



Fraunhofer

ITEM

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM



ANNUAL REPORT
2015

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PERFORMANCE AND RESULTS

ANNUAL REPORT

2015

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FOREWORD TO READERS

Dear Reader,

I would like to use this Annual Report to elaborate specifically on the traditional research area of Fraunhofer ITEM: inhalation toxicology.

Since its foundation 34 years ago, Fraunhofer ITEM has been an acknowledged partner to industry and public authorities with regard to toxicological and preventive health research, hazard identification, and exposure and risk assessment. Detection of health hazards at the earliest possible stage and elucidation of the relevant mechanisms of action to optimally set the stage for the development of safe products and production processes have been the aims of the application-oriented toxicological research performed at Fraunhofer ITEM with both industrial and social policy relevance.

Harmful substances in the air we breathe are a particular hazard, as the lung, providing an inner surface of about 120 m² in an adult breathing in as deeply as possible, is at the same time the primary target organ for airborne pollutants. The lung thus represents the human body's largest interface with the outside world.

From the very beginning, the focus of toxicological research at Fraunhofer ITEM has been on the investigation of potentially harmful airborne contaminants in both gaseous and particulate form. Expert knowledge and a broad range of technology platforms and special laboratories in the areas of aerosol physics, particle analytics and particle measurement technology, analytical chemistry, and inhalation technology, combined with general in-vivo, mechanistic, and lung-specific toxicology, have made Fraunhofer ITEM an internationally acknowledged institute for inhalation toxicology research.

Our studies on diesel engine exhaust with a special focus on soot particles resulted in the recommendation to use exhaust filters already more than two decades ago, so as to minimize the hazard potential for chronic inflammatory and neoplastic reactions in lung tissue. Further research revealed that the insoluble carbon core fraction of diesel exhaust particles and likewise all other poorly soluble particles, if deposited in the lung in large quantities, can induce chronic inflammatory and neoplastic effects, and these findings substantially contributed to the derivation of a general threshold limit value for poorly soluble dusts in the workplace based on the particles' mechanism of action.

First research results about possible health hazards from nanoparticles were also obtained during this era of toxicological research on diesel exhaust particles, as the carbon core of these particles is composed of agglomerated carbon nanoparticles. Titanium dioxide dust, which at that time was investigated in comparison with diesel exhaust particles and carbon dust, equally consisted of insoluble nanoparticles. These early findings about nanoparticles perfectly set the stage for today's studies on the health effects of a broad diversity of nanoparticles conducted at Fraunhofer ITEM within several research projects.

Similarly, we undertook research on the toxic and carcinogenic effects of fibrous dusts such as natural and man-made mineral fibers already more than three decades ago. The resulting insights, leading to derivation of risk-based threshold limits, a recommendation to the mineral fiber industry regarding the manufacture of non-hazardous mineral fibers, and the development and implementation of tests to endorse fibers that do not pose a health hazard, now also prove beneficial in our comprehensive toxicological research on carbon nanotubes and nanoplatelets.

The finding that poorly soluble dusts can lead to lung injury, if the lung clearance mechanism is chronically overloaded, also has an impact on research into the health effects of metals and their different compounds in the form of inhalable dusts. The toxic agent of a metal particle is its bioavailable metal ion, and the amount of bioavailable metal ions influences the magnitude of the toxic effect. Intracellular release of ions from incorporated particles in particular can have a considerable hazard potential. The particle in this case acts as a carrier for the toxic and partly also carcinogenic agent – the metal ion. Decisive parameters in defining a threshold limit for such metal dusts or rating them non-hazardous are bioavailability, the mechanism of toxicity, and the dose-effect relationship for the toxic metal ion. In contrast, the occupational threshold limit for inhalable, poorly soluble, non-bioavailable metal particles without specific surface reactivity could be based on the threshold limit for poorly soluble dusts. As long as such metal particles are inhaled at concentrations that do not overload the particle clearance mechanism of the lung and do not have any systemic toxic effects if swallowed into the gastrointestinal tract, they should not pose any particular health hazard. In this context as well, Fraunhofer ITEM has a long track record of conducting projects on how to adequately determine bioavailability and effects and conduct hazard and risk assessment of different metals and their compounds.

These examples show that Fraunhofer ITEM has been a successful and acknowledged player in inhalation and particle toxicology for three decades already and that the expert knowledge accumulated at the institute over this period is available for hazard identification, product optimization under aspects of human health, and risk assessment of novel substances and products that are released as aerosols during manufacturing processes, further processing, waste disposal, or recycling. Our cooperation partners and clients from industry



and public authorities appreciate this and have engaged in close collaboration with Fraunhofer ITEM in many different ways.

I would like to thank our clients and cooperation partners for our positive and successful cooperation, also in this traditional Fraunhofer ITEM research area, and I am looking forward to further application-oriented joint research.

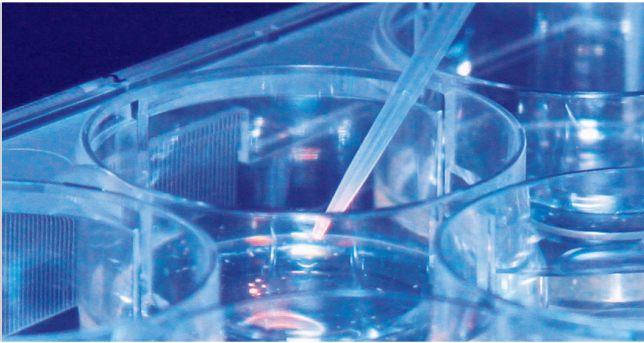
A handwritten signature in black ink, which appears to read 'U. Heinrich'.

Prof. Dr. Dr. Uwe Heinrich
Executive Director

PROFILE OF THE INSTITUTE

Research at 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, 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 15 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 Fraunhofer ITEM, even though the institute's research and services are not limited to these subject areas.





Protecting human health

Health protection includes environmental, occupational, and consumer protection. 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 health hazards are as yet unknown, such as different nanomaterials. They evaluate the human exposure situation and develop suggestions on how to reduce or eliminate these potential hazards. For the experimental part of risk assessment, 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 falling under the European chemicals regulation REACH.

Pre-clinical research and development

With regard to inflammatory and allergic diseases of the respiratory tract 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, 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 cell line to 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).

Early-phase clinical trials in the CRC Hannover

In collaboration with the Hannover Medical School and the Braunschweig-based Helmholtz Center for Infection Research, Fraunhofer ITEM is operating a new clinical study center, the "Clinical Research Center Hannover" (CRC Hannover), which was formally opened in September 2014. This study center offers an optimal infrastructure for conducting early-phase clinical trials (phases I and II) and has 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. In the CRC Hannover, Fraunhofer ITEM has specialized in conducting clinical trials for the registration of pharmaceuticals for the indications allergy, asthma, COPD, and pulmonary fibrosis. The focus is on proof-of-concept studies in compliance with GCP guidelines, managed by highly qualified physicians. Whenever needed, the required investigational medicinal products can be manufactured on site in compliance with GMP guidelines.

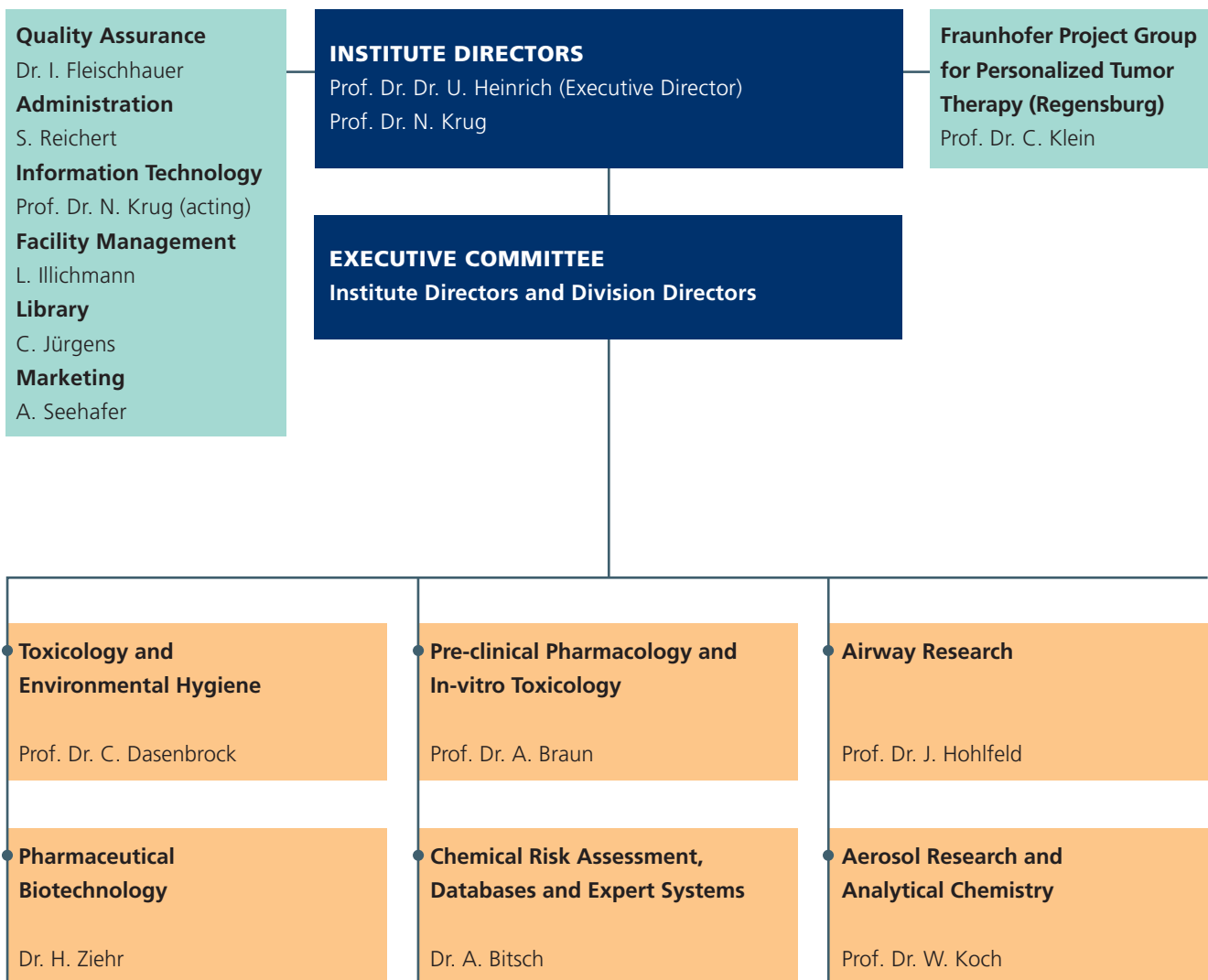
With the Fraunhofer Allergen Challenge Chambers (Fraunhofer ACCs in short), special challenge chambers are available that are among very few of this kind worldwide. In these chambers, pollen, house dust mite and other allergens can be dispersed in the air in a precisely controlled manner. The efficacy 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 ACCs 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.

As a logical consequence, the Department of Medical Inhalation Technology was set up in 2015. Its focus is on conducting and assisting the development of novel technologies for administration of medicinal aerosols and on dealing with issues arising during development of novel formulations. The Fraunhofer scientists have many years of experience in development of medical devices and have at their disposal a broad range of technical equipment and methods for aerosol characterization and generation and for measurement of basic physical parameters.

ORGANIZATIONAL STRUCTURE



(as at December 2015)

Headed by the Institute Directors and the Executive Committee, 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 Fraunhofer ITEM, the Fraunhofer-Gesellschaft, and the University of Regensburg.

DEPARTMENTS AND WORKING GROUPS

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 December 2015).

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. Wronski

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

Dr. F. Dahlmann

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. M. Heine
Dr. S. Duvar

Microbial Cultivation

Dr. A. Roß
Dr. C. Seitz

Downstream Processing

Dr. J. Paulsen
Dr. C. Lüler

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
A. Zwintscher

Veterinary Medicinal Products

Dr. G. Könnecker
Dr. A. Wibbertmann

Exposure Assessment

Dr. S. Hahn

Testing Strategies and Structure-Activity Relationships

Dr. S. Escher

Databases and Information Systems

Dr. R. Kellner

Risk Assessment of Nanomaterials

Dr. S. Escher

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. K. Blümlein

Structure Analytics

Dr. S. Schuchardt

GXP – QUALITY ASSURANCE ACCORDING TO INTERNATIONAL STANDARDS

Fraunhofer ITEM is striving to meet high quality standards with the services and products offered and to ensure maximum safety for trial subjects in clinical studies performed at the institute. Not only are the relevant legal regulations strictly complied with, but state of the art regulatory requirements are invariably taken into consideration. To guarantee that the work performed at Fraunhofer ITEM satisfies internationally accepted quality standards, Fraunhofer ITEM has implemented the GXP quality assurance systems. These include Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP). With their respective scopes of application, these quality assurance systems cover the translational approach in the institute's spectrum of activities. The central service unit "Quality Assurance" is responsible for putting into practice the relevant quality assurance programs.

GLP conformity of non-clinical safety studies

To ensure reliability and traceability 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

By means of study-based and facility-based inspections, the service unit "Quality Assurance" continuously monitors compliance with these principles in the institute's departments of toxicology, safety pharmacology, and analytics. 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. On the occasion of the last inspection in December 2014, the integrity of the GLP studies performed was once again confirmed. The established quality assurance system thus guarantees to all sponsors a recognized quality standard in the institute's non-clinical departments.

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 Fraunhofer ITEM, a broad range of measures ensures that these requirements can be met both in trials falling under the German Drug Act and performed on behalf of international sponsors and also in clinical research projects. The service unit "Quality Assurance" assists the clinical investigators in fulfilling their responsibilities by closely monitoring implementation of the quality-relevant processes under aspects of GCP and by routinely checking the relevant documentation. Both the monitoring authority and the institute's sponsors have assessed the quality level reached to be GCP-compliant.

During setup of the Clinical Research Center Hannover (CRC Hannover), co-operated as a Fraunhofer research institution by Fraunhofer ITEM, the Hannover Medical School (MHH) and the Helmholtz Center for Infection Research (HZI), the service unit "Quality Assurance" assumed lead responsibility in the establishment of a joint quality assurance system for the facilities used by the cooperation partners performing clinical trials according to GCP. During routine operation of the CRC Hannover, the service unit "Quality Assurance" is performing cross-project



The GXP platform at Fraunhofer ITEM includes GMP (Good Manufacturing Practice) in the manufacturing of biopharmaceuticals for clinical trials.

and coordinating tasks in the field of quality assurance, thereby contributing to a steady high level of uniform quality standards in the facilities of the CRC Hannover. The synergies resulting from the scientific cooperation of the partners in the CRC Hannover thus go hand in hand with guaranteed maximum protection of all trial subjects and fulfillment of sponsors' quality requirements.

GMP facilities at the institute's Hannover site

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 (liquid dosage forms) in spatial proximity to the clinical departments, an appropriate GMP facility was successfully established at Fraunhofer ITEM in Hannover a few years ago. Furthermore, the possibility to manufacture ozone according to GMP for use as a challenge substance in clinical inhalation trials has been established and confirmed by the competent authorities. A corresponding GMP manufacturing authorization was granted by the competent authorities, but is dormant for the time being. The service unit "Quality Assurance" ensures that the regulatory conditions for resuming manufacturing operations, whenever needed, are met.

GMP facilities at the institute's Braunschweig site

The Division of Pharmaceutical Biotechnology in Braunschweig has a long and comprehensive history in the development of GMP manufacturing processes for biopharmaceuticals. The division has been manufacturing biopharmaceutical active ingredients by microbial fermentation or animal cell culture and investigational medicinal products in its GMP facilities according to European Union GMP quality regulations since 1998. Since 2012, when GMP regulations were extended to apply

to cell banking, master and working cell banks have been produced according to Annex 2 of the EU GMP Guide. The division also supplies trial-specific challenge agents for early-phase clinical trials.

More recently, the division set up an automated filling machine in a joint project with the Packaging Technology Group of Robert Bosch GmbH for the aseptic fill and finish of vials and ampoules. Filling operations have been successfully validated by repeated media fill studies.

The Braunschweig facilities received their first manufacturing authorization in 1998, which has since been extended several times. The last inspection by the competent authorities in January 2015 resulted in the extension of the manufacturing authorization to include the aseptic fill and finish of small-volume parenterals.



