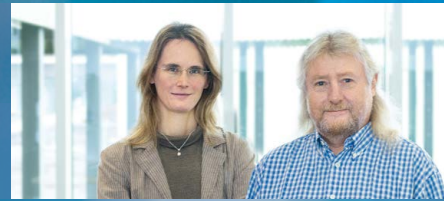


FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

TOXICOLOGY TESTING >



< PRE-CLINICAL PHARMACOLOGY

< EARLY-PHASE CLINICAL TRIALS



< REGISTRATION AND  
RISK ASSESSMENT



ENVIRONMENTAL, OCCUPATIONAL AND CONSUMER PROTECTION >

MANUFACTURING OF BIOPHARMACEUTICALS  
FOR CLINICAL TRIALS >



ANNUAL REPORT  
**2013**



This Annual Report 2013 of the Fraunhofer ITEM gives an insight into the activities and service profiles of the institute's six business units and provides examples of typical contract and pre-competitive research projects performed in each of these areas. The title page and also the opening pages of the different business units in this Annual Report show the business unit spokespersons, who represent, coordinate, and further develop the individual business units to meet market requirements.

---

## **Business units of the Fraunhofer ITEM**

---

Business Unit 1 **Toxicology Testing**

Business Unit 2 **Pre-clinical Pharmacology**

Business Unit 3 **Early-Phase Clinical Trials**

Business Unit 4 **Registration and Risk Assessment**

Business Unit 5 **Environmental, Occupational and Consumer Protection**

Business Unit 6 **Manufacturing of Biopharmaceuticals for Clinical Trials**

**FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM**

**PERFORMANCE AND RESULTS**

**ANNUAL REPORT**  
**2013**

---

## Content

---

Foreword to readers	4
Profile of the institute	6
Organizational structure	9
Competencies	10
GXP – quality assurance to international standards	12
Staff and institute budget performance	14
Advisory board	15
New center for early-phase clinical trials:	
Clinical Research Center Hannover	16
Project Group in Regensburg	18

Business units of the Fraunhofer ITEM	20	Fraunhofer-Gesellschaft	62
		Fraunhofer Group for Life Sciences	63
<b>Business Unit 1</b>			
<b>Toxicology Testing</b>			
Focuses of activity in 2013	22	Names, dates, events	
Projects	26	Publications	64
		Doctorates	67
		Degree dissertations	68
		Master's theses	68
		Bachelor's theses	68
		Invited lectures at congresses and conferences	68
		Contributions to congresses and conferences	70
		Active participation in committees	72
		Research projects	74
		Cooperation with institutions and universities	75
		Exhibitions, congresses, and workshops	77
		Editorial notes	78
<b>Business Unit 2</b>			
<b>Pre-clinical Pharmacology</b>			
Focuses of activity in 2013	30		
Projects	34		
<b>Business Unit 3</b>			
<b>Early-Phase Clinical Trials</b>			
Focuses of activity in 2013	36		
Projects	40		
<b>Business Unit 4</b>			
<b>Registration and Risk Assessment</b>			
Focuses of activity in 2013	42		
Projects	46		
<b>Business Unit 5</b>			
<b>Environmental, Occupational and Consumer Protection</b>			
Focuses of activity in 2013	50		
Projects	54		
<b>Business Unit 6</b>			
<b>Manufacturing of Biopharmaceuticals for Clinical Trials</b>			
Focuses of activity in 2013	56		
Projects	60		

# FOREWORD TO READERS

Dear Reader,

The hallmarks of a Fraunhofer institute are research and development work in cooperation with and on behalf of industry, and excellent application-oriented basic research, also referred to as pre-competitive research. Successful compliance with both these criteria requires that the institutes have precise knowledge about the present and future demands of their industry clients, so as to allow the institutes' service profiles to be optimally adapted to this demand and the relevant fields of study to be further developed as needed. And in fact, it is not unusual to even generate a new demand by a novel and innovative service offer.

The service profiles offered in the different business units of the Fraunhofer ITEM are based on the institute's specific core competencies and their stand-out features. Products and markets are highly dynamic and are influenced, among others, by demand, customers, the competitive situation, and also by the most recent scientific findings. The institute has to continually respond to this dynamics. Constant market and customer observation and analysis and continued further development of scientific competencies are the prerequisites for the institute's work to be scientifically and economically successful.

In 2012 and 2013, the Fraunhofer ITEM underwent a scrutiny process during which its competencies, services, business units, markets, client base, and competitors were evaluated in an analysis of strengths and weaknesses and were checked for topicality and future proofness in an intense, institute-wide discussion process. Based on these results, the institute's core competencies and business units were remodeled and, wherever necessary, newly developed. In a 5-year strategy plan for the institute and its business units, objectives were defined and roadmaps with milestones for the implementation of these objectives were devised.

In an audit with representatives from industry and the public sector, selected as representative clients of the services offered by the Fraunhofer ITEM, and in an intense discussion process with the members of the institute's advisory board, the strategy plan has been further developed, in particular with regard to national and international market attractiveness and the institute's claim for excellent scientific competence and for good networking in the regional, national and international scientific landscapes.

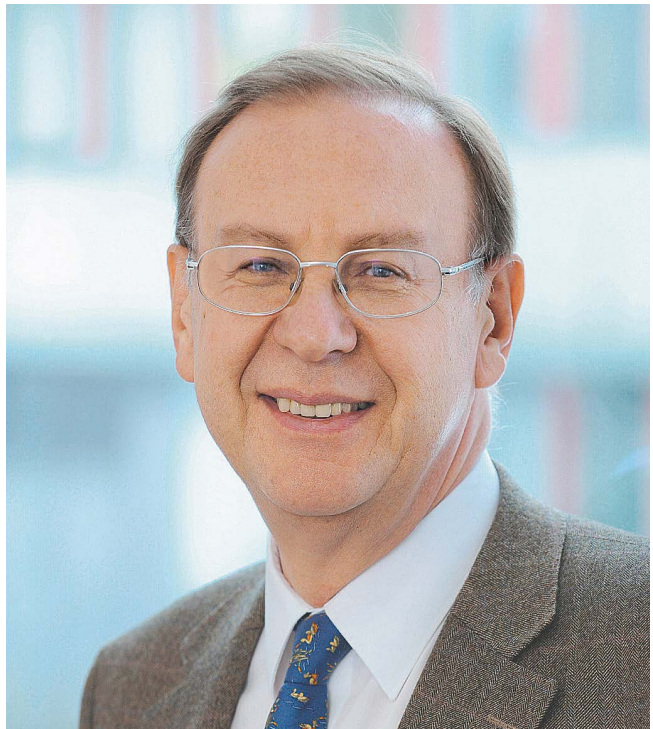
In cooperation with the business unit spokespersons, the institute's marketing department supports project acquisition for the different business units and verifies whether the services offered are in line with current market demands. Institute directors and marketing staff regularly discuss and monitor compliance with the defined roadmaps, not only with regard to their adequate implementation, but in particular also to review whether the defined objectives are still up to future demands and market conditions.

In this Annual Report, you will find descriptions of the institute's six business units and examples of typical contract and pre-competitive research projects performed in each of these areas.

I hope this will help our present and future clients to even better understand the relevance and added value of our service profiles, both in the individual business units and also across these, for the development of their new products and technologies.

I would like to thank our clients who used our services during the past year and I look forward to new cooperations with partners to whom we offer development of customized services.

I would also like to take this opportunity to thank the institute's staff for their highly professional and client-oriented conduct of commissioned projects, for their committed cooperation in the institute's strategy process, and for their outstanding, nationally and internationally acknowledged research work.



A handwritten signature in black ink, which appears to read 'U. Heinrich'.

Prof. Dr. Dr. Uwe Heinrich  
Executive Director

# PROFILE OF THE INSTITUTE

Research at the Fraunhofer ITEM is focused on human health. The emphasis is on two aspects: firstly, on protecting health from potentially harmful, in particular airborne substances, be they gases, aerosols, particles, fibers, or nanomaterials, and secondly, on investigating and developing diagnostic and therapeutic approaches in the field of inflammatory and allergic respiratory conditions. For over 30 years already, the Fraunhofer ITEM has been building up and further enhancing its expertise in the areas of inhalation toxicology and pre-clinical airway research, and for over 10 years, the institute's clinical division has furthermore performed clinical proof-of-concept studies. Airway diseases, inhalation toxicology, and inhalable substances are thus at the focus of research at the Fraunhofer ITEM, even though the institute's work is not limited to these subject areas.







## Protecting human health

Health protection includes environmental, occupational, and consumer protection. The Fraunhofer ITEM supports industry and public authorities in the early identification and prevention of health hazards from new products and processes and thereby also promotes sustainable development of Germany as a business location.

In this context, Fraunhofer scientists investigate novel products and processes whose potential hazards are as yet unknown – such as different nanomaterials –, evaluate the human exposure situation, and develop suggestions on how to reduce or eliminate these potential hazards. For the experimental part of risk assessment, the Fraunhofer ITEM has at its disposal the necessary know-how and toxicological test methods, in particular in the field of inhalation toxicology. For the required tests, complex atmospheres and test aerosols can be generated at laboratory scale and exposure scenarios can be reproduced for in-vitro or in-vivo studies. Special computerized mathematical exposure models are also developed and used for this purpose.

The scientists perform exposure and risk assessment on behalf of clients, based on their own experimental studies, literature searches, and data provided by the client. They prepare reports on test substances and support clients in the registration of chemicals and complex mixtures and in the assessment of substances under the European chemicals regulation REACH.

## Therapies for respiratory diseases: pre-clinical research and development

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. Toxicological and safety pharmacological testing for drug registration is performed in compliance with GLP.

The institute offers a broad range of efficacy and drug safety studies and makes use of a variety of in-vitro test systems and models of inflammation, asthma, and lung infection. Using a tiered approach, the scientists first perform studies in cell culture models and subsequently gain further insights in complex tissue cultures and eventually in animal models. The use of human tissue in particular allows them to obtain human data at an early stage already, data of pivotal importance above all in the testing of biopharmaceuticals.

Throughout this process, the Fraunhofer ITEM follows the 3-Rs concept (“reduce, refine, replace”), consistently trying to reduce the number of laboratory animals needed, to refine research methods, and to replace animal experiments by alternative methods.



### **Biopharmaceutical manufacturing: from the cell line to the investigational medicinal product**

A team of scientists, engineers and technicians in the institute's facilities in Braunschweig advises and assists clients and cooperation partners in the development of novel biopharmaceutical agents – from the development of recombinant production cell lines via the manufacturing of master and working cell banks, bioprocess development and scale-up, to the manufacturing of pilot batches of the novel biopharmaceutical agent and sterile fill and finish of investigational medicinal products in the form of infusion solutions or in vials or ampoules (in compliance with GMP guidelines).

### **Therapies for respiratory diseases: clinical studies**

For the registration of pharmaceuticals for the indications allergy, asthma, and COPD, the Fraunhofer ITEM conducts clinical studies managed by highly qualified physicians, mainly proof-of-concept studies, in compliance with GCP guidelines. Whenever needed, the required investigational medicinal products can be manufactured on site in compliance with GMP guidelines.

With the Fraunhofer Environmental Challenge Chambers (Fraunhofer ECC in short), the institute has its disposal special challenge chambers that are among very few of this kind worldwide. In these chambers, pollen, house dust mite and other allergens can be dispersed in the air in a precisely controlled manner. The efficacy of novel medications, for example, to treat seasonal allergic rhinitis can be tested there under

controlled allergen challenge conditions. And in challenge studies with LPS or ozone, the clinical efficacy of new anti-inflammatory drugs can be verified. The temporary inflammation of the airways in healthy study participants induced by short-term controlled ozone inhalation challenge resembles the inflammatory condition seen in COPD patients.

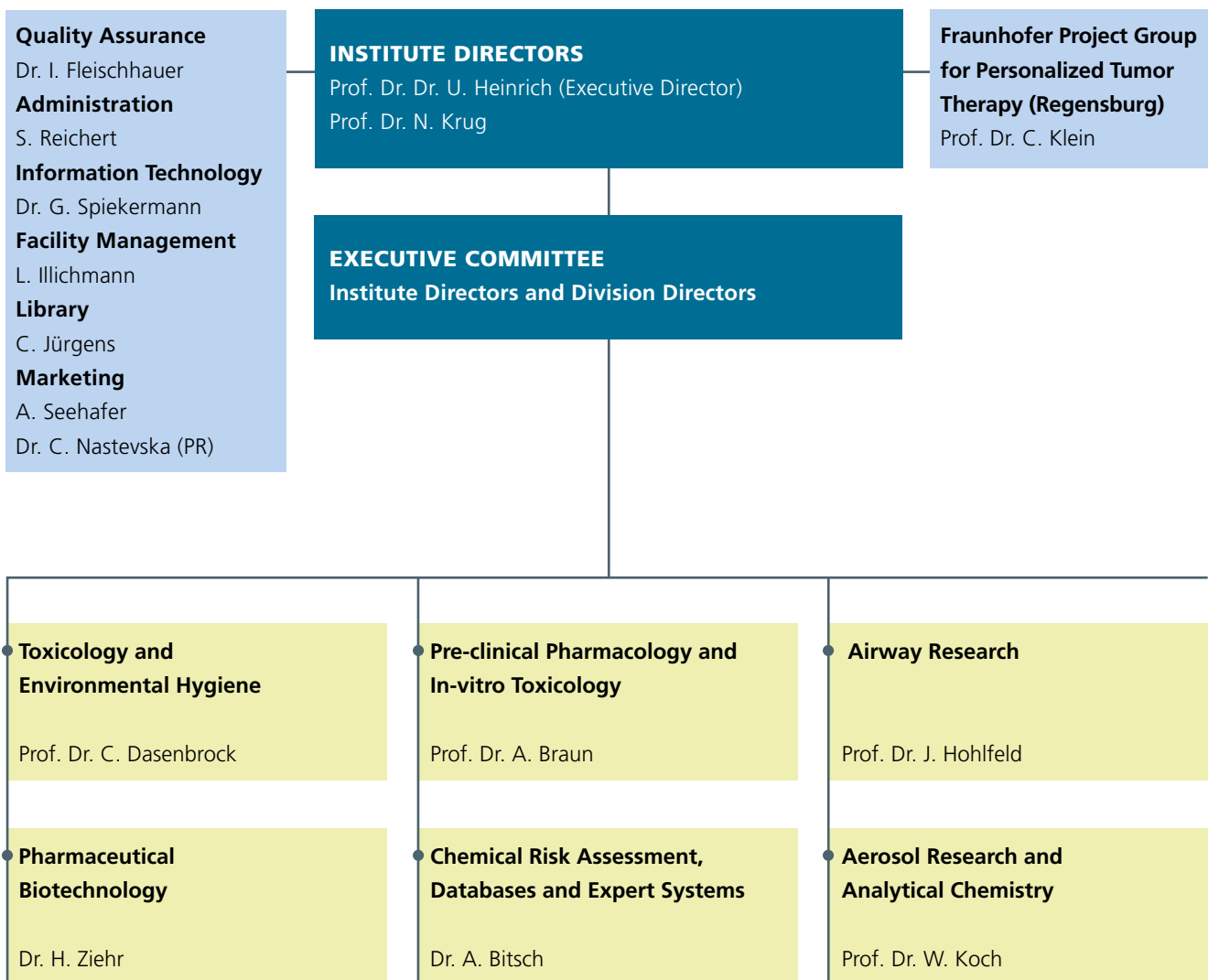
### **Aerosol technology in medicine**

An essential prerequisite for the setup, further development, and operation of the Fraunhofer ECC is the comprehensive expertise and many years of experience of the institute's aerosol technologists. Their know-how on the aerosolization of substances and on the deposition and kinetics of inhaled materials is also important in the development of medicinal aerosols and their formulations and in the development of new technologies for medical application of aerosols.

### **Early-phase clinical studies in the Clinical Research Center Hannover**

A new clinical study center, the "Clinical Research Center Hannover" (CRC Hannover), is being set up as a joint venture of the Fraunhofer ITEM, the Hannover Medical School, and the Braunschweig-based Helmholtz Center for Infection Research. The CRC Hannover will offer an optimal infrastructure for conducting early-phase clinical trials (phases I and II) and will thus set the stage for performing the critical step in medical translational research, which is efficacy and tolerability testing of new drug candidates in human test subjects. First clinical trials in the new study center are planned to begin in fall 2014.

# ORGANIZATIONAL STRUCTURE



(as of 2014)

Headed by the Institute Directors and the Executive Committee, the Fraunhofer ITEM is organized in six divisions. The institute's headquarters are in Hannover (Germany), except for the Division of Pharmaceutical Biotechnology, which has its facilities in Braunschweig on the campus of the Helmholtz Center for Infection Research.

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.

# COMPETENCIES

The Fraunhofer ITEM has pooled the competencies from its various divisions in business units. This chart gives you the contact persons for the individual competencies, working groups, and departments at a glance (as at February 2014).

---

## Toxicology and Environmental Hygiene

---

### Inhalation Toxicology

Dr. O. Creutzenberg  
Prof. Dr. C. Dasenbrock

### General and Regulatory Toxicology

Dr. R. Fuhst

### Reproductive Toxicology

Dr. J. Buschmann

### Pathology

Priv.-Doz. Dr. S. Rittinghausen

### Transgenic Technologies

Dr. R. Halter

### Animal Laboratories

Dr. T. Tillmann

---

## Pre-clinical Pharmacology and In-vitro Toxicology

---

### Airway Pharmacology

Dr. H.-G. Hoymann

### Immunopharmacology and Immunotoxicology

Dr. K. Sewald

### Experimental Immunology

Prof. Dr. A. Braun

### Microbiology and Infection

Dr. S. Rochlitzer

### Genetic Toxicology and Epigenetics

Dr. C. Ziemann

### Pre-clinical Biomarkers and ADME

Dr. T. Hansen

### In-vitro Inhalation Toxicology

Dr. J. Knebel

### Molecular Toxicology and Pharmacology

Dr. M. Niehof

### Primate Research

S. Knauf, D. V. M., Ph. D.

---

## Airway Research

---

### Clinical Airway Research

Prof. Dr. J. Hohlfeld  
Dr. P. Badorrek

### Clinical Method Development

Dr. O. Holz

### Clinical Pharmacology

Prof. Dr. J. Frölich  
Dr. P. Badorrek

### Biomarker Analysis and Development

Dr. M. Müller

---

## **Pharmaceutical Biotechnology**

---

### **Quality Control**

Dr. L. Baydoun  
Dr. U. Pägelow

### **Cell Culturing Techniques**

Dr. S. Duvar  
Dr. V. Hecht

### **Microbial Cultivation**

Dr. A. Ross  
Dr. K. Bohle

### **Downstream Processing**

Dr. J. Paulsen  
Dr. C. Lüer

### **Aseptic Fill and Finish**

Dr. J. Paulsen  
Dr. L. Baydoun

---

## **Chemical Risk Assessment, Databases and Expert Systems**

---

### **Chemicals/REACH**

Dr. G. Könnecker  
Dr. O. Licht

### **Biocides**

Dr. A. Bitsch

### **Veterinary Medicinal Products**

Dr. G. Könnecker  
Dr. A. Wibbertmann

### **Exposure Assessment**

Dr. S. Hahn

### **Testing Strategies and Structure-Activity Relationships**

Dr. S. Escher  
Dr. M. Batke

### **Databases and Information Systems**

Dr. R. Kellner

### **Risk Assessment of Nanomaterials**

Dr. K. Schröder

---

## **Aerosol Research and Analytical Chemistry**

---

### **Aerosol Technology**

Prof. Dr. W. Koch  
Dr. K. Schwarz

### **Medical Inhalation Technology**

Dr. G. Pohlmann

### **Bio- and Environmental Analytics**

Dr. S. Schuchardt  
Dr. E. Berger-Preiß

### **Structure Analytics**

Dr. S. Schuchardt

# GXP – QUALITY ASSURANCE TO INTERNATIONAL STANDARDS

The services and products offered by the Fraunhofer ITEM meet high quality standards, ensuring maximum safety for trial subjects in clinical studies performed at the institute. The relevant legal regulations are complied with and regulatory requirements are invariably taken into consideration. To guarantee that the work performed at the Fraunhofer ITEM satisfies internationally accepted quality standards, the Fraunhofer ITEM has implemented the GXP quality assurance systems. These include Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP). The central service unit “Quality Assurance” is responsible for putting into practice the relevant quality assurance programs.

## **GLP conformity of non-clinical safety tests**

To ensure reliability and reproducibility of the data generated in non-clinical health and environmental safety studies, the GLP principles include, among others, the following requirements:

- Clear assignment of responsibilities within the test facility
- Meticulous planning and qualified performance of every study
- Complete documentation of all procedures and preparation of comprehensive reports

The service unit “Quality Assurance” continuously monitors compliance with these principles in the institute’s toxicological and analytical departments. During the past two decades, the competent authorities have performed regular inspections and certified the institute’s GLP conformity for a broad range of studies.

## **GCP standard of clinical trials**

The ethical principles for biomedical research laid down in the Declaration of Helsinki form the basis of the GCP principles describing the quality standards to be met in clinical trials. At the Fraunhofer ITEM, a broad range of measures ensures that these requirements can be met both in trials performed in the Department of Clinical Airway Research on behalf of international sponsors and in studies initiated by Fraunhofer

*The GMP unit of the Fraunhofer ITEM in Hannover enables patient-specific dilution and aseptic fill and finish of investigational medicinal products in spatial proximity to the institute's clinical department.*



researchers (referred to as “investigator-initiated trials”). The service unit “Quality Assurance” assists the clinical investigators in fulfilling their responsibilities. Both the monitoring authority and the institute’s sponsors have assessed the quality level reached to be GCP-compliant.



#### **CONTACT**

Dr. Ilona Fleischhauer  
Phone +49 511 5350-304  
[ilona.fleischhauer@item.fraunhofer.de](mailto:ilona.fleischhauer@item.fraunhofer.de)

#### **GMP facilities at the institute’s Hannover and Braunschweig sites**

All manufacturing and quality control steps for investigational medicinal products to be used in clinical trials – including challenge agents – are subject to stringent GMP requirements. To enable patient-specific dilution and aseptic fill and finish of investigational medicinal products in spatial proximity to the clinical department, an appropriate GMP facility has been successfully established at the Fraunhofer ITEM in Hannover. This has been confirmed by the competent authorities that granted the corresponding GMP manufacturing authorization.

The institute’s Division of Pharmaceutical Biotechnology in Braunschweig is able to manufacture active biopharmaceutical ingredients and investigational medicinal products in compliance with GMP. The comprehensive expertise of the GMP staff allows GMP-compliant realization of a broad range of projects. The Braunschweig facilities received their first manufacturing authorization in 1998, and it has been extended several times over the years. The last inspection by the competent authorities took place in December 2012.

# STAFF AND INSTITUTE BUDGET PERFORMANCE

At the end of 2013, 292 people were employed at the Fraunhofer ITEM. The following list gives the numbers of employees by occupational groups:

- 87 scientists
- 75 graduates
- 73 technical staff
- 4 Ph. D. students
- 24 laboratory assistants
- 19 other assistants
- 10 apprentices

In 2013, the institute's budget reached a level of 22.8 million euros\*. Financing by acquired funding amounted to 72.9 percent. The share of industrial income in the institute's budget was 40.0 percent – with regard to the Fraunhofer ITEM in Hannover it was 47.0 percent. Investments of the Fraunhofer ITEM amounted to approximately 1.5 million euros.

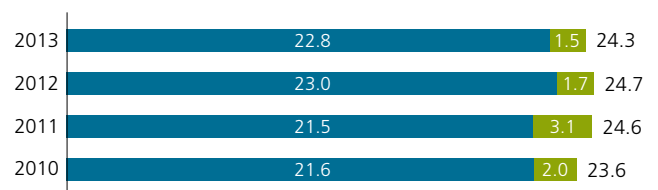
## Staff of the Fraunhofer ITEM

Number of employees



## Total budget of the Fraunhofer ITEM

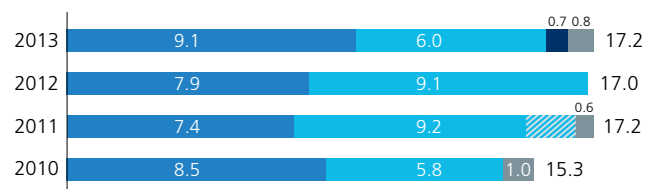
In million euros



- Operating budget
- Investments

## Sponsors and external income of the Fraunhofer ITEM

In million euros



- Industry and commercial associations
- Public sector
- EU
- Other
- ▨ Project-financed investments at the institute's Braunschweig facility

\* Preliminary figures, valid at the time of printing



# 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 2013, 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 HealthCare AG

**Professor Dr. Dieter Bitter-Suermann**

Deputy Chairman of the Advisory Board  
Former 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

**Professor Dr. Ulrich Deschl**

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

**Professor Dr. Paul-Georg Germann**

Head Preclinical Safety Germany, AbbVie Deutschland GmbH

**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,  
University of Carolina at Chapel Hill, USA

**Dr. Edgar Leibold**

Vice President Product Stewardship, BASF SE

**Professor Dr. Reinhard Pabst**

Lower Saxony Professorship in Immunomorphology,  
Hannover Medical School

**Professor Dr. Klaus F. Rabe**

Head of Pneumology, LungenClinic Grosshansdorf;  
Endowed Professorship in Internal Medicine/Pneumology,  
University of Kiel

**Professor Dr. Gerhard Schlüter**

Consultant in Toxicology, former Global Head Toxicology,  
Bayer HealthCare 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

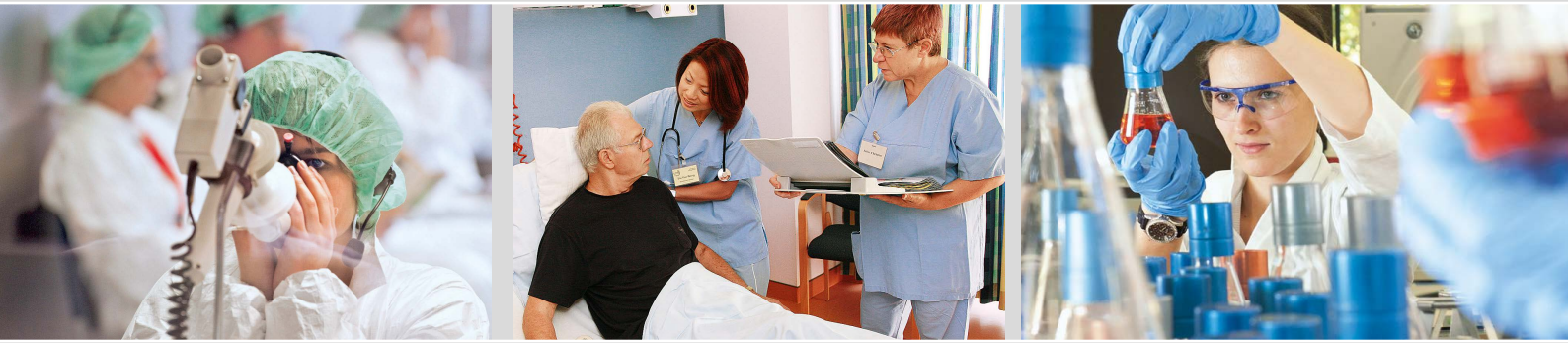
# NEW CENTER FOR EARLY-PHASE CLINICAL TRIALS: CLINICAL RESEARCH CENTER HANNOVER



CRC HANNOVER

Construction of the Clinical Research Center Hannover (CRC Hannover) is almost complete. With this new center erected on the grounds of the Fraunhofer ITEM, infrastructure for clinical trials will be available to the life sciences in the Hannover-Braunschweig area as of 2014. The new center will allow novel methods, therapeutics and diagnostics to be developed further than before within the academic landscape. The CRC Hannover will thus further contribute to closing the gap between health research and medical practice.





