




Facts & Figures 2011

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





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Prevention Research: important for everyone



Research is important because it is the only way of obtaining new findings that are ultimately synonymous with progress. In the world of work, progress can have different meanings including fewer work-related health hazards, fewer accidents, fewer occupational diseases, and healthier work.

The IPA prides itself on its many years of experience in the area of prevention-oriented occupational medical research. The IPA's research concept has always been geared towards the practical requirements of occupational safety and health: the prevention of occupational accidents and diseases.

To efficiently respond to the increasingly complex issues in occupational medical research and prevention, the German Social Accident Insurance and the IPA must continuously develop and expand their own scientific expertise to stay ahead the level of excellence to which the public have become accustomed. At the same time, the complexity of modern-day issues increases the need for co-operations within research associations and networks at both the national and international level.

With its first ever „Facts and Figures“ brochure in English, the IPA is pleased to introduce the key areas of its research to the broader international audience.

We hope you enjoy getting to know us, and look forward to any feedback.

Thomas Brining

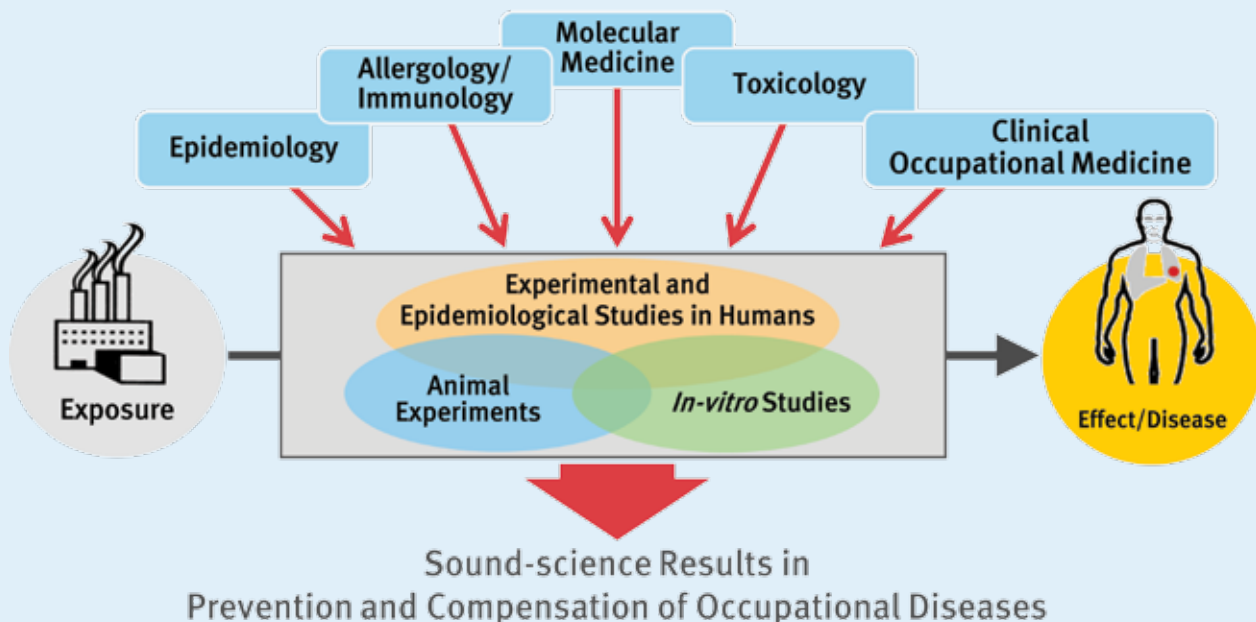
The IPA: a portrait

The Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA) is an institute of the Ruhr-Universität Bochum. It serves as the interface between research and practice in occupational safety and health, safeguarding the health of around 70 million insured individuals at the workplace and in educational establishments. The institute is characterized by its orientation towards preventive health protection institutions.

The IPA's origins date back to the 1920s, when the growing use of machinery in the mining sector led to increases in cases of silicosis. The task of combating silicosis, and of doing so by a preventive approach, was given to the main department for protection against drill dust, which had been created by the German Social Accident Insurance Institution responsible at the time for the mining industry. During the years that followed, the

department progressively extended the scope of its activities. One product of this was the Silicosis Research Institute, the predecessor institute to today's IPA.

The institute's structures, which have been progressively expanded since 2001, are focused firmly on the needs of the member companies insured by the German Social Accident Insurance



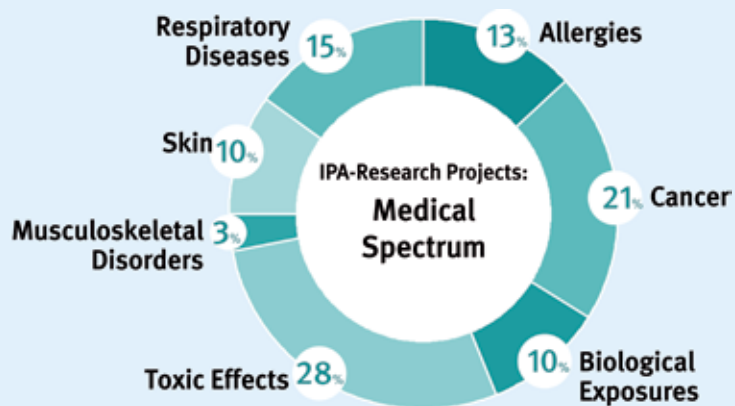
Institutions and their employees. The focal point of research at IPA are the establishment and use of preventive measures at the workplace, a fact reflected not least by its change of name in 2009 from the BGFA Institute for Occupational Medicine to the Institute for Prevention and Occupational Medicine, or IPA.

Over the past 20 years, the focus of IPA's research activities has developed continually in step with the changing requirements of health protection at the workplace. Whereas in the past, the emphasis was on pulmonary diseases – particularly silicosis, but also allergic problems such as the exposure of employees to latex – the key topics are now the synergistic effects of various hazardous substances upon human health, the early diagnosis of cancer, and also exposure measurements at the workplace by means of biological monitoring in humans. The IPA employs state-of-the-art technology and continuously works on the perfection of its methods to the highest scientific standards in the field of occupational and environmental health sciences.

The IPA currently employs some 140 staff from numerous disciplines, including occupational physicians, toxicologists, chemists and biologists. These personnel conduct research at five centers of excellence: those of medicine, allergology/immunology, toxicology, epidemiology, and molecular medicine. The focus is upon molecular and epidemiological studies on humans, conducted at workplaces and on experimental studies in an environmentally controlled exposure laboratory. This research approach is supplemented by experimental laboratory studies such as the use of *in-vitro* cell cultures. Conversely, results from cell cultures can also be reviewed for their actual relevance to human beings and to those obtained in field studies. Altogether, sound-scientific results are produced for the detection and interpretation of workplace-related effects upon human health. Owing to the close co-operation with the accident insurance institutions, these results translate into findings of practical relevance



Medical spectrum of the IPA research projects



for preventive measures and compensation of work-related diseases. This concept is virtually unique anywhere in the world.

Utmost priority is given to scientific quality assurance in all research activities and areas of expertise. Standardization and quality assurance can be considered reliable only because research at IPA is based on the consistent use of good laboratory practice (GLP) and good epidemiological practice (GEP).

The overall aim is to support the accident insurance institutions in their statutory mandate: of structuring the workplace and educational institutions in such a way that all suitable means are used to prevent occupational, school and commuting accidents, occupational diseases, and work-related health hazards. The IPA is always open to new research activities in its fields of research.

IPA division of tasks



The IPA and its competences

The IPA is organized into five closely meshed competence centers: for medicine, toxicology, allergology/immunology, molecular medicine, and epidemiology. The five centers exploit synergy effects to the full.

