Fraunhofer institutes and a Fraunhofer research institution have focused their research on the life sciences. In the Fraunhofer Group for Life Sciences they have pooled their competencies in biology, biomedicine, pharmacology, toxicology, and food technology. With a staff of over 1700, the Fraunhofer Group for Life Sciences is an important R&D partner for the pharmaceutical and biotechnology sectors as well as for the chemicals industry and medical technology companies.

The Fraunhofer Institutes for Biomedical Engineering IBMT, Interfacial Engineering and Biotechnology IGB, Molecular Biology and Applied Ecology IME, Toxicology and Experimental Medicine ITEM, Cell Therapy and Immunology IZI, and Process Engineering and Packaging IVV and the Fraunhofer Research Institution for Marine Biotechnology EMB combine their concentrated expertise to allow for even comprehensive projects to be undertaken for their clients.



Research and development in the Fraunhofer Group for Life Sciences cover on the one hand the preventive areas of environmental and consumer protection, and on the other hand the regenerative areas of medical therapy and ecological recovery. The broad range of methods and equipment available within the Fraunhofer Group for Life Sciences is unrivaled at so high a concentration.

What characterizes the research performed in the Fraunhofer Group for Life Sciences is its closeness to industrial application, aiming to develop solutions that meet clients' actual requirements, always with a view to economic efficiency and sustainability. In addition, the institutes also undertake basic research to develop the basis for future applications in industry. The business units of the Fraunhofer Group for Life Sciences include translational medicine research and biomedical technology, regenerative medicine, healthy foodstuffs, industrial biotechnology, and research aimed at the safety of processes, chemicals, and pesticides.

The Group shows ways of preserving health and the environment in an industrialized world and develops new options for diagnosing and treating diseases in a setting of a more personalized healthcare and for protecting natural resources.

CONTACTS



Fraunhofer Group for Life Sciences
Prof. Dr. Thomas Hirth
(Group Chairman)



Central Office
Dr. Claus-Dieter Kroggel
(Head of the Central Office)
Phone +49 511 5350-103
Fax +49 511 5350-155
claus.kroggel@vls.fraunhofer.de

NAMES, DATES, EVENTS

PUBLICATIONS

- Badorrek, P.; Dick, M.; Emmert, L.; Schaumann, F.; Koch, W.; Hecker, H.; Murdoch, R.; Hohlfeld, J. M.; Krug, N. (2012)
Pollen starch granules in bronchial inflammation.
In: *Annals of Allergy, Asthma & Immunology* 109 (3): 208-214.e6.
doi: 10.1016/j.anai.2012.06.019
- Basma, H.; Gunji, Y.; Liu, X.; Nelson, A.; Farid, M.; Iwasawa, S.; Ikari, J.; Wang, X.; Holz, O.; Müller, K.-C.; Magnussen, H.; Rabe, K.; Rennard, S. I. (2012)
Generation of ips-like cells from COPD lung fibroblasts.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A4966.
- Batke, M.; Aldenberg, T.; Escher, S.; Mangelsdorf, I. (2012)
Relevance of non-guideline studies for risk assessment: the coverage model based on most frequent targets in repeated dose toxicity studies.
In: *Toxicology Letters*. 20 p.
doi: 10.1016/j.toxlet.2012.09.002
- Billr, H.; Schwarz, K.; Windt, H.; Koch, W.; Hohlfeld, J. M. (2012)
Characterization of exhaled particles from the human lung in airway obstruction.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A5747.
- Braun, A.; Ernst, H.; Schaudien, D.; Hoymann, H.-G.; Rittinghausen, S. (2012)
The respiratory tract: Chapter 2.7.
In: Hedrich, Hans J. (Ed.): *The laboratory mouse*. Oxford, UK: Elsevier, p. 271-311. (Handbook of experimental animals.)
doi: 10.1016/B978-0-12-382008-2.00012-X
- Braun, A.; Spies, E.; Rochlitzer, S.; Voedisch, S. (2012)
Neuropeptides influence airway dendritic cell behavior.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A2155.
- Buschmann, J. (2012)
The OECD guidelines for the testing of chemicals and pesticides.
In: Barrow, Paul C. (Ed.): *Teratogenicity testing: methods and protocols*. New York: Springer, p. 37-56. (Methods in molecular biology 947.)
doi: 10.1007/978-1-62703-131-8_4
- Cockayne, D. A.; Cheng, D. T.; Waschki, B.; Sridhar, S.; Ravindran, P.; Hilton, H. Kourteva, G.; Bitter, H.; Pillai, S. G.; Visvanathan, S.; Müller, K.-C.; Holz, O.; Magnussen, H.; Watz, H.; Fine, J. S. (2012)
Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity.
In: *PLoS One* 7 (6): e38629, 12 p.
doi: 10.1371/journal.pone.0038629
- Creutzenberg, O. H.; Ziemann, C.; Hansen, T.; Ernst, H.; Schaudien, D.; Schuchardt, S.; Wiench, K.; Bellmann, B. (2012)
Subacute and subchronic inhalation toxicity and dermal absorption of the nanoscaled zinc oxide Z-COTE® HP1 in the rat.
In: *The Toxicologist* 126 (1): 142-143, Abstr. 658.
- Creutzenberg, O.; Bellmann, B.; Korolewitz, R.; Koch, W.; Mangelsdorf, I.; Tillmann, T.; Schaudien, D. (2012)
Change in agglomeration status and toxicokinetic fate of various nanoparticles in vivo following lung exposure in rats.
In: *Inhalation Toxicology* 24 (12): 821-830.
doi: 10.3109/08958378.2012.721097
- Dutow, P.; Lingner, S.; Bode, J.; Laudeley, R.; Glage, S.; Hoymann, H.G.; Dittich, A. M.; Müller, M.; Braun, A.; Klos, A. (2012)
Chlamydia pneumoniae and asthma bronchiale in a mouse model: Decrease in airway hyperresponsiveness to house dust mite allergen after pneumonia. Proceedings of the 7th Meeting of the European Society for Chlamydia Research. Ouburg, S.; Morré, S. A. (Eds.). VU University Amsterdam, Amsterdam, 204.
- Eydner, M.; Schaudien, D.; Creutzenberg, O.; Ernst, H.; Hansen, T.; Baumgärtner, W.; Rittinghausen, S. (2012)
Impacts after inhalation of nano- and fine-sized titanium dioxide particles: morphological changes, translocation within the rat lung, and evaluation of particle deposition using the relative deposition index.
In: *Inhalation Toxicology* 24 (9): 557-569.
doi: 10.3109/08958378.2012.697494
- Fischer, M.; Koch, W.; Windt, H.; Dasenbrock, C. (2012)
Estimation of the consumer inhalation risk of waterproofing sprays.
In: *Naunyn-Schmiedeberg's Archives of Pharmacology* 385, Suppl. 1: S27, Abstr. 111.
- Fischer, M.; Koch, W.; Windt, H.; Dasenbrock, C. (2012)
A pilot study on the refinement of acute inhalation toxicity studies: The isolated perfused rat lung as a screening tool for surface-active substances.
In: *Alternatives to Laboratory Animals* 40 (4): 199-209.

- Gerhauser, I.; Wohlsein, P.; Ernst, H.; Germann, P.-G. (2012)
Vacuolation and mineralisation as dominant age-related findings in hamster brains. Jan 16 [Epub ahead of print].
In: *Experimental and Toxicologic Pathology*, 7 p.
doi: 10.1016/j.etp.2011.12.001
- Gerhauser, I.; Wohlsein, P.; Ernst, H.; Germann, P.-G.; Baumgärtner, W. (2012)
Lack of detectable diffuse or neuritic plaques and neurofibrillary tangles in the brains of aged hamsters.
In: *Neurobiology of aging* 33 (8): 1716-1719.
doi: 10.1016/j.neurobiolaging.2011.05.012
- Hardy, B.; Apic, G.; Carthew, P.; Clark, D.; Cook, D.; Dix, I.; Escher, S.; Hastings, J.; Heard, D. J.; Jeliaskova, N.; Judson, P.; Matis-Mitchell, S.; Mitic, D.; Myatt, G.; Shah, I.; Spjuth, O.; Tcheremenskaia, O.; Toldo, L.; Watson, D.; White, A.; Yang, C. (2012)
Food for thought ... A toxicology ontology roadmap.
In: *ALTEX* 29 (2): 129-137.
- Hardy, B.; Apic, G.; Carthew, P.; Clark, D.; Cook, D.; Dix, I.; Escher, S.; Hastings, J.; Heard, D. J.; Jeliaskova, N.; Judson, P.; Matis-Mitchell, S.; Mitic, D.; Myatt, G.; Shah, I.; Spjuth, O.; Tcheremenskaia, O.; Toldo, L.; Watson, D.; White, A.; Yang, C. (2012)
Toxicology ontology perspectives.
In: *ALTEX* 29 (2): 139-156.
- Heinrich, U.; Schlichting, A.; Ziemann, C.; Seyock, S.; Haase, D.; Leonhardt, A.; Bellmann, B. (2012)
Suspension of MWCNT for toxicological in vivo and in vitro studies.
In: *The Toxicologist* 126 (1): 143, Abstr. 661.
- Holz, O.; Roepcke, S.; Lauer, G.; Krug, N.; Ernst, P.; Lahu, G.; Hohlfeld, J. M. (2012)
Stable inflammatory phenotype in smokers and smokers with COPD.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A1300.
- Holz, O.; Schaumann, F.; Janssen, O.; Lavae-Mokhtari, B.; Witte, L.; Krug, N.; Heinrich, J. M.; Hohlfeld, J. M. (2012)
Depletion of neutrophils from induced sputum using a novel bead and sieve-separation system.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A2781.
- Holz, O.; Tan, L.; Faulenbach, C.; Müller, M.; Krug, N.; McLeod, A.; Hohlfeld, J. M. (2012)
Reproducibility of serum biomarkers and relationship to airway inflammation following LPS challenge in healthy volunteers.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A3937.
- Hox, V.; Vanoirbeek, J. A.; Alpizar, Y. A.; Voedisch, S.; Bobic, S.; Callebaut, I.; De Vooght, V.; Sharify, A.; van Gerven, L.; Ceuppens, J. L.; de Vries, A.; Braun, A.; Hoet, P.; Talavera, K.; Nemery, B.; Hellings, P. (2012)
Transient potential channel A1 and mast cell activation in bronchial hyperreactivity caused by hypochlorite and OVA in mice.
In: *Allergy* 67, Suppl. 96: 143-144, Abstr. 331.
- Hox, V.; Vanoirbeek, J. A.; Alpizar, Y. A.; Voedisch, S.; Callebaut, I.; Bobic, S.; Sharify, A.; De Vooght, V.; Van Gerven, L.; Devos, F.; Liston, A.; Voets, T.; Vennekens, R.; Bullens, D. M. A.; De Vries, A.; Hoet, P.; Braun, A.; Ceuppens, J. L.; Talavera, K.; Nemery, B.; Hellings, P. W. (2012)
Crucial role of TRPA1 and mast cells in induction of non-allergic airway hyperreactivity in mice. Dec 21 [Epub ahead of print].
In: *American Journal of Respiratory and Critical Care Medicine*: 51 p.
doi: 10.1164/rccm.201208-1358OC
- Hoymann, H. G. (2012)
Lung function measurement in rodents in safety pharmacology studies.
In: *Frontiers in Pharmacology* 3 (156): 1-11.
doi: 10.3389/fphar.2012.00156
- Hueper, K.; Elalfy, M.; Laenger, F.; Halter, R.; Rodt, T.; Galanski, M.; Borlak, J. (2012)
PET/CT imaging of c-Myc transgenic mice identifies the genotoxic n-nitroso-diethylamine as carcinogen in a short-term cancer bioassay.
In: *PLoS One* 7 (2): e30432, 11 p.
doi: 10.1371/journal.pone.0030432
- Jahn, U. von; Ernst, H.; Matthies, H. K.; Albrecht, U. V. (2012)
MicroScout - an assistance system for histological analysis in forensics.
In: *Biomedizinische Technik* 57, Suppl. 1: 34-37.
doi: 10.1515/bmt-2012-4253
- Kirsch, S.; Klein, C. A. (2012)
Sequence error storms and the landscape of mutations in cancer.
In: *Proceedings of the National Academy of Sciences of the United States of America* 109 (36): 14289-14290.
doi: 10.1073/pnas.121224610
- Knauf, S.; Seehase, S.; Switalla, S.; Neuhaus, V.; Zöller, M.; Kaup, F.-J.; Schlumbohm, C.; Fuchs, E.; Lauenstein, H. D.; Sewald, K.; Hohlfeld, J. M.; Braun, A.; Sewald, K. (2012)
A new model for testing human specific anti-inflammatory drugs: LPS-induced lung inflammation in the common marmoset.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A5697.