### Platform for research-intensive studies

The CRC Hannover will be operated by the Fraunhofer ITEM in cooperation with the Hannover Medical School (MHH) and the Braunschweig-based Helmholtz Center for Infection Research (HZI), providing a platform for safety and efficacy testing of novel drugs and methods as part of the registration process. The close dovetailing of the involved partners makes it a clinical test center that combines academic expertise with infrastructure possibilities that are normally found in private commercial testing institutions. The CRC Hannover is thus perfectly predestined for conducting research-intensive studies.

### Strong partners provide an unrivaled environment for clinical studies

The Fraunhofer will relocate to the new center its Division of Airway Research, whose focus has always been on clinical trials. The enhanced capacities will allow the institute's business unit "Early-Phase Clinical Trials" to be further strengthened in this field. Clinical trials in major research areas of the MHH, incorporation of the MHH biobank, and integration of the HZI's epidemiological expertise will provide a scientific environment for clinical studies that is so far unrivaled in Germany. The CRC Hannover, furthermore, is a constituent of the Translational Alliance in Lower Saxony (TRAIN). TRAIN is a cross-disciplinary alliance of university and non-university research institutes in

Lower Saxony, funded by the Lower Saxony Ministry of Science and Culture. Its aim is to develop novel drugs and vaccines and accelerate their transfer from bench to bedside.

### Infrastructure for a broad study portfolio

For the performance of phase-I studies, that is, first-in-man trials with novel drugs to test their safety in a small number of volunteers, and phase-II studies, required to provide the proof of concept of novel medications or therapeutic approaches in man, a total of 50 beds will be available, 30 of which will allow intensive monitoring of study participants. The technical equipment in the new center will enable comprehensive diagnostics, complemented by additional infrastructure of the partners. The CRC Hannover is planned to become operable in 2014: In May, the Germany-wide epidemiological study "National Cohort", investigating public health status and wide-spread medical conditions in Germany under the direction of the HZI, will be initiated, and later this year, the MHH and the Fraunhofer ITEM Division of Airway Research will welcome their first study participants in the new building.



#### CONTACT

Prof. Dr. med. Norbert Krug  
 Phone +49 511 5350-602  
[norbert.krug@item.fraunhofer.de](mailto:norbert.krug@item.fraunhofer.de)

---

## Infrastructure

---

- 30 intensive-monitoring beds (for clinical trials of phases I and IIa)
- 20 beds for study participants who do not require intensive monitoring
- Outpatient section for screening visits
- Infrastructure for study participants incl. cinema, gym, and cafeteria
- 15 rooms for special diagnostics
- Imaging technology (MRI)
- Biomarker laboratory
- Biobank

# PROJECT GROUP IN REGENSBURG

Since 2011, the Project Group for Personalized Tumor Therapy has been a part of the Fraunhofer ITEM. Its focus is on tumor diagnosis, in particular on detection of single circulating tumor cells, and on the development of novel tumor therapies. The group, which meanwhile has reached a size of nine scientists and six technical assistants, is headed by Professor Christoph Klein, who is also holding the Chair of Experimental Medicine and Therapy Research of the University of Regensburg. In 2013, the focus of research was on the characterization of single circulating tumor cells and on the development of diagnostic methods enabling detection and analysis of circulating tumor cells for routine use in hospitals.

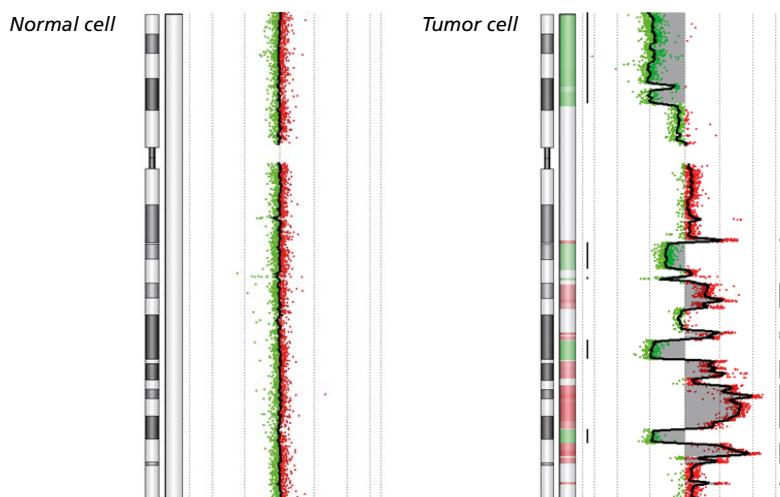
## High-resolution analysis of single-cell genomes

Analysis of minute quantities of genomic DNA is becoming increasingly important in oncology, human genetics, and forensic medicine. Especially in the field of clinical cancer research, the high molecular heterogeneity between individual tumor cells creates ever greater challenges. Here, a robust method to analyze the whole genome of a single cell could pave the way for new diagnostic and therapeutic approaches. During systemic cancer progression, metastases arise in distant organs years after surgical excision of the primary tumor. This process is

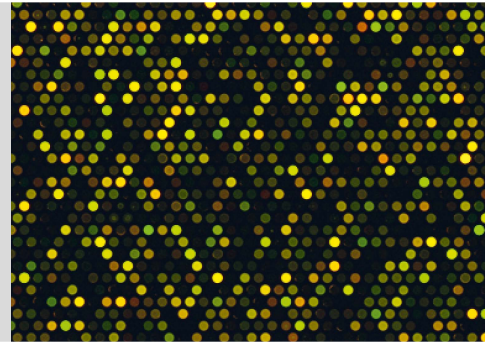
driven by the evolutionary principles of adaptation and selection of aggressive tumor cells, which are based on genomic heterogeneity of single cells.

To allow a better insight into these driving forces of metastasis, scientist of the Fraunhofer Project Proup for Personalized Tumor Therapy recently developed a method that enables – after whole-genome amplification with *Ampli1*<sup>TM</sup> – comprehensive analysis of the complete genome of a single cell. Using single cells from healthy donors and well characterized cancer cell lines it was demonstrated that the newly developed protocol for high-resolution comparative genome hybridization on microarrays (arrayCCH) displays high specificity and accuracy

**Fig. 1:** The method of comparative genome hybridization on microarrays (arrayCGH) allows investigation of the genetic changes in a tumor cell. The figure shows the genomic profile (arrayCGH profile) of chromosome 17 of a normal cell (left part of the figure) compared with that of the breast cancer cell line MDA-MB-453 (right part of the figure). While the profile of the normal cell does not show any deviations from the center-line, the chromosome of the tumor cell displays numerous deviations to the right (red), indicating increased DNA copy numbers, and to the left (green), indicating DNA losses.



*Analysis of the genome and transcriptome of single circulating tumor cells will help develop novel individualized and more effective anti-cancer therapies.*



in the detection of DNA copy number changes in single cells (Fig. 1). The method allows reliable detection of genomic alterations as small as 0.1 Mb in size. Importantly, fixation and staining procedures which are necessary to detect single disseminated cancer cells but potentially harmful to DNA showed no significant impact on the performance of the new aCGH approach, indicating applicability of the method in clinical research or diagnosis. To demonstrate usability of the new workflow in a clinical setting, the genomic profiles of single disseminated cancer cells isolated from a metastatic breast cancer patient were analyzed. To this end, bone marrow was repeatedly sampled during the course of high-dose chemotherapy treatment, single disseminated cancer cells were isolated, and their genome was amplified. Finally, by means of the new aCGH assay it was possible to detect genetic heterogeneity not only of individual disseminated cancer cells, but also as compared to samples from the primary tumor. Additionally, the newly developed approach detected subclones with a distinctive genomic profile among the metastatic precursor cells and allowed their clonal evolution to be monitored over time. In the future, this approach may have considerable practical implication for the selection of targeted therapeutic approaches and prediction of cancer patients' outcome.



#### **CONTACT**

Zbigniew T. Czyz  
Phone +49 941 298480-53  
zbigniew.czyz@item.fraunhofer.de

### **Molecular profiling of single circulating tumor cells in a diagnostic approach**

More than 40,000 patients are enrolled in over 200 clinical studies that are currently exploring clinical exploitation of the detection of circulating tumor cells (CTCs) as a so-called "liquid biopsy". Molecular analysis of these rare CTCs could

contribute to selection of the optimal anti-cancer therapy for each individual patient in the future. To allow this approach to be used in routine clinical diagnosis, however, standardization of the analytical work flow is mandatory.

In an international study, scientists of the Project Group for Personalized Tumor Therapy combined CellSearch®, the gold standard for CTC enrichment and detection, with an automated single-cell isolation system (DEPArray™) and *Ampli1*™, a method to amplify the whole genome of a single cell developed by this project group. In this study, they were able to isolate 510 single CTCs of 66 breast cancer patients as well as 189 single leucocytes as controls. The researchers invented a method to define a genome integrity index (GII) for single cells that reliably predicts success for targeted downstream molecular analysis and that was found to correlate with CTC morphology. During further molecular analysis of these single tumor cells, they detected mutations in the therapy-relevant genes HER2 and PIK3CA in 17 percent and 37 percent of patients, respectively. Interestingly, in many patients these mutations could not be detected in the primary tumor that had been surgically removed years before blood draw. This finding substantiates the hypothesis that advantageous genomic aberrations are selected in disseminated tumor cells after leaving the primary tumor.

In conclusion, the developed work flow for the first time allows comprehensive molecular analysis of single cells with diagnostic intention. By applying this approach in controlled clinical therapy studies, the scientists now want to evaluate if the molecular profile of CTCs can predict success of targeted therapies in individual patients and help uncover emerging therapy resistance at an early time point.



#### **CONTACT**

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

# BUSINESS UNITS OF THE FRAUNHOFER ITEM

## **Expertise pooled in six business units**

The Fraunhofer ITEM has pooled its wide spectrum of expertise (see page 10) in six business units and is thus able to investigate issues of human health on behalf of clients from industry, industry associations, occupational safety and health organizations, and public authorities. If desired, full-package solutions can also be offered, whenever necessary in cooperation with partners.

This Annual Report gives you an insight into the scope of services and selected projects performed in the different business units.

**Business Unit 1** Toxicology Testing

**Business Unit 2** Pre-clinical Pharmacology

**Business Unit 3** Early-Phase Clinical Trials

**Business Unit 4** Registration and Risk Assessment

**Business Unit 5** Environmental, Occupational and Consumer Protection

**Business Unit 6** Manufacturing of Biopharmaceuticals for Clinical Trials

# TOXICOLOGY TESTING

The Business Unit “Toxicology Testing” offers a broad range of toxicological tests enabling assessment of potential risks to human health. Substances we investigate include pharmaceuticals, biopharmaceuticals, chemicals, particles, complex mixtures, and also nanomaterials. The focus is on characterizing inhalable substances. Our expertise ranges from the development of tests to accompanying companies in the registration process. A solid basis is provided by the institute’s core competencies “Inhalation, Fiber and Particle Toxicology” and “Aerosol Research and Chemical Analyses”.

For risk assessment and registration, we offer toxicological, toxicokinetic, pharmacokinetic, and safety pharmacological studies, in addition to in-vitro studies. In compliance with international registration guidelines, these studies are performed under GLP conditions. We furthermore support our clients in the registration of pharmaceuticals, biopharmaceuticals, and phytopharmaceuticals by completing what has been demanded by the competent authorities and preparing the necessary documentation. Clients benefit in particular from the close dovetailing of basic research and applied research. This allows guideline studies to be complemented, whenever necessary, by further investigations using novel toxicological and molecular toxicological methods.

For over 20 years, we have conducted inhalation studies in rodents and thus are experienced also in complex studies. Thanks to our cutting-edge equip-

## Focuses of activity in 2013

In 2013, the focus in the Business Unit “Toxicology Testing” was on toxicological studies with nanomaterials. After all, they have the potential of being hazardous to man and the environment, on the one hand because of their special properties, such as their nano-aspect, large specific surface area, and high potential reactivity, and on the other hand because they are being manufactured and used in large quantities. Please find below brief outlines of selected studies from this field.

---

### Toxic effects of multi-walled carbon nanotubes

---

Multi-walled carbon nanotubes (MWCNT) have been discussed as exhibiting a toxic potential: Because of their length and fiber-like shape, they could produce effects similar to those of asbestos fibers. In view of the broad spectrum of applications of such nanotubes, it seemed desirable to develop a validated in-vitro screening method that would allow fast and low-cost testing of the large variety of MWCNT for their potential health hazard. In a project funded by the German Federal





ment, not only standard fiber and (nano-)particle aerosols can be generated, but also sophisticated exposure atmospheres, such as occupationally relevant bitumen aerosols. Over the past years, the focus of interest in toxicology has expanded and is no longer on fine particulate matter only, but because of their wide range of applications now also includes engineered nanoparticles ( $< 0.1 \mu\text{m}$ ). This is why cross-departmental pilot projects have been initiated at the institute, aimed at establishing robust, validated screening assays that allow the toxic potential of this type of particles to be evaluated. Substance categories currently under investigation are carbon nanotubes (CNT) and graphene, a two-dimensional carbon modification with a regular hexagonal pattern.

Our offer furthermore includes a broad range of in-vitro test methods for pre-clinical testing of active pharmaceutical ingredients and for assessing the cytotoxic and genotoxic potentials of environmentally and occupationally relevant substances. This also includes alternative test methods in line with the current European chemicals policy (REACH). Selection of the appropriate cellular test systems and development of the study design is performed in consultation with the sponsor, governed by a variety of criteria such as relevance of the species, organ, and target site, endpoints to be analyzed, compliance with OECD guidelines, and any additional requirements.

#### **BUSINESS UNIT SPOKESPERSONS**

Dr. Jochen Buschmann  
Phone +49 511 5350-462  
[jochen.buschmann@item.fraunhofer.de](mailto:jochen.buschmann@item.fraunhofer.de)

Dr. Tanja Hansen  
Phone +49 511 5350-226  
[tanja.hansen@item.fraunhofer.de](mailto:tanja.hansen@item.fraunhofer.de)

Ministry of Education and Research, Fraunhofer ITEM scientists are studying the biological effects of MWCNT of different diameters and lengths in vivo in rats and in vitro in human peritoneal mesothelial cells. The data derived from these experiments are being compared with those of long amosite asbestos as positive control; ground MWCNT and a granular dust serve as negative controls.

For the experiments within this study, the Leibniz Institute for Solid State and Materials Research in Dresden, Germany, synthesized MWCNT of different lengths and diameters. To investigate their carcinogenic potential, these were suspended

in medium and injected intraperitoneally into rats, and the carcinogenic potential was observed for two years. In addition to the endpoint of tumorigenesis, proliferation of cells in the diaphragmatic peritoneum and tissue thickening as early markers of chronic toxicity were monitored after 3, 6, and 12 months. Furthermore, migration of MWCNT in lung tissue to the pleura was investigated in an inhalation study. In in-vitro tests, the scientists analyzed cytotoxicity and genotoxicity in human mesothelial cells, monitoring in each case MWCNT size and distribution in the suspension by electron microscopy. According to preliminary results, needle-shaped MWCNT of certain lengths and diameters that do not tend to agglomerate

are able to induce increased cell proliferation, tissue thickening, and also tumor formation after intraperitoneal injection into rats at high number concentrations. Some of the cytotoxic and genotoxic endpoints analyzed in vitro correlated with the in-vivo findings.

---

### Predicting human toxicity of engineered carbon black nanoparticles

---

The joint research project “CarbonBlack”, sponsored by the German Federal Ministry of Education and Research, is aimed at establishing a test system composed of test models of increasing complexity to evaluate the toxic effects of modified and well characterized carbon black nanoparticles (CBNP) on the airways and lungs. The models included in this tiered test system range from a simple cell culture model via tissue models to verification in an animal model by an inhalation study.

The Fraunhofer ITEM is investigating the effects of engineered model CBNP in human cell lines from different regions of the respiratory tract, primary bronchial epithelial cells, and in precision-cut lung slices (PCLS). Pure carbon nanoparticles (Printex 90®) and particles specially loaded with polycyclic aromatic hydrocarbons are being used for these investigations. The aim is to find out whether the toxicity of CBNP depends primarily on their size and geometry or on surface chemistry. In the in-vitro and ex-vivo models, cell viability endpoints are being analyzed, but also production of reactive oxygen species and cytokines, integrity of tight junctions, and genotoxicity. First results have shown that CBNP cause toxic effects in cell cultures and PCLS only at very high doses. Cells from different regions of the respiratory tract respond differently to the model particles. Transferability of the in-vitro and ex-vivo results to the in-vivo situation is now being verified in a final nose-only inhalation study in rats.

---

### 25 years of RITA database

---

On June 10, 2013, Fraunhofer ITEM employees celebrated the 25<sup>th</sup> anniversary of the RITA database together with experts from leading pharmaceutical and chemical companies. RITA, an acronym of “Registry of Industrial Toxicology Animal-data”, is a database for the storage and analysis of so-called historical control data, comprising spontaneous proliferative lesions observed in long-term studies in rats and mice. After 25 years of data collection, the RITA database today contains validated historical control data from

---

### Fraunhofer ITEM is investigating novel nanostructured fire retardants

---

The aim of the EU project PHOENIX is to develop novel nanomaterials with new functionalities that enable their use as halogen-free fire retardant systems. Besides replacing halogen-based fire retardant systems, nanostructured systems will also provide improved thermal and impact properties to the nanocomposites produced with these components. The new fire retardant systems have been manufactured using a water-based sustainable production method forming nanoplatelet structures, hollow nanoparticles, and modified lignins.

As a partner in this project, Fraunhofer ITEM scientists are performing toxicological studies and health analyses. They are investigating the biological effects of various nanomaterials with regard to lung cytotoxicity and genotoxicity. The results obtained will allow the potential risk during manufacture and processing of nanostructured flame retardants to be assessed. For end users of the produced nanocomposites, no evident risk is at present foreseeable.

more than 260 long-term studies. The mark of 100,000 discrete findings will soon be reached. The project was started in early 1988 at the Fraunhofer institute in Hannover – then still called Fraunhofer ITA – under the preliminary name “Registry”, in cooperation with eleven industry partners from Germany and Switzerland. Today, the group comprises leading pharmaceutical and chemical companies from seven European countries, the US and Japan, and has thus become a global cooperation that is the only one of its kind in this field of research.

For more information about the RITA database, please refer to: <http://reni.item.fraunhofer.de/reni/public/rita/index.php>



*Participants of the anniversary celebration in June 2013.*

## Testing and assessment of nanomaterial safety

In the CEFIC project N1 “Tiered Approach to Testing and Assessment of Nanomaterial Safety to Human Health” the nanostructured materials zinc oxide and amorphous silica were investigated in a comprehensive study program, addressing the routes of exposure inhalation and dermal for zinc oxide and inhalation and oral for amorphous silica. The overall aim was to evaluate whether the existing OECD guidelines can also be applied to nanoscaled particles or whether these require an expansion of the endpoint pattern.

Additional endpoints are important for an adequate characterization of nanomaterial toxicity, including an initial physico-chemical analysis and toxicokinetics (dissolution behavior in different pH environments, chemical analysis, and TEM analysis) as part of toxicity testing. Basically, the scientists wanted to figure out whether in-vitro assays allow reliable prediction of in-vivo effects. To this end, they juxtaposed in-vitro and in-vivo tests with the same endpoints. Overall, the in-vitro and in-vivo tests complemented each other and thus confirmed the concept of this project.



### FOCUSES OF ACTIVITY CONTACT

Dr. Otto Creutzenberg  
Phone +49 511 5350-461  
[otto.creutzenberg@item.fraunhofer.de](mailto:otto.creutzenberg@item.fraunhofer.de)

## Equipment highlights

- Scanning electron microscope with energy-dispersive X-ray analysis system
- Transmission electron microscope with energy-dispersive X-ray analysis system
- High-resolution dark field microscope with hyperspectral microscopy
- Multi-headed transmitted light microscope for 21 observers, with digital camera and projection unit
- Slide scanner with image analysis software
- ZetaSizer® for particle measurement in the submicrometer range by dynamic light scattering
- Electron spin resonance spectrometer

## PROJECTS

### OECD-compliant testing of volatile substances

Testing of a volatile substance cannot be performed with the commonly used standard test methods described in OECD guideline 471. This is due to the fact that, because of the high vapor pressure, the test substance will pass to the gaseous phase and escape from the test system already during the first steps of the testing procedure (preparation of the suspension), or during incubation of the standard agar plates at the very latest. In addition, substances with high vapor pressure and/or non-polar characteristics display high volatility from aqueous systems and pronounced mobility in the gaseous phase. To guarantee appropriate testing of gaseous or volatile substances, Fraunhofer ITEM scientists have developed and established a test method based on an experiment described by Zeiger et al. in 1992. The standardized biological test system has been

optimized with regard to the method of application, dosage, and concentration monitoring, and furthermore guarantees that the testing of volatile candidate substances will comply with the relevant guidelines and with the principles of GLP. In addition to the species-specific positive and negative substances, compliance with all acceptance criteria requires a positive control substance with high vapor pressure that allows the proper functioning of the whole test principle (including method of application, dosage, and analytical methods) to be verified. In a first study conducted at the Fraunhofer ITEM, GLP testing of a candidate substance for registration was successfully performed with the newly developed test method.



#### CONTACT

Dr. Jan Knebel  
Phone +49 511 5350-273  
jan.knebel@item.fraunhofer.de

### Prevalidation of the ex-vivo model PCLS for prediction of respiratory toxicity

In acute inhalation toxicity studies, animals inhale substances at defined concentrations. Without additional information, it is difficult to estimate the appropriate starting concentration for in-vivo inhalation studies. In the context of REACH and the principle of the 3 Rs, there is an increasing public demand for alternative methods. The Fraunhofer ITEM was involved in the standardization and prevalidation of precision-cut lung slices (PCLS) as a suitable ex-vivo alternative method to reduce animal numbers in inhalation toxicology. To this end, lung tissue was exposed to increasing concentrations of 20 industrial chemicals in serum-free culture medium under normal submerged culture conditions. Evaluated endpoints included toxicity (WST-1 assay, LDH assay, and BCA assay for total protein content) and inflammation (cytokine IL-1 $\alpha$ ). For each endpoint,

test acceptance criteria were established. All assay endpoints showed excellent inter-laboratory consistency for the data obtained by WST-1 and BCA assays. Toxic effects were found for the majority of substances. Some substances induced a significant increase in IL-1 $\alpha$ . Reproducibility between the participating laboratories appeared to have acceptably low between-laboratory variations for the WST-1 and BCA assays. The results show that the test protocol used can be adequately transferred to practical use and that the tissue model using the WST-1 endpoint for cytotoxicity is reliable. Whether or not the model can be used for reliable prediction of in-vivo toxicity so far remains open.



#### CONTACT

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

*Cosmetic products often contain paraben preservatives. The aim of the EU project ACTICOSPACK is to develop and manufacture alternative packaging products for cosmetics that are able to release natural preservatives at the adequate rate and amount into the cosmetic products. The task of the Fraunhofer ITEM in this project is to investigate the antimicrobial efficacy and toxicity of the novel preservative systems.*



---

## Establishment of pathway-specific gene expression analyses

---

The aim of this study was to establish pathway-specific arrays (Qiagen/SABiosciences) allowing expression of a variety of genes to be assessed simultaneously. These arrays combine real-time PCR performance with the capabilities of micro-arrays, and they are intended to provide a fast, knowledge-based alternative to genome-wide gene expression analysis in toxicogenomics studies.

The herbicide paraquat, which exerts its toxic effects by forming reactive oxygen species (ROS), was used as test substance at the Fraunhofer ITEM. ROS can lead to activation of transcription factors which regulate the transcription of genes relevant for the inflammatory response, cell growth, differentiation, or apoptosis. Paraquat accumulates preferably in type II alveolar

epithelial cells. Therefore, the Fraunhofer ITEM scientists used the alveolar epithelial cell line A549 in this study. Because of the effect of paraquat on the inflammatory response, an array for the NF $\kappa$ B signaling pathway representing 84 genes was used for the establishment. About 40 percent of the tested genes were significantly regulated. A classification of these genes into functions showed, as expected, that a large number of cytokines involved in the inflammatory response were upregulated. To validate the arrays, 15 percent of the genes were selected. Expression of these genes could be completely confirmed by real-time RTqPCR. The results of this study show that establishment of these arrays was successful and that they yield a high precision and quality.



### CONTACT

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

---

## Novel preservative systems for cosmetic products put to test

---

The main objective of the EU project ACTICOSPACK is a reduction of the content of preservatives (especially parabens) in cosmetic products, while assuring the quality and safety for the same shelf life or even longer. Paraben preservatives are used nowadays in a large number of cosmetic packaging products. These preservatives are included in European legislation as components to be reduced in the future. In order to reduce the levels of parabens used, ACTICOSPACK is working on the development and production of new packaging products able to release natural preservatives at the adequate rate and amount into cosmetic products. The task of the Fraunhofer ITEM within the ACTICOSPACK consortium is to assess the

antimicrobial efficacy and toxicity of the novel preservative systems. Antimicrobial efficacy towards a set of bacterial and fungal microorganisms is tested according to ISO and Pharmacopeia documents. Cytotoxicity of the preservative systems towards human skin cells is assessed using standard laboratory procedures (LDH, WST, cytokine secretion). Finally, the most promising preservative systems are assessed for genotoxicity using the bacterial reverse mutation test (Ames test, OECD 471), the in-vitro mammalian chromosome aberration test (OECD 473), and the in-vitro mammalian cell gene mutation test (OECD 476).



### CONTACT

Dr. Tanja Hansen  
Phone +49 511 5350-226  
tanja.hansen@item.fraunhofer.de

### Study on the role of extremely low-frequency magnetic fields in cancer

Extremely low-frequency magnetic fields (ELF-MF) have been discussed to be responsible for childhood leukemia. In the EU project ARIMMORA (Advanced Research on Interaction Mechanisms of electromagnetic exposures with Organisms for Risk Assessment) several research institutes in Europe have joined forces to help elucidate the role of ELF-MF in cancer by means of different approaches. At the Fraunhofer ITEM, the focus was on identifying differentially expressed genes and epigenetic changes in spleens of ELF-MF-exposed mice. In summary, there was no statistically significant effect on gene expression. How-

ever, epigenetic changes which may result in altered expression of genes were found in individual animals for a selected number of genes. Since these results were observed in whole-tissue extracts of the spleen, it was not possible to assign the alterations to a specific cell type. No risk assessment could, therefore, be performed. Macroscopically, animals did not show any histological findings, and no indication of genotoxicity was observed in peripheral blood.



#### CONTACT

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

### Validation of the developmental neurotoxicity test

The developmental neurotoxicity test (OECD 426) is used to investigate possible functional and morphological effects of substances on the developing nervous system. This test is technically demanding and in the future will also be utilized as one module of the enhanced one-generation study (OECD 445). At the Fraunhofer ITEM, the prerequisites for performing both the functional and morphological investigations are satisfied. As preparatory steps, basic data were generated and evidence was provided that the tests are able to correctly map the effects to be expected from a positive control (pharmacological validation). Endpoints included, among others, litter size, viability

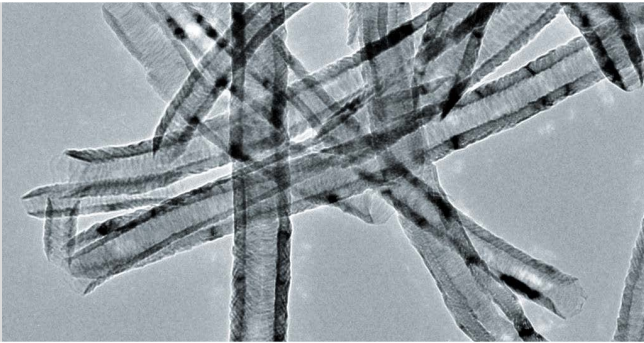
and body weight gain of the offspring, reflex development, and above all behavioral parameters (locomotor activity, auditory startle response, learning behavior), which were determined at different time points (approximately day 20, day 30, and day 70).