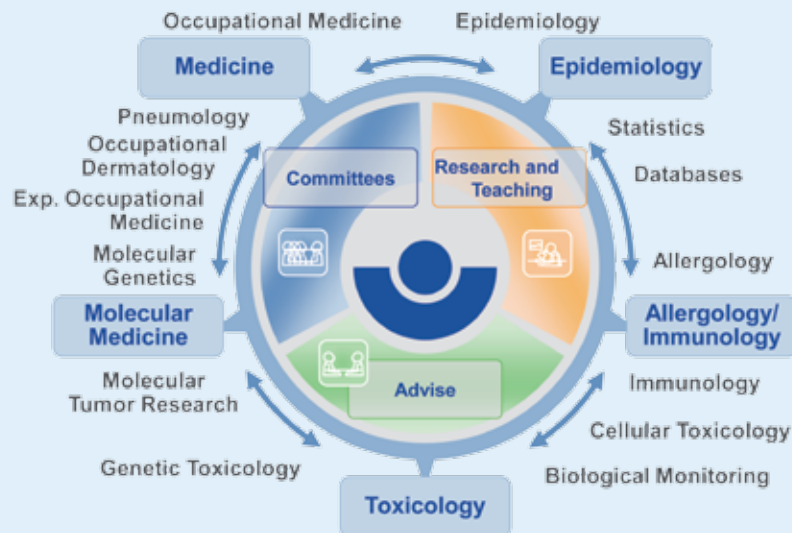
Medicine

The Competence Center Medicine comprises the following sections:

- Occupational medical research and consultancy
- Outpatient clinic/pneumology
- Occupational dermatology
- Experimental occupational medicine

Traditionally, research by the Competence Center Medicine has focused primarily on diseases of the respiratory tract caused by hazardous substances. The problems addressed range from

prevention of and compensation for diseases caused by quartz dust, asbestos and organic dusts, through occupational allergies, to acute and chronic effects of irritants. The center uses a large number of cutting-edge medical diagnostic methods, in some cases in conjunction with the Bergmannsheil University Hospital, in order to prevent and assess occupational diseases. Among these, non-invasive diagnostic methods are growing in importance. 700 to 800 patients are examined in the outpatient clinic each year. To these are added several hundred test subjects taking part in the numerous field studies of the IPA. Problems currently being examined concern for example the health risks



experienced by welders, miners in potash mines and workers in composting plants.

In the area of clinical and experimental occupational dermatology, studies are performed about occupational skin diseases and their prevention. Clinical studies are also conducted about skin cancer caused by UV radiation, and experimental *in-vivo* and *in-vitro* studies about penetration of the skin by hazardous substances. Dermatological assessments are performed in order to assess the occupational contribution to diseases. For particular allergological issues, patients are tested with substances of their own for possible contact allergies of occupational origin. For this pur-

pose, the expertise in occupational dermatology and allergology is combined with the IPA's analytical and toxicological expertise.

The experimental occupational medicine focuses on clarifying the mechanisms of occupational exposure to hazardous substances associated with health risks. Examples of the issues to be addressed are the mutagenic action of carcinogens in cells and acute effects of airway irritants in humans. Methods employed range from experiments on cell cultures to controlled studies on human study participants in the exposure laboratory (Expo-Lab). In the latter, the effects of multiple exposures, such as to particles, hazardous substances or allergens, can be studied simultaneously under highly standardized exposure conditions.



The expertise of the Competence Center Medicine is used on a large scale in consulting with the German Social Accident Insurance (DGUV) and the individual accident insurance institutions on issues of prevention and compensation. In addition, researchers at the competence center are active on further state and research advisory committees.

Besides conducting research studies, the occupational physicians are engaged in medical surveillance of employees of various companies.

Toxicology

The Competence Center Toxicology comprises four closely interconnected sections:

- Human biomonitoring
- Cell biology
- Genetic toxicology
- Toxicological consultancy

Activities focus on biological monitoring at the workplace and general risk assessment of exposure to hazardous substances. For this purpose, analytical and molecular biological methods have been developed for the quantitative assessment of biomarkers. These methods help determine the exposure and action of hazardous substances, in addition to the effects of carcinogenic, mutagenic and reprotoxic substances on humans. Consequently, the hazardous substance intake (inhalative, dermal and oral) by an individual, and the resulting biological effects, can be quantitatively measured. Studies on human subjects are performed concurrently with studies in cells (*in vitro*), in order to decode the precise mechanism of action of the damage caused by the hazardous substances. The results obtained from such analysis yield findings relevant to the practical prevention and compensation work of the accident insurance institutions.

In addition to its research work, the Competence Center Toxicology participates in several national and international committees, including the BEI committee of the ACGIH and the Consumer Product Safety Commission (CPSC) (both in the USA), and the committees of the ISSA (International Social Security Association). At national level, the competence center is represented in a number of working groups of the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) of the German Research Foundation (DFG), and in the AGS Committee for Hazardous Substances of the Federal Ministry of Labour and Social Affairs (BMAS). With these diverse activities, the IPA's Competence Center Toxicology is able to address new developments as they emerge, and to take a proactive role. For example, through its function as a consultant on various toxicological issues, the Center supports the accident insurance institutions in issues of primary and secondary prevention, based upon the latest knowledge, together with the necessary wider perspective. Hazardous substances currently in the spotlight are carcinogenic and reprotoxic substances for which health-based occupational exposure limits are unavailable due to limited data.

In addition to occupational medical/epidemiological studies, studies on the effect of hazardous substances at cellular and molecular level are necessary for the assessment of risks presented by hazardous substances at the workplace. Cell biology methods can be used to study the mechanisms of action of hazardous substances on a particular target tissue *in vitro* by comparing treated and untreated cells.

In addition, the Competence Center Toxicology offers a wide range of human biomonitoring analysis for detecting exposure to hazardous substances commonly found at the workplace. These analysis can be used to clarify scientific issues and to support prevention work conducted in companies. Quality-assured meth-



ods for highly sensitive and specific detection of short-term and long-term markers are available, which also permit assessment of the ubiquitous background exposure of non-occupational origin.

Allergology/Immunology

This competence center comprises the following sections:

- Allergology
- Immunology
- Consultancy and diagnostics

Foci of activity are the study of pathomechanisms which lead to the incidence and persistence of diseases of the respiratory tract caused by occupational allergens and irritative harmful substances. In addition, the effect of complex bioaerosols and individual constituents upon the immune system is studied with particular consideration being given to the components of innate immunity. A further important aspect of the competence center's work is the identification of occupational sources of sensitization. Besides the irritative and sensitizing effects of occupational noxae, substances with unpleasant effects and their influence upon immunological processes are increasingly being addressed. The research activity includes studies of occupational allergies caused by flours, enzymes, mites, fungi, natural rubber latex, animal dander, wood dust, low-molecular substances such as isocyanates and acid anhydrides. Sensitive detection systems are also created for allergens and microbial components. For use in field studies, both cellular and soluble components are sampled from various regions of the respiratory tract and analyzed, among other things for the detection of inflammatory processes. Immunological methods are also used to detect occupational and environmental allergens. Induced sputum and nasal lavage fluids for example were successfully collected and analyzed in this way for the first time on approximately 500 employees before and after shift in the field in the scope of the Human Bitumen Study.

The competence center's findings are channelled into the standardized methods for the diagnosis of allergic diseases of the respiratory tract and into the assessment of the clinical and diagnostic relevance of non-invasive methods. Researchers from the competence center are involved in the creation of national guidelines and international consensus papers on the subjects of allergy diagnostics, the use of non-invasive methods, and the detection and quantification of allergy exposure in the environment and at workplaces. They are also active in the WHO/IUIS Allergen Standardization Committee and the IUIS Allergen Nomenclature Sub-Committee.

For the statutory accident insurance institutions and parties to occupational medicine in the field, the Competence Center Allergology/Immunology offers specific serological antibody detection, primarily to occupational allergens, and also the quantification of selected occupational allergens in material, dust, and atmospheric dust samples. A further focus is the provision of consultancy to the DGUV and its members in all issues of biological exposure and effects upon the immune system, particularly those caused by allergens and components of organic dust.

Molecular Medicine

The Competence Center Molecular Medicine is divided into the following sections:

- Molecular tumour research
- Molecular genetics

The Competence Center Molecular Medicine uses modern molecular biological methods to address a wide range of issues facing the accident insurance institutions and occupational medicine in general. An important objective is the development of new methods for the early detection, diagnosis, and ultimately also treatment of occupational diseases. In this context, the (secondary) prevention of occupational cancer, which has a tremendous

impact upon affected insured individuals, is a particular focus of the research activity. Effective and minimally invasive early detection is a valuable addition to the traditional methods of follow-up treatment.

The competence center conducts research into specific effects of hazardous substances upon the genes and their regulation, and thus the mechanisms by which occupational tumours occur. Cutting-edge analysis methods are employed in order to identify specific patterns in gene expression and new biomarkers for early detection. The priority lies in this case upon validation of these biomarkers in large-scale prospective studies. A further research focus is that into the relationship between sequence variations in the genes of enzymes, which metabolize foreign substances, and susceptibility to occupational noxious substances.

Mechanistic findings from research into cancer and harmful substances also play an important part in the classification of carcinogenic substances and the definition of limit values. As a result, expertise and the latest results from research into molecular interrelationships can be channelled directly into the regulatory committees, such as the MAK Commission of the German Research Foundation (DFG). Staff at the competence center is also active in the working group addressing new mechanisms of carcinogenesis.