NAMES, DATES, EVENTS

- Koch, W.; Behnke, W.; Berger-Preiß, E.; Kock, H.; Gerling, S.; Hahn, S.; Schröder, K. (2012)
Validation of an EDP assisted model for assessing inhalation exposure and dermal exposure during spraying processes [Research Project F 2137].
Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin.
- Krug, N.; Badorrek, P.; Hohlfeld, J. M. (2012)
Experience with an allergen challenge chamber for clinical trials in allergic rhinitis.
In: *Clinical & Experimental Allergy Reviews* 12, Suppl. 2: 14-19.
doi: 10.1111/j.1472-9733.2012.01164.x
- Krug, N.; Gupta, A.; Badorrek, P.; Müller, M.; Casper, A.; Pivovarova, A.; Hilbert, J.; Koenen, R.; Hohlfeld, J. M.; Wood, C. (2012)
CRTH2 antagonist, BI 671800 (BI), reduces nasal symptoms and inhibits nasal cytokines and eosinophils in SAR patients exposed to grass pollen in an environmental challenge chamber (ECC).
In: *American Journal of Respiratory and Critical Care Medicine* 185: A4185.
- Kuhlmann, J.; Bartsch, Y.; Willbold, E.; Schuchardt, S.; Holz, O.; Hort, N.; Höche, D.; Heineman, W. R.; Witte, F. (2012)
Fast escape of hydrogen from gas cavities around corroding magnesium implants. Oct 13 [Epub ahead of print].
In: *Acta biomaterialia*, 8 p.
doi: 10.1016/j.actbio.2012.10.00
- Langer, M.; Booth, J. L.; Patel, V. I.; Duggan, E. S.; Braun, A.; Ramani, V.; Awasthi, S.; Silasi-Mansat, R.; Lupu, F.; Coggeshall, K. M.; Metcalf, J. P. (2012)
Human alveolar epithelial barrier function is impaired by *Bacillus anthracis* lethal toxin.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A3271.
- Langer, M.; Duggan, E. S.; Booth, J. L.; Patel, V. I.; Zander, R. A.; Silasi-Mansat, R.; Ramani, V.; Veres, T. Z.; Prenzler, F.; Sewald, K.; Williams, D. M.; Coggeshall, K. M.; Awasthi, S.; Lupu, F.; Burian, D.; Ballard, J. D.; Braun, A.; Metcalf, J. P. (2012)
Bacillus anthracis lethal toxin reduces human alveolar epithelial barrier function.
In: *Infection and Immunity* 80 (12): 4374-4387.
doi: 10.1128/IAI.01011-12
- Lauenstein, L.; Switalla, S.; Ritter, D.; Knebel, J.; Dasenbrock, C.; Braun, A.; Sewald, K. (2012)
Acute cigarette smoke exposure induces cytotoxicity and inflammation in living tissue of precision-cut lung slices.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A6054.
- Lauenstein, L.; Switalla, S.; Prenzler, F.; Pfennig, O.; Förster, C.; Braun, A.; Sewald, K. (2012)
Assessment of lung toxicity induced by chemical allergens in human precision-cut lung slices.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A4662.
- Le, D. D.; Rochlitzer, S.; Funck, U.; Suhling, H.; Braun, A.; Welte, T.; Din, Q. T. (2012)
Neuro-immune interaction in allergic airway inflammation: expression and function of dendritic cells in sensory airway ganglia neurons.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A2157.
- Lewin, G.; Buschmann, J.; Asmuss, M. (2012)
Influence of extremely low frequency magnetic fields on juvenile development and behaviour in a mouse model.
In: *Reproductive Toxicology* 34 (2): 151-152.
doi: 10.1016/j.reprotox.2012.05.030
- Licht, O.; Voss, J. U.; Mangelsdorf, I. (2012)
Comparison of methods to derive health-based guidance or limit values for chemicals.
In: *Naunyn-Schmiedeberg's Archives of Pharmacology* 385, Suppl. 1: S53, Abstr. 227.
- Lüer, K.; Biller, H.; Windt, H.; Müller, M.; Badorrek, P.; Haefner, D.; Framke, T.; Koch, A.; Ziehr, H.; Krug, N.; Koch, W.; Hohlfeld, J. M. (2012)
Safety and efficacy of house dust mite allergen challenge in patients with allergic rhinitis using a novel technique for inhalation studies in the Fraunhofer Environmental Challenge Chamber.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A4320.
- Mangelsdorf, I.; Voss, J. U. (2012)
Nephrotoxicity of organic solvents from skin exposure.
In: Wilhelm, K.-P.; Zhai, H.; Maibach, H. I. (Eds.): *Dermatotoxicology*. London: Informa Healthcare, chapter 8, p. 66-77.
- May, M.; Huelsenbeck, J.; Schulz, F.; Fritz, G.; Genth, H. (2012)
Cytoprotective effect of the small GTPase RhoB expressed upon Ras glucosylation by *Clostridium sordellii* lethal toxin.
In: *Naunyn-Schmiedeberg's Archives of Pharmacology* 385, Suppl. 1: S40, Abstr. 172.
- McInnes E. F.; Ernst, H.; Germann, P.-G. (2012)
Spontaneous neoplastic lesions in control Syrian hamsters in 6-, 12-, and 24-month short-term and carcinogenicity studies.
In: *Toxicologic Pathology* 41 (1): 86-97.
doi: 10.1177/0192623312448938

Metcalfe, M. P.; Koch, W.; Turner, G. (2012)
Break-up testing of waste-form materials.
In: Mineralogical Magazine 76 (8): 2975-2983.

Michalski, J.; Kanaji, N.; Liu, X.; Nogel, S.; Wang, X.; Basma, H.; Nakanishi, M.; Sato, T.; Gunji, Y.; Fahrid, M.; Nelson, A.; Muller, K.-C.; Holz, O.; Magnussen, H.; Rabe, K. F.; Toews, M. L.; Rennard, S. I. (2012)
Attenuation of inhibitory prostaglandin E2 signaling in human lung fibroblasts is mediated by phosphodiesterase 4.
In: American Journal of Respiratory Cell and Molecular Biology 47 (6): 729-737.
doi: 10.1165/rcmb.2012-00570C

Morenz, K.; Biller, H.; Wolfram, F.; Leonhardt, S.; Ruter, D.; Glaab, T.; Uhlig, S.; Hohlfeld, J. M. (2012)
Detection of air trapping in chronic obstructive pulmonary disease by low frequency ultrasound.
In: BMC Pulmonary Medicine 12 (8): 17 p.
doi: 10.1186/1471-2466-12-8

Nakanishi, M.; Sato, T.; Li, Y.; Nelson, A. J.; Farid, M.; Michalski, J.; Kanaji, N.; Wang, X.; Basma, H.; Patil, A.; Goraya, J.; Liu, X.; Togo, S.; Toews, M. L.; Holz, O.; Muller, K.-C.; Magnussen, H.; Rennard, S. I. (2012)
Prostaglandin E2 stimulates the production of vascular endothelial growth factor through the E-prostanoid-2 receptor in cultured human lung fibroblasts.
In: American Journal of Respiratory Cell and Molecular Biology 46 (2): 217-223.
doi: 10.1165/rcmb.2010-01150C

Neuhaus, V.; Schwarz, K.; Koch, W.; Sewald, K.; Yusibov, V.; Braun, A.; Sewald, K. (2012)
Immunotoxic characterization of a nanoparticle-based inhalable influenza vaccine in murine and human precision cut lung slices.
In: American Journal of Respiratory and Critical Care Medicine 185: A2246.

Pohlmann, G.; Holzinger, K.; Spiegel-Ciobanu, V. (2012)
Vergleichende Untersuchungen zur Charakterisierung ultrafeiner Partikel in Rauchen beim Schweißen und bei verwandten Verfahren – Teil 1: Grundlagen der Untersuchung.
In: Schweissen und Schneiden 64 (5): 267-274.

Pohlmann, G.; Holzinger, K.; Spiegel-Ciobanu, V. E. (2012)
Vergleichende Untersuchungen zur Charakterisierung ultrafeiner Partikel in Rauchen beim Schweißen und bei verwandten Verfahren – Teil 2: Ergebnisse und Diskussion.
In: Schweissen und Schneiden 64 (6): 352-362.

Preiß, A.; Berger-Preiß, E.; Elend, M.; Gerling, S.; Kühn, S.; Schuchardt, S. (2012)
A new analytical approach for the comprehensive characterization of polar xenobiotic organic compounds downgradient of old municipal solid waste (MSW) landfills.
In: Analytical and Bioanalytical Chemistry 403 (9): 2553-2561.
doi: 10.1007/s00216-012-5941-7

Reamon-Büttner, S. M.; Borlak, J. (2012)
Dissecting epigenetic silencing complexity in the mouse lung cancer suppressor gene *Cadm1*.
In: PLoS One 7 (6): e38531, 21 p.
doi: 10.1371/journal.pone.0038531

Reifferscheid, G.; Maes, H.; Allner, B.; Badurova, J.; Belkin, S.; Bluhm, K.; Brauer, F.; Bressling, J.; Domeneghetti, S.; Elad, T.; Flückiger-Isler, S.; Grummt, H.-J.; Gürtler, R.; Hecht, A.; Heringa, M.; Hollert, H.; Huber, S.; Kramer, M.; Ratte, T.; Sauerborn-Klobucar, R.; Magdeburg, A.; Sokolowski, A.; Soldan, P.; Smital, T.; Stalter, D.; Venier, P.; Ziemann, C.; Zipperle, J.; Buchinger, S. (2012)
International round-robin study on the Ames fluctuation test.
In: Environmental and Molecular Mutagenesis 53 (3): 185-197.
doi: 10.1002/em.21677

Repacholi, M.; Grigoriev, Y.; Buschmann, J.; Pioli, C. (2012)
Scientific basis for the Soviet and Russian radiofrequency standards for the general public.
In: Bioelectromagnetics 33 (8): 623-633.
doi: 10.1002/bem.21742

Rittinghausen, S.; Bellmann, B.; Creutzenberg, O.; Ernst, H.; Kolling, A.; Mangelsdorf, I.; Kellner, R.; Beneke, S.; Ziemann, C. (2012)
Evaluation of immunohistochemical markers to detect the genotoxic mode of action of fine and ultrafine dusts in rat lungs. Nov 23 [Epub ahead of print].
In: Toxicology: 10 p
doi: 10.1016/j.tox.2012.11.007

Rochlitzer, S.; Hoymann, H.-G.; Müller, M.; Braun, A. (2012)
Rhinovirus application on the background of allergic airway inflammation in a chronic house dust mite model.
In: American Journal of Respiratory and Critical Care Medicine 185: A1441.