The morphological investigations included measurement of brain weight, enhanced histopathology of the brain (partly after perfusion fixation), and morphometric analyses of the nervous system.



#### CONTACT

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



*Carbon nanotubes are being studied in numerous research projects at the Fraunhofer ITEM. The tiny tubes with diameters of only a few nanometers can be visualized by electron microscopy (copyright: Leonhardt, Leibniz Institute Dresden).*

---

## Study on the mode of action of MWCNT in human bronchial epithelial cells

---

Concerns have been raised about the safety of multi-walled carbon nanotubes (MWCNT) due to their asbestos-like structure. As the most likely route of human exposure to MWCNT is inhalation, investigation of the impact of MWCNT in the bronchial system is crucial. To establish a predictive toxicity screening test, Fraunhofer ITEM scientists therefore performed cytotoxicity assays and gene expression analysis in the human bronchial epithelial cell line Calu-3, after the cells had been treated with MWCNT of a defined length and diameter.

Induction of oxidative stress is considered to be important for the formation of fiber-mediated inflammation. This study,

however, showed no MWCNT-dependent increase in reactive oxygen species. Pathway-specific real-time PCR arrays were carried out to determine MWCNT's influence on gene expression. Regulation of a few genes known to be involved in the regulation of oxidative stress was identified. Additionally, MWCNT changed the expression of genes involved in DNA repair or regulation of the immune response and downregulated the expression of the tumor suppressor gene EGR1. In conclusion, Calu-3 cells are relatively insensitive to MWCNT exposure. Establishment of a predictive toxicity screening for MWCNT requires a more sensitive cell model.



### CONTACT

Dr. Monika Niehof  
Phone +49 511 5350-570  
[monika.niehof@item.fraunhofer.de](mailto:monika.niehof@item.fraunhofer.de)

---

## Kinetics of carbon nanotubes after short-term inhalation exposure

---

Toxicologists of the Fraunhofer ITEM wanted to get a deeper insight into the kinetics of multi-walled carbon nanotubes (MWCNT). To this end, they performed a short-term inhalation study, exposing rats to MWCNT. The aim of the study was to investigate the distribution of MWCNT in the animal body and explore excretion and possible deposition processes. In the first part of the study, the scientists used unlabeled MWCNT for the exposure. In a lung lavage performed one day after the exposure, an inflammatory response was observed, but this was no longer detectable after 28 days. By high-resolution light microscopy, individual MWCNT were detected in liver, kidneys, and in the agarose cast of the pleural cavity.

In the second part of the study, the exposure was performed using Co-60-labeled MWCNT. Gamma-activity was analyzed in different organs, body fluids, and excretion products. By analyzing the lung lavage fluid, the scientists were able to demonstrate that most MWCNT had been phagocytized by macrophages already 1 day after the exposure. Analysis of the agarose cast of the pleural cavity indicated fast translocation of MWCNT from the lung to the pleural cavity (days 0 and 1), followed by rather quick elimination from the pleural cavity (days 14 and 28).



### CONTACT

Anja Hackbarth  
Phone +49 511 5350-415  
[anja.hackbarth@item.fraunhofer.de](mailto:anja.hackbarth@item.fraunhofer.de)

# PRE-CLINICAL PHARMACOLOGY

The Business Unit “Pre-clinical Pharmacology” pools the institute’s competencies in the field of efficacy testing of pharmaceuticals, including biopharmaceuticals in particular. Biopharmaceuticals are evaluated in compliance with the relevant regulations, such as EMA S6. We support our research partners and clients from the development of the study design to the analysis and interpretation of the obtained results.

To comply with legal and public demands on animal protection and also to increase model predictiveness, we use a tiered approach: Starting with in-vitro experiments, we characterize pharmaceutical agents and then develop them further in ex-vivo and in-vivo tests of increasing complexity, up to the proof of concept in man. This approach allows us to obtain human data at an early stage already and compare these with data from other species.

Different in-vitro and in-vivo models of inflammation, asthma, and lung infection, and ex-vivo models such as the standardized precision-cut lung slices (PCLS) are available in this business unit. PCLS enable efficacy testing in living tissue from mice, rats, monkeys, and humans. Using the Fraunhofer-patented P.R.I.T.<sup>®</sup>-ALI culturing and exposure system, PCLS can also be exposed to air-

## Focuses of activity in 2013

In the Business Unit “Pre-clinical Pharmacology”, the focus is on efficacy testing of new medicinal products. In addition, the scientists evaluate the efficacy of methods that play a role in medicine. The below report gives an outline of one such study. The aim of this study was to verify whether UVC irradiation of blood products can help prevent development of a transfusion-associated graft-versus-host reaction.

---

### Efficacy testing of UVC irradiation of blood products

---

Tiny amounts of peripheral blood mononuclear cells (PBMC) can remain in the blood product, when blood components such as concentrates of thrombocytes, erythrocytes or plasma are prepared for transfusion. These cells can then be transferred into the blood of a transfusion recipient, where they can cause a variety of adverse reactions. A side effect often seen in immunosuppressed patients is development of transfusion-associated graft-versus-host disease (TA-GVHD). It is triggered by lymphocytes (a PBMC subgroup) that enter the host organism during blood trans-





borne substances such as gases and aerosols. To meet the client's specific requirements, our models for efficacy testing can be customized and, if need be, developed further.

Numerous new developments are human-specific biopharmaceuticals whose efficacy and safety cannot be sufficiently tested in the classical rodent models. Because of their pronounced homology to humans with regard to anatomy and immunology, pre-clinical disease models in non-human primates, therefore, are often the only possibility to test such novel active pharmaceutical ingredients. In cooperation with the German Primate Center in Göttingen, Fraunhofer ITEM scientists have set up a working group for the development of novel translational animal models in common marmoset monkeys. The aim is to offer translational non-human primate models for pre-clinical testing of human-specific biopharmaceuticals for COPD and asthma treatment. The developed animal models make use of a tiered approach 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.

#### **BUSINESS UNIT SPOKESPERSONS**

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

Dr. Tanja Hansen  
Phone +49 511 5350-226  
tanja.hansen@item.fraunhofer.de

fusion. These cells then start proliferating and produce a strong immunological response against the host's cells and organs.

A current standard method to inactivate such reactive blood cells and thus prevent this disease is precautionary gamma irradiation of the blood component. As an alternative to this method, the blood donation service in Springe (Germany) has developed a new method that inactivates reactive PBMC in blood products by UVC (254 nm) irradiation. Before a new method for GVHD prevention can be authorized for use in man, however, proof must be provided that the irradiation method used is capable of considerably reducing the number of reactive lymphocytes in a blood product. The

Fraunhofer ITEM was commissioned to test the efficacy of the novel irradiation method.

#### **Efficiency of UVC irradiation was demonstrated in vitro**

To this end, Fraunhofer ITEM scientists performed in-vitro and in-vivo tests. In cell cultures, they studied the impact of different types of irradiation – traditional gamma irradiation versus the novel treatment with UVC light – on PBMC that had been added in large quantities to thrombocyte concentrates prior to irradiation. After irradiation treatment, they analyzed the immune status, proliferation activity, and cytokine release of treated versus untreated PBMC. Suitability of the new irradiation method to reduce the quantity of reac-

tive lymphocytes in blood products could be demonstrated in an in-vitro test referred to as limiting dilution assay: After up to 21 days of culture, the number of reactive, dividing lymphocytes was determined prior to and after irradiation, so as to verify the efficiency of the new method for the intended use. The results impressively demonstrated that the UVC irradiation is highly efficient.

#### **In-vivo study confirmed the in-vitro results**

To confirm these results, the scientists conducted an in-vivo study in mice. The aim was to verify whether UVC irradiation was capable of preventing GVHD in mice and whether surviving human cells were detectable in the animals. The following results were found: In the control group that had been injected untreated PBMC, the scientists observed the signs

and symptoms of GVHD and substantial colonization of mouse organs with human cells. What they found in the treatment group was that the transplanted cells had been inactivated by the UVC irradiation, their proliferative capacity was suppressed, and no human cells were detectable in the target organs.

These results obtained by Fraunhofer scientists show that treatment of blood components by UVC irradiation before transfusion is suitable to prevent GVHD.



#### **CONTACT**

Dr. Meike Müller

Phone +49 511 5350-262

meike.mueller@item.fraunhofer.de

---

## **Equipment highlights**

- Facilities for drug administration by inhalation in combination with lung function measurement and feedback dose control system (in animal models)
- Measurement unit for repetitive lung function measurement (in mice, rats, and primates)
- S2 laboratories with integrated animal facility for bacterial, fungal, and viral lung infection models (mouse and rat)
- P.R.I.T.<sup>®</sup> Air/Liquid Interface culturing and exposure system for in-vitro testing of airborne substances
- Equipment for multiplex measurement of biomarkers
- Confocal laser scanning microscope and 2-photon microscope for immunohistochemical and immunocytochemical analyses
- Equipment for genome-wide transcriptome analyses, pathway-specific arrays, and real-time PCR (for analyzing CYPs, proinflammatory genes, cytokines, oxidative stress, proliferation, apoptosis, and transcription factors)

---

## 12<sup>th</sup> workshop "Models of Asthma and COPD"

---

The workshop "Models of Asthma and COPD" has become a regular event at the Fraunhofer ITEM: In January 2013, over 100 international experts from industry and academia got together already for the 12<sup>th</sup> workshop of this series to discuss new scientific approaches and findings. Main topics during the 2013 workshop included model predictiveness and reproducibility of results. Given that the traditional models, mouse models for example, turned out to be largely inappropriate for asthma research, it has become evident that there is a need for new models mimicking the human organism as closely as possible; all the more so, because more than half of all newly developed drugs today are biologics specifically targeting human structures. Great potential thus lies in human tissue slices such as precision-cut lung slices (PCLS), which represent a very useful ex-vivo model. According to Professor Armin Braun, initiator and organizer of this workshop, non-human primate models such as the common marmoset are also very interesting



for future testing strategies. "In the field of models of asthma and COPD, a lot of research will still be necessary in the years to come," says Braun. And if the next workshops are held in the newly constructed Clinical Research Center Hannover, this will certainly place the focus even further on the clinical aspect.



## PROJECTS



### Improved pulmonary fibrosis model with repetitive lung function measurements

Bleomycin-induced lung fibrosis in rodents is a model for efficacy testing of new drugs for treating idiopathic pulmonary fibrosis (IPF). Fraunhofer ITEM scientists have established a model in rats that involves invasive but repetitive lung function measurements. Wistar rats were treated intratracheally with bleomycin aerosol on one or two days by means of a Micro-Sprayer®. On day 14, lung function (lung compliance and lung resistance) was measured in the anesthetized but spontaneously breathing rats, followed by a recruitment maneuver. On day 21, lung function was measured again, followed by lung lavage and preservation.

On day 21, pronounced alveolar/interstitial fibrosis was detected in both bleomycin groups, with elevated collagen and increased

macrophage, neutrophil, and lymphocyte counts. Lung function measurements revealed a marked loss of lung distensibility and elevated tissue and/or airway resistance at both time points. The recruitment maneuver showed reduced lung compliance, indicating much lower recruitability of alveoli. The two-dose regimen resulted in a more homogeneous fibrosis pattern. The lung function tests proved to be useful in monitoring fibrotic alterations without destruction of the organism and may possibly indicate loss in lung stiffness before this becomes histologically detectable. Combined with the pathological examinations, they improve this model for pre-clinical testing of novel therapeutics against IPF.



#### CONTACT

Dr. Heinz-Gerd Hoymann  
Phone +49 511 5350-404  
heinz-gerd.hoymann@item.fraunhofer.de

### Inhalable influenza vaccine

Although traditional vaccination is the only way to get effective protection against influenza, only about one fifth of the population makes use of this prevention measure. In addition, the high variability of influenza viruses requires vaccines that can be produced quickly and inexpensively in the case of an imminent pandemic and that are easy to administer. In cooperation with the Helmholtz Center for Infection Research and the Fraunhofer CMB in the US, Fraunhofer ITEM scientists are developing and testing a novel influenza vaccine that is delivered via a nanoparticle carrier and administered by inhalation. The benefits of this vaccine are that it induces the immune response at the site of infection, that is, in the lung, and that the vaccination is needle-free and thus likely to gain better acceptance by patients.

The novel vaccine consists primarily of the effective influenza antigen produced in plants at the Fraunhofer CMB and bound to inhalable silica dioxide nanoparticles at the Fraunhofer ITEM. Using human precision-cut lung slices, the scientists tested the nano-vaccine for toxicological effects and pharmacological efficacy. At the low concentrations used, hardly any adverse effects were observed. The novel vaccine clearly re-activated a specific T-cell immune response to the influenza protein. The nanoparticles serve two important functions: they stabilize the active ingredient and enhance its effect (Neuhaus, V. et al., 2013).



#### CONTACT

Dipl.-Ing. Vanessa Neuhaus  
Phone +49 511 5350-202  
vanessa.neuhaus@item.fraunhofer.de

*Although traditional vaccination provides effective protection against influenza, relatively few people make use of this prevention measure. A needle-free alternative might reach better acceptance in the future: a novel influenza vaccine delivered via a nanoparticle carrier and administered by inhalation.*

---

## **Worldwide first lung function measurement station for marmosets**

---

Scientists of the Fraunhofer ITEM research group at the German Primate Center in Göttingen, Germany, have set up the first lung function measurement station for marmoset monkeys (*Callithrix jacchus*) worldwide. Lung function measurement in translational non-human primate (NHP) models is essential, because it is part of safety and efficacy testing of novel drug candidates.

The newly developed lung function measurement station allows inhalation exposure to defined doses of test substances and simultaneous recording of an extensive panel of lung function read-out parameters. Similar to tests performed in humans, the scientists used the lung function measurement

device to assess the pulmonary response to a bronchoconstrictor (methacholine) in Fraunhofer's marmoset models of acute and allergic lung inflammation. In both animal models of human obstructive pulmonary disease, they were able to demonstrate airway hyperresponsiveness (AHR) towards methacholine by means of the lung function measurement station. A novel human-relevant read-out parameter has thus been established for the NHP models. Comprehensive lung function testing has characterized the marmoset as a promising translational model for testing human-specific anti-inflammatory drugs (Curths, C. et al., 2014).



### **CONTACT**

Sascha Knauf, D. V. M., Ph. D.  
Phone +49 551 3851-259  
sascha.knauf@item.fraunhofer.de

---

## **Viral infection in a model of chronic asthma**

---

Viral infections can cause a substantial exacerbation of symptoms in asthmatics and even require hospitalization for treatment. A pathogen prominently associated with such asthma exacerbations in humans is human rhinovirus (HRV). An aim of the EU project U-BIOPRED was to investigate viral-induced asthma exacerbation. Within a U-BIOPRED working group, the Fraunhofer ITEM Department of Airway Immunology is involved in the development of a mouse model displaying viral-induced exacerbation in chronic asthma. For this purpose, mice with chronic allergic airway inflammation induced by house dust mite allergens were additionally inoculated with HRV to cause acute respiratory viral infection. Although the superimposed infection in the chronic "asthma phase"

triggered no exacerbation in this model, the scientists observed a clearly deficient anti-viral immune response in the animals with chronic allergic airway inflammation. This condition reflects the clinical picture of the suppressed immune response seen in asthma patients and could be a reason for altered susceptibility to viral infections and, as a result of these, exacerbations at a later time. With its induced deficient immune response to viral infections in chronic asthma, this model thus represents a valuable test system that will enable further investigation of the underlying mechanisms and development of therapeutic agents for an improved protection against viral infections (Rochlitzer, S. et al., 2014).



### **CONTACT**

Dr. Sabine Rochlitzer  
Phone +49 511 5350-444  
sabine.rochlitzer@item.fraunhofer.de

# EARLY-PHASE CLINICAL TRIALS

In our Business Unit “Early-Phase Clinical Trials”, scientists conduct clinical studies to test new pharmaceuticals, develop novel biomarkers, and assess the potential hazards of airborne pollutants. In this subject area, the Fraunhofer ITEM closely cooperates with the Hannover Medical School, with industry, and with different research institutions.

The core activity is the conduct of clinical pharmacological trials in volunteers and patients – trials of phases I and II in particular – to evaluate the efficacy and safety of new anti-inflammatory, anti-obstructive, and anti-allergic medicinal products. These trials are performed to the quality standards of Good Clinical Practice (GCP).

A major focus is on designing and performing proof-of-concept studies for the indications asthma, allergic rhinitis, and COPD. The efficacy of new anti-allergic drugs in patients with allergic rhinitis (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, the Fraunhofer ECC is also used to expose test subjects to birch pollen and house dust mite allergens. Due to the universal patented aerosol generation technology, tests with other allergens, such as cat dander or other types of pollen, will also be possible in the future.

## Focuses of research in 2013

In 2013, one focus of research in the Business Unit “Early-Phase Clinical Trials” was the evaluation of a novel therapeutic concept for treating bronchial asthma in a multicenter study under the direction of the Fraunhofer ITEM. In addition, the feasibility of using magnetic-resonance imaging to monitor a local inflammatory response in the lung, as can be induced by segmental allergen challenge, has been explored. The below articles provide more details about both these studies.

---

### Novel therapeutic principle for treating bronchial asthma: proof-of-concept study in a network of German research centers

---

There is still no satisfactory treatment option for severe courses of bronchial asthma and novel therapeutic principles are required to control the airway inflammation and stabilize the course of disease. Over the past few years, the Fraunhofer ITEM has intensively accompanied the development program of the company sterna biologics GmbH & Co. KG for a novel therapeutic principle and performed a multitude of pre-clinical experiments and clinical trials.



Our clinical research activities furthermore include bronchoscopic examinations after inhalation or instillation of allergens, endotoxin, or medicinal products. A state-of-the-art immunology laboratory enables comprehensive biomarker analyses in a variety of patient samples, for example in blood, sputum, broncho-alveolar or nasal lavage fluid.

Only few institutions worldwide have at their disposal comparable expertise and technical facilities. The existing infrastructure will be further enhanced with the new Clinical Research Center Hannover. More beds and recreation facilities will allow more phase-I trials to be conducted. In addition, numerous rooms for special examinations, a biobank, and cutting-edge imaging technology for use in clinical studies will be available.

As a partner in the German Center for Lung Research, we are conducting clinical research projects to investigate the pathomechanisms of the allergic inflammation in the lung and to develop novel biomarkers.

A high quality standard, leading-edge technology, and professional expertise with an academic background are the hallmarks of this business unit, whose current core competencies are "Respiratory Proof-of-Concept Studies", "Aerosol Research and Chemical Analyses", and "Process Development and GMP Manufacturing of Biopharmaceuticals".

#### **BUSINESS UNIT SPOKESPERSONS**

Dr. med. Philipp Badorrek  
Phone +49 511 5350-681  
philipp.badorrek@item.fraunhofer.de

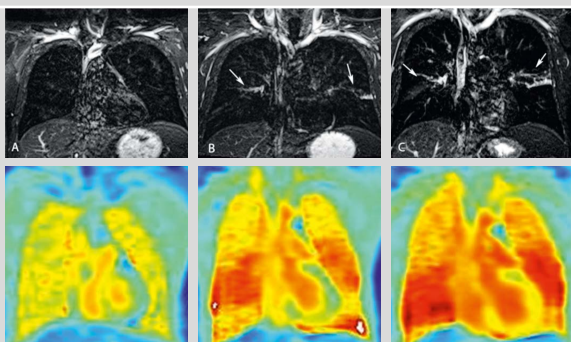
Prof. Dr. med. Jens Hohlfeld  
Phone +49 511 5350-604  
jens.hohlfeld@item.fraunhofer.de

The new therapeutic principle consists in inhibiting the transcription factor GATA-3 by a DNAzyme. The latter binds as an oligonucleotide to the transcription factor and cleaves it enzymatically, leading to its inactivation. Upon completion of the pre-clinical development program in cooperation with the business units "Toxicology Testing" and "Pre-clinical Pharmacology", first trials in man were initiated. For the first time ever, the novel medication, which is administered by inhalation, was given to patients with bronchial asthma. In a first clinical study, we started by testing the safety of single ascending doses in patients with defined hypersensitivity. At the Fraunhofer ITEM, 24 patients with mild to moderate bronchial asthma and

bronchial hyperresponsiveness ( $PC_{20} MCh \leq 4 \text{ mg/ml}$ ) were included in the single-center study. The administration by inhalation proved to be well tolerated and also safe in patients with bronchial asthma. The results of the clinical trial were presented at the annual congress of the European Respiratory Society (<http://www.ers-education.org/events/annual-congress.aspx?idParent=125498>).

In 2013, in the next step of the clinical development program, the safety, tolerability, and general efficacy of inhibiting the transcription factor GATA-3 were studied in patients with bronchial asthma (daily administration of the new medication

## Early-Phase Clinical Trials



Magnetic-resonance images of the local inflammatory response in a patient with allergic bronchial asthma before segmental allergen challenge (left images) and 6 (middle images) and 24 hours thereafter (right images). The upper row shows images generated by turbo-inversion recovery magnitude (TIRM) magnetic-resonance imaging. The bottom row shows intensity maps of the oxygen transfer function in T1-weighted images at 21 and 100 percent oxygen respiration. The differences in intensity correlate well with the inflammatory response found in bronchoalveolar lavage fluid.

over a duration of four weeks). To assess its efficacy in terms of a proof of concept, a standardized inhaled allergen challenge was performed before and after the treatment interval, so as to compare challenge-induced lung function impairment before and after treatment. All in all, over 40 patients were included in the clinical trial. Because of the large number of patients, the clinical trial was designed as a multicenter study under the scientific direction of the Fraunhofer ITEM. This required implementation of uniform operating procedures and identical technical equipment for the inhaled allergen challenge in the seven German institutions involved. In addition, the Fraunhofer ITEM as analysis laboratory took care of quality assurance and analyzed samples of induced sputum. Besides training the involved test centers in the methods of sputum induction, sputum processing and inhaled allergen challenge, the Fraunhofer ITEM performed comprehensive analyses of the immunological biomarkers in blood and sputum and also analyzed the pharmacokinetic samples. After completion of the clinical tests in October 2013, the results of the clinical trial are expected to be available at the end of 2013.

### Imaging-based development of novel biomarkers to quantify airway inflammation

Respiratory diseases such as bronchial asthma, chronic obstructive pulmonary disease, and allergic rhinitis are very frequent and involve chronic inflammation of the airways. To investigate disease triggers and the response to novel therapies, monitoring of the airway inflammation is of pivotal importance.

For non-invasive monitoring of the course of disease, not only measurement of the airway inflammation by exhaled breath analysis, but also imaging of the inflammatory response is

### RIBOLUTION aimed at detecting novel biomarkers

Both for clinical diagnostics and for clinical trials of the pharmaceutical industry, there is an increasing need for specific molecular biomarkers that enable efficient diagnostic algorithms. They can contribute to early detection and individualized treatment of diseases – and thus provide the basic preconditions for a more personalized medicine. With RIBOLUTION (Innovative Ribonucleic acid-based Diagnostic Solutions for Personalized Medicine), a cross-disciplinary research program in the area of molecular diagnostics was launched in 2011. Five Fraunhofer institutes, among them the Fraunhofer ITEM, are involved. The aim is to explore a novel class of molecules with high biomarker potential that so far has hardly been used, referred to as non-coding RNAs (ncRNAs).

The focus of the Fraunhofer ITEM in this project is on biomarkers which, as diagnostic indicators, could provide clues to the development of chronic obstructive pulmonary disease (COPD) or help predict the course of disease or its response

of great interest. In particular the possibility to observe site-resolved processes would be highly valuable with regard to the segmental challenge methods frequently used at the Fraunhofer ITEM. In a first project designed to enable collection of inflammatory cells from patients with bronchial asthma after segmental allergen challenge, scientists investigated potential correlations between alterations in proton-based magnetic resonance images and the cellular inflammatory response in cooperation with the Institute for Diagnostic and Interventional Radiology of the Hannover Medical School.





to therapy. Thanks to the collaboration with the ECLIPSE consortium (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), a large collection of samples with a well characterized data set from a three-year multicenter study is available. In addition, numerous biosamples from different compartments and cell fractions have been collected from 150 COPD patients at the Fraunhofer ITEM, enabling compartment-specific investigation of biomarker signatures.

To this end, four healthy volunteers and eleven patients with mild bronchial asthma were included in the study and subjected to segmental allergen challenge by bronchoscopy. In each study participant, three lung segments were instilled with different allergen doses to evaluate dose dependence and

reproducibility. In addition to cellular and biochemical characterization of the inflammation in bronchoalveolar lavage fluid, magnetic resonance images of the lung were taken before the segmental allergen challenge and 6 and 24 hours thereafter. Several sequences were recorded during each magnetic-resonance imaging procedure. Semi-quantitative parameters such as the degree of local edema in images taken by turbo-inversion recovery-magnitude (TIRM) magnetic-resonance imaging, but also quantification of the oxygen transfer function in T1-weighted images at 21 and 100 percent oxygen respiration yielded good correlation with the cellular severity of inflammation (Fig. 1).

These findings suggest that it is generally feasible to monitor a local inflammatory response in the lung by magnetic-resonance imaging. Further studies are required to improve sensitivity, so as to enable visualization and time-resolved mapping also of less pronounced inflammatory reactions after inhalation challenge.

In the future, it will be possible to conduct studies of this kind under one roof in the Clinical Research Center Hannover. Besides proton-based magnetic-resonance imaging, the use of hyperpolarized xenon to display ventilation and gas transfer will then also be an available option.



#### **FOCUSES OF ACTIVITY CONTACT**

Prof. Dr. med. Jens Hohlfeld  
Phone +49 511 5350-604  
[jens.hohlfeld@item.fraunhofer.de](mailto:jens.hohlfeld@item.fraunhofer.de)

---

## **Equipment highlights**

- Challenge chambers (allergens, ozone)
- Phase-I unit with 25 beds
- GMP unit
- Imaging technology (MRI, PET, CT)
- Multicenter network for inhaled allergen challenge
- Segmental challenge during bronchoscopy
- Exercise testing (spiroergometry)
- Biomarker analysis and biobank
- Patient/volunteer database

# PROJECTS

## Multicenter study made use of Fraunhofer ECC

Novel medications intended for desensitization of patients with seasonal rhinitis are often tested in large trials with participation of numerous study centers. Such large multicenter studies may also benefit from using the Fraunhofer Environmental Challenge Chamber (ECC) at the Fraunhofer ITEM. Because due to stable allergen concentrations and constant ambient conditions, the controlled pollen exposure in the Fraunhofer ECC yields highly conclusive results, even out of the pollen season and with small patient cohorts.

In a study recently conducted on behalf of a large pharmaceutical company, the benefits of a multicenter study were therefore combined with those of pollen exposure in the Fraunhofer ECC. Those patients from the study centers who had volun-

teered to additionally undergo pollen exposure at the Fraunhofer ITEM traveled to Hannover by an organized bus ride. After a night in a nearby hotel, they underwent pollen exposure at the Fraunhofer ITEM – once before and once after treatment with the investigational medicinal product. The study participants then returned to their home cities.