The interpretation of complex interrelationships, coupled with intelligent use of the findings, requires close co-operation with the other competence centers. Together with the Competence Center Epidemiology and the Competence Center Allergology/Immunology, for example, interdisciplinary approaches are pursued to the early detection of cancer in the context of follow-up examinations.



Epidemiology

The Competence Center Epidemiology is divided into the following sections:

- Epidemiology
- Statistics
- Epidemiological consulting

The Competence Center Epidemiology supports the German Social Accident Insurance and its members, and also various other bodies, in evaluating the epidemiological evidence of the effects of hazardous substances upon health. Examples of current research and consulting topics include the health effects of shift work, asbestos, metals, bitumen, dusts (particularly fine quartz dust), polycyclic aromatic hydrocarbons, aromatic amines, solvents, and passive smoking. At national level, the competence center supports the Institute's contribution to the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) of the German Research Foundation (DFG), and on the AGS Committee for Hazardous Substances of the Federal Ministry of Labour and Social Affairs (BMAS). Epidemiological evaluation is of decisive importance in this context as part of the classification of hazardous substances and the setting of occupational exposure limits for them. The interdisciplinary expertise ensures a perspective that also considers mechanisms and molecular aspects.

The key research approach is molecular epidemiological for evaluating the carcinogenicity of hazardous substances and for the

early detection of diseases, particularly where substances have a synergistic effect. In order for sound results to be obtained, multi-center projects are launched and conducted in collaboration with competent partners.

In addition, the Competence Center Epidemiology supports the other competence centers of the institute, thereby assuring the planning and conduct of studies according to Good Epidemiological Practice and adequate statistical analysis of the project results.

In order to obtain robust and quality-assured results, a range of study instruments (such as an operation manual with detailed SOPs), a quantitative assessment of exposure, and comprehensive statistical models are employed. A central element of the evaluation strategies are appropriate statistical methods, which assist in consideration being given to a large number of possible influencing factors during interpretation of the complex datasets.

The IPA is active in national and international research networks

The research competence of the IPA is held in high regard, not only by the German statutory accident insurance institutions, but also by its many national and international partners. Complex and quality-assured research focusing on the health of all insured persons requires competent partners at both the national and international level.

At the national level, the IPA works together with its two sister institutes: the Institute for Occupational Safety and Health (IFA), and the Institute for Work and Health (IAG). An also close cooperation exists with the IGF – Institute for Research on Hazardous Substances. Joint activities are also conducted with other academic and state institutions, such as the Fraunhofer institutes, the Leibniz institutes, and the German Cancer Research Center (DKFZ).

The **WELDOX project** is one of the most comprehensive studies of welders worldwide. In this study, a wealth of data on exposure to welding fumes and metals and on irritative and genotoxic effects assessed with various biomarkers were recorded. Together with researchers at the Technical University of Berlin, the IFA and staff of the prevention and metrological services at various accident insurance institutions, the possible adverse impact upon health caused by welding fumes and the metals contained within them was studied. The study yielded findings for the prevention of work-related health hazards among welders and employees exposed to metals (see page 22).


For research into the risks of multiple exposure to occupational carcinogens in the development of lung cancer, the IPA is co-ordinating the international **SYNERGY project** in conjunction with the International Agency for Research on Cancer (IARC) and the Institute for Risk Assessment Sciences (IRAS). For this purpose, the epidemiological data in occupational and smoking histories from 14 international studies were pooled. The result is the largest data record of its kind to date, containing 17,705 cases of lung cancer and 21,813 controls. A further database has been created containing 374,808 measured concentrations for crystalline silica, asbestos, chromium, nickel and polycyclic aromatic hydrocarbons (PAHs). Based upon this exposure database, a job-exposure matrix was modelled. The project provides the most precise risk assessments available at this time for the lung-cancer risk of the selected carcinogens, adjusted for smoking. The project is to assist in scientific validation of the combined effect of the hazardous substances in cases of occupational cancer, and in the process to generate robust data for prevention and for the legislation governing the formal recognition of cases of occupational disease (see page 19).

In the **STADOCA** multicenter study for the comparison and evaluation of commercial skin prick-test extracts for occupational allergens, patients with allergic respiratory symptoms induced by occupational allergens are being studied by means of prick tests in eight European occupational medical/allergological centers. The data and patient sera are collected, analyzed and evaluated centrally at the IPA. The objective of STADOCA is to optimize the quality of the commercial prick-test extracts for occupational allergens, and to develop international recommendations for standardized diagnosis of occupational asthma in the prevention and assessment of occupational diseases.

COPHES – Consortium to Perform Human biomonitoring on a European Scale – is a pan-European project with the aim of establishing human biomonitoring in all EU Member States as a supplementary instrument for preventive health care. All 27 Member States are involved in this project, with the objective that human biomonitoring develops at the same high level in all states. Two German institutions, the German Federal Environmental Agency (UBA) and the IPA, are responsible for packages of work activity. The COPHES project is for example addressing the harmonization of the analytical methods and quality assurance, and issues in the preanalytical phase and biobanking.

The IPA is a central pillar of **PURE** (Protein Research Unit Ruhr within Europe), founded in 2010. The task of PURE is to detect cancer and neurodegenerative diseases at an early stage, and thus at the same time, promote prevention. For the first time, PURE covers all steps from development of a biomarker concept, through its identification and validation, to development and validation of assays in the field. For this purpose, researchers at the universities of Bochum and Duisburg-Essen have joined forces with the support of the IPA. This research project constitutes a major benefit for primary and secondary prevention (see page 24).

During the **Human Bitumen Study**, the impact of exposure to vapours and aerosols of bitumen exposure upon workers' health during hot laying was examined, particularly upon the respiratory tract. The study was conducted in collaboration with the German Social Accident Insurance Institution for the building trade, the IFA, and university institutes. The results of this study will assist re-evaluation of the classification of bitumen as a Category 2 carcinogen. They will also contribute to redefinition of a limit value based upon human research studies in national and international committees responsible for bitumen (see page 21).



The **UroScreen prospective cohort study** examines whether bladder carcinomas in a study population of persons who have been exposed to aromatic amines at the workplace can be detected better by means of molecular markers than by haematuria or urine cytology. The IPA conducted the study in collaboration with the Institute for Urology at the University of Tübingen, the German Social Accident Insurance Institution for the raw materials and chemical industry (BG RCI) and the occupational medical services of participating industrial enterprises. The initial results indicate that optional inclusion of the tumour marker NMP22 in the principle for occupational medical surveillance of workers exposed to aromatic nitro and amino compounds should be reconsidered based on scientific reasoning due to a large number of false-positive results. The results may also be a useful aid for corresponding occupational medical rules at the German Federal Ministry of Labour and Social Affairs (BMAS) (see page 24).

Research into irritants: in co-operation with the Leibniz Research Center for Working Environment and Human Factors (IfADo) and the IGF, fifteen model substances proposed by the accident insurance institutions were studied with regard to their irritant and odor effects and classified according to their strength of action. For this purpose, the IPA is also engaging in intensive dialogue with the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) and the IFA, within a research network. The resulting findings will be suitable for setting national and international limit values. At the national level, a joint working group responsible for the definition of limit values for local effects has been set up by the MAK Commission of DFG and the Committee on Hazardous Substances (AGS) of the Federal Ministry of Labour and Social Affairs (BMAS) under the direction of the IPA in order to concentrate and co-ordinate the expertise in this area (see page 26).

The IPA advises and is active on committees

Besides its research mandate, it is also important to the IPA that research findings are optimally utilized in the prevention work of the accident insurance institutions and state regulatory bodies. As a result, the institute's expertise is frequently requested. The major effort of IPA is to promptly react to the research and consultancy needs of the statutory accident insurance institutions. This goal is also achieved by a close cooperation between IPA and national and international regulatory bodies and specialist associations.

The IPA is therefore active at the national level in a number of working groups of the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) of the German Research Foundation (DFG), and on the Committee for Hazardous Substances (AGS) of the Federal Ministry of Labour and Social Affairs (BMAS).

The revision and introduction of statutory acts and ordinances – such as adoption of the German gene diagnostics act (GenDG), the Ordinance on hazardous substances and the Ordinance on biological agents, and the introduction of the Ordinance on occupational medical prophylaxis – lead to a considerable increase in the committee work required by the accident insurance institutions for occupational medical issues.

