



IPA

Institute for Prevention and Occupational Medicine
of the German Social Accident Insurance
Institute of the Ruhr University Bochum

Facts & Figures



Medicine



Epidemiology



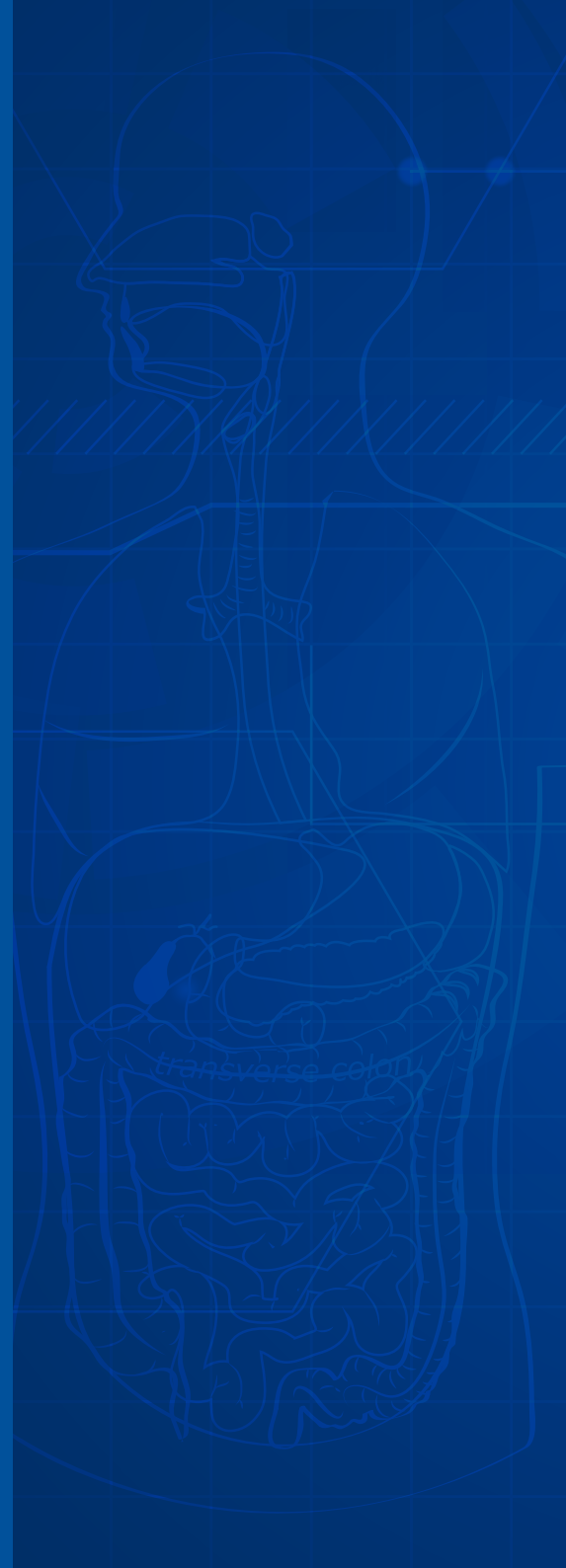
Allergology/Immunology



Toxicology



Molecular Medicine



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Organisation

The IPA in Facts and Figures

The Institute for Prevention and Occupational Medicine (IPA) is the occupational medical research institute of the German Social Accident Insurance. The IPA supports the DGUV (German Social Accident Insurance), and the accident insurance institutions for the industrial and public sectors (the BGs and the public-sector accident insurers respectively) in fulfilling their legal tasks. As a full-fledged research institute of the Ruhr University Bochum it is also responsible for teaching and training in occupational medicine. Thus it is positioned at the interface between occupational medicine research and practice for health protection at the workplace and in educational institutions. With this dual function, the IPA occupies a unique position in the German university landscape.

The world in which we live and work is currently undergoing a profound transformation that comprises all areas of digitalization, industry 4.0, and work 4.0 are just catch phrases that describe this phenomenon. The new technologies and the resulting opportunities – both opportunities and risks – are associated with far-reaching changes for everyone involved.