Feedback of the patients participating in this additional trial was positive without exception, and in a preliminary analysis of the study data the sponsor has meanwhile also come to a positive conclusion. The experience gained thus provides a good basis for similar studies in the future.



### CONTACT

Dr. med. Philipp Badorrek  
Phone +49 511 5350-681  
philipp.badorrek@item.fraunhofer.de

## Establishing a rhinovirus challenge model

U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) is a European Union research project under the Innovative Medicines Initiative, a joint undertaking between the European Union and the pharmaceutical industry association EFPIA. Twenty academic research institutions, 10 pharmaceutical companies, 6 patients' organizations, and 3 small- or medium-sized enterprises are collaborating under this umbrella for a better understanding of severe asthma, a better prediction of different courses of disease, and the development of novel therapies for severe asthma. Aimed at enabling the proof of concept for novel medications against severe asthma already at an early stage of drug development, a challenge model with rhinoviruses in patients with mild bronchial asthma is being developed under the scientific

direction of the Fraunhofer ITEM. This model is planned to be established as a model of severe asthma.

After rhinoviruses have been successfully produced to GMP quality standards, a two-center clinical study for dose finding and characterization of the inflammatory response is currently being performed in patients with bronchial asthma in cooperation with the University of Amsterdam. Comparison of the rhinovirus-induced alterations with data of a large cohort of patients with severe asthma, collected during the U-BIOPRED project, will contribute to establishing the new model.



### CONTACT

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

*First proof-of-concept study in the ozone challenge chamber: Controlled ozone inhalation was used to induce temporary airway inflammation in healthy study participants which resembles the inflammatory condition seen in COPD patients. The trial was performed to test a novel inhalable anti-inflammatory drug.*



---

## Scrutinizing volatile compounds

---

Human exhaled breath is a highly complex mixture. Besides nitrogen, oxygen, and carbon dioxide, the gaseous phase also includes far more than 100 different volatile organic compounds (VOCs). The VOC composition of exhaled breath largely depends on the metabolic processes taking place in the body, but also on an individual's behavior and on ambient factors. Within the German Center for Lung Research and in cooperation with the Leibniz University Hannover, scientists of the Fraunhofer ITEM are using different methods to detect VOCs in exhaled breath and study patient cohorts with different medical conditions. Their aim is to identify specific VOCs or VOC patterns that correlate with certain diseases or degrees of airway inflammation. The exposure and challenge methods established at the Fraunhofer ITEM play a pivotal role in this

search. Ozone or endotoxin allow inflammatory processes resembling those in chronic obstructive pulmonary disease (COPD) to be temporarily induced in the airways of healthy volunteers. Since the resulting VOC pattern in this model is not influenced by any concomitant diseases frequently seen in patients with COPD, inflammation-relevant VOCs can be identified more quickly. These research activities benefit from the combination of analytical expertise available in the Fraunhofer ITEM Department of Bio- and Environmental Analytics and access to well-characterized patients of the institute's Department of Clinical Airway Research.



### CONTACT

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

---

## Ozone challenge for proof of concept

---

Disease models provide a possibility to test the efficacy of novel medicinal products at an early stage of the clinical development process. They enable what is commonly referred to as proof of concept. Substances that prove to be basically effective in such a trial can then be advanced to the next phases of clinical development. An example of such a model is the ozone challenge model, which consists in inhalation exposure of healthy volunteers to ozone under controlled conditions. The resulting airway inflammation resembles the one seen in chronic obstructive pulmonary disease (COPD) in terms of inflammatory cells and biochemical mediators of inflammation. The model can be used to test novel medications for COPD treatment. In a comprehensive validation process performed in close cooperation with the institute's Quality Assurance Unit and the Department of Aerosol Technology, the clinical team

managed to obtain a manufacturing license for ozone as a challenge substance. Such a license became necessary after the last amendment of the German Drug Act to operate the ozone challenge chamber. A first proof-of-concept study has already been performed in this challenge chamber, testing the protective and anti-inflammatory efficacy of a novel inhalable substance in 18 healthy study participants. The study has demonstrated that the cellular and biochemical patterns of the ozone-induced inflammation could be reproduced without any problems on all four exposure days (at two-week intervals) without compromising the safety of the test subjects. Based on these data, the model can be offered for further proof-of-concept studies.



### CONTACT

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

# REGISTRATION AND RISK ASSESSMENT

In our Business Unit “Registration and Risk Assessment”, we offer the studies and services required to assess the potential risks of chemicals to human health and the environment and to register these substances for the intended use. This concerns primarily (industrial) chemicals, biocides, and veterinary medicinal products. Main activities in this business unit include the preparation of registration documents on behalf of industrial clients and contract research for regulatory authorities and associations. For different substances and application areas, we also prepare toxicological expert reports, for example to assess residues or contaminations.

The focus is on the legal requirements valid for the substance in question and its intended use, and on the information necessary to meet these requirements. This information is compiled in cooperation with the client. Our broad range of services includes literature searches, identification of data gaps, and development of a testing strategy, including commissioning and monitoring of the required experimental studies. Furthermore, we determine human and environmental exposure data and compare them with the applicable limit values. All these steps are documented in the required registration and substance dossiers.

## **Focuses of activity in 2013**

In 2013, one of the key topics in the Business Unit “Registration and Risk Assessment” was assessment of the environmental risk from medicinal products. The focus was on veterinary medicinal products, but medicinal products for human use – volatile anesthetics in particular – were also of interest. Assessment of these latter substances poses a particular challenge, given that these anesthetics or their metabolites are first released into the atmosphere, mainly through respiration, before they find their way into soil and water bodies. For more details, please refer to the below report.

---

## **Environmental risk assessment of veterinary medicinal products**

---

Pharmaceuticals used to treat humans or feed animals are detected increasingly in different environmental compartments, where they can also affect terrestrial and aquatic non-target organisms. Most veterinary medicinal products (VMP) are designed to be relatively stable under environmental conditions. Their low-level yet continuous presence in different environmental compartments might have a considerable hazard potential not only for the exposed species and communities, but, via the food chain, also for humans. Last but not least, residues of administered antibiotics have been suspected of



By enhancing the above portfolio in close cooperation with our business units "Toxicology Testing" and "Environmental, Occupational and Consumer Protection", we offer our clients a service tailored to their individual needs. The required studies can be performed at the Fraunhofer ITEM in compliance with international testing guidelines and with the principles of Good Laboratory Practice (GLP). Whenever necessary, we cooperate with other Fraunhofer institutes and also with external contract research institutions that have been our partners for many years.

In the future, alternative methods and tests without animal experiments and also integrated testing strategies shall be used increasingly in chemical risk assessment, so as to keep experimental studies to a minimum. To support this aim, we elaborate scientific basic principles in publicly funded projects and test their applicability in the regulatory context. In addition, our comprehensive activities in risk assessment frequently also spawn ideas for new scientific approaches that may help improve chemical risk assessment methodology in the future. For projects aimed at the development of alternative assessment concepts, such as the TTC concept, we have at our disposal comprehensive databases for toxicological endpoints from studies in rodents, which have been set up and further enhanced in this business unit over the past few years.

#### **BUSINESS UNIT SPOKESPERSONS**

Dr. Oliver Licht  
Phone +49 511 5350-334  
oliver.licht@item.fraunhofer.de

Dr. Monika Batke  
Phone +49 511 5350-344  
monika.batke@item.fraunhofer.de

promoting resistance of exposed bacteria, with possible consequences also for human health.

Growing awareness and concern towards residues of pharmaceuticals found in the environment as well as scientific findings about their fate and behavior have finally led to the incorporation of environmental risk assessments (ERA) into the process of authorization by national and EU competent authorities. VMP legislation meanwhile prescribes assessment of potential adverse effects on non-target organisms in the environment as a prerequisite for granting marketing authorization. A tiered procedure has been introduced for this, starting with a screening exposure assessment to identify those VMP that may get into soil or water in amounts high enough for unacceptable

effects to be worth considering. In this case, investigations on fate (soil biodegradation, adsorption) and ecotoxicity are required.

Guidance documents from the European Medicines Agency (EMA) precisely describe the assessment procedure for the targeted product pathways. With ERA being a relatively new and constantly developing field of research, it is not amazing that for specific issues valuable guidance information, such as details on specific study design and performance, test conditions, and interpretation of study results, is not yet available. But at least, assessors have a certain range of discretion in many cases to develop test strategies and to select and perform appropriate experimental studies. The Fraunhofer institutes

ITEM and IME have been cooperating in this field for several years and have gained considerable experience here, both in experimental testing and in the assessment methodology. Moreover, our experience has impressively demonstrated that it is highly advisable, for scientific and also for economic reasons, to inform the competent authorities (national and EU) about any adaptation in the testing strategy and discuss all options before initiating any studies. In particular for complex compounds exhibiting a special environmental behavior or mode of action, testing may become quite sophisticated and require careful planning to keep the workload and financial burden under control. During our work on several ERAs, it proved very wise to discuss and interpret even notable interim results with the competent authorities during experimental studies with prolonged exposure periods, such as degradation tests in soil.

As another very reasonable option, we offer VMP manufacturers marketing the same active ingredients a cooperation in the performance of the required experimental tests. This is particularly interesting for generics. While each manufacturer has to perform individual notification for each VMP with a separate ERA, experimental studies for active substances (or their main metabolites) can be shared and used for notification purposes. Main advantages of this strategy include not only considerably reduced testing costs, but also avoidance of potentially conflicting study results or of differences in the testing strategy, which otherwise might lead to lengthy discussions with the competent authorities. The willingness to cooperate among all potential partners is, of course, a prerequisite for any data sharing approach, besides the keeping of strict confidentiality on any sensitive company-specific data. During many years of consultant work for industry consortia in the context of industrial chemicals, biocides, and VMP, we have always safeguarded confidentiality of highly sensitive company data, while being regarded as an independent and trustworthy third-party consultant.

### Workshop on environmental risk assessment of veterinary medicinal products

In October 2013, participants from eight EU member states and one non-EU country got together in a workshop on “Environmental Risk Assessment of Veterinary Medicinal Products”, organized by the Fraunhofer institutes IME and ITEM in cooperation with the German Federal Environment Agency.

The workshop offered representatives from the pharmaceutical industry and consulting companies the chance to acquire both background and specific knowledge about dif-

It is foreseeable that the regulatory authorities will place increasing emphasis on the process of environmental risk assessment during future marketing authorizations of VMP, and that data requirements, the complexity of testing strategies, and related costs will likewise increase, similar to what happened in the context of existing chemicals. With all these challenges, the Fraunhofer ITEM can assist VMP manufacturers in fulfilling their obligations in the authorization process effectively and economically, to guarantee safe treatment of food animals not only for the sake of animal and human health, but also for protection of the environment.



#### CONTACT

Dr. Susanne Schwonbeck  
Phone +49 511 5350-357  
susanne.schwonbeck@item.fraunhofer.de

ferent aspects of environmental risk assessment in national and international regulatory contexts. Besides the main target groups, the organizers welcomed also experts from different national competent authorities who wanted to gain a deeper insight into recent developments in new experimental testing guidelines, model calculations, and assessment methodologies. Feedback from participants on this first-time event was invariably positive, fostering the organizers' intention to establish this workshop on a regular two-year basis.



into the wastewater by excretion from the human body. Commonly used volatile inhalation anesthetics, however, are released mainly into the atmosphere, while only minor amounts ( $\leq 5$  percent) are excreted via urine. Until now, no guidelines for estimating environmental risks from atmospheric contamination have been developed. Fraunhofer ITEM scientists, therefore, used an adapted method to calculate PECs of three commonly used inhalation anesthetics for the environmental compartments air, water, and soil. Ozone depletion potential, potential contribution to global warming, and long-distance transport were assessed using literature data. Only for those amounts of the parent compounds and for their metabolites that are expected to reach the water compartment via urinary excretion did they use the conventional method of exposure estimation according to the relevant European guideline. The described procedure from our point of view is an appropriate way of assessing risks from volatile anesthetics for air, water, and soil.

## Environmental risk assessment of human medicinal products: volatile anesthetics

Environmental risk assessment of medicinal products for human use requires calculation of a predicted environmental concentration (PEC) of the compound in surface water. This calculation is based on the assumption that the parent active ingredient gets



### CONTACT

Dr. Stefan Hahn  
Phone +49 511 5350-326  
stefan.hahn@item.fraunhofer.de

## Equipment highlights

### Databases

- RepDose (containing data on repeated-dose toxicity of chemicals)
- FeDTex (containing data on developmental and reproductive toxicity of chemicals)
- PaFtox (containing data on repeated-dose toxicity of nanoparticles)

### Models

- Modeling software for human and environmental exposure assessment

### Documentation

- Literature management with over 100,000 entries in 500 subject areas, with searching possibilities and access to 150 journals

# PROJECTS

## ChemScreen to predict human- and ecotoxicological effects

Since regulatory risk assessment of chemicals is resource-intensive and time-consuming, there is a need for alternative integrated testing strategies where animal tests are replaced to a large extent by more rapid, cost-effective and ethically less controversial alternatives.

The EU project ChemScreen is aimed at developing a prioritization mechanism for chemical compounds in toxicological areas of high regulatory concern, including reproductive toxicity. In-silico pre-screening methods and in-vitro test methods for genotoxicity are relatively well developed. In contrast, few alternative methods for reproductive toxicity testing exist and none of them has reached regulatory acceptance. In the ChemScreen project, Fraunhofer scientists contributed to the development of a tiered testing strategy using novel combi-

nations of existing in-vitro and in-silico tools. To this end, they analyzed in-vivo data from reprotoxicity studies included in the Fraunhofer database FeDTeX (Fertility and Developmental Toxicity in experimental animals). These data are used to:

- Validate in-vitro test results from in-vitro screening of model substances
- Analyze the predictivity of repeated-dose toxicity studies for reproductive toxicity
- Identify critical reprotoxicity endpoints
- Identify structural alerts correlating with toxicological pathways
- Design in-silico methods enabling informed decisions on further in-vitro testing, including a possibility for automated assessments



### CONTACT

Dr. Monika Batke  
Phone +49 511 5350-344  
monika.batke@item.fraunhofer.de

## Fraunhofer scientists are developing concepts in the ETEAM project

The aim of the ETEAM project (Evaluation of Tier-1 Exposure Assessment Models under REACH), sponsored by the German Federal Institute for Occupational Safety and Health, is to evaluate tier-1 assessment models for occupational exposure under REACH. Scientists of the Fraunhofer ITEM and of the Institute of Occupational Medicine (IOM) in Scotland are co-operating in this project to evaluate and validate the commonly used tier-1 occupational exposure assessment models ECETOC TRA, MEASE, EMKG-EXPO-TOOL, Stoffenmanager, and RISKOFDERM. These models have been recommended by the REACH guidance on occupational exposure (R14) to assess

workplace exposure to hazardous substances, and they are commonly used for this purpose under REACH.

The models have generally been designed to provide conservative exposure estimates based on limited descriptive information about the substance and the scenario. However, for most of these models no comprehensive evaluation or validation with measured exposure data has so far been performed to confirm their applicability for exposure assessments under REACH.

Within the ETEAM project, the Fraunhofer ITEM scientists are responsible for conceptual evaluation of the models and qualitative evaluation of their uncertainty. The conceptual evaluation includes a summary of the model algorithms and scope, a short



*With about two square meters, the skin is the largest and also one of the most sensitive organs of the human organism. In particular under the European chemicals regulation REACH, potential dermal exposure has to be thoroughly investigated.*



handling and use description for each model, underlying data, data gaps, and transparency. For the uncertainty evaluation, the ITEM scientists have developed a concept on the basis of the corresponding REACH guidance on uncertainty (R19) and the WHO guidance "Uncertainty and data quality in exposure assessment". This concept includes categorization approaches for input parameter quality, the underlying knowledge base, transparency, and magnitude and direction of uncertainty. A detailed evaluation matrix has been created for each model to allow all potential sources of uncertainty (e.g. single parameters, datasets, assumptions) to be analyzed separately.

## **Dermal exposure to chemicals – sources, measurement, and modeling**

On behalf of the German Federal Ministry for the Environment, the Fraunhofer ITEM has been cooperating in the World Health Organization's (WHO) International Program on Chemical Safety (IPCS) for over 20 years. While during the earlier years the focus was on toxicological evaluation of substances (incl. diesel, polycyclic aromatic hydrocarbons, vinyl chloride, and creosote), the main activity in the past few years was the preparation of reports supporting toxicological risk assessment, for example, on the use of transgenic animals for in-vivo mutagenicity testing and on dermal uptake of chemicals.

For the most recent report, the Fraunhofer ITEM scientists looked into exposure to chemicals via the skin. This route of exposure previously used to be neglected in many cases, but now has to be thoroughly evaluated, for example, for chemical risk assessment under REACH. The report includes information about important sources of dermal exposure and describes approaches for measuring the exposure via this pathway. A very large chapter has been dedicated to dermal

Work within this project is being supported by the members of an advisory board that is composed, among others, of developers of all models under evaluation. For further information on the ETEAM project, please refer to the project homepage <http://www.eteam-project.eu/>.



### **CONTACT**

Dr. Susanne Hesse  
Phone +49 511 5350-366  
[susanne.hesse@item.fraunhofer.de](mailto:susanne.hesse@item.fraunhofer.de)

exposure modeling. Depending on the regulatory context, the particular chemical, biocide, pesticide and country, there are many different approaches that can be used to model the exposure. Last but not least, the report also discusses correlations with dermal conditions, in particular with skin irritation and contact dermatitis.

Once the report had been completed by several Fraunhofer ITEM scientists and external experts, it went through a worldwide review process and was discussed and revised by an expert committee. The final report will be published in 2014 (<http://www.inchem.org/pages/ehc.html>).



### **CONTACT**

Dr. Inge Mangelsdorf  
Phone +49 511 5350-303  
[inge.mangelsdorf@item.fraunhofer.de](mailto:inge.mangelsdorf@item.fraunhofer.de)

## Biocidal products: regulation replaces directive

The Biocidal Products Regulation BPR (528/2012) became effective on September 1, 2013, replacing the Biocidal Products Directive BPD (98/8/EC) that had been in force since 1998. From now on, we will support our clients also with biocide applications in compliance with the new regulation.

The current regulation implicates new requirements for the authorization process, but also new options: Besides national authorizations in individual Member States, authorization throughout the European Union is now also possible. This "Union authorization" process is established in a step-wise approach for individual biocidal product types. Coordination of all processes and final assessment fall within the scope of responsibility of ECHA in Helsinki. Another novelty is that dossiers no longer have to be submitted in Word format, but electronically as a special IUCLID file (module 5.5.1.). The corresponding IUCLID export file (.i5z) has to be uploaded to

the R4BP3 system (Register for Biocidal Products), together with risk assessment documents (Doc II), the listing of end-points, and other supporting documents. Once uploaded, the dossier is considered submitted. Any further inquiries and additional data requests by ECHA are also processed electronically via the user account. Several guidance documents have already been published on the ECHA homepage to support smooth implementation of the BPR.

The services offered by the Fraunhofer ITEM include preparation of dossiers in IUCLID format and their upload to the R4BP3 system. In addition, training or workshops for the new IUCLID module 5.5.1., especially with regard to biocides, can be offered on demand.



### CONTACT

Dipl.-Ing. Ariane Zwintscher  
(Working Group on Biocides, headed by  
Dr. Annette Bitsch)  
Phone +49 511 5350-312  
ariane.zwintscher@item.fraunhofer.de

## DETECTIVE in chemical risk assessment

DETECTIVE stands for **DETE**ction of endpoints and biomarkers for repeated-dose Toxicity using **In-Vitro** syst**Em**s. It is one out of seven projects of the SEURAT research initiative launched by the European Commission and "Cosmetics Europe" (formerly European Cosmetics Association Colipa). Initiated in 2011, this project is aimed at replacing in-vivo repeated-dose systemic toxicity testing by alternative test methods.

Assessment of repeated-dose toxicity data is a standard requirement in human safety evaluation. At present, it relies mainly on animal testing, because alternative methods to date have not reached acceptance by the authorities. The project DETECTIVE is aimed at developing and identifying human biomarkers based on the evaluation of toxic effects observed in the three organs heart, liver, and kidney. Evaluation of complementary functional assays and a battery of "omics" readouts including transcriptomics, proteomics, and metabolomics for selected compounds is expected to provide a better mechanistic insight into human toxicity pathways.



*The Fraunhofer ITEM supports clients in the registration and authorization of biocides under the Biocidal Products Regulation that became effective in 2013. The institute's Working Group on Biocides also offers training and workshops in this area.*

Experts from the Fraunhofer ITEM Department of Chemical Risk Assessment are contributing to an assessment of the usefulness and predictivity of the identified biomarkers for in-vivo toxicity with regard to human health risk assessment. They will support in-vivo versus in-vitro extrapolations based on the Fraunhofer RepDose database ([www.fraunhofer-repdose.de](http://www.fraunhofer-repdose.de)). Within the research initiative SEURAT, they are also cooperating in the risk assessment working group.



#### CONTACT

Dr. Sylvia Escher  
Phone +49 511 5350-330  
[sylvia.escher@item.fraunhofer.de](mailto:sylvia.escher@item.fraunhofer.de)

### Human biomonitoring: derivation of assessment values for novel substances

On behalf of the German Federal Environment Agency, the Fraunhofer ITEM has developed proposals for the derivation of assessment values that can be used to assess substances detected in blood or urine in the context of human biomonitoring. To this end, Fraunhofer scientists analyzed toxicological data, existing limit and guideline values (such as TDI values, i.e. tolerable daily intake), and available information about metabolism in humans or rodents.

Substances for this analysis had been selected within a cooperation project with the German Federal Environment Agency and the German Chemical Industry Association. Initiated in 2010, the aim of this project has been to enhance knowledge about substances that are taken up by the human organism. The focus is primarily on those substances to which the general population is likely to be exposed and that could have an important health impact, but for which no appropriate detection methods in body fluids are, as yet, available. Within this project it is planned to develop methods for 50 substances.

Fraunhofer ITEM scientists so far have completed work on the following substances: 1,2- benzenedicarboxylic acid, 1,2-bis(2-propylheptyl) ester (DPHP, CAS: 53306-54-0); 1,2-cyclohexanedicarboxylic acid, 1,2-diisononyl ester (DINCH, CAS: 166412-78-8); mercaptobenzothiazole (MBT, CAS: 149-30-4); (4-methylbenzylidene)camphor (4-MBC, CAS: 36861-47-9); diphenyl methane-4,4'-diisocyanate (MDI, CAS: 101-68-8). The DINCH dossier was presented during a meeting of the Federal Environment Agency's Human Biomonitoring Commission. The Commission is about to define an HBM-I value for this substance below which no risk for adverse health effects is expected according to current knowledge. The dossier for hexabromocyclododecane (HBCD, CAS: 25637-99-4) is currently being prepared at the Fraunhofer ITEM. Calls for several other substances have been announced by the Federal Environment Agency, and the Fraunhofer ITEM is planning to respond to these.



#### CONTACT

Dr. Oliver Licht  
Phone +49 511 5350-334  
[oliver.licht@item.fraunhofer.de](mailto:oliver.licht@item.fraunhofer.de)

# ENVIRONMENTAL, OCCUPATIONAL AND CONSUMER PROTECTION

The central topic in the business unit “Environmental, Occupational and Consumer Protection” is human exposure to potentially hazardous substances in workplaces, in the environment, and in consumer products. The focus is on inhalation exposure to chemicals, fibers, particles – nanoparticles in particular – and to complex mixtures. To our partners from industry, professional associations, and public authorities, we offer a broad spectrum of methods and services.

Taking into account the relevant regulations, our scientists develop tailored concepts for assessing potential risks to human health, design testing strategies whenever needed, and support clients with issues of product safety and product optimization. Furthermore, they develop customized methods for chemical analyses and aerosol measurement.

Potential inhalation toxicity of substances can be evaluated in different validated in-vitro and animal models. Comprehensive in-vitro test methods and in-silico models for risk estimates are established at the institute – helping to reduce animal experiments. A large variety of aerosols, gaseous atmospheres, and complex mixtures of substances can be generated for use in experimental studies. In addition, technologies for controlled exposure are available.

## **Focuses of activity in 2013**

Spray products are being increasingly used in the food industry, in agriculture, for surface treatment, painting, and also in consumer products. Since spraying processes may generate inhalable aerosols that could be harmful to human health, there is a necessity to assess their potential health hazard. Such assessment first requires the exposure from spray products to be characterized. This was a focus in this business unit in 2013.

---

### **Fraunhofer ITEM characterizes the exposure from spray products**

---

The use of spray products can always result in generation of inhalable aerosols, independent of the spraying technology used and the properties of the spray product. In safety assessment of spray products, increasing emphasis has been placed on the potential release of such inhalable aerosols. Reliable information on the potential release of particles in the health-related size ranges under conditions of use of the product is thus essential. Whenever experimental studies are required, characterization of the inhalation exposure is usually based on the native droplet spray, for example, by means of laser



To characterize the exposure, the Fraunhofer ITEM provides standardized methods, test systems, and model rooms, allowing realistic simulation of pollutant release processes and quantification of the source strength. A focus is on the development of measurement technology for airborne substances, to the point of building prototypes of aerosol measurement devices. Physico-chemical models help determine harmful substances and their emission from building materials, furniture, interior decoration, and consumer products. In addition, Fraunhofer ITEM scientists design exposure scenarios and develop mathematical simulation models for exposure assessment (indoor, environment).

In close cooperation with the business units "Toxicology Testing" and "Registration and Risk Assessment" we are able to offer our clients a comprehensive package of services for the assessment and characterization of substances and products. The required studies are performed in compliance with national and international regulations and with the principles of Good Laboratory Practice (GLP).

#### **BUSINESS UNIT SPOKESPERSONS**

Dr. Katharina Schwarz  
Phone +49 511 5350-139  
katharina.schwarz@item.fraunhofer.de

Dr. Stefan Hahn  
Phone +49 511 5350-326  
stefan.hahn@item.fraunhofer.de

diffraction spectrometry. In general, however, the main fraction of the droplet composition will not be the non-volatile components, but solvents and/or propellants. These will normally evaporate within a few seconds, so that the droplets will shrink to their non-volatile constituents. The spray user, however, will typically remain in the spraying area for more than a few seconds, so that the exposure largely depends on the concentration of this so-called aged or matured aerosol.

For characterization of aged aerosols, scientists of the Fraunhofer ITEM have established a mass balance method. Using this method, they determine the respirable ( $R_{alv}$ ), thoracic ( $R_{thor}$ ), and inhalable ( $R_{inh}$ ) fractions of the released liquid spray for spray products with non-volatile components.