The new approach used to set limit values in occupational safety and health in Germany also involves the introduction of health-based limit values. For this purpose, the health effects of hazardous substances and insured tasks must be evaluated on the basis of medical and scientific findings. In particular carcinogenic substances present a problem, since thresholds cannot normally be determined and risk-based thresholds have to be established rather than health-based thresholds. In order to define risk-based limit values, a risk acceptance concept has been developed in Germany for the first time (Announcement 910) that outlines an acceptable and tolerable risk at the workplace.

Where suitable data are available, the definition of exposure-risk relationships for specific substances allows separate, risk-based limit values to be defined for carcinogenic substances in relation to the previously defined acceptable and tolerable risk. As part of the risk-acceptance concept, three regions of high, medium and low risk have been defined in accordance with the traffic-light principle (red/amber/green), against which preventive OSH measures can be launched.

This is the first time that such a concept has been introduced anywhere in the world. Staff at the IPA are collaborating with relevant working groups responsible for risk acceptance and risk assessment of the BMAS.

Conversely, for non-carcinogenic hazardous substances, the most sensitive reaction is the irritative effect, affecting eyes and the upper respiratory tract, and is therefore particularly significant for defining health-based limit values. Against this background, a generic working group responsible for the definition of limit values for local effects, and headed by the director of the IPA, has been established at national level. The working group's function is to focus its expertise on researching such irritants and developing a basic concept for the definition of occupational exposure limits for hazardous substances with irritative action.



The IPA is also represented on AfAMed (the commission for occupational medicine) of the BMAS. This commission develops rules and provides suggestions for the application of the new Ordinance on occupational medical prophylaxis (ArbMedVV), drafts recommendations for optional check-ups and concepts for workplace preventive healthcare, and advises the BMAS in all issues of occupational medical prophylaxis and occupational medicine. Especially in this commission criteria for mandatory examinations, in particular for carcinogenic substances are also discussed. The Ordinance on occupational medical prophylaxis lists various tasks involving hazardous substances for which mandatory examinations are specified. However, because occupational exposure limits cannot generally be defined for carcinogenic substances, mandatory examinations do not currently exist for all substances. The IPA is therefore closely involved in talks to conceptualize basic principles for the development of action values and to set standards for the implementation of various occupational medical preventive measures.

Owing to the German gene diagnostics act (GenDG) adopted in 2009, the German lower house has for the first time defined statu-

tory framework conditions for genetic studies on human beings. One section of this act governs genetic studies in working life, to ensure that genetic studies performed in the context of occupational medical examinations are not used for other purposes. Based upon the GenDG, a genetic diagnosis commission was set up which provides out guidelines for examinations in the area of genetic diagnosis with reference to good scientific and technical practice. The director of the IPA has been appointed to the genetic diagnosis commission as an expert in the area of occupational medicine.

The scientific expertise of the IPA is also sought after by committees at both the international and national levels. The Directorate General for Health and Consumers of the European Commission (SANCO), for example, has appointed members of staff from the IPA to the scientific committee responsible for consumer protection and to the expert group of scientific advisors on risk assessment. The IPA is also represented on the Chronic Hazard Advisory Panel for phthalates.

The IPA teaches and trains

The IPA is responsible for conducting an Occupational Medicine course at the medical faculty of the Ruhr-Universität Bochum, as part of the standard and pilot medical degree courses. Students attend a series of lectures geared towards the syllabus of learning targets and supplemented by seminars with case presentations. Organized visits to companies in a number of industrial sectors afford students first-hand knowledge on the tasks of occupational physicians.

In the winter term students of the regular course attend lectures on occupational health risks, work-related diseases and preventive measures. These lectures are accompanied by seminars giving the students the opportunity to examine patients with occupational diseases like silicosis and asbestosis. On the occasion of visits to different industries students can learn about strategies and measures of health protection directly at the workplaces and talk to safety experts and occupational physicians in the companies. The programme for the students of the pilot course starts in the summer term and is more directed towards practical education.

In addition, members of the IPA lecture in the areas of immunology, experimental allergology and molecular medicine for students in the faculty of Biology and Biochemistry. Work placements are also offered for these subjects. Doctorates can also

be completed at the IPA at the Ruhr-Universität Bochum. Over ten internal and external doctoral candidates are currently being supervised by scientists at the various competence centers.

Together with the medical association of Westphalia-Lippe, the IPA offers a full course of further training leading to the qualification in occupational medicine and supplementary qualification in occupational medicine. The IPA also conducts monthly training events on various topics relevant to the work of occupational physicians in the field.

The module of Occupational Medical Toxicology is offered in co-operation with the North Rhine-Westphalia Master's course in Toxicology in Düsseldorf.



The IPA researches – traditional epidemiology

Epidemiology is of particular importance for research into hazardous substances. Dose-response relations for hazardous substances at the workplace must be evaluated for this purpose. At the IPA, various „traditional“ epidemiological studies are performed. These comprise also complex exposure estimates. Statistical models enable also the investigation of the shape of dose-response curves to be presented more precisely, the interaction between hazardous substances, and the control of potential confounders. Mixed and multiple exposure are the subject of particular focus. In order to obtain robust results, powerful studies are required in this area. These are conducted jointly with various partner research institutes.

The international, joint **SYNERGY** project examines the interaction of occupational carcinogens in lung cancer development, to produce scientifically sound data for prevention and for the German legislation governing the formal recognition of cases of occupational disease. The project, in which a number of leading epidemiologists are involved, is being co-ordinated by the International Agency for Research on Cancer (IARC), the Institute for Risk Assessment Sciences (IRAS), and the IPA.

For SYNERGY, data on occupational and smoking histories from 14 case-control studies have been pooled in an epidemiological database. With 17,705 cases of lung cancer and 21,813 controls from Europe and Canada, this has produced the largest collection of data for the risk assessment of occupational carcinogens to date.

A wealth of available measured data for quartz dust, asbestos, polycyclic aromatic hydrocarbons, chromium and nickel were identified worldwide for SYNERGY, and transferred to an exposure database. The database currently holds 374,808 measurements from 21 countries. Comprehensive statistical modeling was performed to derive a job-exposure matrix (SYN-JEM) from these

measurements. SYN-JEM presents average exposure estimates for these carcinogens by occupation, calendar year, and region.

By linking SYN-JEM to the occupational histories, the exposures of the cases and controls can be assessed quantitatively. The main effects of the individual carcinogens are first estimated, and then their combined action. Smoking is adjusted as the main confounder of the lung cancer risk of occupational carcinogens. The risk estimation is also performed separately for smokers and non-smokers. Only by means of the comprehensive epidemiological database it is possible to perform analysis among those who have never smoked, and in other important sub-groups.

Parallel to the main objective of SYNERGY, proposals were made for a large number of supplementary studies (subproposals). The results concerning the lung-cancer risk associated with diesel motor emissions have already been published. Additional risk estimations have been conducted to date for exposure to organic dust. The IPA has analysed the risk posed by smoking for the histological subtypes of lung cancer, and is planning more comprehensive analysis, in conjunction with partner institutes, of the lung-cancer risk in miners and welders. Further analysis



are currently being performed for cooks and kitchen workers, painters and decorators, hairdressers and construction workers, among others.

Also of importance for the estimation of lung-cancer risks is the obtaining of reliable results not only for hazardous substances, but also for the risk in certain occupations. The lung-cancer risks estimated from SYNERGY for various occupations are therefore compared with two further comprehensive analysis: the NOCCA (Nordic Occupational Cancer) project, and the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort study. This comparison allows to permit consolidated risk assessments for occupations from different study designs.

The IPA researches – molecular epidemiology

With the aid of molecular epidemiology, in which epidemiological studies are performed by means of the latest biochemical, toxicological, immunological and molecular biological methods, the effects and mechanisms of hazardous substances can now be explained with greater precision.

In such molecular epidemiological studies, the most diverse biomonitoring markers are also studied for detection of hazardous substance exposure, through to the detection of its early effects in human beings.

Besides the use of suitable statistical models for quantification of the risks, the studies also cover new findings regarding molecular mechanisms and the detection of metabolites, DNA damage, DNA methylation, mRNAs, microRNAs and marker proteins.

The Human Bitumen Study

Bitumen is a complex mixture of hydrocarbons, and is produced by the treatment of crude oil. If hot bitumen in the form of mastic asphalt is applied at temperatures of 230-250 °C, complex aerosols and vapours are released and inhalative as well as skin exposure of the workers is possible.

The potential carcinogenic effect has been the principal subject in several studies concerning health risks of bitumen exposure. As early as 1977, the MAK Commission classified vapours and aerosols of bitumen as Category 3, „suspected carcinogens“ (2001: Category 2, „carcinogenic“). The IARC (International Agency for Research on Cancer) likewise classified bitumen as a possible human carcinogen. Few studies have addressed the characterization of non-malignant changes, although some acute effects have been observed during exposure to bitumen, specifically irritation of the mucous membranes and the upper respiratory tract. Health-based studies especially of German workplaces with hot application of bitumen were not available at the beginning of the study.