Rodt, T.; Falck, C. von; Dettmer, S.; Hueper, K.; Halter, R.; Hoy, L.; Luepke, M.; Borlak, J.; Wacker, F. (2012)
Lung tumour growth kinetics in SPC-c-Raf-1-BB transgenic mice assessed by longitudinal in-vivo micro-CT quantification.
In: Journal of Experimental & Clinical Cancer Research 31 (15): 7 p.
doi: 10.1186/1756-9966-31-15

NAMES, DATES, EVENTS

- Rodt, T.; Luepke, M.; Boehm, C.; Hueper, K.; Halter, R.; Glage, S.; Hoy, L.; Wacker, F.; Borlak, J.; Falck, C. von (2012)
Combined micro-PET/micro-CT imaging of lung tumors in SPC-raf and SPC-myc transgenic mice.
In: *PLoS One* 7 (9): e44427, 8 p.
doi: 10.1371/journal.pone.0044427
- Röpcke, S.; Holz, O.; Lauer, G.; Müller, M.; Rittinghausen, S.; Ernst, P.; Lahu, G.; Elmlinger, N.; Krug, N.; Hohlfeld, J. M. (2012)
Repeatability of and relationship between potential COPD biomarkers in bronchoalveolar lavage, bronchial biopsies, serum, and induced sputum.
In: *PLoS One* 7 (10): e46207, 11 p.
doi: 10.1371/journal.pone.0046207
- Schaudien, D.; Knebel, J.; Creutzenberg, O. (2012)
In vitro study revealed different size behavior of different nanoparticles.
In: *Journal of Nanoparticle Research* 14: Art. 1039, 9 p.
doi: 10.1007/s11051-012-1039-6
- Schaumann, F.; Holz, O.; Janssen, O.; Lavae-Mokhtari, B.; Witte, L.; Biller, H.; Krug, N.; Hohlfeld, J. M. (2012)
Low-dose endotoxin inhalation in healthy volunteers: a challenge model for early clinical drug development of novel anti-inflammatory compounds.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A4318.
- Schleh, C.; Rothen-Rutishauser, B. M.; Blank, F.; Lauenstein, H. D.; Nassimi, M.; Krug, N.; Braun, A.; Erpenbeck, V.; Gehr, P.; Hohlfeld, J. M. (2012)
Surfactant Protein D modulates allergen particle uptake and inflammatory response in a human epithelial airway model.
In: *Respiratory Research* 13 (1): 8.
doi: 10.1186/1465-9921-13-8
- Schlepütz, M.; Rieg, A. D.; Seehase, S.; Spillner, J.; Perez-Bouza, A.; Braunschweig, T.; Schroeder, T.; Bernau, M.; Lambermont, V.; Schlumbohm, C.; Sewald, K.; Autschbach, R.; Braun, A.; Kramer, B. W.; Uhlig, S.; Martin, C. (2012)
Neurally mediated airway constriction in human and other species: a comparative study using precision-cut lung slices (PCLS).
In: *PLoS One* 7 (10): e47344, 9 p.
doi: 10.1371/journal.pone.0047344
- Schuchardt, S.; Strube, A. (2012)
Microbial volatile organic compounds in moldy interiors: a long-term climate chamber study. Aug 23 [Epub ahead of print].
In: *Journal of Basic Microbiology* 52: 7 p.
doi: 10.1002/jobm.201200056
- Schwarz, K.; Hohlfeld, J. M.; Biller, H.; Koch, W. (2012)
Single breath particle characterization to detect small airway alterations.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A5748.
- Seehase, S.; Köhncke, S.-P.; Hoymann, H.-G.; Braun, A.; Sewald, K. (2012)
Effect of tiotropium on in vivo and ex vivo lung function in a rat model of bronchoconstriction.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A3586.
- Seehase, S.; Lauenstein, H.-D.; Schlumbohm, C.; Switalla, S.; Neuhaus, V.; Förster, C.; Fieguth, H.-G.; Pfennig, O.; Fuchs, E.; Kaup, F.-J.; Bleyer, M.; Hohlfeld, J. M.; Braun, A.; Sewald, K.; Knauf, S. (2012)
LPS-induced lung inflammation in marmoset monkeys – an acute model for anti-inflammatory drug testing.
In: *PLoS One* 7 (8): e43709, 11 p.
doi: 10.1371/journal.pone.0043709
- Seehase, S.; Neuhaus, V.; Kaup, F. J.; Pfennig, O.; Förster, C.; Hohlfeld, J. M.; Knauf, S.; Braun, A.; Sewald, K. (2012)
Ex vivo lung culture models of marmoset monkeys and humans for anti-inflammatory drug testing.
In: *American Journal of Respiratory and Critical Care Medicine* 185: A4169.
- Sewald, K.; Braun, A. (2012)
Assessment of immunotoxicity using precision-cut tissue slices.
In: *Xenobiotica* 43 (1): 84-97.
doi: 10.3109/00498254.2012.731543
- Solecki, R.; Barbellion, S.; Bergmann, G.; Bürgin, H.; Buschmann, J.; Clark, R.; Comotto, L.; Fuchs, A.; Faqi, A. S.; Gerspach, R.; Grote, K.; Hakansson, H.; Heinrich, V.; Heinrich-Hirsch, B.; Hofmann, T.; Hübel, U.; Inazaki, T. H.; Khalil, S.; Knudsen, T. B.; Kudicke, S.; Lingk, W.; Makris, S.; Müller, S.; Paumgarten, F.; Pfeil, R.; Rama, E. M.; Schneider, S.; Shiota, K.; Tamborini, E.; Tegelenbosch, M.; Ulbrich, B.; Duijnhoven, E. A. J. van; Wise, D.; Chahoud, I. (2012)
Harmonization of description and classification of fetal observations: Achievements and problems still unresolved: Report of the 7th Workshop on the Terminology in Developmental Toxicology Berlin, 4-6 May 2011. Jul 8 [Epub ahead of print]. In: *Reproductive Toxicology* 8 p.
doi: 10.1016/j.reprotox.2012.06.006
- Steinwede, K.; Maus, R.; Bohling, J.; Voedisch, S.; Braun, A.; Ochs, M.; Schmiedl, A.; Länger, F.; Gauthier, F.; Roes, J.; Welte, T.; Bange, F. C.; Niederweis, M.; Bühling, F.; Maus, U. A. (2012)
Cathepsin G and neutrophil elastase contribute to lung-protective immunity against mycobacterial infections in mice.
In: *Journal of Immunology* 188 (9): 4476-4487.
doi: 10.4049/jimmunol.1103346

- Steinwede, K.; Maus, R.; Bohling, J.; Voedisch, S.; Braun, A.; Ochs, M.; Schmiedl, A.; Walter, K.; Bange, F.; Welte, T.; Ehlers, S.; Maus, U. A. (2012)
Cathepsin G and neutrophil elastase contribute to lung protective immunity against mycobacterial infections in mice.
In: American Journal of Respiratory and Critical Care Medicine 185: A3267.
- Switalla, S.; Knebel, J.; Ritter, D.; Dasenbrock, C.; Krug, N.; Braun, A.; Sewald, K. (2012)
Determination of genotoxicity by the Comet assay applied to murine precision-cut lung slices. Dec 27 [Epub ahead of print].
In: Toxicology in Vitro: 6 p.
doi: <http://dx.doi.org/10.1016/j.tiv.2012.12.015>
- Tank, J.; Biller, H.; Heusser, K.; Holz, O.; Diedrich, A.; Framke, T.; Koch, A.; Grosshennig, A.; Koch, W.; Krug, N.; Jordan, J.; Hohlfeld, J. (2012)
Acute ozone-induced airway inflammation does not effect resting human sympathetic nerve traffic.
In: Naunyn-Schmiedeberg's Archives of Pharmacology 385, Suppl. 1: S95, Abstr. 421.
- Tcheremenskaia, O.; Benigni, R.; Nikolova, I.; Jeliakova, N.; Escher, S. E.; Batke, M.; Baier, T.; Porokov, V.; Lagunin, A.; Rautenberg, M.; Hardy, B. (2012)
OpenTox predictive toxicology framework: toxicological ontology and semantic media wiki-based OpenToxipedia.
In: Journal of Biomedical Semantics 3, Suppl. 1: S7, 17 p.
doi: [10.1186/2041-1480-3-S1-S7](https://doi.org/10.1186/2041-1480-3-S1-S7)
- Gluczkiewicz, I.; Batke, M.; Mangelsdorf, I.; Escher, S. (2012)
Derived values and databases for non-cancer endpoints: considerations and concerns.
In: Naunyn-Schmiedeberg's Archives of Pharmacology 385, Suppl. 1: S96, Abstr. 426.
- Ueberberg, B.; Janze, A.-K.; Steinwede, K.; Maus, R.; Magel, L.; Hoymann, H.-G.; Braun, A.; Langer, F.; Jonigk, D.; Kolb, M.; Gauldie, J.; Welte, T.; Maus, U. A. (2012)
Bacterial infection triggers exacerbation of established pulmonary fibrosis in mice: impact on lung protective immunity.
In: American Journal of Respiratory and Critical Care Medicine 185: A3921.
- Veres, T. Z.; Voedisch, S.; Spies, E.; Valtonen, J.; Prenzler, F.; Braun, A. (2012)
Aeroallergen challenge promotes dendritic cell proliferation in the airways. Dec 24 [Epub ahead of print].
In: Journal of Immunology: 8 p.
doi: [10.4049/jimmunol.1200220](https://doi.org/10.4049/jimmunol.1200220)
- Voedisch, S.; Rochlitzer, S.; Veres, T. Z.; Spies, E.; Braun, A. (2012)
Neuropeptides control the dynamic behavior of airway mucosal dendritic cells.
In: PLoS One 7 (9): e45951, 11 p.
doi: [10.1371/journal.pone.0045951](https://doi.org/10.1371/journal.pone.0045951)
- Vogel-Claussen, J.; Schaumann, F.; Renne, J.; Hinrichs, J.; Schoenfeld, C.; Gutberlet, M.; Hüper, K.; Winkler, C.; Faulenbach, C.; Krug, N.; Wacker, F.; Hohlfeld, J. M. (2012)
Semi-quantitative assessment of localized pulmonary inflammation by magnetic resonance imaging in patients with mild allergic asthma following segmental allergen challenge.
In: American Journal of Respiratory and Critical Care Medicine 185: A4319.
- Wiench, K.; Schulte, S.; Champ, S.; Ma-Hock, L.; Schneider, S.; Creutzenberg, O.; Bellmann, B.; Ziemann, C.; Monteiro-Riviere, N.; Ravenzwaay, B. van; Landsiedel, R. (2012)
Zinc oxide – nanosize does not change the toxicological profile.
In: The Toxicologist 126 (1): 300, Abstr. 1392.
- Winkler, C.; Carstens, H.; Müller, M.; Schaumann, F.; Faulenbach, C.; Hohlfeld, J. M. (2012)
Alternative activation of macrophages during the allergic airway inflammation alters antigen presenting capacities.
In: American Journal of Respiratory and Critical Care Medicine 185: A5053.
- Ziegler-Heitbrock, L.; Frankenberger, M.; Heimbeck, I.; Burggraf, D.; Wjst, M.; Haussinger, K.; Brightling, C.; Gupta, S.; Parr, D.; Subramanian, D.; Singh, D.; Kolsum, U.; Boschetto, P.; Potena, A.; Gorecka, D.; Nowinski, A.; Barta, I.; Döme, B.; Strausz, J.; Greulich, T.; Vogelmeier, C.; Bals, R.; Hohlfeld, J. M.; Welte, T.; Venge, P.; Gut, I.; Boland, A.; Olaso, R.; Hager, J.; Hiemstra, P.; Rabe, K. F.; Unmüßig, M.; Müller-Quernheim, J.; Prasse, A. (2012)
The EvA study: aims and strategy.
In: European Respiratory Journal 40 (4): 823-829.
doi: [10.1183/09031936.00142811](https://doi.org/10.1183/09031936.00142811)
- Ziemann, C.; Reamon-Büttner, S.-M.; Schlichting, A.; Brockmeyer, H.; Rahmer, H.; Bellmann, B. (2012)
Human pleural mesothelial MeT-5A cells are a limited in vitro model system in determining potential asbestos-like effects of multiwall carbon nanotubes.
In: Naunyn-Schmiedeberg's Archives of Pharmacology 385, Suppl. 1: 107, Abstr. 473.