Today more than ever, occupational medical research is geared towards creating the basis for effective and efficient preventive work. Both the development of new technologies, a multitude of new hazardous substances and, in some cases, completely new risks for people at the workplace indicate that the exposure scenarios are becoming increasingly complex. All this poses constant new challenges for occupational medical research.

We hope you enjoy the new facts and figures. We are looking forward to your feedback.

A handwritten signature in black ink that reads "Thomas Brüning". The signature is written in a cursive style with a large, looped 'B'.

The IPA *in brief*

The Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA) is an institute of the Ruhr University Bochum. It serves as an interface between research and workplace practice in occupational safety and health, safeguarding the health of around 80 million insured individuals at the workplace and in educational establishments. The institute is characterized by its orientation towards preventive health protection.

The focus of IPA's work lies upon the impact of workplace hazards upon health, such as inflammation, cancer and allergies, and the effects of irritants, hazardous substances and odors, particularly in the context of synergistic, i.e. combined effects of workplace exposures. Further key topics are the effects of particle and fiber exposure, the physical effects of UV radiation, and the impact of shift work upon health.

The IPA pursues an interdisciplinary strategy in developing and applying biomarkers for the early detection of cancer, for use in the field of follow-up screening examinations of insured persons with recognized occupational disease.

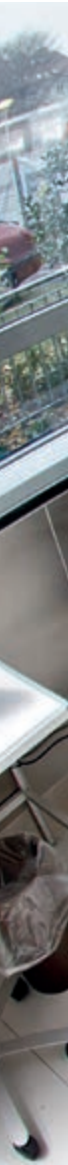
The Institute for Prevention and Occupational Medi-

cine of the German Social Accident Insurance (IPA) in Bochum has five competence centers. Their respective core disciplines are medicine, epidemiology, allergology/immunology, toxicology and molecular medicine.

The competence centers conduct interdisciplinary research in close cooperation with each other. Together, they address issues arising in the field of prevention and occupational diseases. For this purpose, they are in continuous dialogue with the German Social Accident Insurance Institutions. Strategies for solutions are then developed in the form of consulting or research projects, and the results of these projects introduced into practice.

IPA's work focuses on questions concerning the health effects of harmful substances on humans. The IPA is an independent research institute within the German statutory accident insurance system. Its structure is possibly unique worldwide, with the institute conducting research at the interface between occupational medical research, industrial practice, and the safety and health of insured individuals.