CONTACT

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Dr. Neophytos Papamichael
Head of Quality Assurance at the Braunschweig site
Phone +49 531 6181-6200
neophytos.papamichael@item.fraunhofer.de

STAFF AND INSTITUTE BUDGET PERFORMANCE

At the end of 2015, 327 people were employed at Fraunhofer ITEM:

- 10 apprentices
- 48 students (including Ph.D. students)
- 269 scientific, technical, and administrative staff

In 2015, the institute's budget reached a level of 24.3 million euros*. Financing by acquired funding amounted to 67 percent. The share of industrial income in the institute's budget was 42 percent – with regard to Fraunhofer ITEM in Hannover it was 42.4 percent. Investments of Fraunhofer ITEM amounted to approximately 1.8 million euros.

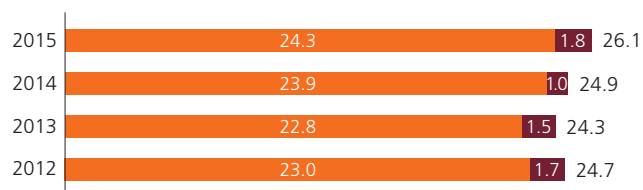
Fraunhofer ITEM staff

Number of employees



Fraunhofer ITEM total budget

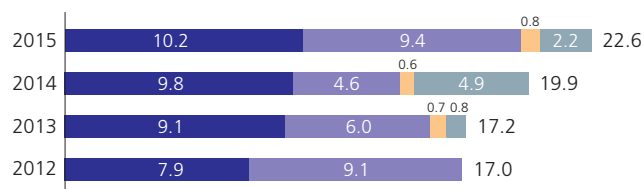
In million euros



- Operating budget
- Investments

Fraunhofer ITEM sponsors and external income

In million euros



- Industry and commercial associations
- Public sector
- EU
- Other

* 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 2015, the Fraunhofer ITEM Advisory Board 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

Prof. Dr. Christopher Baum

Deputy Chairman of the Advisory Board (as of May 28, 2015)
President and member of the Presidential Council responsible for the Division of Research and Teaching of the Hannover Medical School

Dr. Marcus Beiner

Deputy Head of the Department Research and Innovation,
Head of the Division of Life Sciences, Humanities,
Social Sciences, and Sustainable Development,
Lower Saxony Ministry of Science and Culture
(as of July 1, 2015)

Prof. Dr. Dieter Bitter-Suermann

Former President and member of the Presidential Council responsible for the Division of Research and Teaching of the Hannover Medical School

Prof. Dr. Ulrich Deschl

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

Prof. Dr. Paul-Georg Germann

Head Preclinical Safety Germany, AbbVie Deutschland GmbH

Prof. Dr. Thomas Jung

Chief Medical Officer, Delenex Therapeutics AG, Switzerland

Dr. Günther Karmann

Managing Director, Karmann Consulting GmbH

Prof. 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

Prof. Dr. Reinhard Pabst

Lower Saxony Professorship in Immunomorphology,
Hannover Medical School

Prof. Dr. Klaus F. Rabe

Medical Director and Executive Medical Officer,
LungenClinic Grosshansdorf;
Endowed Professorship in Internal Medicine/Pneumology,
University of Kiel

Prof. Dr. Gerhard Schlüter

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

Dr. Thor A. Voigt

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

Dr. Torsten Wagner

Senior Vice President, Corporate Technical Operations,
Merz Pharma GmbH & Co. KGaA
(as of July 1, 2015)

CRC HANNOVER

Center for early-phase clinical trials has been firmly established

In 2015, the Clinical Research Center Hannover (CRC Hannover) became firmly established as a leading-edge study center. The partners Fraunhofer ITEM and Hannover Medical School (MHH in short for "Medizinische Hochschule Hannover") further extended their research activities in the field of early-phase clinical trials; the study center of the "National Cohort" study, operated by the Braunschweig-based partner Helmholtz Center for Infection Research (HZI), successfully went into routine operation; and the splendid conference facilities of the CRC Hannover hosted a variety of high-level meetings.

The close collaboration of MHH clinicians and Fraunhofer ITEM airway researchers and the ideal combination of Fraunhofer and CRC infrastructures enabled completion of several innovative studies in 2015. In cooperation with the MHH Department of Dermatology, the impact of grass pollen count in the air on

atopic dermatitis, long hypothesized by physicians, could eventually be demonstrated, and the research performed on idiopathic pulmonary fibrosis was honored with the "ERS Research Award on Idiopathic Pulmonary Fibrosis 2015". A special success: in toxicity tests and clinical trials with a novel DNzyme-based drug, Fraunhofer ITEM scientists were able to provide the proof of concept for a novel therapeutic principle aimed at treating the allergic airway inflammation in asthmatic patients. The results of the clinical proof-of-concept trial, a collaborative project with industry, were published in the "New England Journal of Medicine".

Two innovative studies have demonstrated with particular clarity that the MRI scanner available in the CRC Hannover for use in research only plays a pivotal role in cutting-edge airway research: in collaboration with MHH scientists, Fraunhofer ITEM airway researchers are investigating whether a drug that has already received regulatory approval for treatment of chronic obstructive pulmonary disease also reduces the strain on the heart of patients by dilating their bronchi. And the xenon polarizer set up in May 2015 puts the Fraunhofer ITEM scientists in a position to visualize by MRI scanning not only lung tissue, but also the air in the lungs – and even the air moving into tissue: a milestone in the search for biomarkers intended to indicate whether lung tissue is healthy or diseased. Such diagnostic biomarkers in turn can then be used to develop new methods for drug testing.

The study activities of the MHH Core Facility likewise gained momentum in 2015, covering a broad portfolio. A biomarker pilot study aimed at investigating the efficacy of influenza vaccination in the elderly, a phase-II study on treatment of post-polio syndrome, a psoriasis study in cooperation with the MHH Department of Dermatology, and a phase-II study in cooperation with the MHH Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation are but a few examples from the broad range of MHH study activities performed at the CRC Hannover.





The CRC Hannover is operated by Fraunhofer ITEM in cooperation with MHH and HZI. It provides 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 yields a unique combination of the academic expertise of three well-established research institutions, each in its particular domain, and the infrastructure possibilities of the CRC Hannover. The CRC Hannover is thus perfectly predestined for conducting research-intensive studies. For the

performance of phase-I studies, that is to say, 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 are available, 30 of which allow intensive monitoring of study participants. The technical equipment in the CRC Hannover enables comprehensive diagnostics, complemented by the partners' additional infrastructure.

The number of examined individuals shows that the study center of the "National Cohort" in the CRC Hannover is also a success: only half a year after the official launch of this nationwide health study, the HZI team was able to welcome the 1000th study participant. An important milestone, as it is planned to interview and examine 10,000 individuals over the next few years within Germany's largest epidemiological study, which is aimed at elucidating the causes for the development of major chronic diseases.

Last but not least, the Hannover Unified Biobank (HUB) in 2015 not only complemented its infrastructure by state-of-the-art robotic technology, but above all invested into the establishment of a quality management system. In November 2015, the HUB as one of only few biobanks in Germany was certified in accordance with DIN EN ISO 9001:2008, thereby substantiating its high quality standards in the handling of biological samples from patients.

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



CONTACT

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CRC HANNOVER

PROJECT GROUP IN REGENSBURG

The Project Group for Personalized Tumor Therapy in Regensburg has been a part of Fraunhofer ITEM since 2011. Its focus is on tumor diagnosis, in particular on detection of single disseminated und circulating tumor cells, and on the development of novel tumor therapies. The group, which meanwhile has reached a size of fourteen scientists, two Ph.D. students, and seven technical assistants, is headed by Prof. Christoph Klein, who is also holding the Chair of Experimental Medicine and Therapy Research of the University of Regensburg. Research activities of the project group in the year 2015 were focused on the development of new technologies for single-cell analysis, on molecular characterization of disseminated cancer cells, and on the development of novel pre-clinical models for systemic cancer therapy.

Circulating tumor cells as biomarkers for early detection of breast cancer resistance to therapy

Breast cancer is the most frequent cancer in women worldwide, and numerous patients still die from generalized metastatic disease. To improve treatment of breast cancer patients, increasing efforts have been made to tailor therapies to a patient's particular tumor. After initially good responses to these therapies, however, the cancer cells in most patients with metastases develop resistance to the administered drugs within a few months, resulting in disease progression. To enable early detection of such effects and appropriate intervention by a change in medication, scientists are striving to gain information about metastatic cancer cells by analyzing circulating tumor cells (CTCs) from the patient's blood (method referred to as "liquid biopsy").

In Germany, the DETECT study group is investigating whether breast cancer patients who, based on analysis of the primary tumor, would not be treated with therapies targeting the oncogene ERBB2, might benefit from anti-ERBB2 treatment nevertheless. The criterion for this treatment is detection of the oncogene in CTCs. In this study, scientists of the Regensburg-based Fraunhofer ITEM Project Group isolate CTCs at different time points during systemic treatment, aiming to discover molecular changes and features associated with either response

or resistance to therapy. For these analyses the scientists have developed a semi-automated workflow for isolation of single cells without contamination. Using this technology, the Fraunhofer scientists so far have isolated 1376 CTCs by means of tumor-specific expression markers and 444 leucocytes, and amplified their genomes with *Ampli1*TM, a method developed by Prof. Christoph Klein, head of the project group in Regensburg. Sampling has been timed such that therapy-resistant cells can be detected and mutations with a potential impact on drug response can be discovered in the course of treatment.

In a project funded by the company Silicon Biosystem, the Fraunhofer researchers are now exploring in CTCs the most relevant genetic alterations in breast cancer. The molecular data obtained from isolated CTCs will then be correlated with the patients' clinical course of disease. The aim is to enable early detection of resistance to therapy and reliable prediction of the efficacy of targeted treatments by means of these CTC tests.

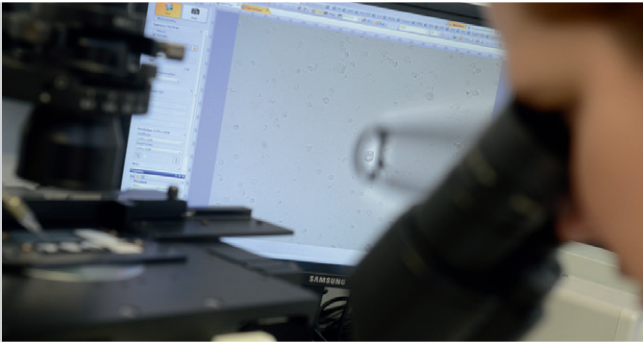


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Innovative approach for evaluation of the tumor status: instead of the traditional histopathological examination using a few sections from different levels of a lymph node, this method detects tumor cells in a single-cell suspension created from minced tissue, independent of their location in the lymph node.

New approach for lymph node staging in malignant melanoma

Analysis of the so-called sentinel lymph node is currently considered to be the most important factor in assessing a patient's prognosis with malignant melanoma. Evaluation of the tumor status, commonly referred to as "staging", in practice at present is usually done by histopathological analysis of sections from different levels of the removed lymph node. This method, however, carries the risk of overlooking tiny clusters of tumor cells and micrometastases. To prevent such faults and to detect and quantify (number of tumor cells per million lymphocytes) even single disseminated tumor cells, Fraunhofer scientists have joined forces with scientists and physicians of the German universities of Regensburg and Tübingen to establish a detection method that allows tumor cells to be demonstrated by immunofluorescence, independent of their location in the lymph node, after tissue mincing and creation of a single-cell suspension (see figure). The aim was to find out whether and to what degree the presence of even single disseminated cancer cells (DCCs) affects the course of disease in patients with malignant melanoma.

More than 1000 melanoma patients with over 1800 removed lymph nodes were investigated in a study over a period of eight years. Lymph nodes were cut into halves and one half each was histopathologically examined by means of sections from different levels, while the other half was disaggregated into a single-cell suspension and immunocytologically stained with a specific melanocytic marker (gp100). The researchers found a correlation between the presence of single DCCs and poorer patient prognosis. Already the presence of up to three DCCs per million lymphocytes was associated with an increased death risk for the patient, and this risk doubled if the DCC value grew by a factor of 10. Taking into account additional prognostic factors such as age and location of the primary tumor, DCCs had a stronger prognostic impact in multivariate

analyses than the results of histopathological examinations. The scientists were able to develop a statistical survival model which, based on tumor thickness, ulceration, and DCC value, allowed the prognosis of survival to be predicted more accurately than based on the currently valid clinical staging concept recommended by the American Joint Committee on Cancer (AJCC).

The results have shown that dissemination of a tumor to regional lymph nodes can be accurately demonstrated by quantitative immunocytology, with less effort than by histopathological analyses. In combination with other features of the primary tumor, this allows an individual prognosis to be established for each patient. Furthermore, an elevated risk of metastasis can be determined for patients who are not taken into consideration by current clinical standards. In collaborative projects with partners from industry and other institutes of the Fraunhofer-Gesellschaft, the Fraunhofer ITEM Project Group is now working on a standardization of the described approach in combination with molecular analysis of single disseminated cancer cells. The aim is to enable more targeted inclusion of melanoma patients in future clinical studies, so as to eventually open up new therapeutic options for treatment of malignant melanoma.

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BUSINESS UNITS OF FRAUNHOFER ITEM

Expertise pooled in six business units


Fraunhofer ITEM has pooled its wide spectrum of expertise (see pages 10/11) 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.

 **Pre-clinical Pharmacology**

 **Toxicology Testing**

 **Manufacturing of Biopharmaceuticals for Clinical Trials**

 **Respiratory Clinical Trials**

 **Environmental, Occupational and Consumer Protection**

 **Registration and Risk Assessment**

BUSINESS UNIT

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 56. 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.[®]-ALI culturing and exposure system, PCLS can also be exposed to air-

Focuses of activity in 2015

The cluster of excellence “From Regenerative Biology to Reconstructive Therapy” (acronym “REBIRTH”) was founded in 2006 by the Hannover Medical School in collaboration with six partner institutions, among them Fraunhofer ITEM. The aim of REBIRTH is to develop new therapies based on regenerative sciences and medicine in conjunction with other scientific disciplines. This subject area has been a focus of activity in the Business Unit “Pre-clinical Pharmacology” in 2015.

REBIRTH unit “Pre-clinical safety and toxicology testing” for cell-based therapies

Stem cell research as a part of regenerative medicine is of rapidly growing social and clinical importance, which is why Fraunhofer ITEM is aiming to evolve as a competent partner for non-clinical safety and toxicology research also in the field of Advanced Therapy Medicinal Products (ATMPs), with a focus on cell-based medicinal products (CBMPs). The institute is specialized in the development of product-specific testing strategies for pre-clinical evaluation of biologics and non-biologics and already has a track record in pharmacology research



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.

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on cell therapies. Toxicological testing of cell-based therapeutics and cell recovery in the host body thus excellently complement the Fraunhofer ITEM portfolio.

New products require new regulations

In its "Guideline on human cell-based medicinal products" (EMA/CHMP/410869/2006), the European Medicines Agency (EMA) describes CBMPs as heterogeneous and considers that product-specific case-by-case testing strategies are needed, rather than conventional non-clinical studies. It further recommends early presentation of these individual, risk-based strategies for pre-clinical evaluation to the drug registration

authorities for discussion. With our long-standing expertise in pre-clinical testing of new drugs, including safety-relevant studies according to GLP, we are in a position to adequately support our clients in all contexts of pre-clinical testing of heterogeneous cell-based therapies. This includes consulting to set up an appropriate testing strategy and early interaction with the competent authorities to ensure regulatory compliance of the developed strategy. The complex assays and studies are then validated and performed according to the relevant quality standards. In this context, Fraunhofer ITEM is uniquely positioned, both technically and with regard to its staff, to move non-standard test systems from the research lab to the GLP environment.

Fraunhofer ITEM as a REBIRTH partner

In the REBIRTH cluster of excellence, the connection of biomedical science and biotechnology with clinical practice and networking of the different groups within the cluster and beyond are of primary importance. The expertise of Fraunhofer ITEM optimally contributes to the focus of the REBIRTH group "Biocompatibility" (Biocompatibility Laboratory BioMedimplant). BioMedimplant is specialized in the assessment of biocompatibility and in regulatory issues regarding pre-clinical evaluation of tissue-engineered medicinal products. In the interdisciplinary REBIRTH working group "Toxicology", together with BioMedimplant and other REBIRTH groups we are developing a REBIRTH network for pre-clinical safety and efficacy testing of ATMPs. In this context, we are focusing on the recovery and immunohistochemical detection of transplanted stem cells in tissues and whole-organ slices.