DOCTORATES

Lorenz Samy Emmert

Die Bedeutung von Pollen und Starch Granules bei der Allergie der Atemwege.
(The role of pollen and starch granules in respiratory allergy.)
Hannover Medical School
April 2012

Annika Lehmbecker

Effekte der Partikeltranslokation von feinen und nanoskaligen Titandioxid-Partikeln nach Inhalation und intranasaler Instillation bei der Ratte.
(Effects of particle translocation of fine and nano-scale titanium dioxide particles upon inhalation and intranasal instillation in rats.)
University of Veterinary Medicine Hannover, Foundation and Center for Systems Neuroscience (ZSN) Hannover
March 2012

Sophie Seehase

Marmoset monkeys as a pre-clinical model in respiratory research.
University of Veterinary Medicine Hannover, Foundation
November 2012

MASTER'S THESES

Jendrik Füller

Untersuchungen zur Verwendung verschiedener chromatographischer Methoden in der Herstellung und Analytik biopharmazeutischer Plasmide.
(Investigations into the use of different chromatographic methods in the manufacture and analysis of biopharmaceutical plasmids.)
Braunschweig Technical University
November 2012

Olga Helwich

Entwicklung eines neuen Prüfverfahrens zur aerosolphysikalischen Charakterisierung von Aerosolherzeugern für neonatologische Beatmungsgeräte.
(Development of a new test method for aerosol-physical characterization of aerosol generators for preterm infant lung ventilators.)
Leibniz University Hannover
October 2012

Dennis Niermeier

Zelllinienentwicklung und Etablierung einer High-Throughput-Methode zur Optimierung einer plattformbasierten Antikörperaufreinigung.
(Cell line development and establishment of a high-throughput method to optimize a platform-based antibody purification procedure.)
Bremerhaven University of Applied Sciences
March 2012

Teresa Wehren

Validierung funktioneller Untersuchungen im Rahmen von Developmental Neurotoxicity Studies entsprechend OECD 426 unter Nutzung einer geeigneten Positivsubstanz.
(Validation of methods in developmental neurotoxicity studies according to OECD 426 by using a suitable positive control substance.)
RWTH Aachen University
December 2012

BACHELOR'S THESES

Christian Augustin

Etablierung pathway-spezifischer Genexpressionsanalysen am Beispiel der Wirkung von Paraquat auf humane Lungenepithelzellen.
(Establishment of pathway-specific gene expression analyses using the effect of paraquat on human lung epithelial cells as an example.)
University of Applied Sciences Emden/Leer
June 2012

Jana Dietrich

Vergleich zweier eukaryotischer Expressionssysteme in der Zelllinienentwicklung.
(Comparison of two eukaryotic expression systems in cell line development.)
Aachen University of Applied Sciences
February 2012

Andy Geizkopf

Vergleich von Protein A- und Kationenaustauschchromatographie bei der Antikörperaufarbeitung aus Zellkulturüberständen: Einfluss der Vorbehandlung des Zellkulturüberstands.
(Comparison of protein A chromatography and cation exchange chromatography in the processing of antibodies from cell culture supernatant: influence of cell culture supernatant pre-treatment.)
Biberach University of Applied Sciences
November 2012

Maren Kleine

Anforderungsanalyse und Auswahl einer Software zur Intranet-präsentation eines Leitfadendokuments – Durchführung am Beispiel des Leitfadens zur Durchführung klinischer Studien nach AMG am Fraunhofer ITEM.
(Requirements analysis and selection of a Web publishing software to be used for an intranet presentation of the guideline for conduct of clinical trials at the Fraunhofer ITEM according to the German Drug Act (AMG).)
Hannover University of Applied Sciences and Arts
February 2012

Adeline Kongtso

Synthesis of N-dodecylethanamide-DTTA and characterization by mass spectrometry, NMR and IR spectroscopy.
Leibniz University Hannover
September 2012

Janina Müller

Untersuchungen zur Entwicklung eines Kultivierungsmediums für eine humane Amniocyten-Zelllinie.
(Investigations aimed at developing a culture medium for a human amniocyte cell line.)
Braunschweig Technical University
September 2012

Martin Weiß

Optimierung der Auswertmethodik zur Quantifizierung von pathologischen Veränderungen durch Carbon Nanotubes.
(Optimization of the analysis method for quantification of pathological alterations caused by carbon nanotubes.)
University of Applied Sciences Emden/Leer
December 2012

INVITED LECTURES AT CONGRESSES AND CONFERENCES

Dr. Annette Bitsch

Exposure and Risk Assessment for Biocidal Active Substances. Workshop at International Fresenius Conference "Human Health Hazard, Exposure and Risk Assessment For Agrochemicals, Biocides and other Chemicals".

Cologne (Germany)
May 21-22, 2012

Prof. Dr. Armin Braun

CGRP as a nerve-derived DC modulator. 11th Workshop "Models of Asthma and COPD".

Hannover (Germany)
January 21, 2012

Innovative in vitro and ex vivo models: precision-cut lung slices. SOT Session: Innovative Models and Techniques for the Investigation of Nanotoxicity. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.

San Francisco (USA)
March 11-15, 2012

Toxicological and pharmacological testing of a new nanoparticle-based inhalable influenza vaccine in murine and human precision-cut lung slices. New cells, new vaccines.

Wilmington, DE (USA)
March 25-28, 2012

Basic technologies for the study of asthma. P³AGI Summer School 2012 – Imaging Innovations of the Lung.

Göttingen (Germany)
April 18, 2012

Neuroimmune interactions in allergic asthma. SFB 587 symposium.

Soltau (Germany)
May 3-4, 2012

Neuroimmune interaction in allergic asthma. Seminar series "Lung Club".

Homburg/Saar (Germany)
June 6, 2012

Neural mechanisms in asthma exacerbations. EAACI/GA²LEN Allergy School on "Asthma exacerbations: Risk factors and management".

Tallinn (Estonia)
August 2-5, 2012

Can we do anything about the neural mechanisms? EAACI/GA²LEN Allergy School on "Asthma exacerbations: Risk factors and management".

Tallinn (Estonia)
August 2-5, 2012

Neuroimmune interactions in allergic asthma. LISA Summer School, session: Lung Inflammation, Asthma, Allergy.

Hannover (Germany)
September 9, 2012

Humane Ex-vivo-Lungenschnitte (PCLS) als nützliches Werkzeug in der translationalen Lungenforschung. Colloquium of the German Center for Lung Research (DZL).

Hannover (Germany)
November 20, 2012

Translationale Methoden in der Asthmaforschung. Workshop Platform Imaging des DZL – Schwerpunkt Mikroskopie. Hannover Medical School.

Hannover (Germany)
November 27, 2012

Dr. Otto Creutzenberg

Ergebnisse toxikologischer Untersuchungen an ausgewählten CNT. IFA-Fachgespräch Nanomaterialien.

Ludwigshafen am Rhein (Germany)
September 28, 2012

In-vitro and in-vivo testing of nano-ZnO. PROSPECT Final Dissemination Workshop – Achievements in Global Nanomaterials Safety.

London (UK)
November 6, 2012

N1 Project: Approach on nanomaterial safety of ZnO and SiO₂ – final results and overall conclusions. 14th Annual CEFIC-LRI Workshop.

Brussels (Belgium)
November 15, 2012

Dr. Heinrich Ernst

INHAND Nomenclature: Proliferative lesions of the skeletal system and teeth in rodents. 10th European Congress of Toxicologic Pathology, ESTP.

Stresa (Italy)
September 13, 2012

Dr. Ilona Fleischhauer

Qualitätssicherung: Audits bei klinischen Studien. Lecture in the advanced training course "Qualifikation zum Prüfarzt/Prüfärztin bzw. Assistenz in klinischen Studien (GCP-Grundkurs)" at the Hannover Medical School.

Hannover (Germany)
May 8 and December 11, 2012

Introduction to GLP and GMP. Hannover Biomedical Research School (HBRS).

Hannover (Germany)
November 28, 2012

Prof. Dr. Jens Hohlfeld

Challenge models in clinical airway research. 78th Annual Conference of the "Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie" (DGPT).

Dresden (Germany)
March 20, 2012

Klinische Studien mit luftgetragenen Stoffen. GDCh course 157/12 (introduction to toxicology for chemists). Fraunhofer ITEM.

Hannover (Germany)
May 10, 2012

Bedeutung neuer Biomarker in der klinischen Forschung für die Indikation COPD. RIBOLUTION Meeting. Fraunhofer IZI.

Leipzig (Germany)
November 20, 2012

Dr. Stefan Kirsch

Biomarker discovery in DCCs/CTCs: Issues and opportunities. Fresenius Kabi Biomarker Workshop.

Munich (Germany)
September 28, 2012

Prof. Dr. Christoph Klein

Mechanism of colorectal cancer dissemination in lymph nodes and distant organs. Falk Symposium 182: Carcinogenesis, Prevention and Treatment of Colorectal Cancer – State of the Art 2012.

Munich (Germany)
February 10, 2012

Stem cells and stroma in metastasis. IABCR: Breakthrough Breast Cancer Conference.

Manchester (UK)
April 18, 2012

Molecular heterogeneity of the minimal residual disease. 4th IMPAKT Breast Cancer Conference.

Brussels (Belgium)
May 4, 2012

Selection and adaptation during metastatic cancer progression. Metastasis Research Conference 2012.

Brisbane (Australia)
September 4, 2012

Genetic disparity between primary tumors, disseminated tumor cells, and manifest metastasis. Advances in Circulating Tumor Cells.

Athens (Greece)
September 26, 2012

The metastatic process. Herrenhausen Symposium on Metastasis.

Seon (Germany)
October 8, 2012

Selection and adaptation of subpopulations of metastatic cancer cells. The 43rd International Symposium of The Princess Takamatsu Cancer Research Fund.

Tokyo (Japan)
November 16, 2012

Sascha Knauf, D. V. M., Ph. D.

A tiered approach to test anti-inflammatory drugs in different species. 11th Workshop "Models of Asthma and COPD".

Hannover (Germany)
January 20, 2012

NAMES, DATES, EVENTS

Prof. Dr. Norbert Krug

Clinical trials (first-in-man, proof-of-concept). Joint symposium of the Fraunhofer-Gesellschaft. Hebrew University of Jerusalem. Jerusalem (Israel)
January 26, 2012

Angewandte Translations-Forschung in der Allergologie. Neue Horizonte in der Allergologie. Foundation symposium for the cross-disciplinary allergy center of the Hannover Medical School. Hannover Medical School. Hannover (Germany)
March 10, 2012

Atemwegsinfektionen – klinische Studien. Fraunhofer Group for Life Sciences meeting on infection biology research. Fraunhofer ITEM. Hannover (Germany)
April 4, 2012

Forschungskonzept und Gebäudestruktur des Clinical Research Centers (CRC) Hannover. Forum patient-oriented research (HIS workshop). Hannover (Germany)
May 10, 2012

Translational research in airway diseases – searching ncRNA biomarkers for COPD. TRX12 Conference. Life Sciences Queensland. Brisbane (Australia)
October 26, 2012

Dr. Bernhard Polzer

Mechanisms of metastatic dissemination – molecular analysis of tumor cell heterogeneity. Pre-conference Workshop II, European CTC Summit 2012. Berlin (Germany)
April 24, 2012

Entwicklung einer neuen diagnostischen Pathologie der systemischen Krebserkrankung. 4th Scientific Symposium of the Commission for Translational Research. Bergisch Gladbach (Germany)
May 18, 2012

Molekulare Charakterisierung von DCC und CTC. UTZ series of seminars of the University of Düsseldorf. Düsseldorf (Germany)
November 5, 2012

Fraunhofer Projektgruppe Personalisierte Tumorthherapie. Acatech Meeting of the University of Regensburg. Regensburg (Germany)
November 15, 2012

Katharina Schwarz

Exhalierte Aerosole – eine Matrix für die nicht-invasive Diagnostik von Lungenkrankheiten? Colloquium on energy technologies and process engineering. Leibniz University Hannover. Hannover (Germany)
November 6, 2012

Dr. Christian Werno

Mechanismen der Metastasierung beim Lungenkarzinom. Symposium Lungenkarzinom “Gegenwart und Zukunft”. Regensburg (Germany)
June 30, 2012

Dr. Axel Wibbertmann

Senkung des Infektionspotenzials durch effiziente Vor-Ort-Sterilisation. Fraunhofer symposium “Netzwerk” 2012. Munich (Germany)
December 4, 2012

Dr. Christina Ziemann

Basis of classic genotoxicity tests in EMF research. EMF Health Risk Research Workshop – Lessons Learned and Recommendations for the Future – Seven Years Later. Monte Verità (Switzerland)
October 23, 2012

CONTRIBUTIONS TO CONGRESSES AND CONFERENCES

Basma, H.; Gunji, Y.; Liu, X.; Nelson, A.; Farid, M.; Iwasawa, S.; Ikari, J.; Wang, X.; Holz, O.; Mueller, K.-C.; Magnussen, H.; Rabe, K.; Rennard, S. I.
Generation of iPS-like cells from COPD lung fibroblasts. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Batke, M.; Lipzig, M. von; Escher, S.; Frain, H.; Knebel, J.; Kroese, D.; Kuper, F.; Mangelsdorf, I.; McMorrow, T.; Reus, A.; Ryan, M.; Schuchardt, S.; Slattery, C.; van Someren, E.; Stierum, R.
Mechanism-based characterisation of toxicity for RepDose database substances: initial results on cytotoxicity and genomics. 14th Cefic-LRI Annual Workshop 2012: Evolution or Revolution? What Research Priorities for Future Risk Assessment?
Brussels (Belgium)
November 14-15, 2012

Berger-Preiss, E.; Apel, E.; Gerling, S.; Creutzenberg, O.
Determination of 3-MCPD and 3-MCPD esters in biological samples. 36th International Symposium on Capillary Chromatography and 9th GCxGC Symposium.
Riva del Garda (Italy)
May 27-June 1, 2012