The methods employed at the IPA's five competence

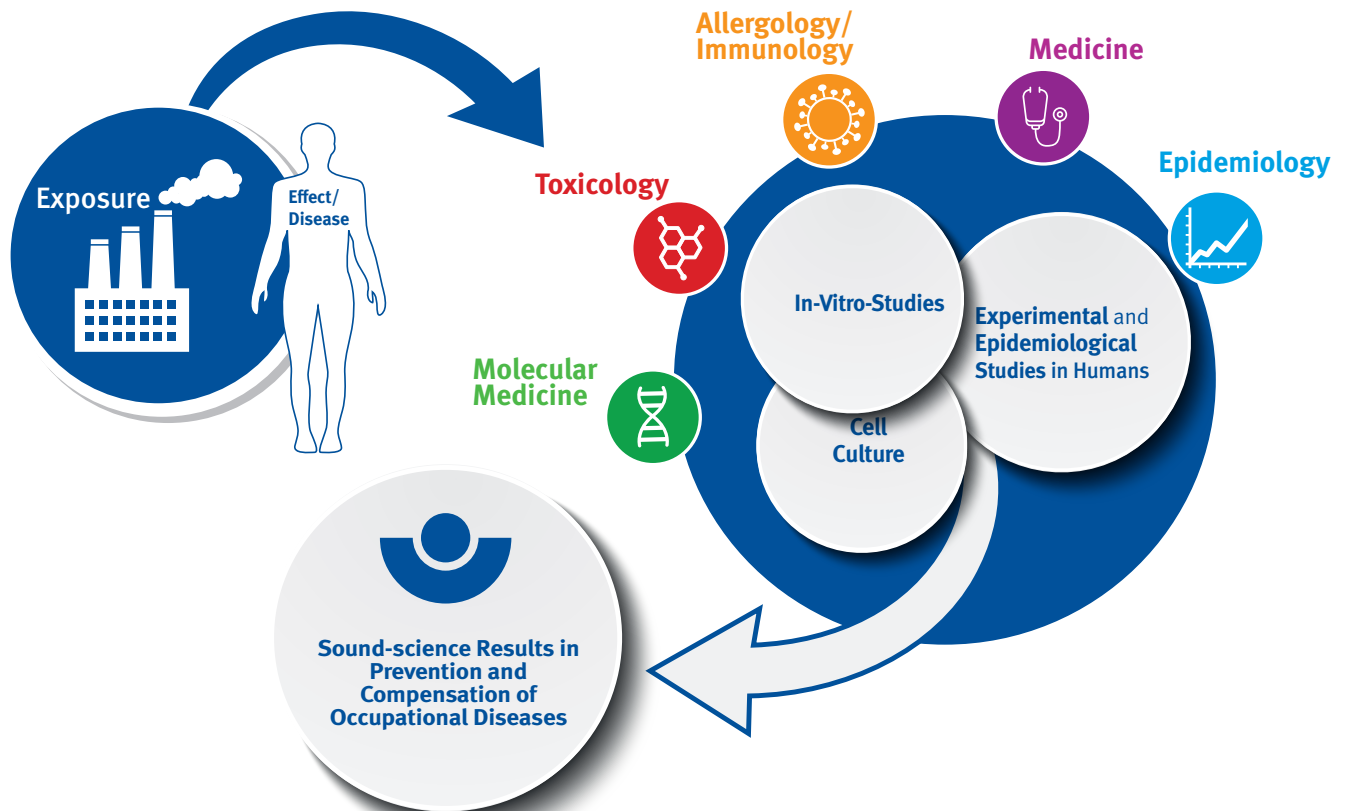


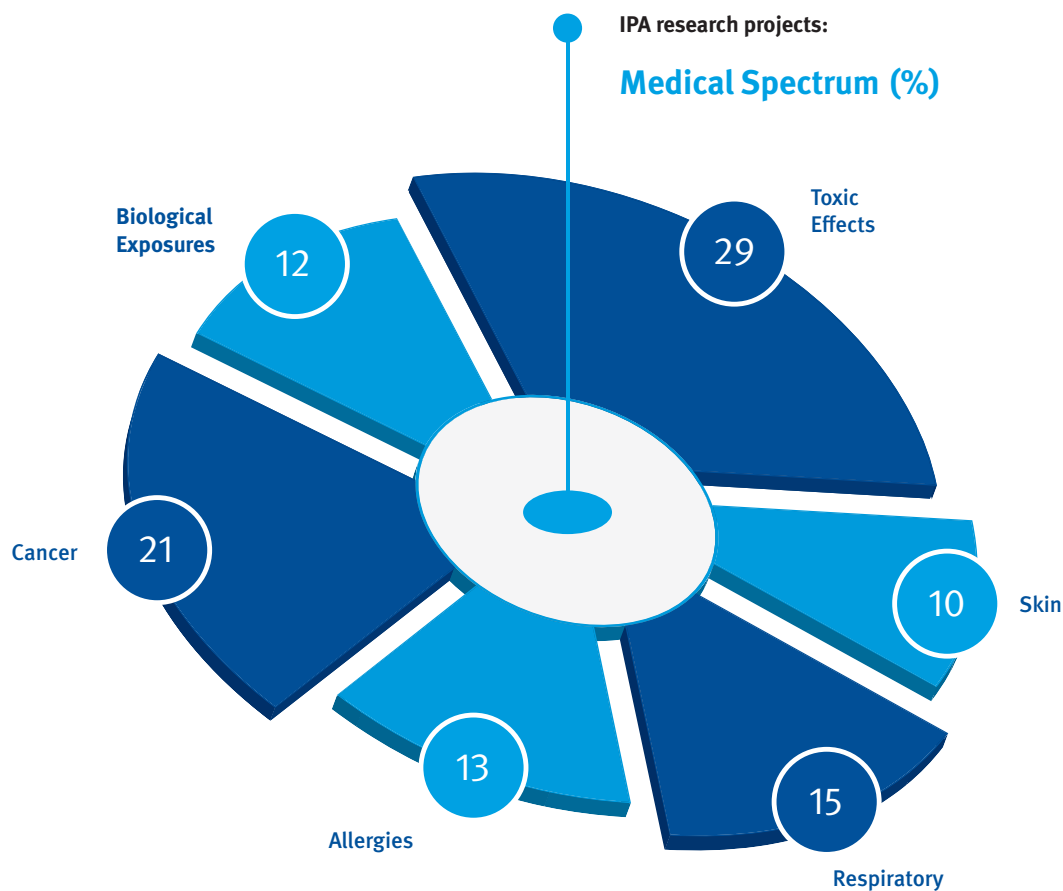


centers comprise modern occupational medical, pneumological and dermatological methods and a wide range of techniques for allergological and toxicological diagnostics and exposure assessment. These include analytical methods as well as *in vitro* methods using cell cultures. In addition, IPA maintains an exposure laboratory for human studies in which standardized conditions for exposure to gases and particles can be

studied with respect to effects upon humans in a standardized manner. Together with the German Social Accident Insurance Institutions, companies, and the insured individuals, the IPA is able to conduct studies directly at the workplace.

No less important for the entire field of prevention and occupational disease is to introduce these research results into the work of regulatory occupational safety