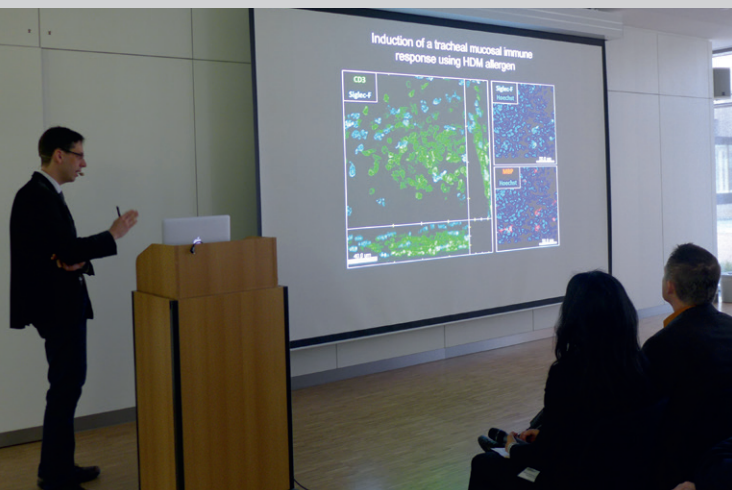
In order to further establish the field of stem cell research and development at Fraunhofer ITEM, we started a collaborative project with the Institute of Experimental Hematology and the Institute for Laboratory Animal Science, both of the Hannover Medical School and integrated members of REBIRTH. The main focus of this project is the characterization of human induced pluripotent stem cells (iPS) and their differentiation into hematopoietic cells in a teratoma-based (embryogenesis) mouse model.

Workshop "Models of Lung Disease"

In early February 2015, experts from academia and industry got together already for the 14th time to discuss the current possibilities of experimental lung research and different experimental approaches. About 130 participants attended this two-day event, most of them from European countries, but a few also from Australia and the US. Compared with the previous events of this workshop series, this year's seminar came up with some novelties – first of all a new name, which changed from "Models of Asthma and COPD" to "Models of Lung Disease". New was also the venue: the meeting took place in the new clinical research center – CRC Hannover. Further novelties were the possibility for participants to present scientific posters, and a small industry exhibition where a few companies got the opportunity to present themselves and their products to the visitors. The seminar was organized by Fraunhofer ITEM in close cooperation with the German Center for Lung Research (DZL).

Hematopoietic stem cells – a highly valued cell type

Hematopoietic stem cells (HSCs) are mainly located in the bone marrow of vertebrates, where they are surrounded by a complex cellular environment. Besides their self-renewing potential, HSCs can develop into any matured blood cell type, as required by the immune or blood system. Bone marrow transplantation is successfully used in the treatment of blood-derived diseases, such as leukemia or innate or acquired immune disorders. Like in all transplantation approaches, however, availability of compatible donors is limited and does not cover the demand. To overcome this shortage, scientists have been investigating protocols for in-vitro generation of HSCs from stem cells, but so far without success. Even though many processes of human hematopoiesis have been uncovered over



Visualization of T-cell activity contributes to a better understanding of the role different cells play in the allergic inflammatory process, explained Tibor Veres from Finland in his talk during this workshop.

For a summary of this event, please refer to the Web page: http://www.item.fraunhofer.de/en/meetings-fairs/own-meetings/Summary_Workshop_2015.html

the past decades, the required time-dependent interactions of different cell types are very complex and so far impossible to adequately mimic in cell cultures.

Study of human hematopoiesis in a mouse model

A new approach to investigating human hematopoiesis is induction of teratoma formation as a model of embryonic development. Teratomas are germ cell tumors that can be induced by injecting stem cells into immunodeficient mice. During tumor growth, the injected cells differentiate into cell types from all three germ layers, reflecting embryonic development to a certain degree. In this process, a small portion of the emerging cells differentiate into functional HSCs – a result so far impossible to achieve in cell cultures. We use this model

primarily to investigate the different cell populations enabling development of transplantable HSCs. To this end, we prepare teratoma tissue for immunohistochemical staining that allows cell types to be identified by their characteristic surface proteins. Furthermore, we test different conditions for their potential to enhance hematopoiesis in teratoma. Gathered insights are planned to be transferred to cell culture methods, so as to get closer to the aim of successful de-novo generation of HSCs from iPS cells.



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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.® 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)

PROJECTS

Infectivity and toxicity testing of inhaled microbial active ingredients

In a study performed on behalf of Sourcon-Padena for registration of a microbial plant protection product, Fraunhofer ITEM scientists evaluated the toxicological risk from inhalation exposure according to OECD guideline 407 and infectiological parameters according to EPA OPPTS 885.3150. To this end, they first optimized nebulization of the microbes to rule out impairment of microbial viability and to ensure the high germ count required for the study. Rats were then exposed to the microbial agent for 4 hours by nose-only inhalation and their health status was subsequently monitored for 21 days. In satellite groups, the germ load in the lung and associated lymph nodes and in other organs and the pulmonary immune response were analyzed by means of differential cell count in bronchoalveolar lavage (BAL) performed at different time

points. Despite the high microbial count, inhalation of the microbial active ingredient caused no adverse effects or mortality. No proliferation of microbes was found, but rather their fast elimination by the host's immune cells. This was also demonstrated by a transient increase in neutrophil granulocytes, the typical effector cells of an immune response directed against microorganisms, in BAL. After a few days only, the inhaled microbes had been degraded and the immune response had subsided. Therefore, no toxicological or infectiological risk is to be expected from potential inhalation exposure to the microbial active ingredient during use of the product.



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Therapeutic nanosystems against pulmonary infections

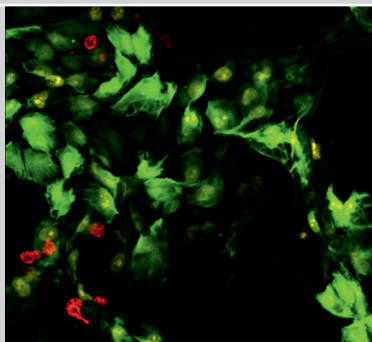
Infections caused by antibiotic-resistant bacteria are among the greatest healthcare challenges worldwide, because there are no effective therapies available. In order to solve this problem, the EU is funding under its 7th Framework Program from 2014 to 2017, among others, the "PneumoNP" consortium, involving 11 working groups from 6 European countries. The key mission of this project is to develop two solutions: 1) a diagnostic system for identification of antibiotic-resistant gram-negative bacteria that cause respiratory infections, and 2) a nanomaterial-based therapeutic for inhaled administration. The scientists are using dextran-based particles and liposomes as nanocarriers, which are being loaded with different innovative, antimicrobially effective peptides. The focus at Fraunhofer ITEM is on

in-vitro studies aimed at ensuring early selection of appropriate nanocarriers and combined nanosystems. To this end, the ITEM scientists perform cytotoxicity tests in cell-based assays using human lung cell lines. In addition, they use microdilution tests to evaluate the efficacy of the combined nanosystems against antibiotic-resistant bacteria. The most promising drug candidates will subsequently be further analyzed both in in-vitro genotoxicity tests according to international guidelines and by means of in-vitro exposure methods in a cell-based air-liquid interface system developed at Fraunhofer ITEM.



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3D confocal microscopy image of GFP-labeled cancer cells (green) that have invaded lung tissue, in contact with lung tissue-resident macrophages (red).

Studying cancer cells in their natural microenvironment

Development of anti-cancer therapeutics often fails because of inadequate test systems that are unable to reflect the tumor's natural environment. Fraunhofer ITEM scientists, therefore, have been using vital precision-cut lung slices with GFP-labeled (GFP = green fluorescent protein) cancer cells to study the behavior and growth of tumor cells in interaction with their natural microenvironment (see figure). Due to the GFP labeling, the cancer cells specifically differ from all other cells in lung tissue. This allows interactions of the tumor with immune cells to be observed within the lung structures. By means of immunohistological confocal microscopy, the morphological dynamics

of cancer cells, their interactions with lung cells, and cancer cell growth can thus be three-dimensionally visualized and quantified. Furthermore, this enables testing of anti-cancer therapeutics interfering with the tumor's microenvironment, such as drugs directed against tumor-associated macrophages. Such analyses provide deeper insights into fundamental interactions between the tumor and its environment. The model is being developed for efficacy testing of anti-cancer therapeutics in vital human lung tissue.



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Inflammasome activation by bacterial and viral infections

Initiation of antibacterial and antiviral immunity in the lung requires recognition of specific pathogen-associated molecular patterns (PAMPs) – structural hallmarks characteristic of a broad spectrum of microorganisms – by cellular receptors. Equally important are cell damage-associated molecular patterns (DAMPs) and their recognition by tissue-resident immune cells. Recognition of both PAMPs and DAMPs can trigger immune cell activation and inflammatory signaling cascades via the inflammasome, a cytosolic protein complex. Fraunhofer ITEM scientists are using precision-cut lung slices (PCLS) to study inflammasome activation via different pathways. They incubate human lung tissue with two different PAMPs to simulate bacterial or viral infection – either with LPS, a membrane component of gram-negative bacteria, or with poly(I:C), a synthetic analogue of double-stranded RNA as a molecular

pattern associated with viral infection. ATP, which is capable of increasing inflammasome activation, is used as DAMP. Human PCLS respond to these stimuli by releasing pro-inflammatory cytokines, analogously to the whole complex organism. This enables testing of pharmaceutical agents targeted at inhibiting the inflammasome. In the described test system, the scientists were able to measure an increase in pro-inflammatory markers after incubation with either LPS or poly(I:C), which was further enhanced by ATP. Inflammasome inhibitors and glucocorticoids attenuated this signal, providing evidence that the system can be used to study inflammasome activation and corresponding pharmacological interventions.



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BUSINESS UNIT 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 2015

In the toxicological studies performed in the Business Unit “Toxicology Testing” in 2015, nanomaterials again played an important role. In the report below, we are presenting an example – a study investigating the carcinogenic potential of multiwalled carbon nanotubes with lengths and structural properties similar to those of asbestos.

Molecular basis of the carcinogenic potential of multiwalled carbon nanotubes

In in-vivo studies, multiwalled carbon nanotubes (MWCNTs) have been shown to cause mesothelioma. Mesothelioma is a malignant tumor originating from mesothelial cells, in particular from pleural and peritoneal squamous epithelium, and has frequently been associated with asbestos exposure. To identify molecular



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

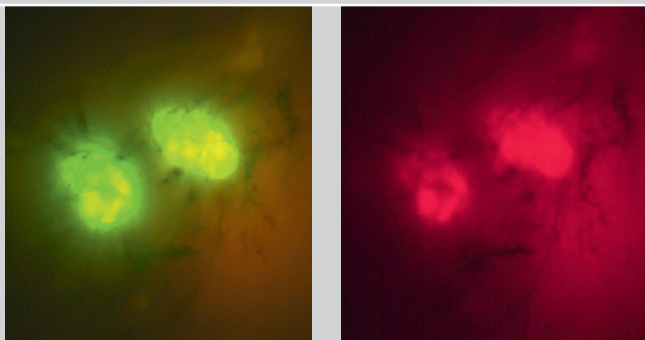
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cues by which MWCNTs induce mesothelioma, Fraunhofer ITEM scientists investigated the carcinogenic potential of different tailor-made, non-functionalized MWCNTs in vitro, using an array of classical cytogenetic and molecular biology approaches. Their model system were primary human peritoneal mesothelial cells (LP9) treated for 24 hours with 3-5 $\mu\text{g}/\text{cm}^2$ of MWCNTs, amosite asbestos as positive control, or milled MWCNTs as material control. In addition, they analyzed tumors induced by the same MWCNTs and asbestos in rats for comparison (Rittinghausen et al., 2014, Part Fibre Toxicol 11: 59).

Human primary peritoneal mesothelial cells

Interestingly, the findings from in-vitro experiments with a highly tumorigenic type of MWCNTs (MWCNT A) revealed markers associated with cellular senescence, a growth arrest in response to different stressors such as persistent DNA damage, disrupted chromatin, and strong mitogenic signals. Cellular senescence is implicated in several pathological processes including aging, tumor suppression, and – paradoxically – tumorigenesis. This broad range of effects can be attributed



LP9 cells treated with multiwalled carbon nanotube MWCNT B. The cells exhibit chromatin abnormalities: The phosphorylated and thus activated histone variant H2A.X (gamma H2A.X) appears in green after immunofluorescence staining with a specific antibody (left images on both pages). DNA counterstaining of the same cells with propidium iodide appears in red (corresponding right images), proving that the stained structures (green and red) are, in fact, DNA.

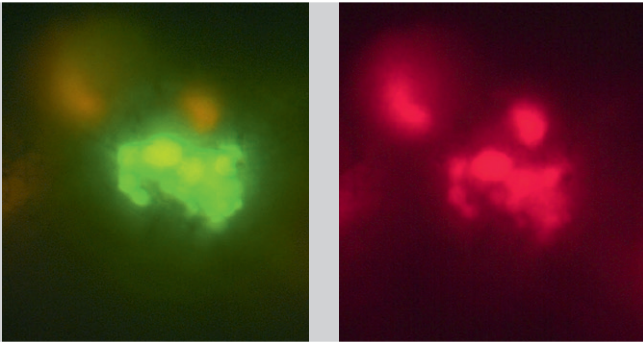
to a senescence-associated secretory phenotype involving pro-inflammatory cytokines, chemokines, growth factors, and proteases, which reinforce senescence, but also affect neighboring cells. In keeping with a senescence-inducing effect of MWCNTs, in their in-vitro experiments the Fraunhofer scientists found, for instance, inhibition of cell division, nuclear fragmentation, chromatin condensation, microtubule disruption, pan-nuclear staining after γ H2A.X immunofluorescence, senescence-associated heterochromatin foci, and enlarged cells exhibiting senescence-associated γ -galactosidase activity.

Using microarray technology, they furthermore determined how the transcriptomic changes induced by MWCNT A differ from those induced by another tumorigenic MWCNT type with albeit lesser potency (MWCNT D), asbestos (amosite), and milled MWCNTs. The scientists found 3788 significantly differentially regulated genes for MWCNT A, 1680 for MWCNT D, 145 for amosite, and only 4 for milled MWCNT. Further bioinformatic analyses comparing the two different MWCNT types and amosite revealed common as well as exclusive candidate biomarkers. Interestingly, many differentially regulated genes implicated in cellular senescence could be identified. For example, the scientists found differential expression of genes associated with a senescence-associated secretory phenotype of cells. Up- and downregulation of these genes was much more pronounced in cells exposed to MWCNT A than in MWCNT D and amosite-exposed cells. The mechanisms leading to mesothelioma induction by MWCNTs are far from clear, but key information obtained from the present microarray experiments, together with the identified senescence markers in MWCNT-exposed cells, suggests a likely role of induction of cellular senescence.

MWCNT-induced mesotheliomas in rats

Epigenetic events are heritable changes in gene expression without alterations in the primary DNA sequence. Misdirection of epigenetic regulation can lead to diseases. Aberrant DNA methylation of gene promoter regions, for example, has been associated with gene silencing in cancer. To better understand the molecular basis of MWCNT-induced carcinogenesis, the Fraunhofer scientists in addition analyzed the transcriptomic and (epi-)genetic landscapes of pathologically well-characterized mesotheliomas induced by MWCNTs and asbestos in rats and compared them with non-pathological peritoneal tissue from control rats. Besides their different inducers, the tumors were a mixture of different pathological types, i.e. squamous, sarcomatoid, epitheloid, and biphasic tumors. Initial bioinformatic analyses of genome-wide transcriptomic data showed that the tumors induced by different MWCNTs and amosite did not essentially differ in the number of significantly differentially regulated genes. Nonetheless, both exclusive and common biomarkers were found among the tumors induced by MWCNTs and amosite.

For further characterization of the tumors, the scientists designed bisulfite sequencing assays to analyze for DNA sequence variations (dbSNPs, somatic mutations) and DNA methylation (CpG and non-CpG methylation) at a single-molecule resolution in the promoter regions of selected genes. A large variety of combinations of genetic and epigenetic changes, even within the same gene, was found in the tumors.



A tumor suppressor gene, *H-Ras-like suppressor (Hrasls)*, for example, was studied in more detail. It was significantly down-regulated both in microarray analysis and in qRT-PCR of 37 individual tumors, and this downregulation was found across different inducers (MWCNTs and amosite) and tumor types. The scientists thereby sequenced a 431-bp fragment encompassing 28 CpGs along the promoter and 5'-untranslated regions (5'-UTR) of *Hrasls*. They detected non-CpG methylations, sequence variations, and increased frequency of methylated CpGs in certain tumors. Non-CpG methylation was detected more frequently in MWCNT-induced tumors than in tumors from asbestos-exposed rats. Several of these (epi-)genetic variations could alter the binding of transcription factors and thereby affect promoter function and activity of the corresponding gene. More importantly, in an MWCNT-induced squamous tumor, an insertion and a transition in cis arrangement within the binding sites of the two tumor suppressors p53 and Mzf1, respectively, was detected in 5 of 8 clones. So far, these two sequence variations have not been identified in other analyzed tumors (i.e. epitheloid, sarcomatoid, or biphasic) or control tissues, nor have they been reported as specific sequence variations in other contexts.