Bludau, E.; Veith, N.; Baydoun, L.; Geiszkopf, A.; Paulsen, J.; Duvar, S.; Hecht, V.; Ziehr, H.
Development of a standardized platform for production of antibodies on basis of CHO cells. PEGS Europe Conference.
Vienna (Austria)
November 6-8, 2012

Bohle, K.
Entwicklung einer Plattformtechnologie für Plasmid-DNA als Biopharmazeutikum. GVC/DECHEMA Vortrags- und Diskussions-tagung – Biopharmazeutische Produktion.
Freiburg (Germany)
May 14-16, 2012

Bohle, K.; Roß, A.
Biopharmazeutische Produktion von Plasmid DNA – Einfluss der Wachstumsrate und Auswirkungen auf das Prozessdesign. GVC/DECHEMA Vortrags- und Diskussions-tagung – Biopharmazeutische Produktion.
Freiburg (Germany)
May 14-16, 2012

Braun, A.; Spies, E.; Rochlitzer, S.; Voedisch, S.
Neuropeptides influence airway dendritic cell behavior. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Buschmann, J.; Chahoud, I.; Kellner, R.; Solecki, R.
The DevTox project: terminology, species, and images updated. 40th Conference of the European Teratology Society.
Linz (Austria)
September 2-5, 2012

Costa Pinheiro, N.; Hahn, S.; Bitsch, A.
Emission Scenario Documents (ESD) for biocidal products: Data refinement via questionnaires. Joint annual conference of SETAC GLB and the division of environmental chemistry and ecotoxicology within the German Chemical Society (GDCh): "Erkennen, Untersuchen, Modellieren – Vom Nutzen des Verstehens".
Leipzig (Germany)
September 10-13, 2012

Costa Pinheiro, N.; Hahn, S.; Bitsch, A.
Emission Scenario Documents (ESD) for biocidal products: Data refinement via questionnaires. Workshop "Environmental monitoring of biocides in Europe – from prioritization to measurements".
Berlin (Germany)
November 5-6, 2012

Creutzenberg, O.
N1 project: approach on nanomaterial safety of ZnO and SiO₂ – Final results and overall conclusions. 14th Cefic-LRI Annual Workshop 2012: Evolution or Revolution? What Research Priorities for Future Risk Assessment?
Brussels (Belgium)
November 14-15, 2012

Creutzenberg, O. H.; Ziemann, C.; Hansen, T.; Ernst, H.; Schaudien, D.; Schuchardt, S.; Wiench, K.; Bellmann, B.
Subacute and subchronic inhalation toxicity and dermal absorption of the nanoscaled zinc oxide Z-COTE® HP1 in the rat. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

NAMES, DATES, EVENTS

- Czyz, T.; Polzer, B.; Klein, C. A.
Single-cell array CGH with 100 kb resolution. 1st meeting
"Advances in Circulating Tumour Cells (ACTC): from Basic Research to Clinical Practice".
Athens (Greece)
September 26-29, 2012
- Dasenbrock, C.
Recommendations for the future – The animal biologist's view.
EMF Health Risk Research Workshop.
Monte Verità (Switzerland)
October 22-25, 2012
- Dutow, P.; Lingner, S.; Bode, J.; Laudeley, R.; Glage, S.; Hoymann, H. G.;
Dittrich, A. M.; Müller, M.; Braun, A.; Klos, A.
Chlamydia pneumoniae and asthma bronchiale in a mouse model:
Decrease in airway hyperresponsiveness to house dust mite allergen
after pneumonia. 7th Meeting of the European Society for Chlamydia
Research.
Amsterdam (The Netherlands)
July 1-6, 2012
- Duvar, S.; Hecht, V.; Finger, J.; Gullans, M.; Ziehr, H.
Developing an upstream process for a monoclonal antibody including
medium optimization. 10th Annual BioProduction.
Berlin (Germany)
October 24-25, 2012
- Fuhst, R.; Runge, F.; Buschmann, J.; von Erichsen, J.; Turowska, A.;
Hoymann, H. G.; Müller, M.; Pohlmann, G.; Sewald, K.; Ziemann, C.;
Schlüter, G.; Garn, H.
Advantageous toxicity profile of an inhaled GATA-3-specific DNzyme
intended for anti-inflammatory treatment of Th2-driven asthma.
European Respiratory Society (ERS) Annual Congress.
Vienna (Austria)
September 1-5, 2012
- Hahn, S.; Bitsch, A.; Schröder, K.; Berger-Preiss, E.; Kock, H.;
Behnke, W.; Koch, W.
Validation of the deterministic indoor air model SprayExpo. 7th Inter-
national Conference on the Science of Exposure Assessment (X2012).
Edinburgh (UK)
July 2-5, 2012
- Hahn, S.; Soyka, T.; Regelman, J.; Könnecker, G.; Licht, O.; Bitsch, A.
At which level is an additional factor for EPM within the risk assess-
ment of the benthic environment justified? Society of Environmental
Toxicology and Chemistry (SETAC) 6th World Congress/Europe 22nd
Annual Meeting.
Berlin (Germany)
May 20-24, 2012
- Hansen, T. and Knebel, J.
Calu-3 cells as a model to estimate the pulmonary absorption of
inhaled drugs for the treatment of COPD. Society of Toxicology (SOT)
51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012
- Hansmann, F.; Herder, V.; Ernst, H.; Baumgärtner, W.
Epidermoidzysten im Rückenmark von Mäusen – ein Zufallsbefund?
55th Annual Meeting of the working group on "Pathology" of the
German Society for Veterinary Medicine (DVG).
Fulda (Germany)
March 10-11, 2012
- Haunschild, G.; Rack, B.; Polzer, B.; Appel, I.; Guzvic, M.;
Blankenstein, T.; Maak, M.; Buchholz, S.; Schlimok, G.; Klein, C. A.
Gene expression profiling of single EpCAM-positive cells isolated from
bone marrow of non-metastatic breast cancer patients and healthy
donors. 1st meeting "Advances in Circulating Tumour Cells (ACTC):
from Basic Research to Clinical Practice".
Athens (Greece)
September 26-29, 2012
- Healy, L.; High, W.; Vahle, J.; Rinke, M.; Ernst, H.; Boyce, R.; Schelling,
S.; Long, P.; Boyle, M.; Bolon, B.; Fossey, S.; Bendele, A.; Jolette, J.;
Roth, D.; Leininger, J.
International Harmonization of Nomenclature and Diagnostic Criteria
for Lesions in Rats and Mice (INHAND): Proposed bone nomenclature.
10th European Congress of Toxicologic Pathology (ESTP).
Stresa (Italy)
September 11-14, 2012
- Heinrich, U.; Schlichting, A.; Ziemann, C.; Seyock, S.; Haase, D.;
Leonhardt, A.; Bellmann, B.
Suspension of MWCNT for toxicological in vivo and in vitro studies.
Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012
- Holz, O.; Roepcke, S.; Lauer, G.; Krug, N.; Ernst, P.; Lahu, G.; Hohlfeld, J. M.
Stable inflammatory phenotype in smokers and smokers with COPD.
American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012
- Holz, O.; Schaumann, F.; Janssen, O.; Lavae-Moktari, B.; Biller, H.;
Krug, N.; Hohlfeld, J. M.
Low-dose inhaled LPS challenge – reproducibility of the inflammatory
response. European Respiratory Society (ERS) Annual Congress.
Vienna (Austria)
September 1-5, 2012

Holz, O.; Schaumann, F.; Janssen, O.; Lavae-Moktari, B.; Witte, L.; Krug, N.; Biller, H.; Hohlfeld, J. M.
Neutrophile Atemwegsentzündung in gesunden Probanden nach niedrig dosierter inhalativer Endotoxin (LPS)-Provokation. 53rd Congress of the German Society for Pulmonology and Respiratory Medicine (DGP).
Nuremberg (Germany)
March 29-April 1, 2012

Holz, O.; Schaumann, F.; Janssen, O.; Lavae-Moktari, B.; Witte, L.; Krug, N.; Heinrich, J. M.; Hohlfeld, J. M.
Depletion von neutrophilen Granulozyten aus induziertem Sputum mittels Antikörper-gebundener Beads und Sieb-Trennsystem. 53rd Congress of the German Society for Pulmonology and Respiratory Medicine (DGP).
Nuremberg (Germany)
March 29-April 1, 2012

Holz, O.; Schaumann, F.; Janssen, O.; Lavae-Moktari, B.; Witte, L.; Krug, N.; Heinrich, J. M.; Hohlfeld, J. M.
Depletion of neutrophils from induced sputum using a novel bead and sieve separation system. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Holz, O.; Tan, L.; Scholl, D.; Faulenbach, C.; Mueller, M.; Hidi, R.; Phillips, P.; Wheeler, J.; Krug, N.; McLeod, A.; Hohlfeld, J. M.
Reproducibility of serum biomarkers and relationship to airway inflammation following LPS challenge in healthy volunteers. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Jan, U. von; Ernst, H.; Matthies, H.; Albrecht, U.
MicroScout – An Assistance System for Histological Analysis in Forensics. 46th Annual Conference of the German Society for Biomedical Engineering – BMT 2012.
Jena (Germany)
September 16-19, 2012

Kellner, R.; Rittinghausen, S.
Workflow for establishing historical control data in the RITA database. 31st Annual Symposium of the Society of Toxicologic Pathology (STP).
Boston (USA)
June 24-28, 2012

Kellner, R.; Rittinghausen, S.
Workflow for establishing historical control data in the RITA database. 10th European Congress of Toxicologic Pathology (ESTP).
Stresa (Italy)
September 11-14, 2012

Kirsten, A.; Holz, O.; Tal-Singer, R.; Magnussen, H.; Watz, H.
The p38 MAP kinase inhibitor diltapimod ameliorates airway inflammation induced by ozone challenge in healthy volunteers. European Respiratory Society (ERS) Annual Congress.
Vienna (Austria)
September 1-5, 2012

Kirsten, A.; Watz, H.; Pedersen, F.; Holz, O.; Smith, R.; Bruin, G.; Koehne-Voss, S.; Magnussen, H.; Waltz, D. A.
The anti-IL-17A antibody secukinumab does not attenuate ozone-induced acute airway neutrophilia in healthy volunteers. European Respiratory Society (ERS) Annual Congress.
Vienna (Austria)
September 1-5, 2012

Knauf, S.
A translational approach to test anti-inflammatory drugs in an LPS-induced acute lung inflammation model in the common marmoset. 2nd Cross Company Respiratory Symposium, Novartis.
Horsham (UK)
September 6-7, 2012

Knauf, S.; Seehase, S.; Switalla, S.; Neuhaus, V.; Zoeller, M.; Kaup, F.-J.; Schlumbohm, C.; Fuchs, E.; Lauenstein, H. D.; Sewald, K.; Hohlfeld, J. M.; Braun, A.
A new model for testing human specific anti-inflammatory drugs: LPS-induced lung inflammation in the common marmoset. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Knebel, J.
Innovative in vitro and ex vivo models as significant tools in inhalation toxicology. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

Kuper, F.; Ernst, H.; van Oostrum, L.; Rittinghausen, S.; Penninks, A.; Ganderup, N.; Wolterbeek, A.
Nasal passages of Göttingen minipigs from the neonatal period to young adult. 40th Annual Conference of the European Teratology Society.
Linz (Austria)
September 2-5, 2012

Langer, M.; Booth, J. L.; Patel, V. I.; Duggan, E. S.; Braun, A.; Ramani, V.; Awasthi, S.; Silasi-Mansat, R.; Lupu, F.; Coggeshall, K. M.; Metcalf, J. P.
Human alveolar epithelial barrier function is impaired by *Bacillus anthracis* lethal toxin. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