Following the suspension of the limit value for vapours and aerosols from bitumen during hot application, the AGS Committee for Hazardous Substances together with the German BITUMEN Forum proposed a study in 2000 of the impact of bitumen exposure upon human beings. Within the Human Bitumen Study, the IPA therefore examined the irritative and genotoxic effects of vapours and aerosols of bitumen. For this purpose, a „cross-shift“ study design was used, and defined outcomes and findings obtained:

In total 500 employees on 80 construction sites throughout Germany were studied. Biomonitoring of selected PAH metabolites in the urine showed an increase of the concentrations exposed to bitumen after shift compared to non-exposed workers, but the concentration of urinary PAH metabolites was substantially lower than at typical PAH workplaces. Smoking is a clear confounding factor of the PAH metabolites in the urine. A weak correlation was identified between the external bitumen exposure and the PAH urine metabolites during shift.

Only among the workers exposed to bitumen inflammatory changes observed in the lower respiratory tract were detectable using analysis of the induced sputum samples. Since this difference between the groups was measurable both before and after the shift, this effect may be the result of repeated exposure.

The scale of oxidative DNA damage in the blood was higher among the exposed workers than among workers of the reference group, both before and after the shift. Owing to the lack



of a correlation with the level of exposure, however, the studied genotoxic damage cannot be attributed clearly to exposure to bitumen or the PAHs contained within it. A dose-effect relationship to a single shift measurement of bitumen exposure could not be established for any of the parameters studied. Mutagenic effects were not detected.

The modulations caused by polymorphisms on the discharge of the two biomarkers studied in the urine were lower in number and scale than the effects observed in an IPA PAH study. Once again, the cause here was possibly the substantially lower PAH exposure at the bitumen workplaces.

The results of this study will contribute to bitumen's classification as a Category 2 carcinogenic substance being re-evaluated, and to a more health based exposure limit value being redefined in national and international bitumen committees. The detailed study results are presented in a special issue of „Archives of Toxicology“.

Study of welders – WELDOX

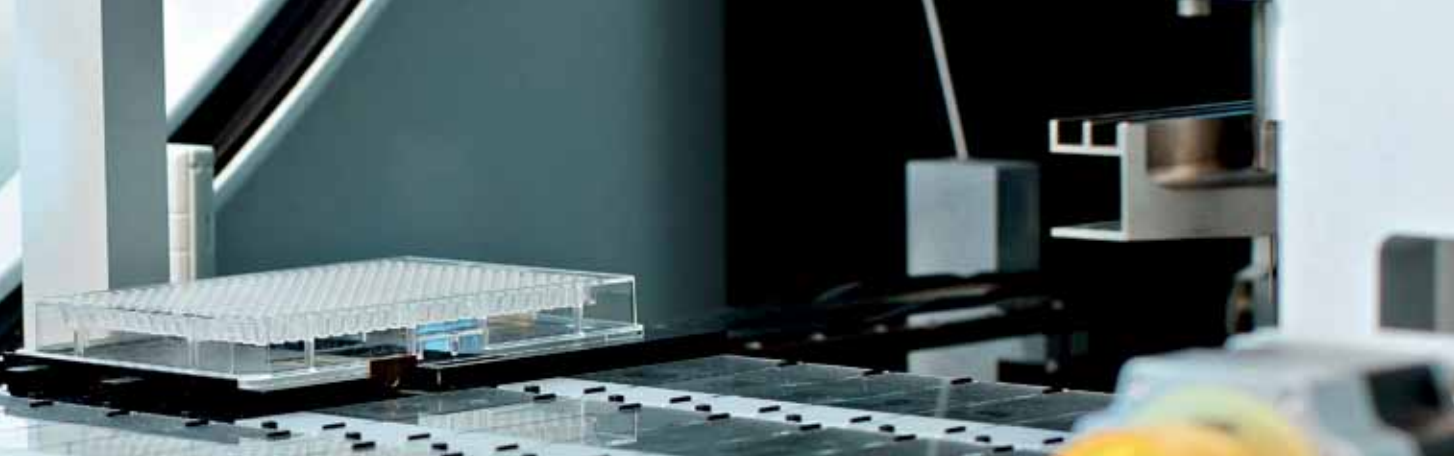
Involving as it does 243 welders, the joint WELDOX study is one of the most comprehensive studies of the impact of metals in welding fumes upon health. A large number of exposure data and biomarkers of exposure and early health effects were recorded. In addition to personal measurements of the inhalable and respirable fractions of the welding fumes, ultrafine particles were measured at some workplaces. In biological samples from various media, the internal exposure to metals, the iron homeo-

stasis, irritative effects and genotoxic changes in white blood cells were determined. New methods for studying the genotoxicity were established in part at the Technical University of Berlin. The exposure data were first interpreted in depth.

The results reveal a very wide spectrum of exposure to welding fumes and metals. Factors influencing the exposure were quantified by means of suitable statistical models. The welding process has a substantial influence on the concentrations of the welding fumes, whereas the exposure to chromium and nickel is determined essentially by the alloy component in the electrode and base metal. In some cases, the occupational exposure limits for respiratory particles were exceeded, particularly where flux-cored wire was used.

The statistical models permit findings that can be used for the prevention of work-related health hazards among welders exposed to particles, chromium, nickel, or manganese. A working group was formed for this purpose; its objective is to validate these models by means of other welding-fume datasets, for example from the MEGA database and that of the British TWI (The Welding Institute).

In consideration of recent studies into the neurotoxicity, the MAK Commission has lowered the proposed occupational exposure limit for manganese to 20 µg/m³ for the respirable and 200 mg/m³ for the inhalable particle fractions. Owing to the thermal metal-treatment process and its relatively low boiling point, the manganese found in welding fumes is predominantly respirable.



On average, the manganese concentrations exceeded the newly recommended occupational exposure limit for the respirable fraction, particularly in common welding techniques such as the metal active gas welding process.

Due to the biological regulation of manganese as essential metal, however, a weak correlation of respirable manganese with manganese in the blood was observed only above an airborne concentration of 50-100 $\mu\text{g}/\text{m}^3$. On average, the manganese concentrations in blood were not elevated. However, some welders exceeded the biological reference value (BAR) value of 15 $\mu\text{g}/\text{l}$ blood.

Direct uptake of manganese into the brain, via the olfactory system cannot be ruled out. In the light of this, possible neurotoxic effects and prevention measures are to be studied in depth in a planned multi-center study among welders. The objective is to assess and improve preventive measures and the medical surveillance of welders.

Impacts of shift work upon health

Shift work is suspected of causing a large number of health complaints and disorders. Employees, particularly those working night shifts, often suffer sleep disorders leading to fatigue, loss of appetite and stomach complaints. Beyond these complaints, epidemiological studies also indicate that shift work may be a contributory factor in the causation of diabetes mellitus, cardiovascular disorders and mental disorders. In 2007, the IARC classified shift work that involves circadian disruption

as „probably carcinogenic for humans“ (Category 2A). This classification is based upon the results of animal experiments, and in particular upon two prospective studies of nurses (Nurses' Health Studies).

The natural alternation between daylight and darkness synchronizes the body's internal clock to the day/night rhythm. This is largely governed by the neurohormone of melatonin, the synthesis of which begins with the onset of darkness and is suppressed by daylight or artificial light at the workplace. Important physiological processes such as sleeping and waking cycles, the metabolism, hormone secretion, immune defence, DNA repair and the degradation of hazardous substances are regulated by circadian rhythms. Disruption of the synchronization of these biological processes by external influence such as night-shift work is termed chronodisruption, and is considered responsible for the occurrence of health disorders. The objective of the interdisciplinary prevention research at the IPA is to examine the mechanisms of chronodisruption on humans, in order to develop concepts for healthy shift systems.

In parallel with this activity and in conjunction with the Bergmannsheil University Hospital in Bochum and the Helmholtz Centre in Munich, a study has been set up to examine the influence of shift work upon sleep, well-being, the hormonal balance and the metabolism. This study, which will be conducted on nurses, is to yield new scientific findings from which recommendations can be derived for healthy shift systems.