Conclusion

The results obtained show that MWCNTs can cause malignant mesothelioma, namely through cellular senescence. Understanding the molecular mechanisms leading to mesothelioma development is crucial for risk assessment of MWCNTs.



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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
- Measurement system: isolated perfused rat lung

PROJECTS

Insight into adverse effects of cerium oxide nanoparticles

Cerium oxide (CeO₂) nanoparticles are used, for example, as diesel additives to optimize combustion processes. They can thus be emitted into outdoor air and may enter the human body by inhalation. There are indications suggesting a toxic potential of these particles, however, the available data are, as yet, insufficient. This is why the German Federal Ministry of Education and Research is funding the project "InhalT90", a 90-day inhalation test in rats aimed at elucidating adverse effects of CeO₂. Histopathological and retention analyses as well as lung lavages are performed during the exposure and subsequent observation period. CeO₂ distribution in the lung is monitored by ion beam microscopy and confocal microspectroscopy. Another important aim of this study is the identification of early indicators of genotoxic and carcinogenic

effects. To this end, the scientists are performing comprehensive gene expression analyses in type-II lung epithelial cells and try to identify marker genes associated with endpoints such as genotoxicity or inflammation and whose expression could be substantially influenced by the exposure. Exposure conditions have been selected to match those of a parallel BASF carcinogenicity study, to enable correlation between the results obtained and chronic exposure data and to allow evaluation of the predictive potential. Transferability of the marker genes identified in vivo to an in-vitro test system is planned to be verified by airborne exposure of a lung cell line in a Fraunhofer ITEM-developed air-liquid interface system.



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Nonhazardous nanostructured flame retardants for synthetic materials

The European industry is in urgent need of novel solutions that will allow halogenated flame retardants (FR) with health and environmental hazard potential to be replaced by less harmful yet effective materials. FR are used to manufacture thermo-plastic or duroplastic component parts, for example for electric or electronic devices, low-voltage cables, or appliances that are potentially at risk of fire. The cross-disciplinary project PHOENIX (<http://www.phoenix-eu-project.eu>), receiving 4-year funding under the 7th EU Framework Program for Research and involving 17 organizations from 8 countries, has taken on this challenge. It is pursuing three major approaches: (1) development of innovative, non-halogenated, nanostructured flame-retardant materials based on graphenes, modified lignins, nano-hydroxides,

and encapsulated phosphates, (2) development of corresponding innovative, functional, cost-effective, and environmentally less harmful processing technologies for plastic materials (material compounding, extrusion, injection molding), and (3) simulation and modeling of plastics processing to develop optimal production methods for nano-composites. For this project, Fraunhofer ITEM is using different lung-relevant in-vitro cell models to comparatively determine the (geno-)toxic and pro-inflammatory potential of newly developed FR, perform hazard assessment, and enable early discarding of novel compounds with high hazard potential.



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Testing of hair cosmetic products: in the lab, natural hair is treated with cosmetic products before thermal straightening to mimic the real-life situation and enable in-vitro testing of the resulting aerosols.



Feasibility study on in-vitro testing of occupationally relevant aerosols from hair care products

Inhalable aerosols may be generated when applying heat to hair in conjunction with hair cosmetic products, for example during thermal straightening of product-treated hair. Toxicological assessment of these aerosols is difficult, because the exact composition of the aerosol droplets resulting from the product's mixture is often unknown. In cooperation between Fraunhofer SCAI and the Fraunhofer ITEM working groups on Analytical Chemistry, In-vitro and Mechanistic Toxicology, and Chemical Risk Assessment, a testing concept involving the use of hair care products under product-relevant conditions has been implemented in an industry project. The generated aerosols are fed into an optimized exposure system (P.R.I.T.®-

ExpoCube®) for in-vitro testing using air-liquid interface cultures from human lung. Measurements regarding acute toxicity or irritant effects in the exposed cell cultures allow detection of potential biological effects. By means of measurements performed in parallel at workplaces under real-life conditions, application-relevant testing of the product in the in-vitro test system, and verification by appropriate positive and negative control substances, the scientists have implemented a testing concept aimed at allowing not only qualitative detection of biological effects, but also quantitative evaluation of the biological alterations with regard to toxicological assessment.



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In-vitro models for prediction of idiosyncratic drug-induced liver injury

The most frequent type of drug-induced organ toxicity leading to market withdrawal of pharmaceuticals is drug-induced liver injury (DILI). Despite comprehensive research in this context, it has not been possible to fully elucidate the mechanisms of liver injury for a large number of pharmaceuticals. Moreover, some drugs have the ability to induce a very rare but particularly severe form of liver injury, referred to as idiosyncratic DILI (iDILI). This form does not exhibit any clear dose dependence and occurs in very few individuals only. This is why, so far, there has been no way of predicting iDILI based on the results of animal experiments, so that the iDILI potential of a drug candidate frequently did not become evident until it had progressed to the clinical phases (I-III) of drug development or the

medicinal product had even been marketed. Fraunhofer ITEM scientists have embarked upon development of cell culture models aimed at enabling investigation of drug candidates for their hepatotoxic potential already at an early development stage. By co-culturing hepatocytes with cells of the immune system or by adding pro-inflammatory cytokines, the sensitivity of these models can be enhanced, allowing recognition of substances prone to cause iDILI. Gene expression analyses are performed in addition to gain a better understanding of the molecular mechanisms of iDILI and help identify appropriate biomarkers.



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BUSINESS UNIT 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 2015

The use of pharmaceutically active biomolecules such as antibodies is becoming more and more important in the treatment of diseases. In this context, development of product-specific manufacturing processes for specially designed proteins such as bispecific antibody-based molecules represents a challenge to bioprocess engineers. The report below presents a project from this subject area.

Single-chain bispecific antibodies – new active pharmaceutical ingredients for tumor immunotherapy

For efficient tumor treatment, the pharmaceutical and biotech industries are increasingly focusing on the body's natural immune defense as a universal therapeutic tool. The challenge here is to use existing immune-active cells with their complete cytotoxic repertoire for therapeutic intervention against different tumors in a targeted and highly specific manner.



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

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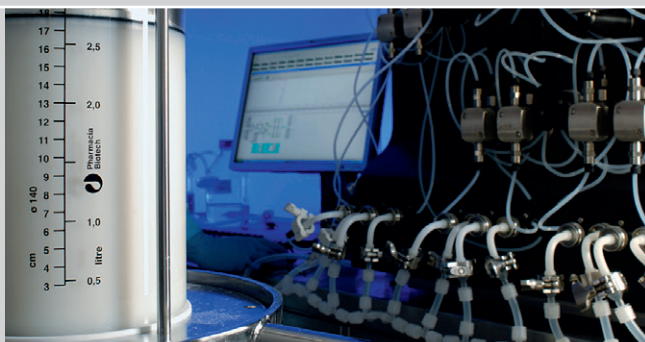
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The Fraunhofer ITEM Division of Pharmaceutical Biotechnology is cooperating for this purpose with a German university spin-off. The aim is to use the anti-neoplastic potential of T cells in a targeted way by directing their cytotoxic machinery towards the eradication of tumor cells. To ensure that they will hit the right targets, T cells in the first place have to get into the molecular vicinity of tumor cell surfaces. Tumor cells and T cells then have to be coupled via molecular bridges. Once this has occurred, the T cell is activated and will exercise its cell-destroying potential, presumably by injecting granzyme into the target cell, leading to tumor cell lysis and phagocytosis of the cell debris by other immune cells – such is the theory.

In practice, however, this means that the T cell must recognize tumor cells with very high specificity, as any non-specific binding and non-specific activation of T cells would equally trigger a T cell-mediated cytokine storm that may result in serious systemic side effects.

Tailored manufacturing approach

For the translation of this concept into a drug candidate, this means that the bispecific bridging molecules have to be highly specific – both, for the tumor and the T cell –, while at the same time any interaction with non-tumor surface markers



Process chromatography system for purification of bispecific antibody fragments.

should be strongly avoided. Bioprocess development and early-stage GMP manufacture of small, bispecific protein molecules with this mode of action was the client's intention when the company approached the Fraunhofer ITEM Division of Pharmaceutical Biotechnology in 2013. The task to be accomplished was to develop the full bioprocess development sequence starting from expression system development and ending with GMP manufacturing processes for those bifunctional immunomodulatory proteins.

In tight cooperation with the client, the Division of Pharmaceutical Biotechnology is developing the expression system (cell line) and manufacturing processes including analytics, and is validating the process and analytical methods. The division will subsequently manufacture the therapeutic proteins in compliance with GMP quality standards, first as a pharmaceutical active component or active ingredient and then as parenteral investigational medicinal product (IMP). Once the IMP will have been released and the clinical trial application will have been approved by the competent authorities, it can be administered to patients in a phase-I clinical trial.

Protein purification

Using CHO protein expression technology established at Fraunhofer ITEM, expression of antibody fragments led to sufficient concentrations in the culture supernatant. A tailored purification sequence had to be established, as platform approaches typically used for full-length antibodies are not transferrable to this molecule class.

Fraunhofer ITEM receives regulatory approval for aseptic fill and finish of small batches of investigational medicinal products

In spring 2015, regulatory approval for the Division of Pharmaceutical Biotechnology was extended to include aseptic, automated fill and finish of small-volume liquid dosage forms in vials and ampoules – at batch sizes of several 100 to a few 1000 units. Fraunhofer ITEM has thus closed a gap that has become increasingly evident over the past few years: it has proven highly difficult, some-

Manufacturing of active ingredients using a modular platform

The client's two bispecific antibody projects that have progressed most are targeting indications in oncology, including leukemia and certain solid tumors. The aim is to develop not only individual biopharmaceutical manufacturing processes, but also modular platform technologies that will allow Fraunhofer ITEM clients to explore further antibody-based approaches for tumor immunotherapy.



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times impossible, to find a suitable partner to perform the last step in the process chain for biopharmaceutical drug candidates developed at the institute on behalf of public institutions or start-up companies, namely the aseptic fill and finish of small batches of an investigational medicinal product (IMP) or batches for stability testing. Fraunhofer ITEM is now able to offer these services in-house, thus covering – as the only institution in Germany’s publicly funded research landscape – the complete process chain to the final IMP released for clinical trials. The filling concept and machine have been newly designed in collaboration with two strong partners: Bosch Packaging Technology in Germany and Nuova Ompi, based in Piombino Dese, Italy.



The new filling suite allows aseptic, automated fill and finish of small-volume liquid dosage forms in vials and ampoules. (Photo courtesy of Robert Bosch GmbH.)

Equipment highlights

- 2000 m² of laboratory space for biopharmaceutical process development
- 600 m² of clean rooms (classes A, B, C, and D) for GMP manufacturing
- Manufacturing authorization since 1997

USP:

- Stainless steel: 50-l STR (batch, fed batch, and perfusion) and 400-l STR (batch and fed batch)
- Single use: 20-l WAVE bioreactor

DSP:

- Chromatography systems (GE Healthcare) with up to 180 l/h
- Preparative HPLC with up to 150 ml/min
- Crossflow filtration system (Sartorius) with up to 6 m²

Filling machine ARF 1010 (by Bosch):

- Semi-automated filling machine for ampoules (1-30 ml) and vials (2-50 ml)
- Nitrogen gassing
- Batch sizes of up to approx. 3500 units

PROJECTS

Alternative method for cell line development

With the traditional method for cell line development, a gene cassette is introduced into a production cell line for subsequent expression of the GOI (gene of interest). The introduction of DNA into the cell is transient in this case. This means that the DNA is introduced into the cell by means of different methods, but its introduction into the cell genome occurs only rarely and in a rather haphazard and non-targeted way. Reliable and targeted introduction of DNA into the cell genome, however, is required to obtain good and stable expression of the GOI. An alternative method for cell line development that has been little used so far is introduction of the DNA into cells by viral particles. The probability for the viral genome to be integrated into the cell genome is far higher, resulting in the generation of a much higher number of cells that may be suitable for

manufacturing of an active pharmaceutical ingredient. The use of lentiviruses, derived from the human immunodeficiency virus, has the benefit that the cells are infected with viral DNA, no matter in what state of the cell cycle they are. The viral genome, including the GOI, is integrated above all into active loci of the cell genome. Aside from lentiviruses, gamma-retroviruses can also be used, although these can infect only dividing cells. This means that their transduction efficiency is slightly lower; however, given that this type of viruses tends to integrate into the loci of transcription start sites, it sometimes allows higher expression levels to be reached.



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Translational research is gaining momentum

Development of drug candidates and, after successful completion of pre-clinical testing, performance of clinical trials with the developed investigational drugs are the hallmarks of translational research. In theory, this special branch of research has long become an established term. But what does it look like in reality? Academic institutions in particular have to cope with numerous challenges to be successful on their way from the idea to the medicinal product. Financial hurdles, due to public funding policy, and increasing regulatory requirements come on top of the researchers' actual tasks, which consist of collecting data on the safety and efficacy of a new drug candidate and ensuring that it is produced to the required standards. The latter in particular is a challenge which the scientists of the

Fraunhofer ITEM Division of Pharmaceutical Biotechnology have taken up, thereby making an important contribution to translational research with regard to quality. This is reflected by current research projects, involving development of manufacturing processes and GMP manufacturing of biopharmaceutical drug candidates for use in humans in clinical trials. Many inquiries have recently been received from academic institutions, indicating on the one hand that translational research in Germany is gaining momentum and on the other hand that Fraunhofer ITEM is optimally positioned to support this kind of research with the services offered.



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So far an unusual method: production of recombinant proteins using fungi.



Protein expression in fungi: an inventive alternative to traditional expression systems

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, to enable customized solutions for specific protein expression requirements. The idea which scientists of the Fraunhofer ITEM Division of Pharmaceutical Biotechnology are currently exploring in cooperation with Professor Fleißner from the Institute of Genetics of Technische Universität Braunschweig aims to develop a fungal expression system that offers this potential. The red bread mold *Neurospora crassa* has been used as a eukaryotic model organism for research for several decades already. Within weeks, it can be reproducibly transformed into a production organism for the desired protein. Over the past three years, the scientists have developed strains that

produce antibody fragments. The manufacturing process was first established in regulated bioprocesses in laboratory reactors (see figure), subsequently scaled up to pilot scale, and the product was successfully isolated. It could be demonstrated that *N. crassa* is suitable for use in bioreactors and that different modes of operation are possible, similar to bacterial fermentation. With this manufacturing system, product amounts in the mg/l range can be produced already. By further optimizing both genetic engineering and process technology parameters, it will be possible in the future to provide an expression system that represents an alternative to traditional systems, also from an economic point of view.



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Collaborative process development: recombinant manufacturing of veterinary vaccines

With increasing requirements on safety, efficacy, and cost efficiency, recombinant manufacturing of veterinary medicinal products has been getting more and more important. Aiming to develop a high-yield fermentation process in *E. coli* for manufacturing of recombinant-antigen veterinary vaccines by the company IDT Biologika, Fraunhofer ITEM and IDT Biologika have joined forces and pooled their expertise. Based on experience gained in similar projects, the Fraunhofer ITEM scientists were able to quickly implement a fully defined, non-proprietary culture medium to replace the complex medium so far used by IDT Biologika. The new culture medium is not only easy to

prepare and attractive from a regulatory point of view; it furthermore proved to support high biomass yields with the production strain used by IDT Biologika and high yields of recombinant antigen. With such promising first results, the Fraunhofer scientists designed and tested a simple, robust, and highly reproducible lab-scale fermentation process. Adopting this process, IDT Biologika achieved the same high biomass and antigen yields as Fraunhofer ITEM. The next step after this successful technology and know-how transfer will be to take this process to technical scale.



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BUSINESS UNIT RESPIRATORY CLINICAL TRIALS

In our Business Unit “Respiratory 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, 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, COPD, and pulmonary fibrosis. The efficacy of new anti-allergic drugs in patients with allergic rhinitis (hay fever) can be tested in the Fraunhofer Allergen Challenge Chamber (Fraunhofer ACC), 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 ACC 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 activity in 2015

Shortly after the opening of the CRC Hannover – the center for early-phase clinical trials – in September 2014, the Attract research group “Clinical and Translational Fibrosis Research” was set up under the leadership of Prof. Antje Prasse. The “Attract” grant program of the Fraunhofer-Gesellschaft offers outstanding external scientists the opportunity to develop their ideas towards actual applications close to the market within an optimally equipped Fraunhofer Institute. The below report presents the activities of this Attract group in the year 2015.