NAMES, DATES, EVENTS

- Lauenstein, L.
Effects of acute exposure of human precision-cut lung slices to chemicals. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo. San Francisco (USA)
March 11-15, 2012
- Lauenstein, L.; Hess, A.; Vogel, S.; Schneider, X.; Martin, C.; Pirow, R.; Liebsch, M.; Landsiedel, R.; Braun, A.; Sewald, K.
Pre-validation of the ex vivo model PCLS for the prediction of respiratory toxicology. 17th European Congress on Alternatives to Animal Testing. Linz (Austria)
September 5-8, 2012
- Lauenstein, L.; Switalla, S.; Prenzler, F.; Förster, C.; Pfennig, O.; Braun, A.; Sewald, K.
Effects of acute exposure of human precision-cut lung slices to chemicals. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo. San Francisco (USA)
March 11-15, 2012
- Lauenstein, L.; Switalla, S.; Prenzler, F.; Förster, C.; Pfennig, O.; Braun, A.; Sewald, K.
Assessment of lung toxicity induced by chemical allergens in human precision-cut lung slices (PCLS). International Conference of the American Thoracic Society. San Francisco (USA)
May 18-23, 2012
- Lauenstein, L.; Switalla, S.; Ritter, D.; Knebel, J.; Dasenbrock, C.; Braun, A.; Sewald, K.
Acute cigarette smoke exposure induces cytotoxicity and inflammation in living tissue of precision-cut lung slices. American Thoracic Society (ATS). San Francisco (USA)
May 18-23, 2012
- Le, D. D.; Rochlitzer, S.; Funck, U.; Suhling, H.; Braun, A.; Welte, T.; Dinh, Q. T.
Neuroimmune interaction in allergic airway inflammation: expression and function of dendritic cells in sensory airway ganglia neurons. American Thoracic Society (ATS). San Francisco (USA)
May 18-23, 2012
- Lewin, G.; Buschmann, J.
Functional development in young rats: basic data for the performance of juvenile animal studies. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo. San Francisco (USA)
March 11-15, 2012
- Lewin, G.; Buschmann, J.; Asmuss, M.
Influence of extremely low-frequency magnetic fields on juvenile development and behavior in a mouse model. 40th Conference of the European Teratology Society. Linz (Austria)
September 2-5, 2012
- Licht, O.; Voss, J.-U.; Mangelsdorf, I.
Comparison of methods to derive health-based guidance or limit values for chemicals. 78th Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT). Dresden (Germany)
March 19-22, 2012
- Long, P.; Ernst, H.; Schelling, S.; Healy, L.; High, W.; Vahle, J.; Rinke, M.; Boyce, R.; Boyle, M.; Bolon, B.; Fossey, S.; Bendele, A.; Jolette, J.; Roth, D.; Leininger, J.
International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice (INHAND): Proposed joint and tooth nomenclature. 10th European Congress of Toxicologic Pathology (ESTP). Stresa (Italy)
September 11-14, 2012
- Müller, M.
Plasmacytoid dendritic cells down-regulate the allergen-induced T cell proliferation in a human in-vitro allergy model. 2nd Cross Company Respiratory Symposium, Novartis. Horsham (UK)
September 6-7, 2012
- Nendza, M.; Schlechtriem, C.; Kühne, R.; Schüürmann, G.; Zwintscher, A.; Hahn, S.; Jöhncke, U.
Modelling specific mechanisms of bioaccumulation: protein binding and active uptake of surfactants. Society of Environmental Toxicology and Chemistry (SETAC) 6th World Congress/Europe 22nd Annual Meeting. Berlin (Germany)
May 20-24, 2012
- Neuhaus, V.; Schwarz, K.; Koch, W.; Sewald, K.; Yusibov, V.; Braun, A.
Immunotoxic characterization of a nanoparticle-based inhalable influenza vaccine in murine and human precision-cut lung slices. American Thoracic Society (ATS). San Francisco (USA)
May 18-23, 2012
- Paulsen, J.; Geiszkopf, A.; Ziehr, H.
DNA reduction in cell culture supernatants of antibody producing CHO cells. 10th Annual BioProduction. Berlin (Germany)
October 24-25, 2012

Pohlmann, G.; Iwatschenko, P.; Koch, W.; Windt, H.; Rast, M.; Taut, F.; De Muyck, C.
Continuous powder aerosolization (CPA): a new device to administer inhalable particle formulations in high concentrations. 2012 AAPS Annual Meeting and Exposition.
Chicago (USA)
October 14-18, 2012

Polzer, B.; Kirsch, S.; Czyn, Z.; Hoffmann, M.; Pasch, S.; Appel, I.; Fontana, F.; Manaresi, N.; Klein, C. A.
Comprehensive molecular analysis of single circulating tumour cells. European CTC Summit 2012.
Berlin (Germany)
April 24-26, 2012

Polzer, B.; Pasch, S.; Rack, B.; Fontana, F.; Fehm, T.; Alberter, A.; Medoro, G.; Manaresi, N.; Klein, C. A.
Whole genome screen of single circulating tumor cells using a semi-automated workflow. 1st meeting "Advances in Circulating Tumour Cells (ACTC): from Basic Research to Clinical Practice".
Athens (Greece)
September 26-29, 2012

Ritter, D. and Knebel, J.
Improved toxicological characterization of inhalable substances in vitro by in situ fluorescence analysis of the cellular status during exposure. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

Rittinghausen, S.; Teloh, J.; Schaudien, D.; Halter, R.
Immunohistochemical characterization of proliferative lung lesions in SP-C/c-raf-1-BxB mice. 31st Annual Symposium of the Society of Toxicologic Pathology (STP).
Boston (USA)
June 24-28, 2012

Rittinghausen, S.; Teloh, J.; Schaudien, D.; Halter, R.
Immunohistochemical characterization of proliferative lung lesions in SP-C/c-raf-1-BxB mice. 10th European Congress of Toxicologic Pathology (ESTP).
Stresa (Italy)
September 11-14, 2012

Rochlitzer, S.
Impaired anti-viral immune response to human rhinovirus 1B infection in chronic allergic airway inflammation does not manifest in asthma exacerbation. 2nd Cross Company Respiratory Symposium, Novartis.
Horsham (UK)
September 6-7, 2012

Rochlitzer, S.; Hoymann, H.-G.; Müller, M.; Braun, A.
Rhinovirus application on the background of allergic airway inflammation in a chronic house dust mite model. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Schaudien, D.; Knebel, J.; Rittinghausen, S.; Creutzenberg, O.
Measurement of diameter of different nanoparticle agglomerates after contact with A549 cells revealed different size behavior. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

Schaudien, D.; Rittinghausen, S.; Creutzenberg, C.
Similar agglomerate size formation of two different titanium dioxide nanoparticles after intratracheal instillation. 31st Annual Symposium of the Society of Toxicologic Pathology (STP).
Boston (USA)
June 24-28, 2012

Schaumann, F.; Holz, O.; Janssen, O.; Lavae-Mokhtari, B.; Witte, L.; Biller, H.; Krug, N.; Hohlfeld, J. M.
Low-dose endotoxin inhalation in healthy volunteers: a challenge model for early clinical drug development of novel anti-inflammatory compounds. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Seehase, S.
Anti-inflammatory drug testing in marmoset monkey models of LPS-induced acute lung inflammation. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

Seehase, S.; Hoymann, H. G.; Braun, A.; Sewald, K.
Effect of tiotropium on in vivo and ex vivo lung function in a rat model of bronchoconstriction. Cross Company Animal Models Symposium.
Horsham (UK)
September 6-7, 2012

Seehase, S.; Köhncke, S.-P.; Hoymann, H.-G.; Braun, A.; Sewald, K.
Effect of tiotropium on in-vivo and ex-vivo lung function in a rat model of bronchoconstriction. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Seehase, S.; Neuhaus, V.; Kaup, F.-J.; Pfennig, O.; Forster, C.; Hohlfeld, J. M.; Knauf, S.; Braun, A.; Sewald, K.
Ex-vivo lung culture models of marmoset monkeys and humans for anti-inflammatory drug testing. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

NAMES, DATES, EVENTS

Seehase, S.; Switalla, S.; Neuhaus, V.; Zöller, M.; Kaup, F.; Schlumbohm, C.; Fuchs, E.; Lauenstein, H.-D.; Knauf, S.; Sewald, K.; Braun, A.
Anti-inflammatory drug testing in marmoset monkey models of LPS-induced acute lung inflammation. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

Shpigelman, O.; Kopf, J.; Hohlfeld, J.; Braun, A.; Sewald, K.
Carbon black nanoparticles exposure induces cytotoxicity and inflammation in living tissue of precision-cut lung slices. 9th International Conference and Workshop on Biological Barriers.
Saarbrücken (Germany)
February 29-March 9, 2012

Shpigelman, O.; Kopf, J.; Ströbele, M.; Hohlfeld, J.; Braun, A.; Sewald, K.
Cell and tissue culture models as an alternative for the assessment of cytotoxicity and inflammation induced by inhalable carbon black nanoparticles. 17th European Congress on Alternatives to Animal Testing.
Linz (Austria)
September 5-8, 2012

Spannagel, D.; Nuppenau, R.; Lüer, C.
Optimierung eines Aufarbeitungsprozesses für biopharmazeutische Plasmide. GVC/DEHEMA Vortrags- und Diskussionstagung – Biopharmazeutische Produktion.
Freiburg (Germany)
May 14-16, 2012

Steinwede, K.; Maus, R.; Bohling, J.; Voedisch, S.; Braun, A.; Ochs, M.; Schmiedl, A.; Walter, K.; Bange, F.; Welte, T.; Ehlers, S.; Maus, U. A.
Cathepsin G and neutrophil elastase contribute to lung protective immunity against mycobacterial infections in mice. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Gluczkiewicz, I.
The Threshold of Toxicological Concern (TTC) for inhalation exposure: New TTC concept for inhalation exposure and derivation of thresholds with the database RepDose. 14th Cefic-LRI Annual Workshop 2012: Evolution or Revolution? What Research Priorities for Future Risk Assessment?
Brussels (Belgium)
November 14-15, 2012

Gluczkiewicz, I.; Batke, M.; Mangelsdorf, I.; Escher, S.
Derived values and databases for non-cancer endpoints: considerations and concerns. 78th Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT).
Dresden (Germany)
March 19-22, 2012

Ueberberg, B.; Janze, A.-K.; Steinwede, K.; Maus, R.; Magel, L.; Hoyman, H.-G.; Braun, A.; Langer, F.; Jonigk, D.; Kolb, M.; Gauldie, J.; Welte, T.; Maus, U. A.
Bacterial infection triggers exacerbation of established pulmonary fibrosis in mice: impact on lung protective immunity. American Thoracic Society (ATS).
San Francisco (USA)
May 18-23, 2012

Veith, N.
Entwicklung einer standardisierten Plattform zur Herstellung von Antikörpern auf Basis von CHO-Zellen. GVC/DEHEMA Vortrags- und Diskussionstagung – Biopharmazeutische Produktion.
Freiburg (Germany)
May 14-16, 2012

Waschki, B.; Schaper, M.; Sack, A. L.; Holz, O.; Kirsten, A.; Meyer, T.; Rabe, K. F.; Magnussen, H.; Watz, H.
Decrease of physical activity in patients with COPD in the course of the disease. European Respiratory Society (ERS) Annual Congress.
Vienna (Austria)
September 1-5, 2012

Wiench, K.; Schulte, S.; Champ, S.; Ma-Hock, L.; Schneider, S.; Creutzenberg, O.; Bellmann, B.; Ziemann, C.; Monteiro-Riviere, N.; v. Ravenzwaay, B.; Landsiedel, R.
Zinc oxide – nanosize does not change the toxicological profile. Society of Toxicology (SOT) 51st Annual Meeting & ToxExpo.
San Francisco (USA)
March 11-15, 2012

Ziemann, C.; Oertel, A.; Murbach, M.; Kuster, N.; Schürmann, D.; Dasenbrock, C.
No direct genotoxic potential of different radiofrequency electromagnetic fields in human MRC-5 fibroblast cells. 26th Meeting of the Gesellschaft für Umwelt-Mutationsforschung e.V. (GUM).
Mainz (Germany)
February 28-March 2, 2012

Ziemann, C.; Reamon-Büttner, S. M.; Schlichting, A.; Brockmeyer, H.; Rahmer, H.; Bellmann, B.
Human pleural mesothelial MeF-5A cells are a limited in vitro model system in determining potential asbestos-like effects of multiwall carbon nanotubes. 78th Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT).
Dresden (Germany)
March 19-22, 2012

ACTIVE PARTICIPATION IN COMMITTEES

Dr. Luma Baydoun

GMP discussion group "GMP-Gesprächskreis" of the Lower Saxony business inspectorate

Dr. Edith Berger-Preiß

Working group on phthalate measurement "Messen von Phthalaten" of the Association of German Engineers (VDI)

Working group on analyses in biological materials "Analysen in biologischem Material" of the German Research Foundation (DFG)