To this end, a defined quantity  $M$  of the spray product is released into a closed chamber (volume,  $V$ ), where it is homogeneously distributed. By means of two aerosol monitors, concentrations of the aged, that is, the exposure-relevant aerosol in the three particle size fractions  $C_{0,alv}$ ,  $C_{0,thor}$  and  $C_{0,inh}$  are measured on-line (Respicon by Helmut Hund GmbH, Wetzlar, Germany) immediately upon completion of the spraying process. The two monitors include scattered-light aerosol photometers that are calibrated gravimetrically by means of integrated particle filters during each experiment. The values measured by the two monitors represent the mass concentrations of non-volatile components in the different size ranges inside the control chamber. Based on these concentrations, the released spray quantity  $M$ , and the volume  $V$ , the mass-

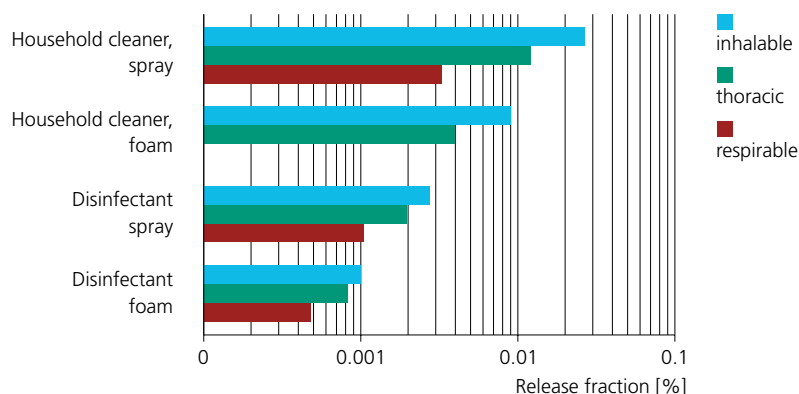
based fractions in the respirable,  $R_{alv}$ , thoracic,  $R_{thor}$ , and inhalable,  $R_{inh}$ , size ranges are calculated using the following equations:

$$R_{alv} = \frac{m_{0,alv}}{M} = \frac{c_{0,alv}V}{M}; R_{thor} = \frac{m_{thor}}{M} = \frac{c_{0,thor}V}{M}; R_{inh} = \frac{m_{0,inh}}{M} = \frac{c_{0,inh}V}{M}$$

In addition, multiplication of the known product spraying rate (mass of spray product released per second) with the calculated mass-based fractions released ( $R_{alv}$ ,  $R_{thor}$  and  $R_{inh}$ ) allows the aerosol release rates to be determined as input parameters for exposure modeling. The three size fractions correspond to the three health-related size classes of airborne particles according to international standards (European standard EN 481 and ACGIH standard), so that the fractions taken into consideration meet the requirements for safety assessment of spray products.

The mass balance method thus enables realistic assessment of the risk from exposure to sprays containing non-volatile components, as it takes into account the aerosol ageing process and the actual exposure scenario, such as surface treatment. Using a large variety of model rooms (from 0.1 to 41 m<sup>3</sup>), we have already successfully used this method at the Fraunhofer ITEM for a broad spectrum of spraying applications, from the use of cosmetic sprays and waterproofing sprays to large-area spraying of lacquers, biocidal products, and surface-active substances used for building protection. Based in particular on direct chemical analysis of the three size fractions in the aerosol

**Fig.1: Foam spraying results in lower aerosol release in the inhalable (blue), thoracic (green) and respirable (red) size fractions than droplet spraying (traditional sprays). For comparison, the figure shows the release fractions during droplet spraying and during foam spraying of a household cleaning agent (pump spray) and of a biocidal product containing non-volatile active ingredients (continuous spraying with a pressurized sprayer).**



## Safety assessment of spray products

Registration of biocidal products (BPR, EU directive 528/2012) and pesticides (EU directive 1107/2009) and risk assessment of chemicals under REACH (EC directive 1907/2006) and the cosmetics regulation (EC 1223/2009) require occupational, consumer, and environmental exposure assessment and, where applicable, identification of appropriate risk mitigation measures. The use of spray products can always result in generation of inhalable aerosols,

samples collected on the integrated filters of the Respicon aerosol monitors, this method furthermore allows us to assess the efficacy of risk-mitigating measures, for example, foam spraying instead of droplet spraying. In addition, we help our clients improve their products, for example, by advising them in selecting the appropriate spraying technology and formulations.

In this context, Fraunhofer ITEM scientists performed first comparative studies on inhalation exposure during foam spraying of an aqueous biocidal solution as compared to traditional droplet spraying under typical conditions of use as part of an investigation on behalf of the German Federal Institute for Occupational Safety and Health. During foam spraying with



independent of the spraying technology used and the properties of the spray product. For safety assessment of spray products, increasing emphasis is being placed on this issue. An amendment (2008/47/EC) to the European Aerosol Dis-

penser Directive (75/324/EEC) for the first time explicitly requires manufacturers to perform hazard analysis addressing the risk resulting from inhalation of the spray under normal and reasonably foreseeable conditions of use. The mass balance method described in the report to the left, which was newly established at the Fraunhofer ITEM, enables realistic assessment of the potential exposure from sprays and therefore represents an important step towards assessment of the risks linked to the use of such products.

low pressure (3 bars), aerosol release was found to be reduced by a factor of three (see Fig. 1). By means of the mass balance approach, we were able to demonstrate that foam spraying of potentially harmful substances is a suitable measure to mitigate the risk from inhalation exposure, but that aerosol formation cannot be totally excluded.

The mass balance method, which enables exposure characterization taking into account chemical and physical properties of the spray formulation, represents an important step towards assessment of the risks from occupational application of spray products in the biocidal regulatory context (Biocidal Products Directive and Regulation, BPD/R) and, in general, from the use of sprays in workplace and consumer contexts.



#### FOCUSES OF ACTIVITY CONTACTS

Dr. Katharina Schwarz  
Phone +49 511 5350-139  
katharina.schwarz@item.fraunhofer.de



Dr. Stefan Hahn  
Phone +49 511 5350-326  
stefan.hahn@item.fraunhofer.de

---

## Equipment highlights

---

- State-of-the-art analytical methods: LC-NMR, LC-MS, ICP-MS (non-target analyses, residue and trace-level analyses, bioavailability)
- Aerosol measurement technology, aerosol generation methods (nebulization, dry dispersion)
- Scanning electron microscope with energy-dispersive X-ray system for elementary analyses
- Spray analyzer
- Battery test rig for accident simulation and quantification of energy release and gas and particle emissions
- Model rooms for exposure characterization (individually equipped, 0.1-41 m<sup>3</sup>)

# PROJECTS

## Investigating resuspension of radioactive materials

In-depth and informed hazard analysis as part of the defense against nuclear hazards requires reliable scientific findings about the risk of resuspension of radioactive materials deposited on (urban) surfaces, for example, as a result of an accident in a nuclear plant or detonation of a dirty bomb. Important issues to be considered during rescue operations include protection of the rescue staff themselves against hazardous radiation and minimization of a carryover of surface contamination. Inhaled resuspended radioactive materials can have a substantial share in the incorporated radiation burden in first aiders and rescue staff. In model experiments, Fraunhofer ITEM researchers have measured wind resuspension rates of respirable particles and their time dependence for representatively contaminated sur-

faces under real-life conditions, taking into account different weather conditions and countermeasures (fixation). In addition, they generated data to enable reproducible, realistic modeling of the factors influencing particle resuspension, for example, from harmed persons or caused by rescuers themselves as a result of walking movements and moving vehicles. The results of the experimental and analytical investigations were used to deduce recommendations for simple protective measures and behaviors of the rescue staff that lead to a considerable reduction of resuspension processes and thus of inhalation exposure to radioactive materials and that can help minimize a carryover of contaminated materials.



### CONTACT

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

## Workplace sampling of semi-volatile substances

Work-related semi-volatile substances such as oil mists and bitumen fumes are two-phase mixtures of droplets and gaseous compounds. From a toxicological point of view, concentrations of the two phases should be able to be monitored separately. Traditional methods, consisting of a filter for collection of the droplets and an absorbent cartridge for the gaseous phase in series, are of limited suitability here, because they cannot rule out the possibility of material transfer from the filter to the absorbent. Fraunhofer ITEM scientists, therefore, have explored

an alternative method that uses a so-called virtual impactor with parallel instead of sequential collection of the gaseous and particle phases. In laboratory tests with a variety of diesel oil mists, two different devices yielded almost identical results. A feature of this method worth pointing out is the unbiased sampling of oil droplets and their vapor phase, irrespective of ambient conditions and sampling duration.



### CONTACT

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



*It goes without saying that first aiders and rescue staff have to protect themselves against radioactive contamination. Rescue operations can cause resuspension of radioactive materials and wind can lead to additional carryover. To minimize resuspension processes and the resulting inhalation exposure to radioactive materials, Fraunhofer ITEM scientists used the results of experimental and analytical investigations to deduce recommendations for simple protective measures and behaviors of the rescue staff.*



## Isolated perfused rat lung as a screening tool for surface-active substances

The isolated perfused rat lung (IPRL) is well suited to screen substances showing acute inhalation toxicity. This has been demonstrated by Fraunhofer ITEM scientists in a study commissioned by the German Federal Institute for Risk Assessment and the German Industry Association for Toiletries and Detergents (IWK). The scientists tested, among others, waterproofing spray formulations for potential lung toxicity each in two male and two female IPRLs. Changes in the respiratory parameters tidal volume, compliance, and resistance, and also edema and atelectasis formation were evaluated and normalized to the inhaled doses. These IPRL results were then compared with available in-vivo results.

Formulations with no acute harmful effects in the IPRL did not show any signs of acute toxicity in in-vivo tests with rats either. In contrast, substances displaying harmful effects such as impaired lung compliance and atelectasis formation in the IPRL also showed alterations in respiratory parameters, even up to mortality, in in-vivo tests. Therefore, for future assessment of surface-active substances, it seems recommendable to perform this screening test prior to an in-vivo inhalation test. For complete risk assessment, formulations displaying no acute harmful effects in the IPRL will still have to be further investigated in vivo. Substances showing strong reactions in the IPRL, however, are most likely to cause lung damage also in vivo and should, therefore, not be tested in live animals.



### CONTACT

Dr. Monika Fischer  
Phone +49 511 5350-409  
monika.fischer@item.fraunhofer.de

## New TTC concept for derivation of threshold values after inhalation exposure

The TTC concept (Threshold of Toxicological Concern) is used to derive threshold values below which no human health risk is assumed given life-time exposure. These thresholds are based on data from oral in-vivo studies. At workplaces and in indoor areas, however, an important route of exposure to chemicals, besides the oral route, is inhalation. The aim of the CEFIC project LRI-B8 was to develop an integrative concept for derivation of threshold values for substance categories of high and low inhalation toxicity. In this project, performed in collaboration with Professor Schüürmann (UFZ, Leipzig), 296 chemicals recorded in the Fraunhofer database RepDose ([www.fraunhofer-repdose.de](http://www.fraunhofer-repdose.de)) with subacute to chronic inhalation toxicity studies were analyzed. On average, locally toxic compounds displayed

higher toxicity than systemically toxic compounds. An integrative approach was used to define groups of substances. Based on structural similarity, about 20 structural features triggering low and high toxicity values were first identified. The structural and toxicological boundaries were then further specified by means of differences in absorption, mechanisms of action, metabolism, and the toxicological profile observed in the in-vivo studies. This resulted in 28 groups: 9 low-toxicity (L) and 19 toxic (T) groups. Compared with the Cramer classes, the L- and T-groups better discriminate between low-toxicity and high-toxicity compounds. About 20 percent of the compounds so far could not be assigned to any of the defined groups.



### CONTACT

Dr. Sylvia Escher  
Phone +49 511 5350-330  
sylvia.escher@item.fraunhofer.de

# MANUFACTURING OF BIOPHARMACEUTICALS FOR CLINICAL TRIALS

The Fraunhofer ITEM team in Braunschweig has 20 years of comprehensive experience and know-how in process development and GMP manufacturing of investigational biopharmaceuticals. Partners from the pharmaceutical and biotech industries and academic institutions much appreciate this expertise, which has enabled successful completion of many of their projects. A cross-disciplinary team of scientists, engineers and technicians stands for quality and experience, supporting and assisting clients in projects from the development of a suitable cell line to manufacturing of the investigational medicinal product.

The first and foremost requirement for a biopharmaceutical process development project is a high-yielding production cell line based on a recombinant microbial or animal cell system. This cell system must feature a well-documented history, robustness, and stability. Once a suitable cell line is available, the next step is the manufacturing of a GMP cell bank that is the starting point for any batch created with the future biotechnological production process. The Fraunhofer ITEM Division of Pharmaceutical Biotechnology manufactures master and working cell banks based on bacteria, yeasts, fungi, and mammalian cells up to safety level S2 in compliance with GMP.

## Focuses of activity in 2013

In 2013, the focus in the Business Unit “Manufacturing of Biopharmaceuticals for Clinical Trials” was on implementing the new aseptic fill-and-finish plant. This plant allowed the process chain from pre-clinical to clinical development of medicinal products to be completed. Fill and finish of investigational medicinal products for clinical trials can thus now be offered to clients from public research institutions and industry. Details about the new plant are given in the following.

---

## Tailored fill and finish: new filling plant for IMPs

---

In January 1997 already, the Division of Pharmaceutical Biotechnology received regulatory approval according to § 13 of the German Drug Act for the manufacturing of biopharmaceutical active ingredients, and in April 2010, this authorization was extended to include aseptic fill and finish of large-volume liquid dosage forms (bags). A new class-B clean room now also enables the automated, aseptic fill and finish of small-volume investigational medicinal products (IMPs) into vials and ampoules in small quantities of 3000 to less than 1000. Within a restricted-access barrier system (RABS) in a class-B clean room, aseptic fill and finish of IMPs in particular



For more than 20 years already, process development for a wide range of biopharmaceutical active ingredients has been the core business of the Division of Pharmaceutical Biotechnology: antibodies, antibody fragments, virus-like particles, bacteriophages, glycoproteins, and nucleic acids, in particular plasmids. The process first has to be thoroughly understood across all phases of process development. GMP elements are successively integrated already during the development phases, resulting in a transferrable GMP process including process analytics that will comply with regulatory requirements. Especially for antibodies and plasmids, manufacturing platforms based on largely pre-developed and pre-validated basic process sequences and process analytics have been developed, which then only have to be adapted to the special requirements of a particular active ingredient.

For GMP manufacture of pilot batches of biopharmaceutical active ingredients and their further processing to investigational medicinal products for use in clinical trials in compliance with regulatory requirements, a GMP facility with grade-C and grade-D clean rooms is available, comprising both USP and DSP suites. Downstream aseptic fill and finish of final dosage forms in ampoules and vials is performed in a grade-B clean room within a class-A RABS (restricted-access barrier system) including an automated filling machine.

#### **BUSINESS UNIT SPOKESPERSONS**

Dr. Kathrin Bohle  
Phone +49 531 6181-6347  
kathrin.bohle@item.fraunhofer.de

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

for clinical trials of phases I and II is performed. Responsibility for the sterile fill-and-finish process lies with Dr. Jens Paulsen and Dr. Luma Baydoun.

#### **Enhanced service portfolio**

“In the past, the manufacturing of the active ingredient was the end of our service chain in Braunschweig, so that we always had to find a partner for our clients who would perform the last step: formulation and fill and finish. Our experience was that, in fact, this often turned out to be the limiting step,” said Dr. Holger Ziehr, head of the Division of Pharmaceutical Biotechnology. One reason for this was the small batch size required for clinical trials; but often the exotic nature of the active ingredient also presented a challenge

which many contract filling companies were quite reluctant to face. “This eventually spawned the idea of enhancing our service portfolio, so as to be able to offer our clients from the pharmaceutical and biotech industries and from academic institutions the complete chain through to the released IMP,” Ziehr further explained.

#### **Cost-effective even for very small batches**

The new plant was developed in cooperation with Bosch Packaging Technology. Special requirements to be met by the new system were defined in advance: “We needed a solution that would support different primary packaging containers and would be cost-effective even for very small batches. The idea was to have a space-saving combined plant that can fill

and seal both vials and ampoules efficiently and in strict compliance with Annex 1 'Manufacture of Sterile Medicinal Products' of the EU GMP guideline, the German Drug Act, and also with the S2 requirements of the German genetic engineering safety regulation GenTSV," Ziehr summarized the requirements. To enable processing of active ingredients such as viruses, bacteriophages and, above all, toxic biological agents and to avoid cross-contamination, an additional requirement was the possibility to decontaminate the room and the plant with vaporized hydrogen peroxide. The plant thus had to be rather robust.

At the beginning of the manufacturing process, multiple-packaged, pre-sterilized ready-to-fill packaging containers are introduced into the class-B clean-room area through the air-lock doors. Via a pizza door, they are passed on into the actual filling plant (class-A clean room), where the staff manually (via the RABS gloves) removes the outer packaging and places them on a ramp. A screw then separates and feeds the packaging containers into a clocked rotating star that transports the individual containers to the different processing stations (e.g. opening, gassing, filling, stoppering and capping including crimping). To avoid an excessive dead volume and thus an unwanted loss of product, the Fraunhofer ITEM plant is operated with only one filling needle. Integrated sensors monitor the whole filling process, and insufficiently finished containers are discarded via a reject outlet.

#### Projects starting in summer 2014

From late 2013 to January 2014, three media fills were performed to finalize validation of the aseptic process and qualification of the plant. "Once regulatory approval for the aseptic fill-and-finish process will have been received, the first projects will be initiated in summer 2014," says Ziehr. Interested visitors can take a look at the plant via a footbridge installed especially for this purpose and can watch a training video to get an insight into the detailed process.



#### FOCUSES OF ACTIVITY CONTACT

Dr. Jens Paulsen  
Phone +49 531 6181-6400  
jens.paulsen@item.fraunhofer.de

---

#### Equipment highlights

---

##### Filling machine ARF 1010 (by Bosch)

- Semi-automated filling machine for ampoules and vials
- Active, open restricted-access barrier system (RABS) including separate ventilation system with HEPA filters in the ceiling
- Class-A air quality in the interior, surrounded by a class-B clean room
- Integrated particle sensor for on-line monitoring of particles (sizes  $\geq 0.5$  and  $\geq 5 \mu\text{m}$ )
- Fast format change between ampoule and vial
- Nitrogen gassing
- Decontamination with vaporized  $\text{H}_2\text{O}_2$
- Fill volume accuracy: 1% for 5 ml, 2% for 2 ml

##### Vial filling

2-50 ml; 2160 vials per hour (10-ml vials)

##### Ampoule filling

1-30 ml; 3600 ampoules per hour (2-ml ampoules); open or closed ampoules

##### Batch sizes

500-10,000 vials; 500-15,000 ampoules

## Fraunhofer ITEM has closed the gap between pre-clinical and clinical product development

Together with about 60 guests from the world of politics, industry and academia, the Division of Pharmaceutical Biotechnology celebrated its new facilities on the campus of the Helmholtz Center for Infection Research in Braunschweig in September 2013. On this occasion, the ITEM scientists also presented the new fill-and-finish plant: In a new class-B clean room, investigational medicinal products can now be filled aseptically into vials and ampoules and released specifically for use in clinical trials.

“With this technology platform, the Fraunhofer ITEM has now closed the last gap between pre-clinical and clinical product development. We are confident that this will make drug development more efficient and will be of great interest to industry and public research institutions,” said Dr. Holger Ziehr, head of the Division of Pharmaceutical Biotechnology. First projects on behalf of public research institutions have been initiated.



Lower Saxony's Minister of Science and Culture Gabriele Heinen-Kljajić expressed her satisfaction over the now available possibility to advance development of novel biopharmaceuticals to investigational medicinal products directly in a publicly funded research institution. The cost of the extensive construction works to remodel and expand the Pharmaceutical Biotechnology facilities amounted to about 6.6 million euros, funded in equal shares by the Fraunhofer-Gesellschaft, the German Federal Ministry of Education and Research, and the government of the *Land* Lower Saxony.



## PROJECTS

### Modular principle allows customized protein expression

There is an ever increasing diversity in the properties of protein-based biopharmaceutical therapeutics. This diversity requires flexible expression systems that can be combined according to a modular principle, enabling customized solutions for specific protein expression requirements. The idea which scientists of the Fraunhofer ITEM Pharmaceutical Biotechnology Division are currently exploring in cooperation with Professor Fleißner from the Institute of Genetics of Braunschweig Technical University aims to develop a fungal expression system that offers this potential. The red bread mold *Neurospora crassa* has been used as eukaryotic model organism in basic research for several decades already. Numerous mutant

strains are available, allowing different properties of this fungus to be combined. Using this collection of strains, which includes deletions for the majority of non-essential genes, the target strain can quite easily be configured according to a modular principle by means of simple crossing procedures to achieve certain properties. "A particularly interesting aspect of this project is that in cooperation with the scientists of the Fraunhofer ITEM it allows our profound expertise from many years of basic research to be advanced towards practical application," says Professor Fleißner.



#### CONTACT

David Havlik  
Phone +49 531 6181-6202  
david.havlik@item.fraunhofer.de

### Searching for the hot spot: RMCE-based stable transgene expression

In the manufacture of glycosylated biopharmaceuticals, high and stable transgene expression is a prerequisite for the manufacturing process to be economic. Traditional methods for the manufacture of production cell lines are based on random integration of the expression vector into the CHO genome. The subsequent selection process aimed at identifying a CHO clone with high and also stable protein expression from among the heterogeneous pool of transfected cells is very time-consuming and labor-intensive. An alternative cell line development strategy consists in targeted integration of a transgene into a precisely identified and characterized, transcriptionally active and exchangeable genomic locus: the hot spot. Fraunhofer ITEM scientists have implemented this strategy by means of recombinase-mediated cassette exchange (RMCE). The individual clones generated so far with this method displayed consistent expression of the target gene, which they stably

produced over three months without use of antibiotics. Specific productivity on average was 0.3 and 0.003 picograms per cell per day for the expression of murine IgG-2 and human tissue-type plasminogen activator, respectively. Expression of different proteins at the same locus thus obviously does not result in comparable productivity rates. The further course of the project includes fed-batch-based process development for clones generated both by RMCE and with traditional methods. The aim is to verify whether RMCE clones display the same homogeneous performance with regard to maximum cell density, titer, and metabolism under optimized identical culturing conditions and also whether their glycosylation structures are similar.



#### CONTACT

Elisabeth Bludau  
Phone +49 531 6181-6340  
elisabeth.bludau@item.fraunhofer.de

*A retraceable, robust, and stable cell bank is the key factor in any biotechnological production process of active ingredients. For 15 years already, the Fraunhofer ITEM in Braunschweig has practiced the GMP standards of a manufacturing license according to § 13 of the German Drug Act for manufacturing master and working cell banks of microbial strains and mammalian cells up to safety level 2.*



## Fraunhofer ITEM provides support with GMP cell bank manufacturing

As of February 2013, Annex 2 of the EU GMP guideline requires appropriate approvals from the national competent authorities also for the manufacturing of cell banks. For recombinant expression systems such as *E. coli* and CHO cells, the corresponding working standard has been practiced for years already. In contrast, for pharmaceutical companies working with non-recombinant organisms, it is relatively new. Scientists of the institute's Division of Pharmaceutical Biotechnology in Braunschweig have embarked upon a large project focused on the development of bacterial, yeast, and even fungal cell banks. The project partner SANUM-Kehlbeck GmbH & Co. KG, a manufacturer of homeopathic preparations using these organisms, wants to switch from external supply of cells to in-house GMP cell banks. Given that some of the bacteria, yeasts, and fungi used are rather extraordinary

microorganisms, the scientists first have to perform a comprehensive feasibility study. In a first step, they will explore experimentally how the required cell banks can be produced in compliance with GMP. According to the project plan, the partner will then test the laboratory cell banks generated in the feasibility study for suitability, before the actual GMP cell bank manufacturing is initiated. The aim is to provide the project partner with GMP cell banks that meet the demands of state-of-the-art pharmaceutical manufacturing, while reasonably complying with regulatory requirements. Counseling in this project is provided by the Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures.



### CONTACT

Dr. Kathrin Bohle  
Phone +49 531 6181-6347  
kathrin.bohle@item.fraunhofer.de

## Firsthand experience: GMP manufacture of a highly toxic active ingredient in *E. coli*

Fraunhofer ITEM biotechnologists in the institute's facilities in Braunschweig are currently working on the implementation of a manufacturing process for a highly efficient protein toxin in *E. coli*, predeveloped by an industrial partner. A special feature of this project is the fact that the partner is bringing in his own manufacturing plant and also members of his own staff who are collaborating with the Fraunhofer team to transfer the process from the development stage to GMP manufacture. The key benefit for the project partner is his staff getting firsthand experience from the setup of the plant to final GMP manufacture of the investigational medicinal product, with direct access to the comprehensive expertise of the Fraunhofer ITEM biotechnologists. After manufacture of the investigational

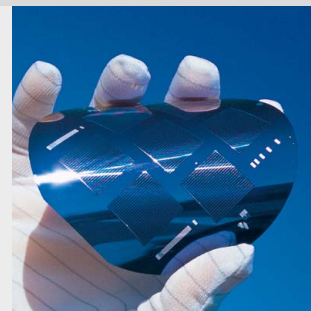
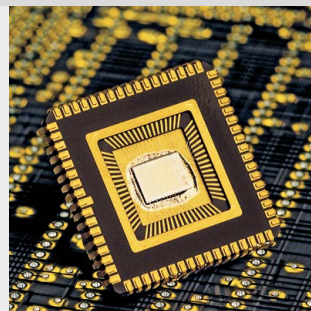
medicinal product, the plant and process will be transferred to the project partner's facilities, where the active ingredient will be manufactured, once authorization will have been received. "Already now, we are getting to know the plant and the process, and we can witness every single step. This will enable us to implement the process at our production site later on and start manufacturing without much delay," explains the scientific expert of the project partner.



### CONTACT

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

# FRAUNHOFER-GESELLSCHAFT



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 67 institutes and research units. The majority of the more than 23,000 staff are qualified scientists and engineers, who work with an annual research budget of 2 billion euros. Of this sum, more than 1.7 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.

International collaborations with excellent research partners and innovative companies around the world ensure direct access to regions of the 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.

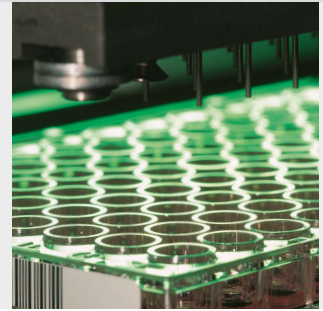
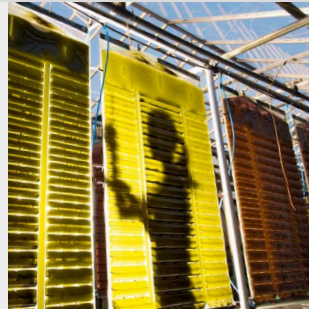
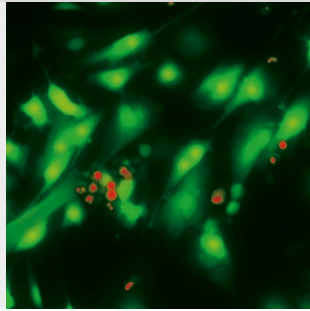
As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills that will allow them to take up positions of responsibility within their institute, at universities, in industry and in society. Students who choose to work on projects at the 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.

[www.fraunhofer.de](http://www.fraunhofer.de)



# FRAUNHOFER GROUP FOR LIFE SCIENCES



Six Fraunhofer institutes and a Fraunhofer research institution have pooled their life sciences expertise and potentiated their capacities within the Fraunhofer Group for Life Sciences. With a staff of over 1700, the Group is an important R&D partner for the pharmaceutical and biotechnology sectors as well as for the chemicals industry and medical technology companies.

With their concentrated expertise and broad range of methods and equipment, 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 are in a position to undertake even comprehensive projects 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.

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 require-

ments, 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 Group 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 remediating the environment.