Successful start of clinical and translational fibrosis research

In the first few months of its existence, the Attract group at Fraunhofer ITEM was primarily concerned with establishing in-vitro models based on primary cells and a humanized animal model of pulmonary fibrosis, including setup of a new collaborative network in Hannover.



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 has been further enhanced with the new Clinical Research Center Hannover. More beds and recreation facilities 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 are now 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 Analytical Chemistry", and "Process Development and GMP Manufacturing of Biopharmaceuticals".

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Benefits from local networking

The Attract group at this location clearly benefits from the comprehensive lung transplantation program of the Hannover Medical School (MHH). In a nationwide unique manner, the network of Fraunhofer ITEM and MHH established within the German Center for Lung Research (DZL) at its Hannover site (BREATH) gives the Attract group access to both fresh lung tissues obtained from human lung explants and to tissues stored in the BREATH biobank. The underlying diseases and clinical characteristics of all lung-transplanted patients were also accurately documented by the Attract group.

The primary cell lines obtained from fresh tissue samples can be used for in-vitro assays in research projects, for example to test pharmaceutical compounds for their mode of action. In parallel with the research laboratory, Dr. Prasse also set up a clinical center for pulmonary fibrosis at the MHH, where more than 400 patients with different types of pulmonary fibrosis were taken care of already in 2015. For the materials resulting from routine diagnostic procedures in these patients, the Attract group has established another biobank, which is used in addition to obtain primary cell lines and for future biomarker research projects. Thanks to the database of healthy volunteers maintained in the CRC Hannover and in the institute's

Department of Clinical Airway Research, the Attract group furthermore has access to materials from healthy control subjects. Within an EU project on idiopathic pulmonary fibrosis, numerous bronchoscopies in healthy volunteers over 60 years of age were already performed at Fraunhofer ITEM in 2015 for collection of appropriate control material.

International collaboration

Based on the available biobanks and databases, the transcriptome (RNA expression) of BAL cells was analyzed in 212 patients with idiopathic pulmonary fibrosis from three independent cohorts in a collaborative project with Yale University, and a genetic signature enabling prognosis of patient survival was developed. Under the lead of Dr. Prasse, this research work has been submitted for publication in a renowned medical journal and has been met with keen interest at international congresses. Partly because of this research, the European Respiratory Society awarded the “ERS Research Award on Idiopathic Pulmonary Fibrosis” to Dr. Prasse in September 2015.

Public project funding is underway

Based on the pulmonary fibrosis biobanks and databases that have been established, Dr. Prasse successfully applied for two scientific projects in 2015, one of these funded by the German Federal Ministry of Education and Research (BMBF) and the other one by the German Research Foundation (DFG). Starting in January 2016, the BMBF will fund a project in the German Center of Lung Research dedicated to personalized medicine for pulmonary fibrosis in the context of DPLD (diffuse parenchymal lung disease). Furthermore, preliminary assessment of a subproject proposal within a DFG Clinical Research Unit (KFO) aimed at correlating molecular biological analyses with

Pollen count affects atopic dermatitis

What scientists have been discussing for no less than 100 years has now been proven by scientific evidence: the grass pollen count in the air has an impact on atopic dermatitis – leading to considerable deterioration of symptoms in those suffering from this skin disorder. This is the result found by a team of scientists of Fraunhofer ITEM and the Department of Dermatology, Allergology and Venerology of the Hannover Medical School. In the Fraunhofer Allergen Challenge Chamber – the so-called “meadow in the lab” – they exposed volunteers with atopic eczema to grass pollen and found that the test subjects exhibited definite exacerbation of their eczema. The results of this study have been published in the “Journal of Allergy and Clinical Immunology”, the leading journal worldwide in the field of allergy research (JACI 2015; 136: 96-103).

PET/CT imaging has been positive. The aim of this subproject is to develop novel radiotracers for pulmonary fibrosis activity characterization in cooperation with the MHH Department of Nuclear Medicine.

Industry projects have been initiated

The Attract Group furthermore was successful in acquiring industry projects in 2015 already. For example, a framework agreement providing for diverse histochemical testing in lung explants from the biobank has been signed with Boehringer Ingelheim Pharma AG. Planning for another collaborative project with Boehringer Ingelheim, aimed at extracting structures from tissue blocks stored in the biobank by laser capture microscopy, is almost complete. This systematically obtained cell material will then be analyzed by RNA sequencing and will be correlated with clinical parameters. The aim of yet another collaborative project with Daiichi Sankyo is to test



Fraunhofer ITEM scientists have brought the meadow to the lab for clinical studies on allergic diseases. In the pollen challenge chamber, "pollen season" is the whole year, with grass pollen being dispersed under controlled conditions – an ideal setup for scientific studies.

the mode of action of a new drug in primary cell lines and develop a microarray-based readout process for a phase-II clinical trial. In addition, the Attract group successfully acquired a phase-I clinical trial to test a new substance for treating idiopathic pulmonary fibrosis on behalf of Roche.

Overall, the Attract group is looking back on a very successful first year and hopefully will continue to grow with many new projects in the offing.



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Equipment highlights

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

PROJECTS

Allergy in culture – in-vitro allergy model for drug testing

Clinical allergic responses in affected individuals show a broad diversity. The related cellular reactions display alterations in the immune system in the sense of a modified T helper cell response. Fraunhofer ITEM scientists have developed an in-vitro allergy model allowing the immunological response taking place in sensitized subjects to be mimicked in cell culture. To this end, they expose dendritic cells to patient-specific allergens and then co-culture these cells with lymphocytes from the same patient. The direct effect of a novel medication can then be evaluated by means of cellular biomarkers. Use of this model requires good clinical characterization of the allergic blood donor and stimulation of the cells with the individually rele-

vant allergens. In a collaborative project, the model was tested to evaluate the effect of immune-deregulating substances in comparison with well-known immunosuppressants. The effects were analyzed by proliferation measurements, flow cytometric measurement of cell surface markers, and determination of cellular cytokine release into culture supernatant. By using cellular material from well-characterized allergic donors in combination with specific allergen stimulation, this model meets the fundamental requirements for successful testing of novel therapeutic strategies and corresponding substances.



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Studies on the relevance of biomarkers in exhaled breath

Exhaled breath contains volatile organic compounds (VOCs). Their composition could play a role for non-invasive monitoring of respiratory diseases, for example during clinical trials. In 2015, the Fraunhofer ITEM Departments of Clinical Airway Research and of Bio- and Environmental Analytics completed three studies exploring the clinical relevance of VOCs in exhaled breath. In one of the largest studies ever performed on VOCs in exhaled breath of patients with chronic obstructive pulmonary disease (COPD), Fraunhofer ITEM scientists examined a total of 190 patients and healthy volunteers (each group comprising both smokers and non-smokers) from the German cities Hannover and Marburg and detected several VOCs that were specifically altered in COPD patients. In a second study, performed in cooperation with the Hannover

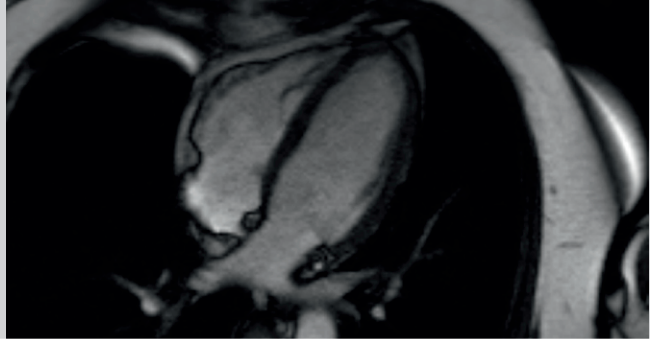
Medical School (MHH), they investigated the correlation between airway inflammation and VOCs in exhaled breath after exposure to ozone and ultrafine particles in 20 healthy volunteers. The time-consuming exposure experiments were completed in September 2015, and analysis of the data is underway. In a third study, again performed in cooperation with the MHH, two measurements each in 54 healthy volunteers were performed to assess the impact of increased physical exercise on the composition of VOCs in exhaled breath. The sophisticated sampling process for this study, taking 14 months in total, has been completed as well, and the data are now being analyzed.



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Magnetic resonance image of the heart. (Image courtesy of Priv.-Doz. Dr. Jens Vogel-Claussen, Hannover Medical School.)



MRI of heart and lung in a COPD study

Thanks to the excellent collaboration with the Institute for Radiology of the Hannover Medical School (MHH), the CRC Hannover offers the possibility to perform studies where a focus of interest is on the examination of organs by magnetic resonance imaging (MRI). One such study is the so-called CLAIM study, aimed at investigating the effects of a bronchodilator therapy on heart function in patients with chronic obstructive pulmonary disease (COPD). It is known that COPD patients frequently suffer from concomitant heart problems. Key to this is the fact that bronchoconstriction leads to hyperinflation of the lung and increased intrathoracic pressure. This results in reduced blood flow back to the heart and impaired heart function. The aim of the CLAIM study is to investigate whether this detrimental chain of events can be interrupted

or improved by treatment with bronchodilator drugs. To this end, 62 patients with COPD are receiving sequential treatment with a combination of two bronchodilators and with placebo. The effects are then evaluated by MRI examination. For comprehensive imaging of heart and lung function, clinically established and innovative methods such as gas-enhanced MRI (see figure) are used and the results are compared with those of well-established methods such as echocardiography, equally performed in close cooperation with the MHH. This study will reveal effects of the administered bronchodilator drugs that go beyond lung function improvement.



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Predictability of the clinical response in the house dust mite challenge chamber

Fraunhofer researchers have recently developed a safe challenge method including production of any kind of allergen particles (e.g. house dust) for use in the Fraunhofer Allergen Challenge Chamber, aimed at inducing symptoms in patients with allergic rhinitis. Symptoms were reproducible in all patients with house dust mite allergy, but showed strong interindividual variability.

To identify possible markers for prediction of an individual's response in the challenge chamber, allergological characterization of 24 house dust mite allergy patients was performed in this research project, using the following test methods: specific immunoglobulin E (Der p1 and Der p2), skin prick test, traditional diagnostic nasal challenge, and intracutaneous test for house dust mite allergy. As resulting variable, the total nasal

symptom score (TNSS), defined as the combined total score of the nasal symptoms congestion, flow, itching, and sneezing, was measured after a 3-hour allergen challenge with house dust in the challenge chamber.

None of the test methods correlated significantly with the TNSS. The best prediction was achieved with a classification model comprising both a blood test for specific IgE (Der p2) and the skin prick test result. These parameters could thus be used to select suitable test subjects for future studies with house dust mite allergen in the challenge chamber.



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BUSINESS UNIT

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 2015

We can be affected by inhalable substances in various ways, for example as users of consumer products, at workplaces, or in the environment. Recently, a major focus in this business unit has been on cabin air quality in aircraft. The below report presents an ongoing project dealing with this subject.

Investigation regarding cabin air quality in aircraft

In the context of health and safety of airline passengers and crew members, air quality inside airplanes has been a subject of debate for over 60 years. The European Aviation Safety Agency (EASA) has commissioned Fraunhofer ITEM and the Hannover Medical School (MHH) with a study to measure and analyze in-flight cabin and cockpit air. Manpower and logistic support for this project is being provided by the companies Lufthansa Technik AG and Condor Flugdienst GmbH. In regard



To characterize the exposure, 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. Physicochemical 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).

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to the number of participating airlines in this project, EASA is planning on an extension in the near future.

Air quality under debate

A distinction has to be made between short-term pollution (as a result of a technical malfunction) and the normal composition of in-flight cabin air, when discussing cabin or cockpit air quality (CAQ) in airplanes. A significant incident affecting in-flight air quality is the leakage of oil fumes from the engines into the cabin and/or cockpit via the bleed air system. Like lubricants, many hydraulic fluids also contain potentially

hazardous substances such as organophosphates, phenyl naphthylamine, and tricresyl phosphate (TCP), which have been associated with health complaints. These health problems are often summarized with little differentiation under the term "aerotoxic syndrome". Incidents referred to as "fume events" do not necessarily have to originate from the engines. Cleaning processes, inflow of outdoor air, passengers etc. can also be sources of contamination leading to "fume events".



Comprehensive analysis of chemical compounds, particles, and aerosols

The origin of a fume event can be manifold and cannot be identified by its odor. It is, therefore, necessary to not only monitor the broad range of possible fume events, but also “normal” in-flight cabin and cockpit air. In order to differentiate between the different air contaminants, the in-flight air is monitored during the different flight phases (take-off, cruise, and landing). In the event of unexpected fume events during a flight, an additional sampling method for volatile organic compounds (VOCs) is in place. The occurrence of an engine-related fume event is considered a very rare and unforeseeable incident and therefore has not been the focus of this study.

Pilot studies as well as comprehensive literature research were conducted prior to the still ongoing measurement campaign, which was initiated in July 2015. The instrumentation currently applied allows detection of VOCs, aldehydes, and organic phosphorous compounds in cabin and cockpit air. In addition to this range of substances, particle and aerosol concentrations are monitored in this campaign. From an analytical chemistry point of view, this measurement campaign, planned by Fraunhofer ITEM and MHH scientists, has proven sufficient to address the issue of the “aerotoxic syndrome”.

Alternative test system for sprays with surface-active substances

Sprays with surface-active substances are widely used for restoration of hydrophobic effects and water-repellent impregnation. Assessment of the acute toxic potential after inhalation of new surface-active agents in waterproofing consumer sprays is performed in vivo according to OECD TG 403. Fraunhofer ITEM scientists investigated the isolated perfused rat lung (IPRL) as a possible alternative test system. To this end, IPRLs were exposed to an aerosolized formulation of a “liquid stain protection product” that has been found to cause respiratory disorders in humans. Clinical signs varied from heavy coughing, dyspnea, and breathless-

Extension of the study is planned

As part of a currently extended study, up to 70 in-flight measurement campaigns have been scheduled within a time window of six to eight months. Almost half of the 70 flights were already conducted in 2015. Future investigations will also include the monitoring of in-flight air in aircraft without bleed-air system. The results will subsequently be evaluated against data sets previously compiled from measurement campaigns in airplanes and other routine air analyses (e.g. in workplaces,

Side view of an open measurement kit with pumps and feed pipes, as mounted in a Boeing 767 (Condor) airliner (left). Measurement kit mounted in an Airbus 321 (Condor), equipped with different sampling systems (middle). Measurement kit of the same type with additional particle detector in an Airbus 321 (Condor) cockpit (right).

ness to pneumonitis and lung edema. These findings are consistent with the results of the IPRL exposure to matured aerosols generated from the liquid spray formulation. Online monitoring of respiratory parameters such as tidal volume, compliance, resistance, lung weight, and partial pressures showed severe lung injury even at very low doses of the active ingredient. Thus, the IPRL model is well suited to screen formulations for acute “physical” inhalation toxicity and can thus contribute to reducing in-vivo trials in animals.



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indoor air, outdoor air). The insights gained in this study will be used to design another comprehensive study on cabin air quality in airplanes, focusing on the impact of technical problems in the air supply system and in-flight air quality.



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Equipment highlights

- State-of-the-art analytical methods: LC-NMR, LC-MS, ICP-MS (non-target analyses, residue and trace-level analyses, bio-availability)
- Aerosol measurement technology, aerosol generation methods (nebulization, dry dispersion)
- Scanning electron microscope with energy-dispersive X-ray system for elementary analyses
- Determination of exposure from spray products
- Battery test rig for accident simulation and quantification of energy release and gas and particle emissions
- Model rooms for exposure characterization

PROJECTS



Integrated testing strategies for airborne cosmetic ingredients

Cosmetic products are used as leave-on or rinse-off products, in either case leading to direct exposure of the human body. Commonly, the products are evaluated to be safe for the intended use. Nevertheless, chemical changes are possible under extreme or very specific application conditions (e.g. hot showering, hot hair drying), leading to possible health risks especially with respect to inhalation during use.

Fraunhofer ITEM scientists support industry and professional users in the development of specific safety assessment concepts for such products. To this end, a comprehensive characterization of inhalation exposure is carried out, including droplet

size analysis and consideration of the aged/matured aerosol from spray products as well as identification and analysis of by-products. For the performance of valid in-vitro testing of possibly toxic substances or mixtures, the relevant exposure atmospheres can be applied to cell- and tissue-based models by using the P.R.I.T.[®] air-liquid exposure technique. In addition, in-silico approaches, such as read-across, are applied. Finally, considering all available data, Fraunhofer ITEM scientists perform risk assessment tailored to the specific problem.