Reviewer for international journals in analytics and biomonitoring

Dr. Annette Bitsch

Commission on food additives, flavorings, and processing aids "Lebensmittelzusatzstoffe, Aromastoffe und Verarbeitungshilfen" of the German Federal Institute for Risk Assessment (BfR)

Expert panel on wood preservatives in timber construction of the German Federal Institute for Construction Technology (DIBt)

Working committee on probabilistic exposure and risk assessment "Probabilistische Expositionsabschätzung"

Member of the GUM working group on threshold mechanisms of genotoxins

Prof. Dr. Armin Braun

Reviewer for international journals in respiratory medicine and immunology (incl. American Journal of Respiratory and Critical Care Medicine and Journal of Allergy and Clinical Immunology)

Reviewer for international foundations (incl. The Swedish Foundation for Strategic Research and the Fonds National de la Recherche Luxembourg)

PhD commission of the Hannover Medical School (MHH)

Scientific advisory committee of the German Society for Allergology and Clinical Immunology (DGAKI)

Dr. Jochen Buschmann

Working committee on reproductive toxicity "AK Reproduktionstoxizität" of the toxicology advisory board of the German Committee on Hazardous Substances (AGS)

Dr. Otto Creutzenberg

Reviewer for international journals in particle and fiber toxicology (Particle and Fibre Toxicology, Inhalation Toxicology)

Prof. Dr. Clemens Dasenbrock

Committee on Non-Ionizing Radiation, German Radiation Protection Board (SSK)

Editorial board of the journal "Experimental and Toxicologic Pathology"

Treasurer of the German Society for the Promotion of Biomedical Research

Dr. Heinrich Ernst

Editorial board of the journal "Experimental and Toxicologic Pathology"

"Guess What" Committee of the European Society of Toxicologic Pathology (ESTP)

INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) organ working groups "Soft Tissue" and "Skeletal System"

Reviewer for the international journal "Toxicologic Pathology"

Dr. Ilona Fleischhauer

Working groups on GLP quality assurance/monitoring "GLP: Qualitätssicherung/Überwachung", GLP analytics "GLP: Analytik", and GCP quality management "GCP: Qualitätsmanagement" of the German Society for Good Research Practice (DGGF)

Dr. Stefan Hahn

Working committee on chemical risk assessment (deputy head) of the division of environmental chemistry and ecotoxicology "Umweltchemie und Ökotoxikologie" within the German Chemical Society (GDCh)

Prof. Dr. Dr. Uwe Heinrich

Research Committee of the Health Effects Institute (HEI), Boston, USA

DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission): working groups on the definition of threshold limit values for dusts, on the definition of occupational exposure limits, and on the classification of carcinogens; ad-hoc working groups on metals and on nanoparticles

Committee on Hazardous Substances under the German Federal Minister of Labor and Social Affairs: Subcommittee III; Subcommittee III working group on fibers and dusts; Subcommittee III working group on metals (chairman)

Committee supporting the public authorities responsible for the approval of animal experiments (Animal Protection Commission)

Invited member of the working groups on particles, fibers, diesel engine exhaust, polycyclic aromatic hydrocarbons, metals, irritant gases, and air pollution for the compilation of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Scientific advisory committee of the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)

Advisory committee of the Institute for Prevention and Occupational Medicine (IPA) of the German Social Accident Insurance (DGUV)

Advisory committee "VDI Area of Competence Biotechnology" of the Association of German Engineers (VDI)

Editorial board of the journal "Umweltmedizin in Forschung und Praxis"

Editorial board of the "International Journal of Hygiene and Environmental Health"

Co-editor of the manual "Gefährdungsabschätzung von Umweltschadstoffen" (hazard assessment of environmental pollutants)

Prof. Dr. Jens Hohlfeld

Reviewer for international journals (incl. American Journal of Respiratory and Critical Care Medicine, European Respiratory Journal, Journal of Allergy and Clinical Immunology)

External expert for the German Research Foundation (DFG)

Deputy spokesman of the DFG Collaborative Research Center SFB 587 "Immune Reactions of the Lung in Infection and Allergy"

Dr. Rupert Kellner

Councilor for electronic communication and member of the Executive Board of the European Society of Toxicologic Pathology (ESTP)

Global Editorial and Steering Committee (GESC) for the initiative "International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice" (INHAND)

Prof. Dr. Christoph Klein

Member of the Health Research Council of the German Federal Ministry of Education and Research (GFR), working group on an action plan for individualized medicine "Aktionsplan Individualisierte Medizin"

Prof. Dr. Wolfgang Koch

Editorial board of the "Journal of Aerosol Science"

Lecturer at Clausthal University of Technology on dissemination of pollutants in the atmosphere and on aerosols in the environment

ECETOC task force "Lung Overload"

Dr. Gustav Könnecker

Working group on European chemicals policy "Europäische Chemikalienpolitik" of the 6th governmental commission "Energie- und Ressourceneffizienz" of the *Land* Lower Saxony.

Prof. Dr. Norbert Krug

Reviewer for international journals in respiratory medicine and allergy (incl. American Journal of Respiratory and Critical Care Medicine, Thorax, European Respiratory Journal, Journal of Allergy and Clinical Immunology, Allergy, and Clinical and Experimental Allergy)

External expert for the German Research Foundation (DFG)

Panel of non-university health research institutions "Ausschuss der nicht-universitären Forschungseinrichtungen in der Gesundheitsforschung" of the German Health Research Council (GFR)

Scientific advisory board of the German Society for Allergology and Clinical Immunology (DGAKI)

Board of "Biomedical Research in Endstage And Obstructive Lung Disease Hannover" (BREATH) within the German Center for Lung Research (DZL)

Advisory board of the expertise network "Asthma und COPD"

Scientific board of the U-BIOPRED project under the Innovative Medicines Initiative (IMI)

Dr. Oliver Licht

Working committee on regulatory toxicology "Regulatorische Toxikologie" of the German Society of Toxicology within the German Society of Clinical and Experimental Pharmacology and Toxicology (DGPT)

Member of the public relations committee of the German Society of Toxicology within the German Society of Clinical and Experimental Pharmacology and Toxicology (DGPT)

Lecturer at RWTH Aachen University on toxicology and risk assessment

Dr. Norbert Lüthe

Working group on electronic data processing "EDV" of the German Society for Good Research Practice (DGGF)

Fraunhofer quality management network

Dr. Inge Mangelsdorf

Indoor Air Hygiene Committee of the German Federal Environment Agency

Temporary advisor in the WHO International Program on Chemical Safety (IPCS)

Priv.-Doz. Dr. Susanne Rittinghausen

Editorial board of the journal "Experimental and Toxicologic Pathology"

Co-optive member of the ESTP board: representative for nomenclature and RITA

Global Editorial and Steering Committee (GESC) for the initiative "International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice" (INHAND)

"Guess What" Committee (chair) of the European Society of Toxicologic Pathology (ESTP)

INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) organ working groups "Respiratory System", "Endocrine System", and "Soft Tissue"

Reviewer for the international journal "Toxicologic Pathology"

Dr. Anton Roß

Member of the advisory board, DECHEMA section of bioprocess engineering

Dr. Katrin Schröder

Working committee on probabilistic exposure and risk assessment "Probabilistische Expositions- und Risikoabschätzung"

Commission on exposure assessment and exposure standardization "Expositionsschätzung und -standardisierung" of the German Federal Institute for Risk Assessment (BfR)

Dr. Sven Schuchardt

Associate editor of the journal "Biological Chemistry"

Speaker of the Society for Biochemistry and Molecular Biology (GBM) study group "Bioanalytics"

Reviewer for international journals in biochemistry and analytics (incl. Journal of Proteome Research, Electrophoresis, Proteomics, and Talanta)

Dr. Katherina Sewald

Reviewer for the international journals Toxicology Letters, Toxicology in vitro, Nanotoxicology, and for international research grants

Steering Group for the Respiratory Toxicity Workshop

Dr. Holger Ziehr

Association of German Engineers (VDI) committee 6305 "Technical Good Manufacturing Practice"

GMP discussion group "GMP-Gesprächskreis" of the Lower Saxony business inspectorate

Dr. Christina Ziemann

Working group "Genotoxicity" of the DIN NA 119 Water Practice Standards Committee, NA 119-01-03-07-03 AK

Member of the GUM working group on threshold mechanisms of genotoxins

Member of the working group on carcinogenesis "Carcinogenese" of the German Society of Toxicology (GT)

RESEARCH PROJECTS

National

DFG (German Research Foundation)

From Regenerative Biology to Reconstructive Therapy (REBIRTH 2). Excellence cluster

DFG bundle project "Diagnostik und Verlaufskontrolle von Lungenerkrankungen anhand exhalierter Aerosole"

Using exhaled aerosols to diagnose and monitor human respiratory diseases

DFG priority program "Mast Cells – Promoters of Health and Modulators of Disease" (SPP 1394)

Characterization of mast cell anatomy and function in primate airways – interaction with the nervous system. DFG Br2126/3-1

Federal Environment Agency

Carcinogenicity and mutagenicity of nanoparticles – assessment of existing knowledge as a regulatory basis. R&D project 3709 61 220

Toxicology of nanoparticles, mechanisms of action, and carcinogenicity. R&D project 3710 62 221

Human biomonitoring of "novel" hazardous substances, sub-project 1: Preparation of substance dossiers for five substances/substance categories. R&D project 3710 62 220 1

Investigation of non-lipid-based bioaccumulation behavior of compounds. R&D project 3711 63 405/01

Chronic toxicity/carcinogenicity assessment of selected nanomaterials. R&D project 3712 61 206

Federal Institute for Occupational Safety and Health (BAuA)

Health effects of fine and ultrafine particle toxicity in the lung – genotoxicity. Research project F 2135

Dispersion and retention of ultrafine and nanoparticles in the lungs. Research project F 2133

Toxic effects of different modifications of a nanoparticle after inhalation. Research project F 2246

Evaluation of tier 1 exposure assessment models under REACH. Research project F 2303

Federal Institute for Risk Assessment (BfR)

Subacute toxicity studies with 2-MCPD diester and 2-MCPD including subsequent proteomics analyses

Toxicokinetics study to characterize the uptake and distribution of silver nanoparticles in Wistar rats

Further scientific development of the DevTox project

Federal Ministry of Education and Research (BMBF) funding program NanoCare: "Auswirkungen synthetischer Nanomaterialien auf den Menschen" (impact of synthetic nanomaterials on human health)

Project: CarbonBlack

Prediction of the human-toxicological effect of synthetic carbon black nanoparticles

Project: CarboTox

Development of screening methods to analyze cancerogenous potential of carbon nanotubes

Federal Ministry of Education and Research (BMBF) funding program "Ersatz und Ergänzungsmethoden zum Tierversuch" (alternatives and complements to animal experiments)

Extended prevalidation study for examination of the toxic impact of substances effective via inhalation (gases) after direct exposure of human lung cells at the layer between air and liquid

Development of a strategy for establishing categories and defining new categories for the endpoints subacute, subchronic, and chronic toxicity to minimize animal experiments under REACH

Federal Ministry of Education and Research (BMBF) funding program “Vermeidung von Tierversuchen” (avoiding animal experiments)

Validation of the ex-vivo model PCLS for prediction of respiratory toxicological effects

Federal Office for Agriculture and Food

Studies on the bioavailability and metabolism of glycidyl fatty acid esters

Federal Office for Radiation Protection

Impact of low-frequency electromagnetic fields on the developing hematopoietic system, the immune system, and the CNS in vivo

Determination of time dependence of the resuspension of deposited radioactive contamination from urban surfaces, taking into account different environmental influences and countermeasures

German Center for Lung Research

Allergy and Asthma

SFB 587 “Immune Reactions of the Lung in Infection and Allergy”

Neuroimmune interactions in chronic asthma. Project B4

Interaction between the allergic inflammation and the pulmonary surfactant system in asthma. Project B8

Lung function measurements. Project Z2

International

EFSA project:

Combined toxicokinetic and in-vivo genotoxicity study on Alternaria toxins

EU project: ACTICOSPACK

Development of antimicrobial packaging materials for cosmetic products

EU project: ARIMMORA

Advanced research on interaction mechanisms of electromagnetic exposures with organisms for risk assessment

EU project: ChemScreen

Chemical substance in-vitro/in-silico screening system to predict human- and ecotoxicological effects

EU project: Detective

Detection of endpoints and biomarkers for repeated-dose toxicity using in-vitro systems

EU project: Innovative Medicines Initiative (IMI) “Understanding Severe Asthma”