The IPA researches – early detection of cancer

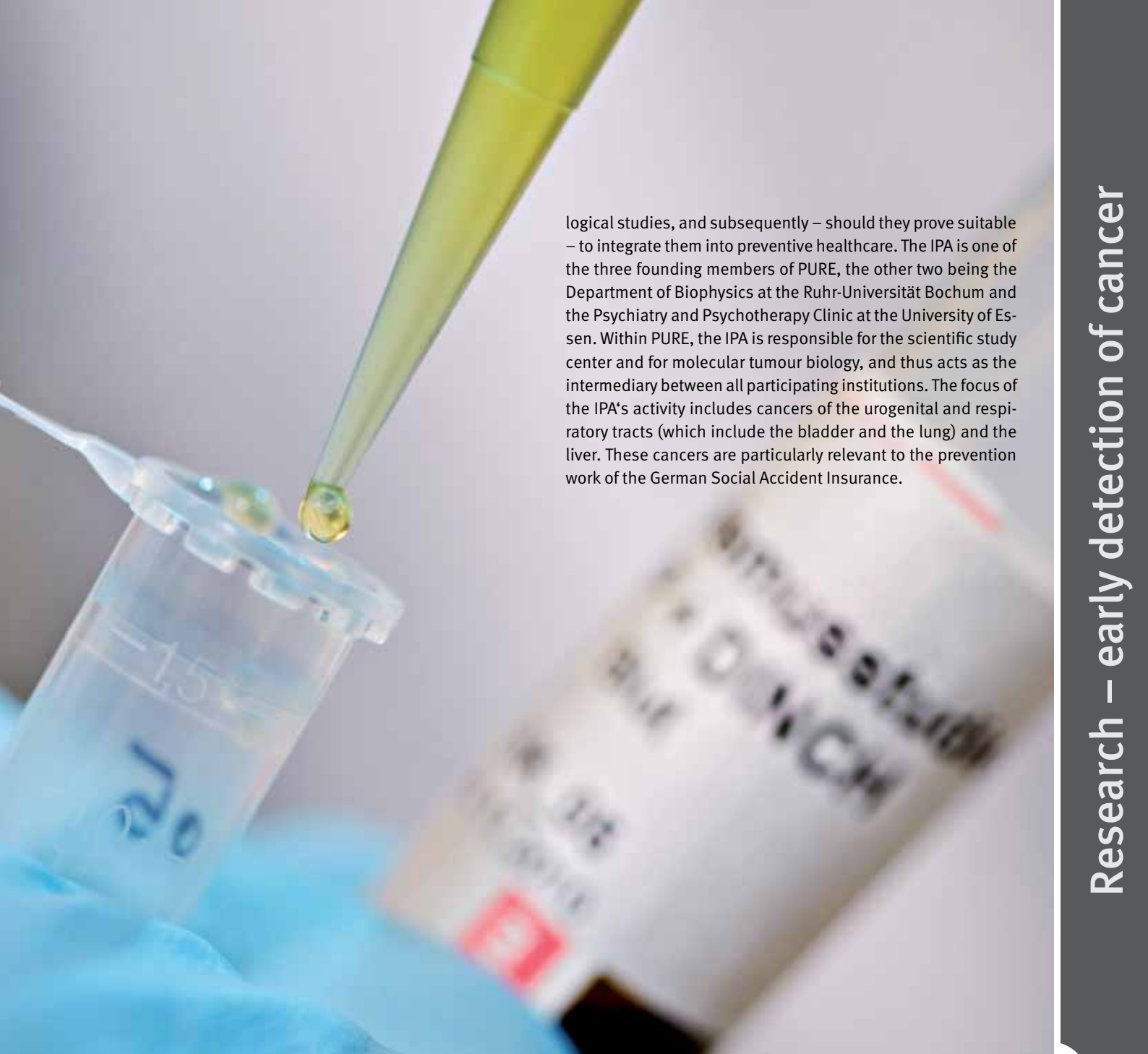
A further important focus of the IPA's research work is the early detection of cancer. Early diagnosis of the diseases is crucial for a successful therapeutic approach. In contrast to radiological methods, the analysis of molecular markers does not involve exposure to radiation. Such examinations therefore meet with greater acceptance among the population.

The „MoMar“ project (molecular markers for early detection of cancer) is concerned with the development and validation in medical practice of molecular markers for the early detection of asbestos-related tumours of the lung and pleura. Mesothelioma, a pleural tumour caused by asbestos constitutes a highly significant occupational health issue owing to its long latency and rising number of cases. Therefore substantial research efforts are still needed. The objective of the prevention study is to validate new molecular markers for early detection in high-risk collectives using the longitudinal design. The markers are determined non-invasively in blood or other body fluids. In addition, the method does not involve radiation exposure for the patient, in contrast to radiological methods. The high-risk collective will comprise 2,000 workers formerly exposed to asbestos and exhibiting asbestosis, who will be examined annually over a period of five years. In contrast to previous, less selective approaches, the prospective study of high-risk collectives enables biomarkers for early detection to be evaluated under substantially more realistic conditions for use in medical practice.

The joint „UroScreen“ project concerning the early detection of bladder cancer is studying the performance of molecular markers for the early diagnosis of bladder carcinomas. Every year, some 28,000 people in Germany are newly diagnosed with bladder cancer. If the tumour can be detected and treated in the early stages of development, the patient's chances of survival are high. Within this study, workers who have been exposed to carcino-

genic aromatic amines and have been examined by the ODIN organizational service for annual surveillance will in addition be offered to the standard program an early detection scheme based on urine-based tumour markers. The aim of this prospective study was to validate the tumour markers studied and to estimate their performance in screening for bladder cancer. The results indicate that the low incidence of bladder cancer impairs the positive predictive value of urine-based tumour markers. Therefore, bladder cancer screening should not be performed in asymptomatic subjects but in the clinical follow-up of cases on recurrence. The relapse rate is very high; a follow-up screening at close intervals is therefore necessary. Reliable non-invasive markers would enable the frequency of painful cystoscopies to be reduced.

PURE (Protein Research Unit within Europe) is an association of several research institutes at the universities of Bochum and Essen. Its aim is to identify biomarkers for the early detection of widespread diseases, particularly cancer and neurodegenerative diseases such as Alzheimer's and Parkinson's. For this purpose, the research institutions involved have been awarded approximately €7.9 million per year until the end of 2014 by the Ministry of Innovation, Science, Research and Technology for the region of North Rhine-Westphalia. The underlying objective is to identify biomarkers for the early detection of cancer and neurodegenerative diseases using a clinical network across Germany, to validate them in large-scale molecular epidemio-



logical studies, and subsequently – should they prove suitable – to integrate them into preventive healthcare. The IPA is one of the three founding members of PURE, the other two being the Department of Biophysics at the Ruhr-Universität Bochum and the Psychiatry and Psychotherapy Clinic at the University of Essen. Within PURE, the IPA is responsible for the scientific study center and for molecular tumour biology, and thus acts as the intermediary between all participating institutions. The focus of the IPA's activity includes cancers of the urogenital and respiratory tracts (which include the bladder and the lung) and the liver. These cancers are particularly relevant to the prevention work of the German Social Accident Insurance.

The IPA researches – Exposure laboratory

Inhalative exposure by gases, dusts and aerosols pose the most common form of health hazard at the workplace. Studies performed under controlled exposure conditions yield valuable findings for the prevention of acute and chronic diseases caused by dusts and hazardous substances, particularly for the setting of exposure limits.

In the IPA's new exposure laboratory (ExpoLab), studies can be performed simultaneously on four test subjects and with simulation of a defined physical (cycle ergometry) and psychological and mental (computer) workload. Besides measurements performed within the project for differentiation between „annoying“ and „irritative“ effects of hazardous substances, neuropsychological test methods are employed in order to record impairments to concentration and attention.

Exposure related effects on airways and lung are also investigated by means of the non-invasive measures established in recent years at the IPA. The ExpoLab can further be used to study resorption of aerosols precipitating on the skin and the correlation between external (inhalative and dermal) and internal exposure. Internal exposures, metabolites of the incorporated substances, and early biological effects can be detected using the institute's biomonitoring methods.

The Expolab technology allows not only exposures to hazardous chemicals, but also to particles and allergens. Co-exposures are common at workplaces and can be simulated by means of two separate ventilation circuits. The safety of the study subjects is assured by validated exposure methods and defined exposure conditions, with a utmost stable temporal and spatial constancy of concentrations in the room air. The exposure conditions are monitored and documented continually by redundant measurements.

Research into irritants

Numerous substances capable of causing unpleasant effects, odors and irritation, health complaints, and in some cases clear disorders of the upper and lower respiratory tracts can be found in workplace atmospheres. Around half of the German limit values for hazardous substances at workplaces relate to the avoidance of irritation. Controlling these effects by means of health-based limit values is often difficult, since human data of validated quality are rather rare.