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Sunscreen spray products containing nanoparticles: exposure characterization

Risk assessment of nano-sized materials is currently an important issue in safety assessment of chemicals and products. Nanomaterials such as titanium dioxide and zinc oxide are used as UV filters in sunscreens. For spray products, the amount of aerosol able to reach the lower respiratory tract is of major relevance from the toxicological point of view. Furthermore, the number of nanoparticles released during spray application is of interest. Conventional methods for determination of potential aerosol exposure are of limited suitability here. Fraunhofer ITEM scientists, therefore, have developed a method that allows determination of aerosol release, or directly of titanium dioxide or zinc oxide release in the size fractions relevant for inhalation exposure assess-

ment. This method is based on mass balance analysis of the non-volatile aerosols or nanomaterials generated in the respirable and thoracic size ranges under realistic conditions of spray application. Furthermore, it allows sunscreen spray products to be characterized in view of the number of particles generated in the nano-range ($< 0.1 \mu\text{m}$). Providing the basis for exposure calculations with established exposure models, this development supports safety assessment of sunscreen products. The method could also be used for exposure characterization of any aerosolized products and applications containing nanomaterials.



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The use of cosmetic spray products can result in generation of inhalable aerosols. Fraunhofer ITEM scientists support industry and professional users in the development of specific safety assessment concepts for sprays and other cosmetic products.

Isocyanates in the workplace

Isocyanates are chemical compounds containing NCO groups, which can lead to acute airway irritation and sensitization. Diphenylmethane diisocyanate (MDI) in monomer or polymer form serves as a base material used in large quantities for production of flexible and rigid foams, surface coatings etc. These products are manufactured through stoichiometric transformation with polyols, namely through a polyaddition reaction of the isocyanates' NCO groups with the polyols' OH groups. Spraying techniques, among others, are frequently used for this, for example, for wall insulation, all-weather roof coating, and to protect surfaces against mechanical stresses. In application-specific, well-controlled processes, the isocyanates and polyols are brought together and mixed under high pressure in a mixing and spray head and are subsequently sprayed onto

the surface to be treated. Occupational safety and environmental protection require the release of unbound MDI from the overspray cloud to be minimized. To characterize the aerosol formation, two typical spraying processes were analyzed in an application center of a leading manufacturer of polyurethane products. Using a universally applicable method developed at Fraunhofer ITEM, the mass fractions of inhalable and respirable aerosol in relation to the total amount of released spray product were measured and the content of unbound MDI was determined.



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Reference aerosol generator for ultrafine particles

The number concentration of suspended ultrafine aerosol particles in outdoor air, at workplaces or in exhaust gas is a parameter of increasing importance in toxicological and regulatory contexts. A broad range of methods is available for continuous measurement of number concentration and number size distribution, including condensation nucleus counters, optical particle spectrometers, and electric mobility spectrometers. Depending on the specific requirements, these have to be operated in combination with complex systems to condition the sample air, such as dilution systems. Like any other complex measurement system, these require periodic checks for correct functioning and also calibration. Over the past few years, Fraunhofer ITEM scientists have developed a simple method for these purposes, enabling reproducible generation

of ultrafine test aerosols with predictable properties, in particular with a defined number concentration. The physical basis of this method is coagulation of condensed, supersaturated vapor of a non-toxic, low-volatile, organic substance. This aerosol physical process allows the resulting aerosol parameters to be related to simple parameters such as temperature inside the vaporizer and aerosol flow rate through the device, in addition to the duration of the coagulation process. Several devices manufactured at Fraunhofer ITEM are being tested at present in a French reference laboratory and by a manufacturer of aerosol measurement systems.



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BUSINESS UNIT 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 2015

Integrated testing strategies – their use and further development – again were a focus in the Business Unit “Registration and Risk Assessment” in 2015. A field of activity in this context are trainings and workshops to support companies with regard to testing strategies, risk assessment, and authorization in connection with animal-free assessment of substances under REACH. The report below presents a few examples.

Animal-free assessment under REACH

The European chemicals policy stipulates the use of alternative methods for risk assessment in a variety of regulatory contexts, for example under REACH Annex XI. The aim of taking into account in-silico methods such as read-across and quantitative structure-activity relationships (QSAR) is to optimize the use of existing knowledge and minimize the need for animal experiments. On behalf of the German Federal Environment Agency (Umweltbundesamt, UBA in short), Fraunhofer ITEM is organizing three international expert workshops dedicated to the topic of QSAR and read-across. The aim of the UBA-funded



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 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.

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projects is to promote the use of these in-silico methods and improve the quality of registration dossiers. Fraunhofer ITEM is organizing these workshops together with EurA Consult AG and is accompanying the whole process, providing information material, documenting the results of discussions, and preparing a practical guidance document.

Use of computerized calculations such as quantitative structure-activity relationships

The aim of the UBA research project “Support for the use of computerized calculations such as quantitative structure-activity relationships (QSAR methods) to reduce animal experiments

under REACH” is to support small and medium-sized enterprises in the use of QSAR methods for substance registration. QSAR models describe relationships between a chemical structure and a biological activity for a data set of chemicals and can be used to predict the activity of new substances that have not yet been tested.

A first professional workshop with experts from academia, industry, and representatives of regulatory authorities was held at UBA in Dessau, Germany, in June 2015. It was organized based on the results of a questionnaire. The aim of this workshop was to analyze the participants’ experience, wishes, and problems in connection with the use of QSAR models under

REACH, with a focus on QSAR models for predicting the (eco-) toxicity of chemicals under REACH. It became apparent that the main reason for not using QSAR models is not a lack of available models, but rather a lack of acceptance. The following requirements whose fulfillment would contribute to a broader acceptance of QSAR methods were identified in the course of the workshop:

- Create guidance documents with examples supporting preparation of registration dossiers in compliance with regulatory requirements and providing guidance, for example, on dealing with uncertainties.
- Analyze existing databases to get a broader basis of high-quality data for use with the available models, so as to improve regulatory acceptance.

- Use QSAR not in an isolated manner, but in conjunction with other in-silico methods.
- Try to implement an improved, qualified professional training, both for the users of QSAR methods and the staff of regulatory authorities.

The above described workshop will be followed by a second workshop built upon the first one. It is scheduled to take place in June 2016. The target group of the second workshop are mainly representatives from small and medium-sized enterprises involved in the implementation of the REACH regulations. The workshop will provide information about the applicability of QSAR and will offer the opportunity to discuss special requirements of small enterprises with the regulatory authorities and consultants with regard to the last registration phase in May 2018.

Initiative for regulatory drug research and development

Bringing together the best of both worlds, Fraunhofer ITEM has launched a cross-functional initiative to combine its excellence in laboratory-based and clinical research with its chemical regulatory expertise. With this effective combination, the institute is uniquely positioned to support clients also in regulatory affairs of pharmaceutical development. Our scientists research, develop, and validate new approaches to manufacture, characterize, and test innovative medicinal products, ensure regulatory acceptance of these approaches, and implement them in product development in conjunction with the client.



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Further development and application of read-across

Another UBA-funded research project is aimed at promoting the use of read-across by different players under REACH. A read-across approach means that the relevant data of “similar” substances (source substances) are used to extrapolate the toxicity of a substance which has not yet been tested (target substance). Predictions can be made on a 1:1 (analogue approach) or N:1 basis (category approach). The similarity hypothesis in most cases is based on an analysis of chemical and biological similarity of the source and target substances. Statistical analysis of the submitted REACH dossiers has shown that read-across is currently the in-silico method used most frequently to avoid animal experiments.

Based on the results of a literature search and of a survey on the experience gained with read-across by representatives from academia and industry, an expert workshop with a focus on ecotoxicological endpoints will be organized by Fraunhofer ITEM. Besides discussion of recent developments and methodological approaches, it is planned to address in particular the



Optimal use of existing knowledge to assess novel substances: in-silico methods such as read-across and quantitative structure-activity relationships play a key role in this effort.

Toxicity testing for the 21st century

Fraunhofer ITEM has joined the project EU-ToxRisk, an international consortium of 39 partners. The consortium will work on the integration of new concepts into regulatory chemical safety assessment. The new concepts involve human-relevant, non-animal in-vitro methods and in-silico computational tools to provide the basis of a mechanism-based toxicity testing, e.g. the use of adverse outcome pathways.

EU-ToxRisk is focused on systemic toxicity after repeated exposure in four key targets: liver, kidney, lung, and neurotoxicity. Furthermore, a better mechanistic understanding of developmental and reproductive toxicity will be developed. This aim will be achieved by testing four different types of case studies, starting with data-rich read-across (RAX) groups. Fraunhofer ITEM will contribute to the selection of the RAX groups by

analyzing in-vivo data from the Fraunhofer databases RepDose (repeated-dose toxicity) and FeDTex (reproductive toxicity). The institute will also contribute to physiologically based toxicokinetic (PBTK) models, for example by developing a PBTK database and in-vitro measurement of relevant data. Fraunhofer experts will furthermore explore the integration of data from human precision-cut lung/liver slices (PCLS). PCLS will help to bridge the gap between in-vitro systems and in-vivo studies. Finally, Fraunhofer toxicologists will guide the integration of "novel" data, e.g. fit-for-purpose testing batteries, into a pragmatic risk assessment framework that is in line with regulatory needs.



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possibilities of standardizing the read-across approach and harmonizing the documentation in registration dossiers. The workshop will offer a platform for sharing experiences between stakeholders from academia, industry, and the authorities. In addition, it is aimed at preparing a best-practice guidance document for ecotoxicological endpoints.



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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

REACH – Bundeswehr’s use of hazardous substances

In the course of implementing REACH, the authorities are identifying substances of potential concern, whose use could pose an unacceptable risk to human health or the environment. As a result, there is a constant increase in the number of substances requiring authorization. The aim being to substitute substances of high concern by less harmful materials in order to improve occupational, consumer and environmental protection, such hazardous chemicals will be banned from the market after a date fixed by the European Chemicals Agency ECHA. Wherever substitution by a technically equivalent substance is not feasible for a specific application, the manufacturer is required to demonstrate in a comprehensive authorization process, taking several years in most cases, how the substance in question can be safely used for the particular application. The outcome of this authorization process is not known in advance,

the decision is up to the EU and will be based on an assessment made by ECHA and national authorities. For substances that cannot be substituted and whose continued use is imperative in the interest of national defense, applications can be filed with the respective EU Member States and the decision is then at their discretion. Bundeswehr suppliers can file applications with the German Federal Office of Bundeswehr Equipment, Information Technology and In-Service Support, whose working group IPT-REACH, established especially for this purpose, will deal with these applications and finally submit them for decision to the German Federal Ministry of Defense. Since 2014, Fraunhofer ITEM has been actively participating in this group, where it is responsible for substance- and application-specific safety assessment according to REACH.



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Biocides: BPR article 95 listing – important deadline in 2015

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. In 2015, an important deadline had to be met: as of September 1, 2015, biocidal products are only allowed on the EU market, if the supplier of either the biocidal product or the relevant active substance in the corresponding product type is included in a list of approved suppliers. Consequently, the supplier of an active substance or a biocidal product is required to hold a dossier himself or have a letter of access (LoA) to a dossier from the data owner. The objective of article 95 of the Biocidal Products Regulation is to ensure that the

costs of generating data and supporting active substances are shared fairly. The article 95 list will be updated regularly by ECHA.

Fraunhofer ITEM supports its clients in either preparing their own dossiers for article 95 submission to ECHA or in negotiations to receive a letter of access to an already submitted dossier from the data owner. Furthermore, Fraunhofer ITEM advises its clients in borderline issues, e.g. the listing of in-situ generated substances and the listing of a manufacturer in the supply chain.



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Evaluation of substances contained in e-waste

In recent years, the hazard and risk from inappropriate disposal of electronic waste has come more and more into the focus. E-waste may contain potentially harmful substances, and information on their long-term impact is needed as well as corresponding management strategies. Due to transportation, the exponentially growing amount of waste from electrical and electronic equipment has become a worldwide pollution problem. Following the adoption of Directive 2011/65/EU (RoHS 2), requesting the European Commission to develop a science-based methodology for assessment of future substances, the Austrian Environment Agency published the final manual on the requested methodology in January 2014. On behalf of an industry client, Fraunhofer ITEM in cooperation with Fraunhofer IPA prepared a report on a flame retardant

according to this methodology manual and evaluated data gaps and uncertainties. In this evaluation, the properties of the substance that present a hazard to human health and the environment were gathered, and an exposure assessment for waste treatment was conducted based on established assumptions and models as used for the assessment of other substances under RoHS. The methodology manual furthermore recommends that consideration be given to substitutes of the emerging substances and that a socio-economic analysis be performed. Overall, the evaluation of this substance based on the currently available information led to the conclusion that a restriction under RoHS 2 is not necessary.



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Risk assessment of carcinogenic substances

In accordance with the 2005 amendment of the Hazardous Substances Ordinance, the German Committee on Hazardous Substances (AGS) has developed a concept for assessing the risk associated with the exposure to carcinogenic substances. It includes the definition of substance-independent risk limits: an acceptable risk below which there is only a low, acceptable risk of cancer and above which a medium risk – to be controlled by defined measures – is tolerated. For a transition period, this risk has been set at 4:10,000 and shall be reduced to 4:100,000 by 2018 at the latest. The tolerable risk has been set at 4:1000. Exposures above this value pose a high risk that is considered non-tolerable. The risks refer to a working life of 40 years with continuous workplace exposure. Derivation of exposure-risk relationships (ERR) allows substance-specific

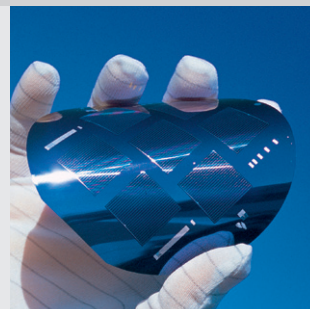
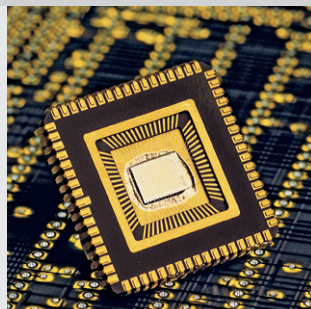
levels to be determined for the acceptable and tolerable risks. These ERR are finally published by the German Federal Ministry of Labor and Social Affairs in its Announcement on Hazardous Substances 910. By May 2015, such values were available for 17 substances. Proposals for further substances are currently being discussed by the AGS. Fraunhofer ITEM scientists so far have analyzed the comprehensive toxicological data for two substances and have prepared reports on the derivation of ERR for these substances. These reports will be presented and discussed in a meeting of Subcommittee III of the AGS and will subsequently serve as basis for ERR justification.



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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 nearly 24,000 staff are qualified scientists and engineers, who work with an annual research budget of more than 2.1 billion euros. Of this sum, more than 1.8 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.

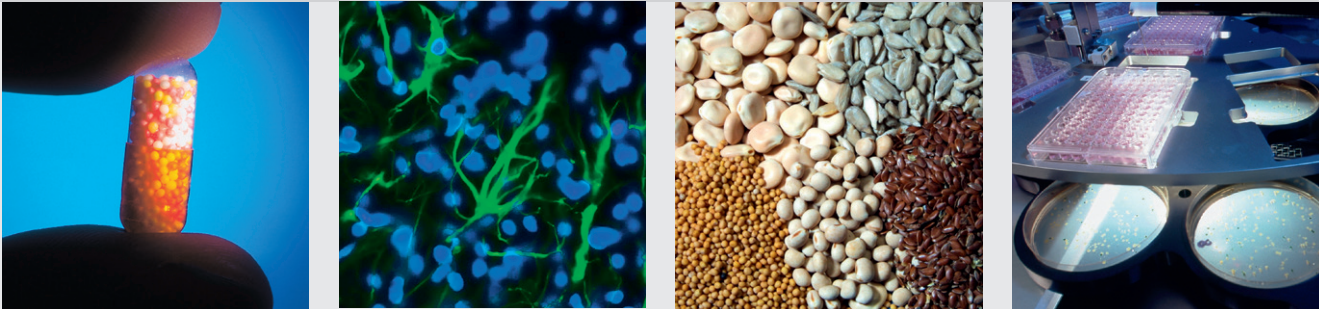
With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits 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.