## 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 5466-440

Fax +49 511 5466-445

[claus.kroggel@vls.fraunhofer.de](mailto:claus.kroggel@vls.fraunhofer.de)

[www.lifesciences.fraunhofer.de](http://www.lifesciences.fraunhofer.de)

## Publications

- Abraham, K.; Appel, K.; Berger-Preiß, E.; Apel, E.; Gerling, S.; Mielke, H.; Creutzenberg, O.; Lampen, A.  
Relative oral bioavailability of 3-MCPD from 3-MCPD fatty acid esters in rats.  
In: Archives of Toxicology 87 (2013), No. 4, pp. 649-659.  
doi: 10.1007/s00204-012-0970-8
- Albrecht, M.; Preston-Hurlburt, P.; Hoymann, H.-G.; Dittrich, A.  
Minor role of neutrophils in Th17 mediated airway collateral priming towards new antigens.  
In: Allergo Journal 22 (2013), No. 6, p. 420, Abstract P 60.
- Appel, K. E.; Abraham, K.; Berger-Preiß, E.; Hansen, T.; Apel, E.; Schuchardt, S.; Vogt, C.; Bakhiya, N.; Creutzenberg, O.; Lampen, A.  
Relative oral bioavailability of glycidol from glycidyl fatty acid esters in rats.  
In: Archives of Toxicology 87 (2013), No. 9, pp. 1649-1659.  
doi: 10.1007/s00204-013-1061-1
- Batke, M.; Aldenberg, T.; Escher, S.; Mangelsdorf, I.  
Relevance of non-guideline studies for risk assessment: the coverage model based on most frequent targets in repeated dose toxicity studies.  
In: Toxicology Letters 218 (2013), No. 3, pp. 293-298.  
doi: 10.1016/j.toxlet.2012.09.002
- Batke, M.; Gundert-Remy, U.; Helma, C.; Kramer, S.; Kleppe-Nordqvist, S.; Maunz, A.; Partosch, F.; Seeland, M.; Bitsch, A.  
New strategies for the generation of chemical categories under REACH.  
In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S6, Abstract 016.
- Berger-Preiß, E.; Gerling, S.  
Pyrethrum and pyrethroid metabolites (after solid phase extraction) in urine [Biomonitoring Methods, 2013].  
In: DFG/Commission for the investigation of health hazards of chemical compounds in the work area: The MAK-collection for occupational health and safety. Part 4, Biomonitoring methods: Vol. 13. Weinheim: Wiley-VCH, 2013, pp. 179-214.  
doi: 10.1002/3527600418.bi800334e0013b
- Berger-Preiß, E.; Gerling, S.; Kock, H.; Koch, W.  
Indoor biocide concentrations after application of biocidal aerosol sprays.  
In: ISEE – International Society for Environmental Epidemiology: Environment and Health – Bridging South, North, East and West: Conference of ISEE, ISES and ISIAQ, 2013, Abstract 3905.
- Buist, H.; Aldenberg, T.; Batke, M.; Escher, S.; Klein, E. R.; Kühne, R.; Marquart, H.; Pauné, E.; Rorije, E.; Schüürmann, G.; Kroese, D.  
The OSIRIS weight of evidence approach: ITS mutagenicity and ITS carcinogenicity. 26 Jan 2013 [Epub ahead of print].  
In: Regulatory Toxicology and Pharmacology 67 (2013), No. 2, pp. 170-181.  
doi: 10.1016/j.yrtph.2013.01.002
- Buschmann, J.  
The OECD guidelines for the testing of chemicals and pesticides.  
In: Barrow, Paul C. (ed.): Teratogenicity Testing. Methods and Protocols (Methods in molecular biology 947). New York/NY: Springer, 2013, pp. 37-56.  
doi: 10.1007/978-1-62703-131-8\_4
- Buschmann, J.; Chahoud, I.; Kellner, R.; Solecki, R.  
The DevTox project: a comprehensive source of information on developmental abnormalities.  
In: The Toxicologist 52 (2013), No. 1, p. 219, Abstract PS 1027.
- Buschmann, J.; Fuhst, R.; Tillmann, T.; Ernst, H.; Kolling, A.; Pohlmann, G.; Preiß, A.; Berger-Preiß, E.; Hansen, T.; Kellner, R.; Rusch, G. M.  
Unexpected brain lesions in lactating Sprague-Dawley rats in a two-generation inhalation reproductive toxicity study with pentafluoropropane (HFC-245fa).  
In: Experimental and Toxicologic Pathology 65 (2013), No. 6, pp. 875-882.  
doi: 10.1016/j.etp.2012.12.006
- Creutzenberg, O.; Kock, H.; Schaudien, D.  
Biokinetics of nanoscaled europium oxide particles following an acute inhalation in rats.  
In: The Toxicologist 52 (2013), No. 1, p. 507, Abstract PS 2374.
- Curths, C.; Becker, T.; Kaup, F. J.; Schlumbohm, C.; Sewald, K.; Hohlfeld, J. M.; Dunker, S.; Braun, A.; Knauf, S.  
Ein translationales Tiermodell für das allergische Asthma des Menschen im Weißbüschelaffen (*Callithrix jacchus*).  
In: Pneumologie 67 (2013), No. 6, A11.  
doi: 10.1055/s-0033-1343971
- Curths, C.; Braun, A.; Knauf, S.  
Ein translationales Tiermodell für das allergische Asthma des Menschen im Weißbüschelaffen (*Callithrix jacchus*).  
In: Allergo Journal 22 (2013), No. 1, p. 64, V46.

- Curths, C.; Wichmann, J.; Becker, T.; Kaup, F.-J.; Hohlfeld, J. M.; Sewald, K.; Windt, H.; Dunker, S.; Braun, A.; Knauf, S.  
A translational non-human primate model for human asthma in the common marmoset (*Callithrix jacchus*).  
In: American Journal of Respiratory and Critical Care Medicine 187 (2013), Suppl., A2687.
- Curths, C.; Wichmann, J.; Dunker, S.; Windt, H.; Hoymann, H.-G.; Lauenstein, H. D.; Hohlfeld, J. M.; Becker, T.; Kaup, F.-J.; Braun, A.; Knauf, S.  
Airway hyper-responsiveness in lipopolysaccharide-challenged common marmosets (*Callithrix jacchus*). 23 Jul 2013 [Epub ahead of print].  
In: Clinical Science 126 (2014), No. 2, pp. 155-162.  
doi: 10.1042/CS20130101
- Dasenbrock, C.; Tillmann, T.; Oertel, A.; Brockmeyer, H.; Murbach, M.; Capstick, M.; Kuster, N.; Ziemann, C.  
No direct genotoxic potential of different radiofrequency electromagnetic fields in MRC-5 cells and B6C3F1 mice.  
In: The Toxicologist 52 (2013), No. 1, p. 319, Abstract PS 1490.
- Dutow, P.; Lingner, S.; Laudeley, R.; Glage, S.; Hoymann, H.-G.; Dittrich, A.-M.; Fehlhaber, B.; Müller, M.; Braun, A.; Klos, A.  
Severity of allergic airway disease due to house dust mite allergen is not increased after clinical recovery of lung infection with *Chlamydia pneumoniae* in mice.  
In: Infection and Immunity 81 (2013), No. 9, pp. 3366-3374.  
doi: 10.1128/iai.00334-13
- Duvar, S.; Hecht, V.; Finger, J.; Matthias, G.; Ziehr, H.  
Developing an upstream process for a monoclonal antibody including medium optimization.  
In: BMC Proceedings 7 (2013), Suppl. 6, P34, 3 pp.  
doi: 10.1186/1753-6561-7-S6-P34
- Escher, S. E.; Batke, M.; Hoffmann-Doerr, S.; Messinger, H.; Mangelsdorf, I.  
Interspecies extrapolation based on the RepDose database: A probabilistic approach.  
In: Toxicology letters 218 (2013), No. 2, pp.159-165.  
doi: 10.1016/j.toxlet.2013.01.027
- Escher, S.; Hoffmann-Doerr, S.; Batke, M.; Mangelsdorf, I.  
Assessment factors in human health risk assessment and their associated level of safety.  
In: The Toxicologist 52 (2013), No. 1, p. 418, Abstract PS 1965.
- Fehrenbach, H.; Müller, B.; König, P.; Hansen, T.; Bockhorn, H.  
CarbonBlack: a joint research project to establish a test system for predicting human-toxicological effects of synthetic carbon black nanoparticles.  
In: Pneumologie 67 (2013), No. 12, p. 699, A 15.  
doi: 10.1055/s-0033-1357063
- Fischer, M.; Dasenbrock, C.; Koch, W.  
The isolated perfused lung (IPL) as a screening tool for aerosol products.  
In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S22, Abstract 082.
- Fuhst, R.; Runge, F.; Buschmann, J.; Ernst, H.; Praechter, C.; Hansen, T.; Erichsen, J. von; Turowska, A.; Hoymann, H.-G.; Müller, M.; Pohlmann, G.; Sewald, K.; Ziemann, C.; Schlüter, G.; Garn, H.  
Toxicity profile of the GATA-3-specific DNzyme hgd40 after inhalation exposure.  
In: Pulmonary Pharmacology & Therapeutics 26 (2013), No. 2, pp. 281-289.  
doi: 10.1016/j.pupt.2012.12.005
- Gibeon, D.; Wagener, A. H.; Yang, X.; Sousa, A. R.; Corfield, J.; Shaw, D. E.; Fowler, S.; Flemming, L. J.; Jeyasingham, E.; Rowe, A.; Fichtner, K.; Robberts, G.; Bakke, P.; Singer, T.; Geiser, T.; Frey, U.; Horvarth, I.; Polosa, R.; Bonnelykke, K.; Krug, N.; Middelveld, R.; Dahlen, S.-E.; Dahlen, B.; Hedlin, G.; Hashimoto, S.; Nordlund, B.; Musial, J.; Woodcock, A.; Murray, C. S.; Pahu, L.; Myles, D.; Compton, C.; Higenbottam, T. W.; Montuschi, P.; Vestbo, J.; Larsson, L.; Sandstrom, T.; Bisgaard, H.; Wagers, S. S.; Howarth, P. H.; Bel, E. H.; Djukanovic, R.; Sterk, P. J.; Chung, K. F.  
U-BIOPRED asthma cohort: Inflammatory markers and corticosteroid use.  
In: European Respiratory Journal 42 (2013), Suppl. 57, 634s, A 3029.
- Hackbarth, A.; Schaudien, D.; Bellmann, B.; Ernst, H.; Ziemann, C.; Leonhardt, A.; Heinrich, U.; Rittinghausen, S.  
Toxic effects of multiwall carbon nanotubes (MWCNT) in vivo and in vitro.  
In: Pneumologie 67 (2013), No. 12, p. 695, A2.  
doi: 10.1055/s-0033-1357050
- Hackbarth, A.; Ziemann, C.; Albrecht, L.; Steinberg, P.; Bellmann, B.  
Multiwall carbon nanotubes exhibit a cytotoxic but not directly DNA-damaging potential in human LP9/TERT-1 peritoneal mesothelial cells.  
In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S30, Abstract 113.  
doi: 10.1089/jamp.2012.0996
- Hackermuller, J.; Ahnert, P.; Christ, S.; Hohlfeld, J. M.; Horn, F.; Krug, N.; Lindemann, E.; Löffler, M.; Lorenz, S.; Reiche, K.; Sohn, K.; Specht, M.; Miller, B. E.; Locantore, N. W.; Tal-Singer, R.  
Assessment of long noncoding RNA expression using whole transcriptome sequencing of COPD blood samples from the ECLIPSE cohort.  
In: American Journal of Respiratory and Critical Care Medicine 187 (2013), A5513.
- Hahn, T.; Diamond, J.; Doubson, S.; Howe, P.; Kielhorn, J.; Könecker, G.; Lee-Steere, C.; Mangelsdorf, I.; Schneider, U.; Sugaya, Y.; Taylor, K.; Van Dam, R.; Stauber, J. L.  
Predicted no effect concentration derivation as a significant source of variability in environmental hazard assessments of chemicals in aquatic systems: An inter-national analysis. 10 Dec 2013 [Epub ahead of print].  
In: Integrated Environmental Assessment and Management (2013), pp. 30-36.  
doi: 10.1002/ieam.1473
- Hansen, T.; Kopf, J.; Danov, O.; Ströbele, M.; Braun, A.; Sewald, K.; Bockhorn, H.; Fehrenbach, H.  
In vitro and ex vivo toxicity screening for predicting toxicological effects of synthetic carbon black nanoparticles in humans.  
In: Pneumologie 67 (2013), No. 12, p. 699, A17.  
doi: 10.1055/s-0033-1357065
- Hansen, T.; Kopf, J. C.; Danov, O.; Ströbele, M.; Braun, A.; Sewald, K.; Steinberg, P.; Fehrenbach, H.  
Effects of carbon black nanoparticles on human pulmonary cell lines and precision cut lung slices.  
In: The Toxicologist 52 (2013), No. 1, p. 95, Abstract PS 444.
- Happle, C.; Henning, C.; Skuljec, J.; Hoymann, G.; Meyer-Bahlburg, A.; Hansen, G.  
A decisive role for B cells in priming of allergy and tolerance by preconceptual immunization of the mother.  
In: European Respiratory Journal 42 (2013), Suppl. 57, 328s, P1578.
- Helwich, O.; Koch, W.; Iwatschenko, P.; Windt, H.; Taut, F. J. H.; De Muynck, C.; Pohlmann, G.  
Performance testing of a novel Continuous Powder Aerosolizer (CPA) for inhalative administration of surfactant to preterm neonates.  
In: Journal of Aerosol Medicine and Pulmonary Drug Delivery 26 (2013), No. 2, p. A-14, Abstract O-39.
- Hess, A.; Lauenstein, L.; Schneider, X.; Vogel, S.; Ma-Hock, L.; Kolle, S.; Martin, C.; Pirow, R.; Steinfath, M.; Liebsch, M.; Landsiedel, R.; Braun, A.; Sewald, K.  
Pre-validation of the ex vivo model precision cut lung slices (PCLuS) for the prediction of respiratory toxicology.  
In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S34, Abstract 131.
- Hittinger, M.; Czyn, Z. T.; Huesemann, Y.; Maneck, M.; Botteron, C.; Kaeuffl, S.; Klein, C. A.; Polzer, B.  
Molecular profiling of single Sca-1<sup>+</sup>/CD34<sup>+</sup> cells – the putative murine lung stem cells.  
In: PLoS One 8 (2013), No. 12: e83917, 10 pp.  
doi: 10.1371/journal.pone.0083917
- Hoffmann, R.; Braun, A.; Knauf, S.; Kaup, F.-J.; Bleyer, M.  
Distribution of ciliated epithelial cells in the trachea of common marmosets (*Callithrix jacchus*). 29 Aug 2013 [Epub ahead of print].  
In: Journal of Medical Primatology 43 (2014), No. 1, pp. 55-58(4).  
doi: 10.1111/jmp.12075
- Hohlfeld, J.; Lüer, K.; Krug, N.; Turowska, A.; Renz, H.; Garn, H.; Homburg, U.  
Safety profile and pharmacokinetics of an inhaled GATA-3-specific DNzyme in a phase Ib study in patients with stable allergic asthma.  
In: European Respiratory Journal 42 (2013), Suppl. 57, 1027s, A 4856.
- Hohlfeld, J. M.; Sharma, A.; Noord, J. A. van; Cornelissen, P. J.; Derom, E.; Towse, L.; Peterkin, V.; Disse, B.  
Pharmacokinetics and pharmacodynamics of tiotropium solution and tiotropium powder in chronic obstructive pulmonary disease. 25 Oct 2013 [Epub ahead of print].  
In: Journal of Clinical Pharmacology (2013), 10 pp.  
doi: 10.1002/jcph.215
- Holz, O.; Gaida, A.; Schuchardt, S.; Lavae-Mokhtari, B.; Biller, H.; Rosano, M.; Hanrahan, J. P.; Hohlfeld, J. M.  
Volatile organic compounds (VOC) in exhaled breath after experimental ozone exposure.  
In: American Journal of Respiratory and Critical Care Medicine 187 (2013), A4101.
- Holz, O.; Janssen, O.; Lavae-Mokhtari, B.; Hohlfeld, J. M.  
Repeatability of sputum composition in healthy subjects over 6 months.  
In: American Journal of Respiratory and Critical Care Medicine 187 (2013), A4094.
- Holz, O.; Roepcke, S.; Lauer, G.; Faulenbach, C.; Hohlfeld, J. M.  
The prognostic value of serum, BAL and sputum biomarkers of smokers with and without COPD – a 5-year follow-up.  
In: American Journal of Respiratory and Critical Care Medicine 187 (2013), A1515.

- Hox, V.; Vanoirbeek, J. A.; Alpizar, Y. A.; Voedisch, S.; Callebaut, I.; Bobic, S.; Sharify, A.; Vooght, V. de; Gerven, L. van; Devos, F.; Liston, A.; Voets, T.; Vennekens, R.; Bullens, D. M. A.; Vries, A. de; Hoet, P.; Braun, A.; Ceuppens, J. L.; Talavera, K.; Nemery, B.; Hellings, P. W.  
Crucial role of transient receptor potential ankyrin 1 and mast cells in induction of nonallergic airway hyperreactivity in mice.  
In: *American Journal of Respiratory and Critical Care Medicine* 187 (2013), No. 5, pp. 486-493.  
doi: 10.1164/rccm.201208-13580C
- Janssen, O.; Schaumann, F.; Holz, O.; Lavae-Mokhtari, B.; Welker, L.; Winkler, C.; 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.  
In: *BMC Pulmonary Medicine* 13 (2013), No. 19, 11 pp.  
doi: 10.1186/1471-2466-13-19
- Jiménez Delgado, S. M.; Danov, O.; Braun, A.; Pfenning, O.; Förster, C.; Hohlbaum, A.; Audoly, L.; Hohlfeld, J.; Sewald, K.  
IL-13-induced cytokine release and hyperresponsiveness in precision cut lung slices of different species – characterization of a model potentially suitable for translational research of asthma cellular events.  
In: *European Respiratory Journal* 42 (2013), Suppl. 57, 1064s, A 5026.
- Jonigk, D.; Al-Omari, M.; Maegel, L.; Müller, M.; Izykowski, N.; Hong, J.; Hong, K.; Kim, S.-H.; Dorsch, M.; Mahadeva, R.; Laenger, F.; Kreipe, H.; Braun, A.; Shahaf, G.; Lewis, E. C.; Welte, T.; Dinarello, C. A.; Janciauskiene, S.  
Anti-inflammatory and immunomodulatory properties of alpha1-antitrypsin without inhibition of elastase.  
In: *Proceedings of the National Academy of Sciences of the United States of America*. PNAS 110 (2013), No. 37, pp. 15007-15012.  
doi: 10.1073/pnas.1309648110
- Karbe, E. (ed.); Drommer, W. (ed.); Germann, P.-G. (ed.); Morawietz, G. (ed.); Kellner, R. (ed.)  
Classic examples in toxicologic pathology.  
European Society of Toxicologic Pathology (ESTP), CD-ROM, 5<sup>th</sup> edition, 2013: 11<sup>th</sup> European Congress of Toxicologic Pathology. Ghent, Belgium, September 10-13, 2013. ESTP series of current topics in toxicologic pathology.  
ISBN 978-3-9814653-3-4.
- 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 airway neutrophilia in healthy volunteers.  
In: *European Respiratory Journal* 41 (2013), No. 1, pp. 239-241.  
doi: 10.1183/09031936.00123612
- Krug, N.; Gupta, A.; Badorrek, P.; Koennen, R.; Mueller, M.; Pivovarova, A.; Hilbert, J.; Wetzel, K.; Hohlfeld, J. M.; Wood, C.  
Efficacy of the oral chemoattractant receptor homologous molecule on TH2 cells antagonist BI 671800 in patients with seasonal allergic rhinitis.  
In: *The Journal of Allergy and Clinical Immunology* (2013), 14 pp. 8 Dec 2013 [Epub ahead of print].  
doi: 10.1016/j.jaci.2013.10.013
- Kuhlmann, J.; Bartsch, Y.; Willbold, E.; Schuchardt, S.; Holz, O.; Hort, N.; Höche, D.; Heineman, W. R.; Witte, F.  
Fast escape of hydrogen from gas cavities around corroding magnesium implants.  
In: *Acta Biomaterialia* 9 (2013), No. 10, pp. 8714-8721.  
doi: 10.1016/j.actbio.2012.10.008
- Lauenstein, H. D.; Quarcio, D.; Welte, T.; Braun, A.; Groneberg, D. A.  
Expression of VPAC1 in a murine model of allergic asthma.  
In: *Journal of Occupational Medicine and Toxicology. Online journal* 8 (2013), No. 1, Art. 28, 4 pp.  
doi: 10.1186/1745-6673-8-28
- Lewin, G.; Batke, M.; Escher, S.; Mangelsdorf, I.  
Analysis of the indicative value of repeated dose toxicity studies for reproductive toxicity  
In: *Naunyn-Schmiedeberg's Archives of Pharmacology* 386 (2013), Suppl. 1, S6-S7, Abstract 017.
- Licht, O.; Voß, J.-U.; Wahnschaffe, U.; Mangelsdorf, I.  
Proposal for biomonitoring values according to the extended approach of the HBM commission.  
In: *Naunyn-Schmiedeberg's Archives of Pharmacology* 386 (2013), Suppl. 1, S47, Abstract 190.
- Liu, Q.; Liu, J.; Roschmann, K. I. L.; Egmond, D. van; Golebski, K.; Fokkens, W. J.; Wang, D.; Drunen, C. M. van  
Histone deacetylase inhibitors up-regulate LL-37 expression independent of toll-like receptor mediated signalling in airway epithelial cells.  
In: *Journal of Inflammation* 10 (2013), Art. 15, 6 pp.  
doi: 10.1186/1476-9255-10-15
- Morimoto, Y.; Oyabu, T.; Horie, M.; Kambara, T.; Izumi, H. Kuroda, E.; Creutzenberg, O.; Bellmann, B.; Pohlmann, G.; Schuchardt, S.; Hansen, T.; Ernst, H.  
Pulmonary toxicity of printer toner following inhalation and intratracheal instillation.  
In: *Inhalation Toxicology* 87 (2013), No. 4, pp. 679-690.  
doi: 10.3109/08958378.2013.835010
- Mueller, A. N.; Ziemann, S.; Treitschke, S.; Abmann, D.; Doehlemann, G.  
Compatibility in the *ustilago maydis*-maize interaction requires inhibition of host cysteine proteases by the fungal effector Pit2.  
In: *PLoS Pathogens* 9 (2013), No. 2: e1003177, 13 pp.  
doi: 10.1371/journal.ppat.1003177
- Neuhaus, V.; Schwarz, K.; Hartman, C.; Shoji, Y.; Chichester, J.; Koch, W.; Sewald, K.; Yusibov, V.; Braun, A.  
The new nanoparticle-based influenza vaccine induces a protective effect in a murine mouse model.  
In: *American Journal of Respiratory and Critical Care Medicine* 187 (2013), A5494.
- Neuhaus, V.; Schwarz, K.; Klee, A.; Seehase, S.; Förster, C.; Pfennig, O.; Jonigk, D.; Fieguth, H.-G.; Koch, W.; Warnecke, G.; Yusibov, V.; Sewald, K.; Braun, A.  
Functional testing of an inhalable nanoparticle based influenza vaccine using a human precision cut lung slice technique.  
In: *PLoS One. Online journal* 8 (2013), No. 8: e71728, 10 pp.  
doi: 10.1371/journal.pone.0071728
- Niehof, M.; Hansen, T.  
Cytochrome P450 monooxygenases expression in human epithelial lung cell lines.  
In: *The Toxicologist* 52 (2013), No. 1, p. 59, Abstract PS 282.
- Paranjpe, M.; Neuhaus, V.; Finke, J. H.; Richter, C.; Gottsch, T.; Kwade, A.; Büttgenbach, S.; Braun, A.; Müller-Goymann, C. C.  
In vitro and ex vivo toxicological testing of sildenafil-loaded solid lipid nanoparticles.  
In: *Inhalation Toxicology* 25 (2013), No. 9, pp. 536-543.  
doi: 10.3109/08958378.2013.810315
- Pohlmann, G.; Holzinger, K.; Spiegel-Ciobanu, V. E.  
Comparative investigations in order to characterise ultrafine particles in fumes in the case of welding and allied processes.  
In: *Welding and Cutting* 12 (2013), No. 2, pp. 97-105.
- Pohlmann, G.; Iwatschenko, P.; Koch, W.; Windt, H.; Rast, M.; Gama de Abreu, M.; Taut, F. J. H.; De Mynck, C.  
A novel continuous powder aerosolizer (CPA) for inhalative administration of highly concentrated recombinant surfactant protein-C (rSP-C) surfactant to preterm neonates.  
In: *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 26 (2013), No. 6, pp. 370-379.
- Polzer, B.; Klein, C. A.  
Metastasis awakening: the challenges of targeting minimal residual cancer.  
In: *Nature Medicine* 19 (2013), No. 3, pp. 274-275.  
doi: 10.1038/nm.3121
- Reamon-Büttner, S. M.; Hackbarth, A.; Voepel, I. R.; Brockmeyer, H.; Bellmann, B.; Ziemann, C.  
Human peritoneal mesothelial LP9 cells as a model system to determine the toxic and genotoxic potential of multiwalled carbon nanotubes (MWCNTs).  
In: *Naunyn-Schmiedeberg's Archives of Pharmacology* 386 (2013), Suppl. 1, S65, Abstract 262.
- Reamon-Büttner, S. M.; Sattler, E.; Ciribilli, Y.; Inga, A.; Wessel, A.; Borlak, J.  
Transcriptional defect of an inherited NKX2-5 haplotype comprising a SNP, a nonsynonymous and a synonymous mutation, associated with human congenital heart disease.  
In: *PLoS One* 8 (2013), No. 12: e83295, 9 pp.  
doi: 10.1371/journal.pone.0083295
- Rittinghausen, S.; Bellmann, B.; Creutzenberg, O.; Ernst, H.; Kolling, A.; Mangelsdorf, I.; Kellner, R.; Beneke, S.; Ziemann, C.  
Evaluation of immunohistochemical markers to detect the genotoxic mode of action of fine and ultrafine dusts in rat lungs.  
In: *Toxicology* 303 (2013), pp. 177-186.  
doi: 10.1016/j.tox.2012.11.007
- Rochlitzer, S.; Hoymann, H.; Müller, M.; Braun, A.  
No exacerbation but impaired anti-viral mechanisms in a rhinovirus-chronic allergic asthma mouse model. 3 Jul 2013 [Epub ahead of print].  
In: *Clinical Science* 126 (2014), No. 1, pp. 55-65.  
doi: 10.1042/cs20130174
- Schlichting, A.; Ziemann, C.; Leonhardt, A.; Rittinghausen, S.; Schaudien, D.; Bellmann, B.  
Toxic effects of MWCNT in vivo and in vitro.  
In: *The Toxicologist* 52 (2013), No. 1, pp. 98, Abstract PS 460.
- Schlick, S.; Kopf, J.; Ströbele, M.; Fehrenbach, H.  
Airway region-specific effects of carbon black nanoparticles (CBNP).  
In: *Pneumologie* 67 (2013), No. 12, p. 700, Abstract A19.  
doi: 10.1055/s-0033-1357067

Schröder, K.; Pohlenz-Michel, C.; Voß, J.-U.; Simetska, N.; Escher, S.; Mangelsdorf, I. Development of a database on toxic effects of nano-objects. In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S74, Abstract 302.

Schulz, F.; Batke, M.; Lewin, G.; Escher, S.; Mangelsdorf, I. FeDTeX Database - A versatile tool condensing data from developmental and reproductive toxicity studies. In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S75-S76, Abstract 309.