Unbiased biomarkers for the prediction of respiratory disease outcomes (U-BIOPRED)

– WP3 Cross-sectional and longitudinal cohort

– WP4 Bronchoscopy studies

– WP5 Clinical models

– WP6 Pre-clinical laboratory models

EU project: NANODEVICE

Novel concepts, methods, and technologies for the production of portable, easy-to-use devices for the measurement and analysis of airborne engineered nanoparticles in workplace air

EU project: PHOENIX

Synergic combination of high-performance flame retardant nano-layered hybrid particles as real alternative to halogen-based flame retardant additives

EU project: SEAWIND

Sound exposure and risk assessment of wireless network devices

EU project: SILICOAT

Industrial implementation of processes to render RCS safer in manufacturing processes

COOPERATION WITH INSTITUTIONS AND UNIVERSITIES

National

Augsburg University Hospital
– Medical Clinic II
– Urological Clinic

Braunschweig University of Technology
– Department of Biotechnology
– Institute for Drug Delivery Systems
– Institute of Biochemical Engineering
– Institute of Genetics
– Institute of Microbiology

Center of Allergy & Environment (ZAUM), Munich

Charité, Berlin
– Institute of Clinical Pharmacology and Toxicology
– Department of Pediatrics, Division of Pneumology and Immunology

Charité Research Organization, Berlin

ECT Oekotoxikologie GmbH, Flörsheim

Federal Environment Agency, Berlin and Dessau

Federal Institute for Occupational Safety and Health (BAuA), Berlin and Dortmund

Federal Institute for Risk Assessment (BfR), Berlin

Federal Ministry of Food, Agriculture and Consumer Protection

Federal Office for Agriculture and Food, Bonn

Federal Office for Radiation Protection (BfS), Salzgitter

Freie Universität Berlin, Institute of Animal and Environmental Hygiene

German Center for Lung Research (DZL)
– Airway Research Center North (ARCN), Borstel/Lübeck/Kiel/Grosshansdorf
– Universities Giessen and Marburg Lung Center (UGMLC), Giessen and Marburg
– Translational Lung Research Center Heidelberg (TLRC-H), Heidelberg
– Comprehensive Pneumology Center (CPC-M), Munich

German Primate Center, Göttingen

Hamburg University of Applied Sciences, Department of Biotechnology

Hannover Clinical Trial Center (HCTC), Hannover

Hannover Medical School
– Center for Anatomy
– Clinic for Dermatology
– Clinic for Pediatric Pneumology and Neonatology
– Clinic for Pneumology
– Department of Conservative Dentistry, Periodontology and Preventive Dentistry
– Department of Immunology and Rheumatology
– Institute for Clinical Pharmacology
– Institute for Functional and Applied Anatomy
– Institute for Medical Microbiology and Hospital Epidemiology
– Institute for Radiology
– Institute of Experimental Hematology and Oncology
– Institute of Immunology
– Institute of Pharmacology
– Biobank
– Excellence Cluster REBIRTH
– Quality Management in Clinical Research
– SFB 587 Junior Research Group

Helmholtz Center for Environmental Research – UFZ, Leipzig

Helmholtz Center for Infection Research, Braunschweig
– Department of Vaccinology and Applied Microbiology
– Working Group on Immunoregulation

Helmholtz Zentrum München – German Research Center for Environmental Health, Munich

Hospital Grosshansdorf – Center for Pneumology and Thoracic Surgery	University of Giessen, Institute of Anatomy and Cell Biology
Institute of Pharmacology and Preclinical Drug Safety (IPAS), Nycomed: a Takeda company, Barsbüttel	University of Göttingen, Center of Pharmacology and Toxicology, Department of Pharmacology
IPA – Institute for Prevention and Occupational Medicine of the German Social Accident Insurance at Ruhr-Universität Bochum	University of Konstanz, Molecular Toxicology Group
Karlsruhe Institute of Technology, Division of Combustion Technology at the Engler-Bunte Institute	University of Lübeck, Institute of Anatomy
Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures, Braunschweig	University of Mainz – Department of Pneumology – Institute of Informatics
Leibniz University Hannover – Institute of Inorganic Chemistry – Institute of Technical Chemistry	University of Marburg, Faculty of Medicine, Department of Pneumology, Working Group on Cell Biology of the Lung
Research Center Borstel, Priority Area “Asthma and Allergies” – Department of Clinical Medicine, Lab Group Molecular and Clinical Allergology – Department of Immunochemistry and Biochemical Microbiology, Lab Group Lung Pharmacology – Division of Experimental Pneumology	University of Munich, gynecological and maternity hospital and ambulant clinic
Robert Koch Institute, Berlin – Department of Hospital Hygiene, Infection Prevention and Control – Center for Biological Threats	University of Regensburg – Chair of Dermatology and Venerology – Chair of Experimental Medicine and Therapy Research – Chair of Gynecology and Obstetrics – Chair of Immunology – Chair of Neurology – Chair of Pathology – Chair of Statistical Bioinformatics – Chair of Surgery – Chair of Thoracic Surgery – Chair of Trauma Surgery – Chair of Urology
RWTH Aachen University, Institute of Pharmacology and Toxicology	University of Rostock, Medical Clinics, Division of Pulmonology
Technische Universität München (TUM) – Chirurgische Klinik und Poliklinik (surgical and ambulant clinic) – Department of Informatics	University of Tübingen – Department of Dermatology – Department of Gynecology and Obstetrics – Institute for Clinical Epidemiology and Applied Biometry
TWINCORE (center for experimental and clinical research on infections), Hannover	University of Veterinary Medicine Hannover, Foundation – Department of Pharmacology, Toxicology and Pharmacy – Institute for Animal Welfare and Behavior – Institute for Food Toxicology and Analytical Chemistry – Institute for Pathology
Ulm University, Institute of Human Genetics	
University Hospital Carl Gustav Carus Dresden, Department of Hospital Hygiene and Environmental Protection	
University Hospital Düsseldorf – Department of General, Visceral and Pediatric Surgery – Department of Gynecology	
University of Freiburg – Department of Pneumology – Institute of Physics	

NAMES, DATES, EVENTS

International

Centro Ceramico – Bologna, Bologna (Italy)	Swiss Federal Institute of Technology Zurich (ETH), Zurich (Switzerland)
European Food Safety Authority (EFSA), Parma (Italy)	TNO Quality of Life, Zeist (The Netherlands)
Fraunhofer USA – Center for Molecular Biotechnology, Newark, DE (USA)	University of Amsterdam, Academic Medical Center (The Netherlands)
Hebrew University of Jerusalem, Jerusalem (Israel)	University of Basel, Institute of Biochemistry and Genetics (Switzerland)
Imperial College, London (UK)	University of Eastern Finland, Department of Environmental Science, Kuopio (Finland)
Institute of Occupational Medicine, Edinburgh (UK)	University of Sonora, Hermosillo (Mexico)
Instituto de Tecnología Cerámica, Castellón (Spain)	University of Southampton (UK)
IT'IS Foundation for Research on Information Technologies in Society, Zurich (Switzerland)	University of Virginia, Charlottesville, VA (USA)
King Mongkut's University of Technology Thonbure, Bangkok (Thailand)	University of Zurich, Institute of Veterinary Pharmacology and Toxicology (Switzerland)
Life Sciences Queensland, Brisbane (Australia)	US Environmental Protection Agency (EPA), Chapel Hill, NC (USA)
McMaster University Medical Centre, Hamilton, Ontario (Canada)	US Environmental Protection Agency (EPA), Washington, DC (USA)
Ministry of Public Health – Department of Medical Sciences, Nonthaburi (Thailand)	World Health Organization (WHO), Geneva (Switzerland)
National Institute of Cancer Research, Genoa (Italy)	
National Institutes of Health, New Bethesda, MD (USA)	
OECD QSAR Expert Group (France)	
Osaka University, Osaka (Japan)	
Queensland Clinical Trials Network (QCTN), Toowong, Queensland (Australia)	
RIVM National Institute of Public Health and the Environment, Bilthoven (The Netherlands)	
Swiss Federal Institute of Aquatic Science and Technology (EAWAG), Department of Environmental Chemistry, Dübendorf (Switzerland)	

VISITING SCIENTISTS

Aiko Hibino

Osaka University, Osaka (Japan)

Dr. Pasi Jalava

University of Eastern Finland, Kuopio (Finland)

Chungeera Youkong Jongjangklang

Biochemical Engineering and Pilot Plant Research and Development Unit, King Mongkut's University of Technology Thonbure, Bangkok (Thailand)

Panit Kitsubun

Biochemical Engineering and Pilot Plant Research and Development Unit, King Mongkut's University of Technology Thonbure, Bangkok (Thailand)

Rodolfo Munguia Soto

University of Sonora, Hermosillo (Mexico)

Sarunya Poma

Biochemical Engineering and Pilot Plant Research and Development Unit, King Mongkut's University of Technology Thonbure, Bangkok (Thailand)

Suthida Tuntigumthon

Ministry of Public Health, Department of Medical Sciences, Nonthaburi (Thailand)

Pornkamol Unrean, Ph.D.

Biochemical Engineering and Pilot Plant Research and Development Unit, King Mongkut's University of Technology Thonbure, Bangkok (Thailand)

EXHIBITIONS, CONGRESSES, AND WORKSHOPS

January 20-21, 2012

11th Workshop "Models of Asthma and COPD"

Fraunhofer ITEM
Hannover (Germany)

March 11-15, 2012

SOT 2012

Annual Meeting of the Society of Toxicology and ToxExpo
San Francisco, CA (USA)

May 9-10, 2012

Deutsche Biotechnologietage

German Biotechnology Days
Frankfurt/Main (Germany)

May 18-23, 2012

ATS 2012

International Conference of the American Thoracic Society
San Francisco, CA (USA)

May 23, 2012

Kooperationsforum "Biopharmaceuticals"

Benediktbeuern (Germany)

June 18-21, 2012

BIO International Convention 2012

Boston, MA (USA)

June 24-28, 2012

STP 2012

Annual Symposium of the Society of Toxicologic Pathology
Boston, MA (USA)

October 5-8, 2012

EUSAAT 2012

European Congress of the European Society for Alternatives
to Animal Testing
Linz (Austria)

November 12-14, 2012

Bio-Europe 2012

Hamburg (Germany)

EDITORIAL NOTES

Coordination and editorial work
Dr. Cathrin Nastevska

Translation
Karin Schlemminger

Photographs and illustrations
auremar (Fotolia) – front cover (right)
BioPark Regensburg – p. 13
Derege (Fotolia) – p. 63 (top)
focus finder (Fotolia) – p. 65
Fraunhofer ITEM (Rainer Meier, BFF/Nathalie Meier) –
pages: front cover (second and third from the left), 7, 8, 15
(left and middle), 22-23, 39, 42-43, 47, 53, 56-57, 67, 74-75
Nico Herzog – p. 15 (right)
HZI/Sondermann – p. 9
Sascha Knauf – p. 31
MEV-Verlag GmbH – pages: 21 (middle), 54, 79
Ralf Mohr – all portrait photos (unless stated otherwise)
Nickl und Partner – p. 10/11
Alexander Raths (Fotolia) – front cover (left)
Silicon Biosystems SpA – p. 35
Silver-John (Fotolia) – p. 70

All other photographs and illustrations: ©Fraunhofer ITEM,
Fraunhofer-Gesellschaft.

All rights reserved. Reproduction only with permission from
Fraunhofer ITEM.

© Fraunhofer Institute for Toxicology and Experimental Medicine
Hannover 2013

CONTACTS: MARKETING AND PR



Dr. Franz Drenk
Phone +49 511 5350-402
franz.drenk@item.fraunhofer.de



Dr. Cathrin Nastevska
Phone +49 511 5350-225
cathrin.nastevska@item.fraunhofer.de



Karola Neubert
Phone +49 511 5350-413
karola.neubert@item.fraunhofer.de

Fraunhofer Institute for Toxicology and
Experimental Medicine ITEM
Nikolai-Fuchs-Straße 1
30625 Hannover
Germany
Main entrance: Stadtfelddamm
Phone +49 511 5350-0
Fax +49 511 5350-155
info@item.fraunhofer.de
www.item.fraunhofer.de

Fraunhofer ITEM
Pharmaceutical Biotechnology
Inhoffenstraße 7
38124 Braunschweig
Germany
Phone +49 531 6181-6001
Fax +49 531 6181-6199
info@item.fraunhofer.de
www.item.fraunhofer.de