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FRAUNHOFER GROUP FOR LIFE SCIENCES



Six Fraunhofer Institutes and a Fraunhofer research institution have pooled their complementary areas of expertise in the life sciences and potentiate 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 food and chemicals industries 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 complex and cross-disciplinary 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 orientation to application. The aim is to develop innovative solutions that meet clients' actual requirements. Translational research – the translation of research results into practical applications – is the Group's everyday business, due to its closeness to universities and other research

institutions on the one hand and to companies, hospitals, and users on the other hand. In addition, the Fraunhofer Institutes also undertake basic research to develop the basis for future applications in industry. The Group has an international outlook that reflects the globalized nature of this scientific field and the related commercial market.

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 health-care and for remediating the environment.

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NAMES, DATES, EVENTS

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Doctorates

Hackbarth, Anja
Biologische Wirkungen synthetisch hergestellter Multiwall-Carbon-Nanotubes am Tiermodell und in der Zellkultur.
University of Veterinary Medicine Hannover, Foundation, 2015

Janßen, Ole
Niedrig dosierte inhalative Endotoxin-Provokation bei gesunden Probanden als Modell in der klinischen Atemwegsforschung.
Hannover Medical School, 2015

Master's theses

Schröder, Simon
Generierung einer Produktionsplattform zur Herstellung von APIs.
Technische Universität Braunschweig, 2015

Bachelor's theses

Kale, Mehmet
Wachstumslimitierende Faktoren für *E. coli* in Schüttelkultur.
Technische Universität Braunschweig, 2015

Knickmeier, Saskia
In-vitro-Untersuchungen zur Wirkung von nanostrukturiertem Carbon Black an Lungenepithelzellen.
Hamburg University of Applied Sciences, 2015

Invited lectures

Dr. Luma Baydoun
Neue Biopharmazeutika: von der Idee zum Prüfartzneimittel. Etablierung einer aseptischen Abfüllung für Kleinstchargen am ITEM.
Symposium of the German Pharmaceutical Association, Section of drug control and pharmaceutical analytics "Arzneimittelkontrolle/Pharmazeutische Analytik", section meeting 2015 "Maßgeschneiderte Proteine als Arzneimittel"
Braunschweig (Germany)
March 11, 2015

Dr. Annette Bitsch
Biozide.
FARBEUNDLACK Seminar
Kassel (Germany)
February 25, 2015

Understanding biocides and the latest regulation: Pre-congress Tutorial.
European Coatings Congress
Nürnberg (Germany)
April 19, 2015

E-Zigarette: ein Verdampfer mit Fluch und Segen?
University of Würzburg, Institute of Pharmacology and Toxicology, Department of Toxicology
Würzburg (Germany)
July 14, 2015

Regulation von Bioziden.
DGPT course "Regulatory Toxicology" at the Governmental Institute of Public Health of Lower Saxony (NLGA)
Hannover (Germany)
August 31 – September 4, 2015

How to perform toxicological risk assessment.
Mapping Workshop "Fume and Smell Events" (FuSE), German national aeronautics and space research center (DLR)
Cologne (Germany)
November 5-6, 2015

Prof. Dr. Armin Braun
A toxicological view on therapeutic antibodies.
81st Annual Conference of the German Society of Experimental and Clinical Pharmacology and Toxicology (DGPT), Symposium "Advances in Antibody Therapy"
Kiel (Germany)
March 10-12, 2015

Integrierte Teststrategien – von der Zelle zum Primaten.
56th Congress of the German Respiratory Society, Symposium "Raus aus der 'Mausefalle' – präklinische pneumologische Forschung der nächsten Generation"
Berlin (Germany)
March 18-21, 2015

Evaluation of biological mechanisms in lung toxicity using precision-cut lung slice technology.
IVTIP Spring Meeting 2015, AOPs in Developmental and Lung Toxicity – an in-vitro route to mechanistic understanding and AOP-based testing
Copenhagen (Denmark)
May 28-29, 2015

Modellierung von Asthma im Mausmodell und mögliche Alternativen.
111th Annual Conference of the German Society of Pediatrics and Adolescent Medicine (DGKJ)
Munich (Germany)
September 2-5, 2015

Dendritic cell-nerve interaction in allergic airway inflammation.
XXIV World Allergy Congress (WAC 2015)
Seoul (South Korea)
October 14-17, 2015

Precision-cut lung slices for inhalation toxicology.
IVTS 2015
Birmingham (UK)
November 10-11, 2015

Biologische Effekte von Medizinprodukten auf Gewebe mit In-vitro- und Ex-vivo-Methoden/In-vivo-Tiermodelle.
Symposium on "functional implants and implant surfaces"
Bremen (Germany)
December 2-3, 2015

Dr. Jochen Buschmann
From experiments to labeling – the European reproductive toxicology perspective.
RIFM Expert Panel Meeting
Cannes (France)
September 15-16, 2015

Dr. Otto Creutzenberg

Inhalation toxicology.
1st Joint Symposium on Nanotechnology
Nanomaterials and Nanoparticles: Application, Research and Regulation – Risk Assessment and Risk Communication
Berlin (Germany)
March 6, 2015

Inhalation toxicity testing of nanopowders.
Workshop on Nanosafety and Nanotoxicology (NanoSaTox)
Hannover (Germany)
October 27, 2015

Dr. Ilona Fleischhauer

Introduction to the principles of GLP.
Laboratory Animal Course on Primates, German Primate Center
Göttingen (Germany)
November 25, 2015

Introduction to GLP and GMP.
Training course at the Hannover Biomedical Research School (HBRS)
Hannover (Germany)
December 9, 2015

Principles of quality management – which manifestations exist?
TRAIN Academy
Hannover (Germany)
December 10, 2015

Anke Friede

Qualitätssicherung in der klinischen Prüfung: Audits.
Lecture in the training course “Qualifikation zum Prüfarzt/Prüfärztin bzw. Assistenz in klinischen Studien” (GCP basic class), Hannover Medical School
Hannover (Germany)
June 26 and December 11, 2015

Dr. Stefan Hahn

Environmental Risk Assessment of veterinary hygiene products (PT3).
4th International Fresenius Conference “Environmental Risk Assessment of Biocides”
Cologne (Germany)
October 21-22, 2015

Overview of use of OECD 308 and 309 in different regulations.
Scientific workshop “Identifying limitations of the OECD water-sediment test (OECD 308) and developing suitable alternatives to assess persistence”, ECETOC/CEFIC LRI
Dübendorf (Switzerland)
October 6, 2015

Prof. Dr. Dr. Uwe Heinrich

Staubbedingte Erkrankungen – Prävention durch wirkungsmechanistische Erkenntnisse.
55th Scientific Annual Conference of the German Society of Occupational and Environmental Medicine (DGAUM)
Munich (Germany)
March 18-20, 2015

Prof. Dr. Jens Hohlfeld

Allergische Rhinitis – Wirksamkeitsprüfung neuer Medikamente im Allergen-provokationsraum.
Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine Hannover, Foundation
Hannover (Germany)
January 14, 2015

Klinische Studien mit luftgetragenen Stoffen.
Lecture in the German chemical society's (GDCh) training course “Introduction to toxicology for chemists”
Hannover (Germany)
June 17, 2015

Environmental challenge chamber – efficacy testing and more.
Symposium on Adjuvants in Allergy, Bencard/Allergy Therapeutics
Amsterdam (The Netherlands)
July 2-4, 2015

Dr. Stefan Kirsch

Combined high-resolution single-cell genome and transcriptome analysis for clinical samples.
7th Annual Next Generation Sequencing Congress & 3rd Annual Single Cell Analysis Congress & Genome Editing Congress 2015
London (UK)
November 12-13, 2015

High-resolution analyses of genome and transcriptome of single disseminated tumor cells.
5th Munich Biomarker Conference 2015
Munich (Germany)
December 1-2, 2015

Prof. Dr. Christoph Klein

Molecular characterization of single disseminated and circulating tumor cells.
18th International AEK Cancer Congress 2015
Heidelberg (Germany)
March 18–20, 2015

The dynamics of early systemic cancer: Consequences for the development of adjuvant cancer therapies.
11th International Symposium in Translational Oncology
Barcelona (Spain)
May 7-8, 2015

Early dissemination and metastasis in breast cancer.
6th International Conference on Tumor Microenvironment and Angiogenesis
Monte Verità (Switzerland)
May 17-20, 2015

Genetic alterations driving metastatic colony formation are acquired outside the primary tumor in patients with melanoma.
Second Annual DEPAArray User Meeting
Bologna (Italy)
November 10-11, 2015

The dynamics of early cancer progression: consequences for the prevention of metastasis.
7th AuF Symposium
Dresden (Germany)
November 19-21, 2015

Prof. Dr. Wolfgang Koch

Light scattering technology and application in ambient air quality monitoring.
Group Seminar, China National Environmental Monitoring Center
Beijing (China)
February 5, 2015

Anwendungsbezogene Charakterisierung ultrafeiner Partikel.
TSI Seminar “Nanoparticle Sizing”, Paderborn University
Paderborn (Germany)
September 29, 2015

Dr. Gustav Könnecker

Erfahrungen aus 10 Jahren REACH – Handlungsempfehlungen für kleine und mittlere Unternehmen.
REACH Experience Sharing Meeting, German Association of the Chemical Industry (VCI e.V.), Regional Association North
Laatzen (Germany)
September 16, 2015

Stoffregistrierung – Von der Datenlückenanalyse bis zur erfolgreichen REACH-Registrierung.
REACH – eine Herausforderung für die Wehrtechnik. Seminar WW 1.06, Carl-Cranz-Gesellschaft e.V., Fraunhofer Institute for Chemical Technology ICT Pfinztal/Karlsruhe (Germany)
September 29-30, 2015

Prof. Dr. Norbert Krug

Allergen-induced asthma responses modified by a GATA-3-specific DNase.
10th German Allergy Congress “Gemeinsam gegen Allergien – für mehr Toleranz”
Cologne (Germany)
October 1-3, 2015

Exacerbations of obstructive lung disease.
International Congress 2015 of the European Respiratory Society, postgraduate course “PG2 Asthma and COPD. Updates in assessment and treatment.”
Amsterdam (The Netherlands)
September 26, 2015

Dr. Oliver Licht

TRGS 910 – Risikobezogenes Maßnahmenkonzept für Tätigkeiten mit krebserzeugenden Gefahrstoffen und praktische Beispiele für Exposition-Risiko-Beziehungen.
Symposium on the handling of chemicals “Umgang mit Chemikalien”, Bundeswehr Educational Center (BiZBw)
Mannheim (Germany)
November 3-5, 2015

Toxikologische Datenanforderungen unter REACH.
REACH – eine Herausforderung für die Wehrtechnik. Seminar WW 1.06, Carl-Cranz-Gesellschaft e.V., Fraunhofer Institute for Chemical Technology ICT Pfinztal/Karlsruhe
September 29-30, 2015

Stoffbewertung und Risikoabschätzung.
DGPT course “Regulatory Toxicology” at the Governmental Institute of Public Health of Lower Saxony (NLGA)
Hannover (Germany)
August 31 – September 4, 2015

Dr. Ute Pägelow

Introduction to GLP and GMP.
Training course at the Hannover Biomedical Research School (HBRS)
Hannover (Germany)
December 9, 2015

Dr. Neophytos Papamichael

Introduction to GLP and GMP.
Training course at the Hannover Biomedical Research School (HBRS)
Hannover (Germany)
December 9, 2015

Dr. Bernhard Polzer

Molecular analysis of single circulating tumor cells: opportunities and challenges for personalized medicine.
FP7 EUROCAN Workshop
Oslo (Norway)
May 18, 2015

Molecular profiling of single circulating tumor cells.
GTCbio Conference "Cancer Markers and Liquid Biopsy"
San Diego, California (USA)
June 11, 2015

Molecular profiling of single circulating tumor cells.
Workshop "Image-based, semi-conductive cell sorting: analysis of CTCs and heterogeneity"
Regensburg (Germany)
July 6, 2015

Clinical aspects of CTC single-cell analysis.
1st DCC-Net-Retreat
Düsseldorf (Germany)
August 13, 2015

Dr. Florian Schulz

Toxikologische Wirkmechanismen und Grenzwertableitungen von Metallen.
31. Münchner Gefahrstoff- und Sicherheits-Tage
Munich (Germany)
November 25-27, 2015

Dr. Katherina Sewald

Neuro-immune mechanisms in viral lung infections.
LISA summer academy
Hannover (Germany)
August 20, 2015

Use of ex vivo organotypic lung tissue in translational research of respiratory injury and inflammation diseases.
EUSAAT 2015 – 16th Annual Congress of the European Society for Alternatives to Animal Testing
Linz (Austria)
September 22, 2015

Dr. Henning Weigt

Principles of quality management – risk management, audits, deviation and change management.
TRAIN Academy
Hannover (Germany)
December 10, 2015

Dr. Axel Wibbertmann

SteriHealth®: Senkung des Infektionspotenzials durch effiziente Vor-Ort-Sterilisation.
Fraunhofer internal networking symposium "Netzwerk" 2015.
Munich (Germany)
January 27, 2015

Dr. Christina Ziemann

Gentoxikologische Testung und Bewertung von Nanomaterialien – eine Herausforderung.
Meeting of the Fraunhofer Nanotechnology Alliance (FNT)
Aachen (Germany)
November 24, 2015

Active participation in committees

Dr. Luma Baydoun

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

Dr. Annette Bitsch

German Federal Institute for Risk Assessment (BfR) Committee for Food Additives, Flavorings and Processing Aids

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

Expert panel 110 on cooling lubricants "Kühlschmierstoffe" of the Association of German Engineers (VDI) Technical Division 1 "Production Technology and Manufacturing Methods"

Reviewer for international journals published by Elsevier (incl. "Regulatory Toxicology and Pharmacology")

Dr. Katharina Blümlein

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

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")

External assessor 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)

ECHA expert group on the Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a, Section R.7.6 "Reproductive Toxicity"

Dr. Otto Creutzenberg

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

Prof. Dr. Clemens Dasenbrock

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

Editorial board of the journal "Experimental and Toxicologic Pathology"

Scientific Expert Group (SEG) of the International Commission on Non-Ionizing Radiation Protection (ICNIRP)

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. Sylvia Escher

Threshold of Toxicological Concern Task Force, ILSI Europe (co-chair)

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 of the German Chemical Society (GDCh) division of environmental chemistry and ecotoxicology "Umweltchemie und Ökotoxikologie"

Prof. Dr. Dr. Uwe Heinrich

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

Invited member of the IARC 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 group on the definition of threshold limit values for dusts; working group on the definition of occupational exposure limits; working group on the classification of carcinogens; ad-hoc working group on heavy metals

Committee on Hazardous Substances (AGS) under the German Federal Minister of Labor and Social Affairs; AGS Subcommittee III (UA III); Subcommittee III: working groups on metals (chairman) and on fibers/dust

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)

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

Prof. Dr. Jens Hohlfeld

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

External expert for the German Research Foundation (DFG)

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

Dr. Heinz-Gerd Hoymann

Working group of German safety pharmacologists

Michéla Kaisler

Working group on archiving "Archivierung" of the German Society for Good Research Practice (DGGF)

Dr. Rupert Kellner

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

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

Prof. Dr. Christoph Klein

External assessor for "Lichtenberg Professorships" of the Volkswagen Foundation

External expert for the German Research Foundation (DFG)

Reviewer for international journals in oncology

Prof. Dr. Wolfgang Koch

Reviewer for international journals in aerosol physics and aerosol technology (incl. "Journal of Aerosol Science", "Aerosol Science and Technology" and "Annals of Occupational Hygiene")

Dr. Gustav Könnecker

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

Integrated REACH project team, German Federal Office of Bundeswehr Equipment, Information Technology and In-Service Support

Prof. Dr. Norbert Krug

External expert for the German Research Foundation (DFG)

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

Board member of the interdisciplinary allergy center of the Hannover Medical School

Chair of the Clinical Trial Board of the German Center for Lung Research (DZL)

Steering committee 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

German Federal Institute for Risk Assessment (BfR) Committee for Contaminants and other Undesirable Substances in the Food Chain; chair of the panel on per- and polyfluorinated alkyl substances "Per- und Polyfluoralkylsubstanzen (PFAS)"

Expert panel "Basic module and perfluorinated tensides" of the German Federal Institute for Risk Assessment's MEAL (= meals for exposure assessment and analysis of foods) study within the Total Diet Study (TDS) in Germany

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

Dr. Norbert Lütke

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

Fraunhofer quality management network

Dr. Bernhard Polzer

Reviewer for international journals in pathology and oncology ("British Journal of Cancer", "International Journal of Cancer", and "Journal of Histochemistry and Cytochemistry")

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

"Guess What" committee 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)

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

Reviewer for the international journal "Toxicologic Pathology"

Dr. Anton Roß

Member of the advisory committee for the DECHEMA/GVC division of bioprocess engineering

Dirk Schaudien, Ph.D.

INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) working group "Non-rodents: minipig"

"Pathology 2.0" committee of the European Society of Toxicologic Pathology (ESTP)

"Webinar" committee of the International Federation of Societies of Toxicologic Pathology (IFSTP)

Dr. Sven Schuchardt

GBM – Society for Biochemistry and Molecular Biology

Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V. (Leibniz Institute for Analytical Sciences)

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

Dr. Katherina Sewald

Reviewer for the international journals "Toxicology Letters", "Toxicology in Vitro", "Nanotoxicology", and "ATOX"

External assessor for international research grants

Steering group of the workshop "Respiratory Toxicity"

Steering group of the workshop "Translational Aspects of in vitro and in vivo Models for Inflammatory Diseases"

Dr. Holger Ziehr

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

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

Center for Pharmaceutical Process Engineering (PVZ) at Technische Universität Braunschweig

BioPharma-Translationsinstitut e. V.

Dr. Christina Ziemann

Working group "Genotoxicity" of the DIN Water Practice Standards Committee

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

Research projects

National

Chemie Wirtschaftsförderungs-GmbH

Collection of information for refinement of the environmental emission scenario for metalworking fluids (PT13) under the EU Biocide Regulation

DFG – German Research Foundation

Experimental exposure to air pollutants and sympathetic nerve activity in human subjects

Surfactant inactivation, alveolar collapsibility and their role in the progression to pulmonary fibrosis in animal models of lung injury and fibrosis

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

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

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

Support for the use of computerized calculations such as quantitative structure-activity relationships (QSAR methods) to reduce animal experiments under REACH. R&D project 3714 67 413 0

Basic toxicological data for derivation of EU-LCI values for 5 substances from construction products. R&D project 3715 61 288 0

Time extrapolation of the effect of local irritants after inhalation exposure. R&D project 40191

Integrated assessment of mercury based on the data collected by the German Environmental Specimen Bank (UPB). Project number 32 842

Human biomonitoring of “novel” substances: substance dossier for Lysmeral – derivation of toxicological assessment values for human biomonitoring. Project number 58 759

Human biomonitoring of “novel” substances: substance dossier for 2,6-di-tert-butyl-4-methylphenol – derivation of toxicological assessment values for human biomonitoring. Project number 59 000

Federal Institute for Occupational Safety and Health (BAuA)

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

Histopathological examination of samples from a long-term inhalation study. Research project F 2325

Method for the identification of granular biopersistent dusts at workplaces. Research project F 2336

Comparison of inhalation and instillation as testing methods for characterization of granular biopersistent particles (GBP). Research project F 2364

Comparative research on measurement methods for quantification of the protective effect of personal protective equipment against dermal exposure. Investigation no. 517753

Federal Institute for Risk Assessment (BfR)

Further scientific development of the DevTox project and Website translation into Chinese

Federal Ministry for Economic Affairs and Energy

Central Innovation Program for SMEs (ZIM), subproject on the service life of implants under the project “Flexible Individualized Active Medical Implants – 3D Printing of Silicone Rubber Connectors and Electrodes (FINAMI)”

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: InhaIT90

90-day inhalation testing with CeO₂ in the rat and subsequent analysis of gene expression profiles for the early detection of toxic/carcinogenic effects

Project: NanoCOLT

Long-term effect of modified carbon black nanoparticles on healthy and damaged lungs

Project: CaNTser

Investigation of the toxic potency of carbon nanotubes following long time inhalation

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

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 Office for Radiation Protection

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)

German Society for Plant and Reactor Safety (GRS)

Study on respirable, aerosol-borne radioactivity release resulting from an explosive event during transportation of nuclear fuel – detection and quantification of the released respirable aerosols

Investigation and assessment of barrier failure and release processes resulting from an event with projectile-forming charges – determination of respirable particle release

Statutory Accident Insurance (DGUV)

Evaluation of usability of the physical characteristics of endogenously generated exhaled aerosols in the diagnosis of occupational lung diseases

International

CEFIC-LRI project: ECO18

Identifying limitations of the OECD water-sediment test (OECD 308) and developing suitable alternatives to assess persistence

CEFIC-LRI project: N5-FRAU

Histopathology of rats exposed to Barium sulfate nanoparticles by life-time inhalation exposure – Effects and Biokinetics

EASA project: (CAQ) Preliminary Cabin Air Quality Measurement Campaign

EFSA project: Testing a procedure for the identification of emerging chemical risks in the food chain

ESIG (European Solvents Industry Group)

Verifying the effectiveness of solvent risk management measures

EU program FP7: Primomed

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

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: CELL-PID

Advanced cell-based therapies for the treatment of primary immunodeficiency

EU project: Detective (SEURAT-1 Research Initiative)

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

EU project: Innovative Medicines Initiative (IMI) – eTOX

Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the in silico prediction of toxicities

EU project: Innovative Medicines Initiative (IMI) – iABC

Inhaled antibiotics in bronchiectasis and cystic fibrosis

WP2B Pre-clinical Inhalation Toxicology and DMPK

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: PHOENIX

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

EU project: PLATOX

In-vitro and in-vivo investigations to generate validated toxicity data of graphene nanoplatelets vs. a carbon black reference

EU project: PneumoNP

Nanotherapeutics to treat antibiotic-resistant Gram-negative respiratory infections

EU project: SILICOAT

Industrial implementation of processes to render RCS safer in manufacturing processes

EU project: SILIFE

Production of quartz powders with reduced crystalline silica toxicity

Helmholtz-Zentrum Dresden-Rossendorf, Dresden

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

IDT Biologika GmbH, Dessau-Rosslau

Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA), Sankt Augustin

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

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

Kiel University

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

Leibniz Institut für Analytische Wissenschaften (ISAS), Dortmund

Leibniz Research Center for Working Environment and Human Factors (IfADo), Dortmund

Leibniz University Hannover

LungenClinic Grosshansdorf GmbH

Mainz University Medical Center

Molecular Networks GmbH, Erlangen

PMS Professional Management Support, Hamburg

QuoData, Gesellschaft für Qualitätsmanagement und Statistik mbH, Dresden

Research Center Borstel

Robert Bosch GmbH – Packaging Technology, Crailsheim

Roche Diagnostics GmbH, Mannheim and Penzberg

RWTH Aachen

Sirion Biotech GmbH, Martinsried

Technische Universität Braunschweig

Technische Universität Dresden

Technische Universität München (TUM), Munich

TRAIN – biomedical translation alliance in Lower Saxony, Hannover

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

Ulm University

Universitätsmedizin Göttingen

University Hospital Carl Gustav Carus Dresden

University Hospital of Munich (LMU)

University Medical Center Hamburg-Eppendorf (UKE)

University of Düsseldorf

University of Cologne

University of Freiburg

University of Giessen

University of Leipzig

University of Lübeck

University of Marburg

University of Regensburg

Cooperation partners

National

Augsburg University Hospital

BioMedVet Research GmbH, Walsrode

Boehringer Ingelheim Pharma GmbH & Co. KG

Center of Allergy & Environment (ZAUM), Munich

Charité, Berlin

Charité Research Organization, Berlin

Clausthal University of Technology

ECT Oekotoxikologie GmbH, Flörsheim a. M.

Essen University Hospital

European Aviation Safety Agency (EASA), Cologne

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 Office for Radiation Protection (BfS), Salzgitter

FOBIG, Forschungs- u. Beratungsinstitut Gefahrstoffe GmbH, Freiburg

Fraunhofer ICT-IMM, Mainz

Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Stuttgart and Würzburg

Freie Universität Berlin

Friedrich Schiller University Jena

GEMoaB Monoclonals GmbH, Dresden

GeneXplain GmbH, Wolfenbüttel

German Cancer Research Center (DKFZ), Heidelberg

German Center for Infection Research (DZIF)

German Center for Lung Research (DZL)

German Primate Center, Göttingen

Gesellschaft für Anlagen- und Reaktorsicherheit (GRS), Cologne

Hannover Clinical Trial Center (HCTC), Hannover

Hannover Medical School

Heidelberg University Hospital

Helmholtz Center for Environmental Research – UFZ, Leipzig

Helmholtz Center for Infection Research, Braunschweig

University of Tübingen

University of Veterinary Medicine Hannover, Foundation

Vakzine Projekt Management GmbH, Hannover

Vetter Pharma International GmbH, Ravensburg

International

Adenium Biotech, Copenhagen (Denmark)

ARTTIC, Paris (France)

AstraZeneca (Sweden)

Babeş-Bolyai University Cluj, Cluj-Napoca (Romania)

Biomedical Primate Research Center, Rijswijk (The Netherlands)

BIOTOX S.R.L., Cluj (Romania)

CeMM – Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna (Austria)

Centro Ceramico – Bologna, Bologna (Italy)

Cosmetics Europe, Brussels (Belgium)

École européenne de chimie, polymères et matériaux (ECPM), Strasbourg (France)

Erasmus Medical Center, Rotterdam (The Netherlands)

Española de Nuevos Tratamientos S. A., Alicante (Spain)

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

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

Fundación CIDETEC (CID), San Sebastián (Spain)

GEPACK – Empresa Transformadora de Plásticos, SA, Aveiras de Cima (Portugal)

GlaxoSmithKline Research and Development Ltd., Brentford (UK)

HANSABIOMED Ltd., Tallinn (Estonia)

IBMCC (Instituto de Biología Molecular y Celular del Cáncer), Salamanca (Spain)

Imperial College of Science, Technology and Medicine, London (UK)

INDUPLAST S.P.A., Bolgare (Italy)

Ingeniatics, Sevilla (Spain)

Institute of Occupational Medicine (IOM), Edinburgh (UK)

Instituto de Tecnología Cerámica, Castellón (Spain)

International Agency for Research on Cancer, Lyon (France)

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

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

Janssen Labs (a Johnson&Johnson company), La Jolla – San Diego (USA)

JRC – Joint Research Center, European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM), Ispra (Italy)

Kazan Federal University, Kazan (Russia)

King Mongkut's University of Technology Thonburi (KMUTT), Bangkok (Thailand)

Laboratorios Almirall S. A., Barcelona (Spain)

LAMEPLAST S.P.A., Novi di Modena (Italy)

Lhasa Ltd., Leeds (UK)

Life Sciences Queensland, Brisbane (Australia)

Liverpool John Moores University, Liverpool (UK)

McMaster University Medical Center, Hamilton, Ontario (Canada)

Medical University of Innsbruck, Innsbruck (Austria)

National Institute of Occupational Health, Oslo (Norway)

NC State University, Raleigh, North Carolina (USA)

Novartis (Switzerland)

OECD QSAR Expert Group (France)

PathoFinder, Maastricht (The Netherlands)

Procter and Gamble (UK)

Quretec OÜ, Tartu (Estonia)

RIVM National Institute of Public Health and the Environment, Bilthoven (The Netherlands)

Rochem Group AG, Zug (Switzerland)

SetLance, Siena (Italy)

Swiss Federal Institute of Aquatic Science and Technology (EAWAG), Dübendorf (Switzerland)

TNO Quality of Life, Zeist (The Netherlands)

UCB Pharma S. A., Brussels (Belgium)

Umaps Communication, Paris (France)

Unilever (UK)

Universidad Autónoma de Madrid, Madrid (Spain)

Université catholique de Louvain, Louvain (Belgium)

University College Cork, Cork (Ireland)

University of Alberta, Alberta (Canada)

University of Amsterdam, Amsterdam (The Netherlands)

University of Aveiro, Aveiro (Portugal)

University of Basel, Basel (Switzerland)

University of Bern, Bern (Switzerland)

University of Eastern Finland, Kuopio (Finland)

University of Groningen, Groningen (The Netherlands)

University of Leiden, Leiden (The Netherlands)

University of Maastricht, Maastricht (The Netherlands)

University of Southampton, Southampton (UK)

University of Utrecht, Utrecht (The Netherlands)

University of Virginia, Charlottesville, Virginia (USA)

University Pompeu Fabra, Barcelona (Spain)

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

Vrije Universiteit Brussel (VUB), Brussels (Belgium)

Weizmann Institute of Science, Rehovot (Israel)

World Health Organization (WHO), Geneva (Switzerland)

Prizes

In 2015, Fraunhofer ITEM researchers were awarded the following prizes for their work:

Prof. Dr. Antje Prasse

Prize: ERS Research Award on Idiopathic Pulmonary Fibrosis 2015
Prize for extensive and outstanding research work in the field of idiopathic pulmonary fibrosis.

Awarded on September 27, 2015 during the ERS International Congress 2015 in Amsterdam (The Netherlands).

Sharon Melissa Jiménez Delgado

Prize: Poster prize in the Junior Member and Affiliates (JMA) Poster Session
Prize for the presented poster entitled "Passively sensitized human organotypic tissue as asthma model to study mast cell-nerve interaction".

Awarded in June 2015 at the EAACI Congress 2015 of the European Academy of Allergy and Clinical Immunology in Barcelona (Spain).

Exhibitions, congresses and workshops

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 2015, the institute hosted or played an active role in the following events:

January 26-27, 2015

DZL Annual Meeting

Hamburg (Germany)

February 5-6, 2015

14th Fraunhofer Seminar "Models of Lung Disease"

Hannover (Germany)

February 20-24, 2015

AAAAI 2014

Annual Meeting of the American Academy of Allergy, Asthma and Immunology
Houston, Texas (USA)

March 4-6, 2015

28th Meeting of the German Society for Environmental Mutation Research (GUM)

Düsseldorf (Germany)

March 9-11, 2015

BIO-Europe Spring

Paris (France)

March 10-12, 2015

81st Annual Conference of the German Society of Pharmacology and Toxicology (DGPT)

Kiel (Germany)

March 11-12, 2015

Forum Life Science 2015

Garching (Germany)

March 18-21, 2015

DGP Congress 2015

56th Annual Congress of the German Respiratory Society (DGP)
Berlin (Germany)

March 22-26, 2015

SOT 2015

54th Annual Meeting of the Society of Toxicology; including Fraunhofer ITEM
Exhibitor-Hosted Session on "Alternative methods in inhalation toxicology"
San Diego, California (USA)

April 14-16, 2015

in-cosmetics 2015

Barcelona (Spain)

April 19-21, 2015

European Coatings Congress

Nürnberg (Germany)

April 25-30, 2015

IOHA 2015

10th International Scientific Conference of the International Occupational Hygiene Association
London (UK)

May 3-7, 2015

SETAC Europe 2015

25th European Annual Meeting of the Society of Environmental Toxicology and Chemistry
Barcelona (Spain)

May 15-20, 2015

ATS 2015

International Conference of the American Thoracic Society
Denver, Colorado (USA)

May 28-29, 2015

IVTIP Spring Meeting

International Congress of the In Vitro Testing Industrial Platform
Copenhagen (Denmark)

May 30 – June 3, 2015

20th ISAM Congress

Congress of the International Society for Aerosols in Medicine
Munich (Germany)

June 6-10, 2015

EAACI 2015

European Academy of Allergy and Clinical Immunology Congress
Barcelona (Spain)

June 15-18, 2015

BIO International Convention 2015

Philadelphia, Pennsylvania (USA)

June 16-19, 2015

Cosmetics Europe Week 2015

Brussels (Belgium)

June 29 – July 1, 2015

42nd Annual Meeting of the Japanese Society of Toxicology

Kanazawa-City (Japan)

September 13-16, 2015

EUROTOX 2015

51st Congress of the European Societies of Toxicology
Porto (Portugal)

September 20-23, 2015

EUSAAT 2015

16th Annual Congress of the European Society for Alternatives to Animal Testing.
Linz (Austria)

September 26-30, 2015

ERS Congress 2015

25th International Congress of the European Respiratory Society
Amsterdam (The Netherlands)

October 6-8, 2015

BIOTECHNICA 2015

Hannover (Germany)

October 7-9, 2015

AusBiotech 2015 – Australia's Life Sciences Conference

Melbourne (Australia)

October 21-23, 2015

7th EMBRN International Mast Cell and Basophil Meeting

Marseilles (France)

November 2-4, 2015

BIO-Europe 2015

Munich (Germany)

November 17-19, 2015

PCT 2015

Partnerships in Clinical Trials
Hamburg (Germany)

December 2-3, 2015

Otti Symposium on "functional implants and implant surfaces – from material to clinical use"

Bremen (Germany)

December 4, 2015

Symposium of the SEURAT-1 Research Initiative

Brussels (Belgium)

EDITORIAL NOTES

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Priv.-Doz. Dr. Jens Vogel-Claussen – p. 45

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