and health committees. These primarily include the committees of the statutory accident insurance system, but also those of the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) of the German Re-

search Foundation (DFG), the AGS Committee for Hazardous Substances and the Committee for Occupational Medicine of the Federal Ministry of Labour and Social Affairs (BMAS), and the Commission on Genetic Testing (GEKO).

Many scientific findings are equally important for prevention and the formal recognition of occupational diseases. This specifically concerns not only the prevention of occupational diseases, but also their diagnosis,

exposure assessment, and establishment of criteria for the formal recognition of occupational diseases. In order to ensure lasting occupational medicine care of companies and public institutions, IPA as an institute

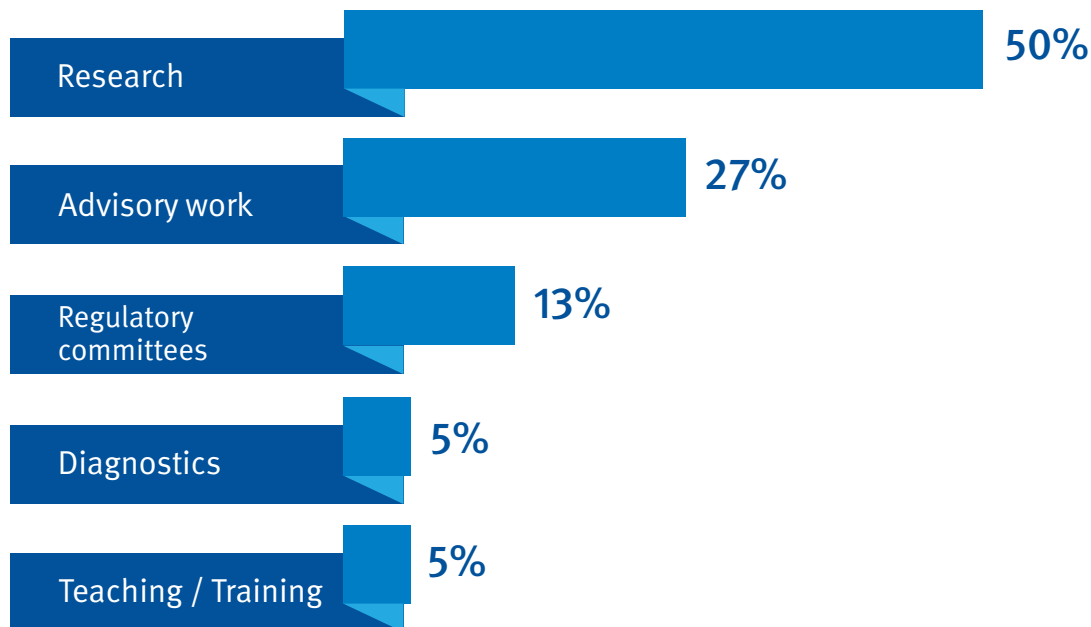


of the Ruhr University Bochum is responsible for medical academic research and teaching in occupational medicine at the Ruhr University and is also active in the advanced training and continuing education of physicians.