Since 2003, the German Social Accident Insurance (DGUV) has been supporting an association of research bodies comprising the IPA – Institute for Prevention and Occupational Medicine, the Institute for Research on Hazardous Substances of the BGRCI (IGF), and the Leibniz Research Centre for Working Environment and Human Factors at TU Dortmund University (IfAdo), in order to develop valid study methods and to produce data of assured quality.

The objective of the research at the IPA is to obtain data permitting an overall evaluation of the large number of relevant irritants, based upon the data for individual irritants.

The importance of research into irritants is also reflected by the creation of a working group for the determining of limit values for local effects. The working group was created by the MAK Commission of the German Research Foundation (DFG) and

Subcommittee III of the AGS Committee for Hazardous Substances at the BMAS. Led by the IPA, the working group will consolidate scientific expertise in the area of irritant research, and co-ordinate the work of the MAK Commission, the AGS, and the DGVV and its members.

The aim of the working group is to develop a decision tree for the derivation of occupational exposure limits for hazardous substances with irritative effects. This process will also include the generation of mathematical models to derive safety for limit-setting in national and international bodies and the determination of limit values (DNELs) in the context of REACH.



The IPA researches – Identification, evaluation and measurement of hazardous chemicals

Human biomonitoring

Biological monitoring determines hazardous substances and their metabolites in body fluids. Additionally, it allows for the differentiation between occupational and non-occupational exposures to ubiquitous environmental substances. In contrast to ambient monitoring, biological monitoring covers all exposure pathways, i.e. not only the inhalative but also the dermal and oral uptake.

As a function of the elimination kinetics of specific metabolites, human biomonitoring yields information on both short term hazardous substance exposure occurring over hours, or the last shift (short-term markers), and longer term exposure over days and months (long-term markers). Therefore, at the IPA biomonitoring methods are frequently employed in studies that either detect several metabolites of a hazardous substance simultaneously, or several methods are used in parallel on one particular substance to create the most comprehensive picture of the exposure situation.

In the previous year, several highly specific and sensitive biomonitoring methods were newly developed and implemented in response to a need by the German Social Accident Insurance Institutions to perform organic trace analysis. Methods were designed to measure bisphenol A in plasma, organophosphate pesticides in urine, organophosphate flameproofing agents in urine, metabolites of isocyanates in urine, metabolites of the

solvent n-methylpyrrolidone in urine, and 2,3-dihydroxypropionamide as an oxidative metabolite of acrylamide.

With the newly implemented methods, both internal exposure attributable to the workplace and background exposures among the general population caused by ubiquitous environmental substances could be measured. In addition, an existing method for determining the haemoglobin adducts of aromatic amines was improved to include additional aromatic amines and optimized whereby smaller quantities of blood could be used for analysis.

In the future it is predicted that analysis would require higher detection sensitivity coupled with the greatest possible specificity. To meet these requirements, two analysis systems with the most up-to-date technologies have been established, employing gas chromatography coupled with tandem-mass spectroscopy.

In all methods, priority is placed on acquiring reliable and accurate results, a goal which is achieved by also following the specification of the highest scientific standards. The accuracy of the results is guaranteed by thorough quality control measures within the laboratory and by participation in external quality control measures, such as round-robin tests. At the same time, the IPA's human biomonitoring is, for the first time, also driving round-robin tests at the European level.





The IPA detects diseases simply and early by means of non-invasive methods

Effect monitoring detects biochemical and biological effects which occur in the chain of events between exposure and the resulting health disorder. At the IPA, non-invasive methods (NIMs) such as analysis of nasal lavage fluids, exhaled breath (exhalate), exhaled breath condensate (EBC) or the induced sputum are increasingly applied for the monitoring of effects of occupational exposures on the upper and lower respiratory tract and the lung.

Measurement of the nitrogen monoxide (FeNO) level in the exhalate is a standardized procedure; mobile measurement equipment for this purpose can be used at the workplace. The results support more objective assessment of workplace-related health disorders, and are also used in the production of expert opinions. EBC is used only for research projects. The material properties of the condensation and collecting surfaces of the equipment employed have been identified as major factors influencing the detection of effect biomarkers in EBC. During the evaluation of possible health disorders of occupational origin, non-occupational confounding factors must also be assessed. Analysis of EBC has for example produced information on inflammatory changes in the lung in otherwise asymptomatic smokers.

An analysis of the composition of EBC may also assist in determining the exposure to foreign substances within the target organ 'lung'. During welding work, in particular, metals may also enter the respiratory tract. In a pilot study of asymptomatic welders, promising results indicated that particular exposure conditions at the welder's workplace are reflected in the metal concentrations measurable in the EBC. EBC is therefore an attractive matrix for reflecting both the scale of the exposure and its consequences in the target organ 'lung'.

In-vitro studies to assess chemical hazards and risks

In order to evaluate the risks of hazardous substances at the workplace, studies at the cellular and molecular level are necessary to substantiate and explain findings from occupational epidemiological studies. In turn, results acquired at the bench can then be used to design further studies in the field. At the IPA, cultured cells are treated with various hazardous substances and the resulting changes at the cellular level are determined by comparing treated versus untreated cells allowing the study of their modes of action. The exposure conditions in such model systems can be defined precisely and modified systematically, making it possible to study the effects of single substances, their reactive metabolites, and the mutual action in complex mixtures. The spectrum of cell biological parameters ranges from early changes, such as the induction of enzymes, to late parameters, such as cell death – the final consequence of toxic action. Within the scope of studying the effects of hazardous substances also the Syrian hamster embryo (SHE) cell transformation assay is used to predict the carcinogenic potential of hazardous substances in vitro. This assay has been implemented at the IPA, and is particularly relevant to the work of the German Social Accident Insurance Institutions, especially in the context of risk assessment and the classification of hazardous substances. It is intended to introduce the SHE assay results at both national and international regulatory committee meetings, and to contribute to a scientifically-based classification of hazardous substances. Owing to the potential importance of this test, helping to predict the carcinogenic potential of hazardous substances, tests with several aromatic amines are planned for the near future and it is intended to expand the testing to other substance classes.

The IPA researches – identification, evaluation and measurement of biological hazards



Exposure to wood dust

Around three million workers in Germany are exposed to wood dust. On the one hand, wood dust is classified as a carcinogen; on the other, exposure to it increases the risk of respiratory complaints which could be caused by pathomechanisms of either an allergic or a non-allergic nature. In collaboration with researchers at the Department of Environmental and Occupational Medicine of the University of Aarhus in Denmark, the IPA studied the incidence of sensitization to beech and spruce wood among workers exposed to wood dust.

Allergic reactions of the immediate type were studied closely for a number of woods. Since wood allergens differ widely, specific wood-dust extracts must be studied for each expo-

sure situation. Studies conducted at the IPA showed that the sensitization potential of beech and pine wood dust to be low; in contrast, other wood types, such as tropical woods, exhibit a substantially higher sensitization prevalence. The study of occupational allergies requires not only quality control of the diagnostic instruments, but also refinement of the diagnostic process in consideration of serological and in some cases cellular tests. By characterization of the complex wood-dust allergens and successful identification of proteins not previously known to be allergens, the IPA has been able in recent years to extend wood-dust allergy diagnostics. It is unique in Germany in this respect. The demand for these diagnostic instruments is evidence of their high importance.

Exposure of workers in the waste materials sector to bioaerosols

At workplaces in the waste management industries, exposure to bioaerosols may cause health impairment among workers in the form of irritation of the respiratory tract and skin, up to and including inflammatory changes and allergies. Currently exposed compost workers, former compost workers, and non-exposed control subjects were examined in a cross-sectional study. Compost workers suffered more often from cough and irritation of the eyes compared to the controls. Former compost workers reported similar work-related complaints, but most symptoms had improved or disappeared after cessation of bioaerosol exposure. Lung function parameters of compost workers were within the reference ranges. Nevertheless, forced vital capacity (FVC) was significantly lower than in controls. Since many of the workers were already examined thrice since 1996/7, a follow-up study was performed in this group of workers. After 13 years significantly more workers complained of cough than did so in the first survey. Further preliminary results showed no higher incidence of deterioration of pulmonary function over the study period. Workers in composting plants exhibited on average higher concentrations of antibodies to fungi, whereas the control subjects were more often sensitized to environmental allergens.

The findings from these studies regarding the underlying immunological and toxicological effects of bioaerosols from the area of composting and waste collection/disposal have been published and made available to the accident insurance institutions. A repeat of the examination of the workers also permits evaluation of the protective measures taken in the meantime, and of their effectiveness. The protective measures can be improved further in particular cases as a result. In addition, repeated examination of the workers permits better estimation of the clinical relevance of pro-inflammatory biomarker concentrations.