Schwarz, K.; Holz, O.; Koch, W.; Hohlfeld, J. M. Sampling and analysis of exhaled breath particles. In: Journal of Aerosol Medicine and Pulmonary Drug Delivery 26 (2013), No. 2, p. A-45, Abstract P-073.

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.; Knauf, S. Ein translationales LPS-Modell zur präklinischen Testung anti-inflammatorischer Substanzen im Weißbüschelaffen (*Callithrix jacchus*). In: Pneumologie 67 (2013), No. 6, A10. doi: 10.1055/s-0033-1343970

Seidel, V.; Hoffmann, R.; Braun, A.; Seehase, S.; Knauf, S.; Kaup, F.-J.; Bleyer, M. Distribution and morphology of Clara cells in common marmosets (*Callithrix jacchus*). In: Journal of Medical Primatology 42 (2013), No. 2, pp. 79-88. doi: 10.1111/jmp.12038

Sewald, K.; Braun, A. Assessment of immunotoxicity using precision-cut tissue slices. In: Xenobiotica 43 (2013), No. 1, pp. 84-97. doi: 10.3109/00498254.2012.731543

Sewald, K.; Lauenstein, L.; Vogel, S.; Hess, A.; Schneider, X.; Martin, C.; Pirow, R.; Liebsch, M.; Landsiedel, R.; Braun, A. Prevalidation of the ex vivo model precision cut lung slices (PCLS) for the prediction of respiratory toxicology. In: The Toxicologist 52 (2013), No. 1, p. 315, Abstract PS 1469.

Sharma, A.; Hohlfeld, J.; Cornelissen, P.; van Noord, J.; Derom, E.; Towse, L.; Peterkin, V.; Disse, B. Comparison of the pharmacokinetics and pharmacodynamics of once daily tiotropium Respimat® and tiotropium HandiHaler® in COPD patients. In: European Respiratory Journal 42 (2013), Suppl. 57, 981s, A 4631.

Solecki, R.; Barbellion, S.; Bergmann, B.; 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. Harmonization of description and classification of fetal observations: Achievements and problems still unresolved. Report of the 7<sup>th</sup> Workshop on the Terminology in Developmental Toxicology, Berlin, May 4-6, 2011. 8 Jul 2012 [Epub ahead of print]. In: Reproductive Toxicology 35 (2013), pp. 48-55. doi: 10.1016/j.reprotox.2012.06.006

Stephan, M.; Suhling, H.; Schade, J.; Wittlake, M.; Tasic, T.; Klemann, C.; Pabst, R.; Jurawitz, M.-C.; Raber, K. A.; Hoymann, H.-G.; Braun, A.; Glaab, T.; Hoffmann, T.; Schmiedl, A.; Hoersten, S. von Effects of dipeptidyl peptidase-4 inhibition in an animal model of experimental asthma: A matter of dose, route, and time. In: Physiological Reports 1 (2013), No. 5: e00095, 9 pp. doi: 10.1002/phy2.95

Switalla, S.; Knebel, J.; Ritter, D.; Dasenbrock, C.; Krug, N.; Braun, A.; Sewald, K. Determination of genotoxicity by the Comet assay applied to murine precision-cut lung slices. In: Toxicology in Vitro 27 (2013), No. 2, pp. 798-803. doi: 10.1016/j.tiv.2012.12.015

Tluczkiwicz, I.; Batke, M.; Kroese, D.; Buist, H.; Aldenberg, T.; Pauné, E.; Grimm, H.; Kühne, R.; Schürmann, G.; Mangelsdorf, I.; Escher, S. E. The OSIRIS weight of evidence approach: ITS for the endpoints repeated-dose toxicity (RepDose ITS). In: Regulatory Toxicology and Pharmacology 67 (2013), No. 2, pp. 157-169. doi: 10.1016/j.yrtph.2013.02.004

Urbanus, J.; Berger-Preiß, E.; Elend, M.; Koch, W. Evaluation of two sampling methods for the determination of gas oil mist and vapour in workplace air. In: ISEE – International Society for Environmental Epidemiology: Environment and Health – Bridging South, North, East and West: Conference of ISEE, ISES and ISIAQ, 2013, Abstract 4898.

Veres, T. Z.; Voedisch, S.; Spies, E.; Valtonen, J.; Prenzler, F.; Braun, A. Aeroallergen challenge promotes dendritic cell proliferation in the airways. In: The Journal of Immunology 190 (2013), No. 3, pp. 897-903. doi: 10.4049/jimmunol.1200220

Vermeire, T.; Aldenberg, T.; Buist, H.; Escher, S.; Mangelsdorf, I.; Pauné, E.; Rorije, E.; Kroese, D. OSIRIS, a quest for proof of principle for integrated testing strategies of chemicals for four human health endpoints. 4 Feb 2013 [Epub ahead of print]. In: Regulatory Toxicology and Pharmacology 67 (2013), No. 2, pp. 136-145. doi: 10.1016/j.yrtph.2013.01.007

Wagener, A. H.; Gibeon, D.; Yang, X.; Sousa, A. R.; Corfield, J.; Shaw, D. E.; Fowler, S.; Flemming, L. J.; Riley, J.; Jeyasingham, E.; Rowe, A.; Fichtner, K.; Robberts, G.; Bakke, P.; Singer, T.; Geiser, T.; Frey, U.; Horvarth, I.; Polosa, R.; Bonnelykke, K.; Krug, N.; Middelvelde, R.; Dahlen, S.-E.; Dahlen, B.; Hedlin, G.; Hashimoto, S.; Nordlund, B.; Musial, J.; Woodcock, A.; Murray, C. S.; Pahus, L.; Chanez, P.; Myles, D.; Compton, C.; Higenbottam, T. W.; Montuschi, P.; Vestbo, J.; Larsson, L.; Sandstrom, T.; Bisgaard, H.; Wagers, S. S.; Howarth, P. H.; Bel, E. H.; Djukanovic, R.; Chung, K. F.; Sterk, P. J. Associated factors with persistent airflow limitation in asthma in U-BIOPRED. In: European Respiratory Journal 42 (2013), Suppl. 57, 662s, P3142.

Walter, D.; Niehof, M.; Hackbarth, A.; Hansen, T. Studies on the mode of action of multi-walled carbon nanotubes onto human bronchial epithelial cells. In: ALTEX Proceedings 2 (2013), No. 13, p. 129.

Wichmann, J.; Curths, C.; Dunker, S.; Windt, H.; Hoymann, H.-G.; Lauenstein, H.-D.; Becker, T.; Kaup, F.-J.; Braun, A.; Knauf, S. Invasive lung function measurement in common marmosets (*Callithrix jacchus*). In: American Journal of Respiratory and Critical Care Medicine 187 (2013), A4066.

Ziemann, C.; Reamon-Büttner, S. M.; Hackbarth, A.; Brockmeyer, H.; Rahmer, H.; Bellmann, B. Human pleural mesothelial MeT-5A cells are a limited in vitro model for detection of potential asbestos-like genotoxic effects of multiwall carbon nanotubes. In: The Toxicologist 52 (2013), No. 1, p. 92, Abstract PS 434.

Ziemann, C.; Tillmann, T.; Oertel, A.; Brockmeyer, H.; Murbach, M.; Capstick, M.; Kuster, N.; Dasenbrock, C. Evaluation of the genotoxic potential of different radiofrequency electromagnetic fields in MRC-5 cells and B6C3F1 mice. In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S95, Abstract 390.

Zwintscher, A.; Bitsch, A. Use of biocides - toxicological effects versus microbiological efficacy. In: Naunyn-Schmiedeberg's Archives of Pharmacology 386 (2013), Suppl. 1, S10, Abstract 030.

---

## Doctorates

---

### Elisabeth Apel

Entwicklung und Validierung analytischer Methoden zur Untersuchung der Bioverfügbarkeit und Metabolisierung von potentiell toxischen Kontaminanten in Lebensmitteln. (Development and validation of analytical methods to investigate bioavailability and metabolization of potentially toxic contaminants in foods.) Leibniz University Hannover December 2013

### Johannes Claudius Kopf

Biologische Wirkungen von nanostrukturiertem Carbon Black auf pulmonale Zielzellen. (Biological effects of nanostructured carbon black on human pulmonary cells.) University of Veterinary Medicine Hannover, Foundation June 2013

### Katharina Schwarz

Zur Entstehung, Charakterisierung und diagnostischen Nutzbarkeit in der menschlichen Lunge endogen generierter, exhalierter Aerosole. (Formation, characterization, and diagnostic usability of exhaled aerosols endogenously generated in the human lung.) Clausthal University of Technology March 2013

---

## Degree dissertations

---

### Arne Gaida

Etablierung und Optimierung eines Verfahrens zum Nachweis volatiler Substanzen in der Ausatemluft.  
(Setup and optimization of a method for detection of volatile substances in exhaled breath.)  
Braunschweig Technical University  
February 2013

### Almir Omerovic

Optimierung und Anwendung einer Feed-Lösung zur Steigerung der Antikörperproduktion einer von Amniocyten stammenden humanen Zelllinie.  
(Optimization and use of a feed solution to increase antibody production of an amniocyte-derived human cell line.)  
Darmstadt University of Applied Sciences  
March 2013

---

## Master's theses

---

### Philipp Biechele

Expression rekombinanter Proteine mit Hilfe des Rekombinase-vermittelten Kassettenaustauschverfahrens.  
(Expression of recombinant proteins by using the method of recombinase-mediated cassette exchange.)  
Ulm University  
June 2013

### Sharon Melissa Jiménez Delgado

IL-13-induced inflammation and hyperreagibility in precision-cut lung slices of different species.  
University of Veterinary Medicine Hannover, Foundation  
April 2013

### Roland Scholz

Regulatorische Anforderungen an Informationen zur dermalen Absorption und deren wirtschaftliche Auswirkungen mit besonderem Fokus auf der Biozid-Zulassung.  
(Regulatory requirements for dermal absorption data and their economic impact with a special focus on biocide registration.)  
Kiel University  
November 2013

### Felicitas Vernen

Heterologe Proteinexpression in *Neurospora crassa*: Wachstums- und Produktbildungsverhalten im Single-Use-System.  
(Heterologous protein expression in *Neurospora crassa*: growth and product formation behavior in a single-use system.)  
Braunschweig Technical University  
April 2013

### Dorothee Walter

Untersuchungen zum Wirkmechanismus von Multi-Walled Carbon Nanotubes an Bronchialepithelzellen.  
(Investigation of the mechanism of action of multi-walled carbon nanotubes in bronchial epithelial cells.)  
Charité Berlin  
January 2013

---

## Bachelor's theses

---

### Julia Boos

Rekrutierung von Teilnehmern für klinische Studien mit modernen Medien – am Beispiel von Facebook und der Abteilung Klinische Atemwegsforschung des Fraunhofer ITEM.  
(Recruitment of subjects for clinical trials via modern media – as exemplified by Facebook and the Fraunhofer ITEM Department of Clinical Airway Research.)  
Hannover University of Applied Sciences and Arts  
January 2013

### Tobias Graef

Differenzierte THP-1-Zellen als Modell für die Testung von Nanopartikeln.  
(Differentiated THP-1 cells as a model for nanoparticle testing.)  
University of Applied Sciences Emden/Leer  
February 2013

### Annabelle Helberg

Erstellung eines Informationsportals zum Thema: "Validierung GXP-relevanter computergestützter Systeme am Beispiel der Vorgehensweise des Fraunhofer ITEM".  
(Implementation of an information portal on the subject: "Validation of GXP-relevant computerized systems by way of the example of the process established at the Fraunhofer ITEM.")  
Hannover University of Applied Sciences and Arts  
February 2013

### Mandy Schott

GATA3-Punktmutationen in einzelnen Krebszellen.  
(GATA3 point mutations in single cancer cells.)  
Martin Luther University Halle-Wittenberg  
July 2013

### David Spannagel

Auslegung einer Metallsalzfällung in der Aufarbeitung pharmazeutischer Plasmid DNA mittels statistischer Versuchsplanung.  
(Layout of metal salt precipitation during purification of pharmaceutical plasmid DNA by means of a statistical experimental design.)  
Mannheim University of Applied Sciences  
January 2013

### Jessica Willner

Einfluss der Coproduktion von Chaperonen und einer Zellwandhydrolase auf die scFvD1.3-Sekretion mit *Bacillus megaterium*.  
(Influence of coproduction of chaperones and a cell wall hydrolase on scFvD1.3 secretion in *Bacillus megaterium*.)  
University of Applied Sciences Emden/Leer  
February 2013

### Sebastian Zahn

Vergleichende Untersuchungen zur Toxizität verschieden geformter Kohlenstoff-Nanomaterialien.  
(Comparative investigations into the toxicity of differently shaped carbon nanomaterials.)  
Coburg University of Applied Sciences and Arts  
December 2013

---

## Invited lectures at congresses and conferences

---

### Dr. Philipp Badorrek

Pharmaindustrie – Akquisition in stark regulierten Märkten.  
Fraunhofer Marketing Day 2013, Acquisition in Key Sectors.  
Munich (Germany)  
November 7-8, 2013

### Dr. Luma Baydoun

Fast access to sterile investigational medicinal products for clinical trials.  
Crailsheim Pharma Day 2013.  
Crailsheim (Germany)  
May 14-15, 2013

Fast access to sterile investigational medicinal products for clinical trials.  
Pharma Day 2013.  
Moscow (Russia)  
September 18, 2013

### Dr. Annette Bitsch

Regulation von Bioziden. DGPT course "Regulatory Toxicology" at the Governmental Institute of Public Health of Lower Saxony (NLGA).  
Hannover (Germany)  
September 9-13, 2013

### Prof. Dr. Armin Braun

Models of pulmonary diseases and physiology. Workshop on Translational Aspects of Cardiovascular and Pulmonary Imaging (TACPI 2013) – EU FP7 Pulmonary Imaging Network.  
Madrid (Spain)  
March 1-2, 2013

Asthma models for the evaluation of investigational new drugs. European College of Veterinary Pharmacology and Toxicology, Workshop in Immunopharmacology and Immunotoxicology.  
Hannover (Germany)  
May 13-17, 2013

Human disease models. Fraunhofer Delaware Technology Summit.  
Wilmington, Delaware (USA)  
March 17-20, 2013

Neuroimmune interaction in the lung. 3<sup>rd</sup> International Symposium of the Collaborative Research Center SFB 587 "Immune Reactions of the Lung in Infection and Allergy".

Hannover (Germany)  
May 30-31, 2013

Virus-induced neurogenic inflammation in the lung. Postgraduate course "Immune and inflammatory responses to respiratory viruses – drivers of asthma?" at the European Academy of Allergy and Clinical Immunology & World Allergy Organization (EAACI/WAO) Congress 2013.

Milan (Italy)  
June 22, 2013

Neuroimmune interactions in allergic asthma. Session "Lung Inflammation, Asthma, Allergy". LISA Summer School.

Hannover (Germany)  
August 22, 2013

Use of precision-cut lung slices for pharmacological and toxicological evaluations. ProDoc Retreat, Swiss Ph. D. program "Toxicology".

Emmeten (Switzerland)  
September 19, 2013

Ex-vivo-Lungenschnittmodelle für die pharmakologische und toxikologische Untersuchung neuer Therapieansätze. 715<sup>th</sup> DECHEMA Colloquium.

Frankfurt/Main (Germany)  
October 31, 2013

The use of precision-cut lung slices to evaluate lung immune responses in situ. Transregio Collaborative Research Center Berlin-Giessen-Marburg "Innate Immunity of the Lung".

Giessen (Germany)  
November 26, 2013

Airway hyperreactivity in animal models. ERS research seminar "Translational animal models of asthma".

Barcelona (Spain)  
November 29-30, 2013

#### **Dr. Otto Creutzenberg**

Toxizitätstestung von Kohlenstoffnanoröhren (CNT) unter Aspekten der Arbeitsplatz- und Verbrauchersicherheit. Inno.CNT 2013 – Annual Conference of the Innovation Alliance Carbon Nanotubes.

Stuttgart/Fellbach (Germany)  
February 20-21, 2013

#### **Dr. Ilona Fleischhauer**

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

Hannover (Germany)  
August 28, 2013

Analysis of clinical trial samples: What is important for a GLP laboratory according to the EMA reflection paper? 1<sup>st</sup> European QA Conference.

Bonn (Germany)  
September 26, 2013

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

Hannover (Germany)  
December 11, 2013

#### **Dr. Stefan Hahn**

Regulatorische Bewertung von Chemikalien am Beispiel von Bioziden. First Forum of Young Environmental Scientists.

Blomberg (Germany)  
May 27-29, 2013

#### **Prof. Dr. Dr. Uwe Heinrich**

Calculation of a human equivalent – no observed adverse effect concentration for biopersistent otherwise non-toxic granular dust. 87<sup>th</sup> Meeting of the Scientific Committee on Occupational Exposure Limits.

Luxemburg/Gasperich (Luxembourg)  
March 20-21, 2013

#### **Prof. Dr. Jens Hohlfeld**

Interaction between allergic inflammation and the pulmonary surfactant system in asthma. 3<sup>rd</sup> International Symposium of the Collaborative Research Center SFB 587 "Immune Reactions of the Lung in Infection and Allergy".

Hannover (Germany)  
May 30-31, 2013

Klinische Studien mit luftgetragenen Stoffen. GDCh course 157/13 (introduction to toxicology for chemists).

Hannover (Germany)  
June 4-6, 2013

Models of COPD: Aktuelle Erkenntnisse aus der Grundlagenforschung. 38<sup>th</sup> Annual Congress of the "Norddeutsche Gesellschaft für Pneumologie".

Hamburg (Germany)  
November 1-2, 2013

Clinical challenge models for airway inflammation using (segmental) provocation with LPS, particles, allergen or ozone. AIT Annual Conference 2013.

Hannover (Germany)  
November 5-7, 2013

#### **Dr. Heinz-Gerd Hoymann**

Nichtinvasive und invasive Lungenfunktionsmesstechniken in sicherheitspharmakologischen Prüfungen. Annual meeting of the working group of German safety pharmacologists.

Darmstadt (Germany)  
April 18-19, 2013

#### **Prof. Dr. Christoph Klein**

What do we mean by cancer dormancy? Cancer Forum Workshop on Cancer Latency and Dormancy, Arizona State University.

Tempe, Arizona (USA)  
February 28 – March 1, 2013

Insights from the direct analysis of minimal residual cancer: Chances and consequences for personalized therapies. Forum Life Science.

Munich (Germany)  
March 13-14, 2013

Genetic heterogeneity and cellular plasticity in melanoma metastasis. Symposium "Trends in Melanoma Research".

Bonn (Germany)  
June 4-5, 2013

Selection and adaptation during metastatic cancer progression. Nature – CNIO Cancer Symposium "Frontiers in Tumor Heterogeneity and Plasticity".

Madrid (Spain)  
October 27-30, 2013

#### **Prof. Dr. Norbert Krug**

Environmental exposure to nanoparticles. European Academy of Allergy and Clinical Immunology & World Allergy Organization (EAACI/WAO) Congress 2013.

Milan (Italy)  
June 22-26, 2013

The value of a challenge chamber for clinical trials in allergy. 63<sup>rd</sup> Annual Meeting of the Japanese Society of Allergology.

Tokyo (Japan)  
November 28-30, 2013

Recent updates in the pathophysiology of allergic rhinitis as an inflammatory disease. 63<sup>rd</sup> Annual Meeting of the Japanese Society of Allergology.

Tokyo (Japan)  
November 28-30, 2013

#### **Dr. Oliver Licht**

Stoffbewertung und Risikoabschätzung. DGPT course "Regulatory Toxicology" at the Governmental Institute of Public Health of Lower Saxony (NLGA).

Hannover (Germany)  
September 9-13, 2013

#### **Dr. Bernhard Polzer**

Comprehensive molecular analysis of single cells. "Cancer Cell Heterogeneity" webinar by Silicon Biosystems SpA.

February 27, 2013

Molekulare Diagnostik an disseminierten Tumorzellen. 33<sup>rd</sup> Annual Meeting of the German Senology Society.

Munich (Germany)  
June 27-29, 2013

Morphology and DNA integrity are defining criteria for molecular profiles of single CTCs. 23<sup>rd</sup> Annual Conference of the German Society of Cytometry.

Dresden (Germany)  
October 9-11, 2013

#### **Priv.-Doz. Dr. Susanne Rittinghausen**

Progress of INHAND. 11<sup>th</sup> European Congress of Toxicologic Pathology.

Ghent (Belgium)  
September 10-13, 2013

#### **Priv.-Doz. Dr. Susanne Rittinghausen and Dirk Schaudien, Ph. D.**

Effects of nanomaterial in the respiratory tract – special labeling techniques and imaging. AIT Annual Conference 2013.

Hannover (Germany)  
November 5-7, 2013

#### **Dr. Anton Roß**

Technical safety measures. State-approved training course "Gene Technology, Biosafety and Biosecurity", Hannover Medical School.

Hannover (Germany)  
September 10-11, 2013

**Dr. Katherina Sewald**

Use of precision-cut lung slice technique (PCLS) for assessment of toxicity and immunotoxicity. Workshop "Inhalation Toxicity: Pathways to Better Methods". Washington, District of Columbia (USA)  
May 1-3, 2013

**Dr. Holger Ziehr**

Fast access to sterile investigational medicinal products for clinical trials. Parenteral Drug Association conference "Parenteral Drug Development – Clinical Trial Materials". Ulm (Germany)  
February 12-13, 2013

**Dr. Christina Ziemann**

Genetische Toxikologie. GDCh course 157/13 (introduction to toxicology for chemists). Hannover (Germany)  
June 4-6, 2013

---

## Contributions to congresses and conferences

---

Batke, M.; Kramer, S.

Strategien zur Entwicklung von chemischen Kategorien für REACH. Working Group on Regulatory Toxicology, advanced course "Read-Across und Grouping zur Füllung von Datenlücken unter REACH" at the University of Halle/Saale. Halle/Saale (Germany)  
March 4, 2013

Batke, M.; Bitsch, A.; Gundert-Remy, U.; Guetlein, M.; Helma, Ch.; Kramer, S.; Maunz, A.; Partosch, F.; Seeland, M.; Stahlmann, R.

New strategies to develop chemical categories in the context of REACH – work in progress. EUROTOX 2013. 49<sup>th</sup> Congress of the European Societies of Toxicology. Interlaken (Switzerland)  
September 1-4, 2013

Batke, M.; Bitsch, A.; Gundert-Remy, U.; Guetlein, M.; Helma, Ch.; Kramer, S.; Maunz, A.; Partosch, F.; Seeland, M.; Stahlmann, R.

Strategies to develop chemical categories in the context of REACH – work in progress. OpenTox Euro 2013: OpenTox InterAction Meeting. Innovation in Predictive Toxicology. Mainz (Germany)  
September 30 – October 2, 2013

Bitsch, A.

From skin contact to internal exposure: data gaps and regulatory accepted approaches with a focus on biocidal products. Occupational and Environmental Exposures of Skin to Chemicals (OEESC 2013). Amsterdam (The Netherlands)/Osnabrück (Germany)  
June 2-5, 2013

Bludau, E.; Veith, N.; Beuerle, B.; Schwager, C.; Hecht, V.; Ziehr, H. Shortened timeline for cell line development – adaption of recombinase-mediated cassette exchange (RMCE) to suspension CHO cells. Fraunhofer Delaware Technology Summit. Newark, Delaware (USA)  
March 5-6, 2013

Bludau, E.; Veith, N.; Beuerle, B.; Schwager, C.; Hecht, V.; Ziehr, H. Shortened timeline for cell line development – adaption of recombinase-mediated cassette exchange (RMCE) to suspension CHO cells. European Society for Animal Cell Technology Meeting (ESACT). Lille (France)  
June 23-26, 2013

Bludau, E.; Veith, N.; Hecht, V.; Ziehr, H. Shortened timeline for cell line development – adaption of recombinase-mediated cassette exchange (RMCE) to suspension CHO cells. 11<sup>th</sup> Conference on Protein Expression in Animal Cells (PEACe). Kananaskis, Alberta (Canada)  
September 22-26, 2013

Brodbeck, C.; Ritter, D.; Knebel, J.

Influence of the geometry of the aerosol-conducting system on the deposition of particles from inhalable aerosols on cellular surfaces in vitro. European Aerosol Conference (EAC). Prague (Czech Republic)  
September 1-6, 2013

Creutzenberg, O.

In-vivo inhalation tests – state of the art and future approaches for toxicity testing of carbon nanotubes. Society of Toxicology (SOT), 52<sup>nd</sup> Annual Meeting and ToxExpo. San Antonio, Texas (USA)  
March 10-14, 2013

Creutzenberg, O.; Ziemann, C.; Hansen, T.; Ernst, H.; Schaudien, D.; Schuchardt, S.; Bellmann, B. CEFIC-LRI N1 Project: Final results and overall conclusions on nanomaterial safety of ZnO and SiO<sub>2</sub>. Inhaled Particles XI. Nottingham (UK)  
September 23-25, 2013

Curths, C.; Wichmann, J.; Becker, T.; Kaup, F. J.; Hohlfeld, J. M.; Dunker, S.; Braun, A.; Knauf, S. Modelling allergic asthma in the common marmoset (*Callithrix jacchus*). 25<sup>th</sup> Mainz Allergy Workshop 2013. Mainz (Germany)  
March 7-8, 2013

Curths, C.; Wichmann, J.; Becker, T.; Kaup, F. J.; Hohlfeld, J. M.; Sewald, K.; Windt, H.; Dunker, S.; Braun, A.; Knauf, S. A translational non-human primate model for human asthma in the common marmoset (*Callithrix jacchus*). 8<sup>th</sup> German Allergy Congress. Bochum (Germany)  
September 5-7, 2013

Curths, C.; Wichmann, J.; Becker, T.; Kaup, F. J.; Hohlfeld, J. M.; Windt, H.; Dunker, S.; Hoymann, H. G.; Braun, A.; Knauf, S.: Lung function assessment in the common marmoset (*Callithrix jacchus*) for the evaluation of translational nonhuman primate models of lung inflammation. Fall Conference of the German Respiratory Society sections of Cell Biology and Infectiology & Tuberculosis. Marburg (Germany)  
October 25-26, 2013

Escher, S.

New Threshold of Toxicological Concern (TTC) for inhalation exposure and derivation of thresholds with the database RepDose. 15<sup>th</sup> Cefic-LRI Annual Workshop. Brussels (Belgium)  
November 20-21, 2013

Escher, S.; Tluczkiewicz, I.; Kühne, R.; Ebert, R. U.; Schüürmann, G.; Mangelsdorf, I. TTC: A new concept for inhalation exposure. EUROTOX 2013. 49<sup>th</sup> Congress of the European Societies of Toxicology. Interlaken (Switzerland)  
September 1-4, 2013

Escher, S.; Tluczkiewicz, I.; Kühne, R.; Ebert, R. U.; Schüürmann, G.; Mangelsdorf, I. TTC: A new concept for inhalation exposure. 15<sup>th</sup> Cefic-LRI Annual Workshop. Brussels (Belgium)  
November 20-21, 2013

Geizskopf, A.; Veith, N.; Paulsen, J.

Improvements in reduction of residual DNA during purification of recombinant antibodies. European Society for Animal Cell Technology Meeting (ESACT). Lille (France)  
June 23-26, 2013

Hackbarth, A.