Animal allergens

Occupational contact with laboratory animals or livestock may induce allergic reactions. Workers in research laboratories in the pharmaceutical industry and at universities, veterinary institutes, livestock traders and veterinary surgeons are primarily at risk. The allergies are caused by proteins contained in the hair, skin scale, urine, saliva and serum of the animals and which are released during contact with them.

Around one-third of exposed persons develop an allergy to laboratory animals. The most frequent symptoms are asthma, rhinitis and conjunctivitis, and more rarely contact urticaria. Of particular relevance in the development of a laboratory animal allergy are the major allergens found in rat and mouse urine. These proteins exhibit the tendency to bind to small particles with very good suspension properties. As a result, they can easily be transported through the air and be inhaled.

For study of the relationship between exposure and the diseases on the one hand, and for creation of suitable measures for reducing or avoiding the allergen exposure on the other, the allergen exposure must be quantified by measurements. These are relatively time-consuming, and consist of dust sampling at the workplace, followed by analysis of the allergens in the laboratory, which is generally performed with the aid of highly sensitive and specific immunological detection methods, such as ELISA. ELISA is currently available at the IPA for the quantification of cow-hair allergens and of mouse and rat urine allergens. The airborne mouse allergens are currently being quantified in collaboration with the Helmholtz Centre in Munich and the German Social Accident Insurance Institution for the administrative sector (VBG) in a laboratory animal facility with a total of 52,000 mice, in order to assess the exposure to laboratory animal allergens in a variety of different cage systems.



The IPA researches – studies of occupational skin exposure

Wet work and protection of the skin

Workers in occupations involving contact to moisture (such as nursing, geriatric care, hairdressing) are exposed to a range of substances which are potentially harmful to the skin (see the TRGS 401 technical rules for hazardous substances). For this reason, moisture-proof gloves are worn. The gloves, which are manufactured from a wide range of materials, provide protection against harmful substances. Beneath them however, irritation and even irritant contact eczema is more likely to occur. This is attributed to the occlusion effect, which is associated with a build-up of moisture (caused in particular by increased perspiration). For these reasons, primary prevention in the form of skin-protection agents is available from a number of manufacturers. These agents are intended for use under gloves, and manufacturers have claimed that these agents stabilize and strengthen the horny layer and prevent it from swelling.

The purpose of the project was to analyze whether the claimed favorable effects upon the skin barrier can actually be expected from the use of skin-protection products under gloves. In an experimental study, occlusive exposure was generated

on test subjects by means of moisture-proof glove material, thereby permitting analysis of the positive and negative effects of the use of typical, commercial skin-protection products under gloves. This was achieved by quantification of sweat and by the recording of irritative skin symptoms by means of non-invasive bioengineering methods for measurement of the skin physiology and by clinical scoring. After occlusion for a defined period of time, an additional standardized irritation followed the occlusion periods, in order to examine the skin's barrier functionality by means of clinical and skin physiology parameters. A subsequent user test determined subjective parameters such as wear comfort, reduction in perspiration, etc.

The results of the study were made available to the accident insurance institutions, and are intended to motivate companies to request evidence for the effectiveness of the skin-protection agents against glove occlusion which are offered to them. For this purpose, manufacturers and accident insurance institutions should reach a consensus in joint committees and discussion fora.



Uptake of hazardous substances through the skin

Toxicologically relevant concentrations of hazardous substances in the human body may be caused by dermal penetration, either separately or in combination with inhalative resorption. Various methods can be used to evaluate dermal resorption. For example *in-vitro* data, including those acquired from the Franz-Kammer model employing human skin, yield initial pointers concerning the quantity of the penetrating substance and the kinetics of resorption. Such *in-vitro* models can also be performed with strongly irritative or carcinogenic substances.

However, only by suitable *in-vivo* systems, such as microdialysis, findings on other relevant factors can be studied, such as damage to the skin barrier or the influence of skin-protection agents. Since uptake of hazardous substances may also occur percutaneously directly from the atmosphere, the contribution made by dermal exposure from the gas phase to the overall exposure can be analyzed in the laboratory in a quality-assured procedure and as a function of the exposed skin area and the physical stress.

In order to assess the dermal resorption of hazardous substances, a combined procedure and comparative study of the hazardous substance under consideration is considered necessary at the IPA, with all stated *in-vitro* and *in-vivo* methods. This procedure is to be conducted within the DermaTox project, which is being performed with the support of the German Social Accident Insurance Institution for the energy, textiles, electrical and media products sector (BG ETEM).

Individual barrier alterations of the skin can also be quantified by means of bioengineering methods established at the IPA. They are applied, as part of the wider procedure, to measure the skin function and skin barrier at the exposed areas. The battery of tests enables a large number of different hazardous substances to be tested with regard to their skin-penetration properties. The results will provide a scientific basis for consulting with the accident insurance institutions on dermatological and toxicological issues and for the development of concepts for primary prevention for workplace substances capable of penetrating the skin.



Studies of UV Radiation Exposure

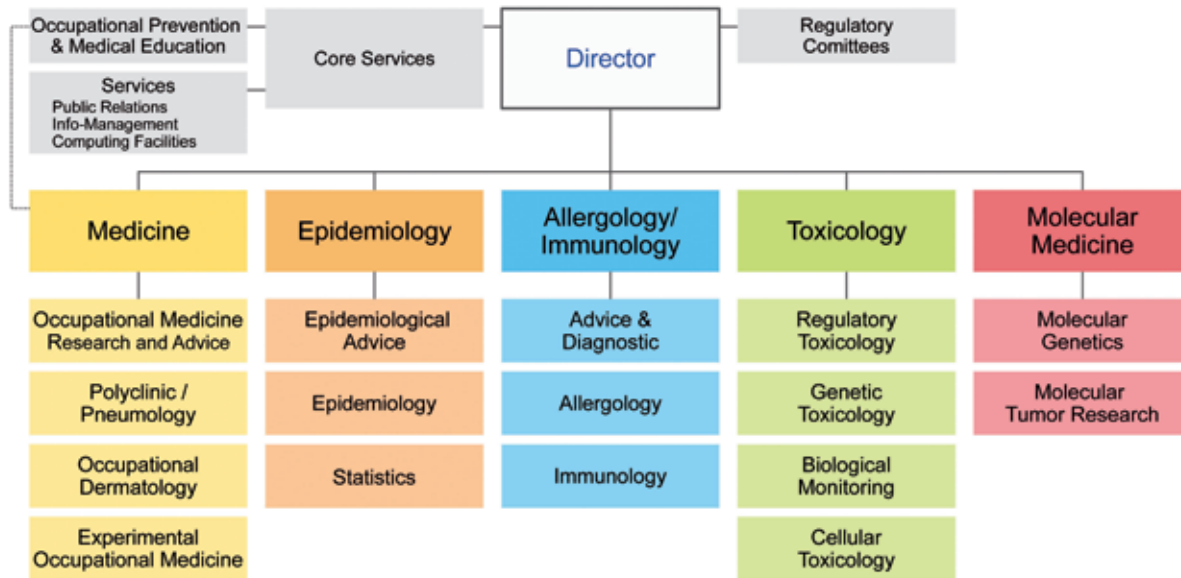
The aim of this dermatological/occupational medical multicentre study is to develop and validate instruments for dermatological recording and quantification of the damage caused to the skin by UV radiation by occupational and non-occupational exposure.

For this purpose, a number of university institutes and the IPA will join in studying age-defined collectives in order to establish a grading system that enables the severity of skin damage caused by UV light to be determined uniformly. This is particularly relevant, since it is known that the occurrence of squamous-cell carcinomas of the skin, including actinic keratoses, may also be relevant in cases of occupational exposure to UV radiation. To date however, uniform, evidence-based criteria have been lacking by which occupational and non-occupational causes may be distinguished clearly and demonstrably.

In the research project, standardized, reproducible instruments are to be developed for dermatological recording and quantification of the damage caused by light on occupationally and non-occupationally exposed skin areas in collectives. At the same time, standards will be established in conjunction with the IFA and the prevention services of affected individual accident insurance institutions for determining and evaluating occupational and non-occupational exposure.

Altogether, the research project is expected to develop and validate criteria which enable a case of skin cancer caused by occupational factors to be distinguished from one caused by non-occupational factors. These criteria are absolutely essential for expert reports on the occupational origin of skin cancer. The results of the research project are to be incorporated into recommendations for expert reports, such as the Bamberg Medical Bulletin.

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