In-vivo subchronic screening toxicity test. Proliferation of diaphragm after intraperitoneal injection of MWCNT. Society of Toxicology (SOT), 52<sup>nd</sup> Annual Meeting and ToxExpo. San Antonio, Texas (USA)  
March 10-14, 2013

Hackbarth, A.; Ziemann, C.; Leonhardt, A.; Rittinghausen, S.; Schaudien, D.; Bellmann, B. Toxic effects of MWCNT in vivo and in vitro. Society of Toxicology (SOT), 52<sup>nd</sup> Annual Meeting and ToxExpo. San Antonio, Texas (USA)  
March 10-14, 2013

Hahn, S.

Regulatory affairs: legal requirements for an environmental risk assessment. Workshop "Environmental Risk Assessment of Veterinary Medicinal Products". Hannover (Germany)  
October 22-24, 2013

Hansen, T.; Kopf, J.; Danov, O.; Ströbele, M.; Braun, A.; Sewald, K.; Fehrenbach, H. In vitro and ex vivo toxicity screening for predicting toxicological effects of synthetic carbon black nanoparticles in humans. CarbonBlack Scientific Symposium. Borstel (Germany)  
October 24-25, 2013



- Havlik, D.; Vernen, F.; Bohle K.  
Development of a fungal expression system for the production of antibody fragments. 44<sup>th</sup> Annual Meeting of the German Genetics Society.  
Braunschweig (Germany)  
September 23-25, 2013
- Hesse, S.; Schröder, K.; Hahn, S.; Mangelsdorf, I.; Lamb, J.; van Tongeren, M.  
Evaluation of Tier 1 Exposure Assessment Models: Conceptual evaluation and uncertainty analyses. Environment and Health – Bridging South, North, East and West. Conference of ISEE, ISES and ISIAQ.  
Basel (Switzerland)  
August 19-23, 2013
- Hohlfeld, J.  
Safety profile and pharmacokinetics of an inhaled GATA-3-specific DNzyme in a phase-1b study in patients with stable allergic asthma. ERS Annual Congress 2013.  
Barcelona (Spain)  
September 7-11, 2013
- Jalava, P.; Knebel, J.; Ritter, D.  
Building up a co-culture and surfactant model for routine use in ALI exposures. SSCT Workshop.  
Charlottenlund (Denmark)  
September 25-27, 2013
- Jiménez, S.; Danov, O.; Braun, A.; Hohlbaum, A.; Sewald, K.  
IL-13 induced cytokine release and hyperreagibility in precision-cut lung slices of different species. ERS Annual Congress 2013.  
Barcelona (Spain)  
September 7-11, 2013
- Kirsch, S.; Czyz, Z. T.; Polzer, B.; Klein, C. A.  
High-resolution analysis of genome and transcriptome of a single cell. World CTC Summit.  
Berlin (Germany)  
April 24-25, 2013
- Knauf, S.  
Modeling asthma and COPD in marmoset monkeys. 12<sup>th</sup> Workshop "Models of Asthma and COPD".  
Hannover (Germany)  
January 18-19, 2013
- Knauf, S.  
Translational non-human primate models for airway inflammation. AIT Annual Meeting 2013.  
Hannover (Germany)  
November 5-7, 2013
- Könnecker, G.  
Quality of data – regulatory purpose. Workshop "Environmental Risk Assessment of Veterinary Medicinal Products".  
Hannover (Germany)  
October 22-24, 2013
- Krome, K.  
Environmental risk assessment of veterinary medicines. CIR Chemical Industries Regulations: Informa Life Science.  
Barcelona (Spain)  
September 4-5, 2013
- Krome, K.  
Cost saving approaches: co-operations. Workshop "Environmental Risk Assessment of Veterinary Medicinal Products".  
Hannover (Germany)  
October 22-24, 2013
- Krome, K.; Hahn, S.; Könnecker, G.  
Volatile anaesthetics – an approach assessing environmental risks. SETAC Europe 23<sup>rd</sup> Annual Meeting: Building a Better Future: Responsible Innovation and Environmental Protection.  
Glasgow (UK)  
May 12-16, 2013
- Lauenstein, L.; Hess, A.; Vogel, S.; Schneider, X.; Martin, C.; Pirow, R.; Liebsch, M.; Landsiedel, R.; Braun, A.; Müller, M.; Sewald, K.  
Effects of acute exposure of human precision-cut lung slices to chemicals. Society of Toxicology (SOT), 52<sup>nd</sup> Annual Meeting and ToxExpo.  
San Antonio, Texas (USA)  
March 10-14, 2013
- 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 precision-cut lung slices (PCLS) for the prediction of respiratory toxicology. Society of Toxicology (SOT), 52<sup>nd</sup> Annual Meeting and ToxExpo.  
San Antonio, Texas (USA)  
March 10-14, 2013
- Lauenstein, L.; Hess, A.; Vogel, S.; Schneider, X.; Martin, C.; Steinfath, M.; Pirow, R.; Liebsch, M.; Landsiedel, R.; Braun, A.; Sewald, K.  
Pre-validation of the ex vivo model PCLS for the prediction of acute inhalation toxicity. EUSAAT 2013 – 18<sup>th</sup> European Congress on Alternatives to Animal Testing.  
Linz (Austria)  
September 15-18, 2013
- Lewin, G.; Buschmann, J.; Reamon-Buettner, S. M.  
Identifying placental epigenetic alterations in intrauterine growth retardation (IUGR) in a rat model induced by gestational protein deficiency. 42<sup>nd</sup> Conference of the European Teratology Society.  
Stresa (Italy)  
September 7-10, 2013
- Licht, O.  
Human-Biomonitoring von "neuen" Schadstoffen – Vorschläge für die Ableitung von Beurteilungswerten. Working committee on chemical risk assessment of the division of environmental chemistry and ecotoxicology "Umweltchemie und Ökotoxikologie" within the German Chemical Society (GDCh).  
Frankfurt/Main (Germany)  
October 9, 2013
- Licht, O.; Wahnschaffe, U.; Mangelsdorf, I.  
DINCH: Development of a criteria document as basis for the assessment of human biomonitoring data. 45<sup>th</sup> session of the Human Biomonitoring Commission.  
Berlin (Germany)  
June 6-7, 2013
- Liebsch, M.; Pirow, R.; Smirnova, L.; Tharmann, M.; Luch, A.; Bauer, M.; Graebisch, C.; Linsel, G.; Troeller, S.; Huettig, N.; Berger-Preib, E.; Kock, H.; Oertel, A.; Ritter, D.; Knebel, J.  
BMBF prevalidation study on direct in-vitro exposure of human lung cells to gases. Symposium "Lung as the target organ – models for toxicity testing" during the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT) Annual Meeting 2013.  
Halle/Saale (Germany)  
March 5-7, 2013
- Pägelow, U.  
GMP requirements – how to be compliant. In-house seminar "Introduction to GLP and GMP".  
Hannover (Germany)  
December 11, 2013
- Papamichael, N.  
GMP regulatory requirements in Europe. In-house seminar "Introduction to GLP and GMP".  
Hannover (Germany)  
December 11, 2013
- Pohler, P.; Müller, M.; Sewald, K.; Müller, T. H.; Seltsam, A.  
UVC-treatment of residual leukocytes in platelet concentrates prevents xGVHD development in a NOD SCID gamma (NSG) mice model. DGTI 2013 – 46<sup>th</sup> Annual Congress of the German Society for Transfusion Medicine and Immunohematology.  
Münster (Germany)  
September 24-27, 2013
- Polzer, B.; Medoro, G.; Pasch, S.; Fontana, F.; Zorzino, L.; Pestka, A.; Andergassen, U.; Meier-Stiegen, F.; Czyz, Z.; Alberter, B.; Treitschke, S.; Schamberger, T.; Sergio, M.; Bregola, G.; Doffini, A.; Gianni, S.; Calanca, A.; Signorini, G.; Bolognesi, C.; Sandri, M. T.; Rack, B.; Fehm, T.; Gorgini, G.; Manaresi, N.; Klein, C. A.  
Morphology and DNA integrity are defining criteria for diagnostic profiles of single CTCs. Selected oral presentation during the 9<sup>th</sup> International Symposium on Minimal Residual Cancer (ISMRC).  
Paris (France)  
September 25-27, 2013
- Reamon-Buettner, S. M.; Brockmeyer, H.; Voepel, I. R.; Rahmer, H.; Ziemann, C.  
Mechanistic insights into MWCNT-induced DNA damage in human peritoneal mesothelial LP9 cells. 2013 German-French DNA repair meeting on epigenetics and genome integrity.  
Strasbourg-Illkirch (France)  
October 7-10, 2013
- Reamon-Buettner, S. M.; Hackbarth, A.; Voepel, I. R.; Brockmeyer, H.; Leonhardt, A.; Bellmann, B.; Ziemann, C.  
Human peritoneal mesothelial LP9 cells as a model system to determine the toxic and genotoxic potential of multiwalled carbon nanotubes (MWCNTs). German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT) Annual Meeting 2013.  
Halle/Saale (Germany)  
March 5-7, 2013

- Ritter, D.  
In-vitro human cell culture systems and air-liquid interface techniques.  
AIT Annual Meeting 2013.  
Hannover (Germany)  
November 5-7, 2013
- Ritter, D.; Knebel, J.; Brodbeck, C.; Jalava, P.  
Biological effects of inhalable compounds – improvements of the in-vitro testing method. SSCT Workshop.  
Charlottenlund (Denmark)  
September 25-27, 2013
- Schröder, K.; Pohlenz-Michel, C.; Voss, J.-U.; Simetska, N.; Escher, S.; Mangelsdorf, I.  
Particle and fiber toxicity database – PaFtox. EUROTOX 2013. 49<sup>th</sup> Congress of the European Societies of Toxicology.  
Interlaken (Switzerland)  
September 1-4, 2013
- Schröder, K.; Pohlenz-Michel, C.; Voss, J.-U.; Simetska, N.; Escher, S.; Mangelsdorf, I.  
Development of the particle and fiber toxicity database – PaFtox.  
10<sup>th</sup> International Particle Toxicology Conference – IPTC 2013.  
Düsseldorf (Germany)  
June 4-7, 2013
- Schürmann, D.; Ziemann, C.; Capstick, M.; Oertel, A.; Barekati, Z.; Focke, F.; Murbach, M.; Kuster, N.; Dasenbrock, C.; Schär, P.  
Investigations of the genotoxic potential of wireless communication electromagnetic fields. BioEM2013.  
Thessaloniki (Greece)  
June 10-14, 2013
- Schwarz, K.; Bitsch, A.; Hahn, S.; Berger-Preiß, E.; Koch, W.  
Application-oriented inhalation toxicity by classification of spray products using the RESPICON method. Inhaled Particles XI.  
Nottingham (UK)  
September 23-25, 2013
- Schwarz, K.; Bitsch, A.; Hahn, S.; Berger-Preiß, E.; Koch, W.  
Application-oriented inhalation toxicity by classification of spray products using the RESPICON method. AIT Annual Meeting 2013.  
Hannover (Germany)  
November 5-7, 2013
- Schwonbeck, S.  
Physical and chemical testing of VMPs – the good, the bad and the ugly.  
Workshop “Environmental Risk Assessment of Veterinary Medicinal Products”.  
Hannover (Germany)  
October 22-24, 2013
- Sewald, K.  
Use of the precision-cut lung slice technique for asthma research.  
12<sup>th</sup> Workshop “Models of Asthma and COPD”.  
Hannover (Germany)  
January 18-19, 2013
- Pluczkiewicz, I.  
OECD QSAR Toolbox – Füllen von Datenlücken durch Read-Across und Grouping. Working Group on Regulatory Toxicology, advanced course “Read-Across und Grouping zur Füllung von Datenlücken unter REACH” at the University of Halle/Saale.  
Halle/Saale (Germany)  
March 4, 2013
- Troeller, S.; Linsel, G.; Huettig, N.; Bauer, M.; Graebisch, C.; Smirnova, L.; Pirow, R.; Liebsch, M.; Berger-Preiß, E.; Kock, H.; Oertel, A.; Ritter, D.; Knebel, J.  
Air/liquid interface (ALI) technique for toxicity testing of gaseous compounds on human lung cells. EUROTOX 2013. 49<sup>th</sup> Congress of the European Societies of Toxicology.  
Interlaken (Switzerland)  
September 1-4, 2013
- Troeller, S.; Linsel, G.; Huettig, N.; Bauer, M.; Graebisch, C.; Smirnova, L.; Pirow, R.; Liebsch, M.; Berger-Preiß, E.; Kock, H.; Oertel, A.; Ritter, D.; Knebel, J.  
Is the air/liquid interface (ALI) technique a promising in-vitro alternative for in-vivo acute inhalation toxicity testing? In Vitro Biology Meeting of the Society of In Vitro Biology.  
Providence, Rhode Island (USA)  
June 15-19, 2013
- Veith, N.; Reamon-Buettner, S. M.  
Understanding epigenetic silencing landscapes in recombinant protein production in Chinese hamster ovary (CHO) lines. 44<sup>th</sup> Annual Meeting of the German Genetics Society.  
Braunschweig (Germany)  
September 23-25, 2013
- Wichmann, J.; Curths, C.; Delgado, S. M. T.; Becker, T.; Bleyer, M.; Kaup, F. J.; Braun, A.; Sewald, K.; Knauf, S.  
Allergen-induced early airway response of monkey lung tissue after passive sensitization of monkey lung tissue with human blood plasma is comparable to human tissue. EMBRN-COST International Mast cell and Basophil Meeting 2013.  
Udine (Italy)  
August 28-30, 2013
- Wichmann, J.; Curths, C.; Delgado, S. M. T.; Becker, T.; Bleyer, M.; Kaup, F. J.; Braun, A.; Sewald, K.; Knauf, S.  
Passive sensitization of monkey lung tissue with human blood plasma. EMBRN-COST International Mast cell and Basophil Meeting 2013.  
Udine (Italy)  
August 28-30, 2013
- Wichmann, J.; Curths, C.; Dunker, S.; Windt, H.; Hoymann, H. G.; Lauenstein, H.-D.; Becker, T.; Kaup, F. J.; Braun, A.; Knauf, S.  
Invasive lung function measurement in common marmosets (*Callithrix jacchus*). European Primate Veterinarians 13<sup>th</sup> Symposium.  
Göttingen (Germany)  
November 28-29, 2013
- Ziemann, C.  
In vitro testing of multi-walled carbon nanotubes, a real challenge – hints and pitfalls. Society of Toxicology (SOT), 52<sup>nd</sup> Annual Meeting and ToxExpo.  
San Antonio, Texas (USA)  
March 10-14, 2013

---

## 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 “Lebensmittel-zusatzstoffe, 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. Boehringer Ingelheim Foundation)

External expert for the German Research Foundation (DFG)

Ph. D. commission of the Hannover Medical School (MHH)

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

Member of the German Center for Lung Research (DZL)

### 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)

Scientific Council on Electromagnetic Fields of the Swedish Radiation Safety Authority (SSM)

Editorial board of the journal “Experimental and Toxicologic Pathology”

Treasurer of the German Society for the Promotion of Biomedical Research

**Uta Dörfel**

Working group on GLP analytics "GLP-Analytik" of the German Society for Good Research Practice (DGGF)

**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" 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

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

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

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)

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)

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

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"

Steering committee of the research network "Biomedical Research in Endstage And Obstructive Lung Disease Hannover" (BREATH) within the German Center for Lung Research e.V. (DZL)

Scientific advisory group of the European Medicines Agency (EMA)

**Dr. Olaf Holz**

Reviewer for international journals (incl. "European Respiratory Journal", "PLoS One", "Respiratory Research", and "BMC Pulmonary Medicine")

European Respiratory Society taskforce "Exhaled biomarkers in lung disease" (TF-2012-11)

**Dr. Heinz-Gerd Hoymann**

Working group of German safety pharmacologists

**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)

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

Reviewer for the international journals "Journal of Zoo and Wildlife Medicine", "PLoS One", and "International Journal of Primatology"

Auditor of the European Association of Zoo and Wildlife Veterinarians (EAZVV)

Primate specialist group, Africa section of the Species Survival Commission (SSC) in the International Union for Conservation of Nature (IUCN)

**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 6<sup>th</sup> governmental commission "Energie- und Ressourceneffizienz" of the Land Lower Saxony.

**Dr. Kristin Krome**

Working committee on soil "Boden" of the division of environmental chemistry and ecotoxicology "Umweltchemie und Ökotoxikologie" within the German Chemical Society (GDCh)

**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 the research network "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)

Public relations delegate 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 Lütke**

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

Fraunhofer quality management network

**Dr. Inge Mangelsdorf**

Ad-hoc working group on indoor guidelines of the Indoor Air Hygiene Committee and of the Supreme State Health Authorities

Human-Biomonitoring Commission 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 committee for the DECHEMA/GVC division 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 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 on the use of exhaled aerosols to diagnose and monitor respiratory diseases "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

Expert report: Human biomonitoring of "novel" hazardous substances – substance dossier for hexabromcyclododecane (HBCD), development of toxicological assessment values. Project number 27434

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)**

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

Aerosol release during application of biocidal foam products

**Federal Institute for Risk Assessment (BfR)**

Development and validation of a test for lung toxicity assessment of formulations containing surface-active substances. FK 3 1329-486 6463044

Further scientific development of the DevTox project

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

**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

ExlTox – Explain Inhalation Toxicity. Development of an integrated testing strategy for the prediction of toxicity after repeated-dose inhalation exposure: a proof of concept

**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 Radiation Protection**

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

Experimental development of simple methods to minimize dispersion of surface contamination after incidents with open resuspendable radioactive materials

**German Center for Lung Research**

Allergy and Asthma

Chronic Obstructive Pulmonary Disease (COPD)

**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****EU program FP7: Primomed**

Use of PRImate MOdels to support translational MEDicine and advance disease-modifying therapies for unmet medical needs

**EFSA project:** Combined toxicokinetic and in-vivo genotoxicity study on Alternaria toxins

**EFSA project:** Preparation of pre-evaluation documents, including toxicological and non-toxicological data, for the re-evaluation of food additives permitted in the European Union

**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: CELL-PID**

Advanced cell-based therapies for the treatment of primary immunodeficiency

**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 nanolayered hybrid particles as real alternative to halogen-based flame retardant additives

**EU project: SILICOAT**

Industrial implementation of processes to render RCS safer in manufacturing processes

**European Commission Joint Research Centre (JRC), Institute for Health and Consumer Protection (IHCP)**

Endocrine Active Substances Information System (EASIS) content provision.  
JRC/IPR/2013/1.05/0023/NC

**NIOSH (Norway)**

Characterization of a virtual impactor for sampling of oil mists

German Primate Center, Göttingen

- Cost Center Primate Facilities
- Infection Biology Unit/Virology
- Pathology Unit
- Primate Genetics Laboratory

Gesellschaft für Anlagen- und Reaktorsicherheit (GRS), Cologne

Hamburg University of Applied Sciences, Department of Biotechnology

Hannover Clinical Trial Center (HCTC), Hannover

Hannover Medical School

- Biobank
- 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 Experimental Pneumology
- Department of Immunology
- Department of Mass Spectrometry/Proteomics
- Excellence Cluster REBIRTH
- 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 Laboratory Animal Science, Experimental Pathology
- Institute of Pathology
- Institute of Pharmacology
- 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 Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research

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

Hospital Grosshansdorf – Center for Pneumology and Thoracic Surgery

Institute of Pharmacology and Preclinical Drug Safety (IPAS), Nycomed: a Takeda company, Barsbüttel

IPA – Institute for Prevention and Occupational Medicine of the German Social Accident Insurance at Ruhr-Universität Bochum

Karlsruhe Institute of Technology, Division of Combustion Technology at the Engler-Bunte Institute

Kiel University

- Institute of Organic Chemistry
- Institute of Toxicology

Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures, Braunschweig

Leibniz University Hannover

- Institute of Inorganic Chemistry
- Institute of Multiple-Phase Flows
- Institute of Technical Chemistry
- Institute of the Basics of Electrical Engineering, Sensor Technology Section
- Institute of Turbo-Engines and Fluid Dynamics

LungenClinic Grosshansdorf GmbH

Research Center Borstel, Priority Area “Asthma and Allergies”, Division of Experimental Pneumology

Robert Koch Institute, Berlin

- Center for Biological Threats
- Department of Hospital Hygiene, Infection Prevention and Control

RWTH Aachen University

- Institute of Pharmacology and Toxicology
- University Hospital Aachen, Institute and Out-patient Clinic of Occupational Medicine

---

## Cooperation with institutions and universities

---

**National**

Augsburg University Hospital

- Medical Clinic II
- Urological Clinic

BioMedVet Research GmbH, Walsrode

Boehringer Ingelheim Pharma GmbH & Co. KG, Div. Research Germany

Bonn University

- Institute of Human Genetics

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

- Department of Internal Medicine/Infectious Diseases and Respiratory Medicine
- Department of Gynecology and Gynecologic Oncology
- Institute of Clinical Pharmacology and Toxicology

Charité Research Organization, Berlin

Clausthal University of Technology, Institute of Particle Technology

Cologne University Hospital, Institute of Medical Microbiology, Immunology und Hygiene

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

Technische Universität München (TUM), Munich  
– Chirurgische Klinik und Poliklinik (surgical and ambulant clinic)  
– Department of Informatics

TWINCORE (center for experimental and clinical research on infections),  
Hannover

Ulm University  
– Institute of Human Genetics  
– University Hospital, Department of Gynecology and Obstetrics

University Hospital Carl Gustav Carus Dresden  
– Department of Hospital Hygiene and Environmental Protection  
– Medizinische Klinik und Poliklinik I (medical and ambulant clinic)

University Hospital Düsseldorf  
– Department of General, Visceral and Pediatric Surgery  
– Department of Gynecology

University Medical Center Hamburg-Eppendorf, Institute of Experimental  
Immunology and Hepatology

University of Freiburg  
– Department of Pneumology  
– Institute of Physics

University of Giessen  
– Institute of Anatomy and Cell Biology  
– Veterinary Clinic, Department of Small-Animal Internal Medicine

University of Göttingen  
– Center of Pharmacology and Toxicology, Department of Pharmacology  
– Department of Diagnostic Radiology

University of Konstanz, Molecular Toxicology Group

University of Lübeck, Institute of Anatomy

University of Mainz  
– Department of Pneumology  
– Institute of Informatics  
– Institute of Toxicology (University Medical Center)

University of Marburg, Faculty of Medicine, Department of Pneumology,  
Working Group on Cell Biology of the Lung

University of Munich, gynecological and maternity hospital and ambulant clinic

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

University of Rostock, Medical Clinics, Division of Pulmonology

University of Tübingen  
– Department of Dermatology  
– Department of Gynecology and Obstetrics  
– Institute for Clinical Epidemiology and Applied Biometry

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

#### International

Biomedical Primate Research Center, Department of Immunology, Rijswijk  
(The Netherlands)

Centro Ceramico – Bologna, Bologna (Italy)

EATRIS – European Infrastructure for Translational Medicine, Amsterdam  
(The Netherlands)

European Food Safety Authority (EFSA), Parma (Italy)

Fraunhofer USA – Center for Molecular Biotechnology, Newark, Delaware (USA)

Imperial College, London (UK)

Institute of Occupational Medicine, Edinburgh (UK)

Instituto de Tecnología Cerámica, Castellón (Spain)

Instituto Tecnológico del Plástico, Valencia (Spain)

IT'IS Foundation for Research on Information Technologies in Society, Zurich  
(Switzerland)

ITENE Instituto Tecnológico del Embalaje, Transporte y Logística,  
Paterna/Valencia (Spain)

Life Sciences Queensland, Brisbane (Australia)

McMaster University Medical Centre, Hamilton, Ontario (Canada)

National Institute of Occupational Health, Oslo (Norway)

National Institutes of Health, New Bethesda, Maryland (USA)

OECD QSAR Expert Group (France)

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)

Swiss Federal Institute of Technology Zurich (ETH), Zurich (Switzerland)

TNO Quality of Life, Zeist (The Netherlands)

University of Amsterdam, Academic Medical Center (The Netherlands)

University of Basel, Institute of Biochemistry and Genetics, Basel (Switzerland)

University of Bern, Institute of Immunology, Bern (Switzerland)

University of Eastern Finland, Department of Environmental Science,  
Kuopio (Finland)

University of Virginia, Charlottesville, Virginia (USA)

University of Zurich, Institute of Veterinary Pharmacology and Toxicology  
(Switzerland)

US Environmental Protection Agency (EPA), Chapel Hill, North Carolina (USA)

US Environmental Protection Agency (EPA), Washington, District of Columbia  
(USA)

World Health Organization (WHO), Geneva (Switzerland)

---

## Exhibitions, congresses and workshops

---

The Fraunhofer ITEM presents its research and the services it offers at national and international congresses and exhibitions. In addition, the institute organizes a variety of seminars and workshops. In 2013, the institute hosted or played an active role in the following events:

January 18-19, 2013

**12<sup>th</sup> Workshop "Models of Asthma and COPD"**

Fraunhofer ITEM  
Hannover, Germany

February 20, 2013

**Lower Saxony GMP discussion group meeting**

Fraunhofer ITEM  
Braunschweig (Germany)

March 10-14, 2013

**SOT 2013**

Annual Meeting of the Society of Toxicology and ToxExpo  
San Antonio, Texas (USA)

March 13-14, 2013

**Forum Life Science 2013**

Garching (Germany)

April 22-25, 2013

**BIO International Convention 2013**

Chicago, Illinois (USA)

May 17-20, 2013

**ATS 2013**

International Conference of the American Thoracic Society  
Philadelphia, Pennsylvania (USA)

June 16-20, 2013

**STP 2013**

Annual Symposium of the Society of Toxicologic Pathology  
Portland, Oregon (USA)

June 17-19, 2013

**40<sup>th</sup> Annual Meeting of the Japanese Society of Toxicology**

Tokio-Chiba, Makuhari (Japan)

June 23-26, 2013

**ESACT 2013**

23<sup>rd</sup> Annual Meeting of the European Society for Animal Cell Technology  
Lille (France)

September 15-18, 2013

**EUSAAT 2013**

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

October 8-10, 2013

**Biotechnica 2013**

Hannover (Germany)

October 22-24, 2013

**Workshop "Environmental Risk Assessment of Veterinary Medicinal Products"**

Hannover (Germany)

October 29-November 1, 2013

**AusBiotech**

Brisbane (Australia)

November 4-6, 2013

**BioEurope 2013**

Vienna (Austria)

November 5-7, 2013

**Annual Meeting of the Association of Inhalation Toxicologists (AIT)**

Hannover (Germany)

## EDITORIAL NOTES

Coordination and editorial work  
Dr. Cathrin Nastevska

Translation  
Karin Schlemminger

Photographs and illustrations  
Adimas (Fotolia) – p. 39  
Jan Benz (Fraunhofer ITEM) – p. 59  
britta60 (Fotolia) – p. 53  
Pavel Chernobrivets (Fotolia) – p. 27  
Adam Gregor (Fotolia) – p. 34  
Nico Herzog – p. 17 (right)  
Leonhardt, Leibniz Institute Dresden – p. 29  
Rainer Meier/BFF, Nathalie Meier (Fraunhofer ITEM) – p. 6, 7, 8, 13, 41, 61  
Ralf Mohr – all portrait photos  
Nickl und Partner – p. 16  
Frank Oppermann (Fotolia) – p. 55  
Z. Schank (Fotolia) – p. 47  
Maurizio Targhetta (Fotolia) – p. 49  
Thinkstock – front cover  
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 ITEM  
Hannover 2014



### CONTACTS

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



Annegret Seehafer  
Marketing  
Phone +49 511 5350-402  
annegret.seehafer@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 6181-6099  
info@item.fraunhofer.de  
www.item.fraunhofer.de

**Further informations:** [www.item.fraunhofer.de](http://www.item.fraunhofer.de)