The simultaneous positioning of the IPA in the areas of research, committee work, teaching, continuing education and training, together with its close coopera-

tion with the accident insurance institutions, ensures that high-level research is conducted with practical relevance, consulting is appropriate and competent, and committee work is efficient and productive. Issues arising in industry and regulatory committees can be addressed directly by IPA's research projects, and its findings fed back swiftly into industrial practice and regulatory committees.

IPA: Major Tasks



Challenges of *Occupational Medicine*

*in tomorrow's
World of Work – an Interview*

3

Questions

Professor Thomas Brüning
Director of the IPA



The digitalization of work – better known under the slogan “Industry 4.0” – has triggered not only a dynamic development, but also a discourse about its consequences. Digitalization promises economic advantages and increased technical safety, the latter having positive consequences for health at the workplace. As always, however, progress

has its downsides: new health risks and previously unknown health hazards will emerge with potentially negative consequences for worker’s health. In this interview, Professor Brünig answers questions concerning the challenges that occupational safety and health will face in the future as a result of the technical revolution.

1

Professor Brüning, what opportunities does digitalization offer for occupational safety and health?

Future-oriented occupational safety and health must exploit modern technologies – especially those of industry! In many areas, such as Industry 4.0 or highly automated driving, occupational safety and health will in fact benefit from these technologies. Consider, for example, sensor-controlled, intelligent measurement and control systems that can significantly minimize health hazards.

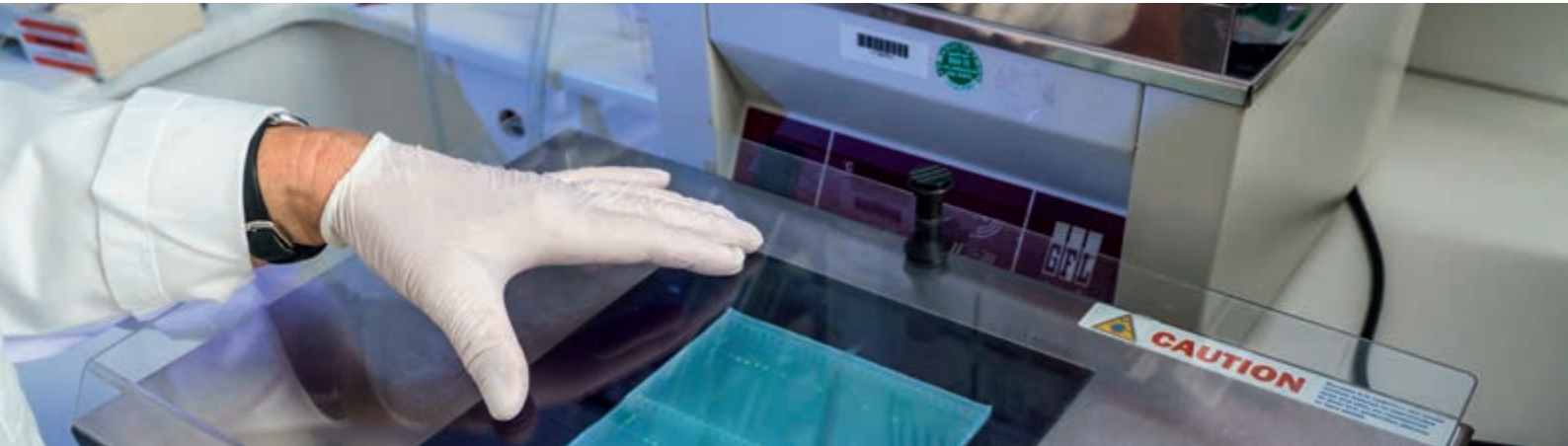
More importantly digitalization will result in rapid medical progress. An example is biomedical research, in which quality-assured prevention measures – such as diagnostic measures for the early detection of neurodegenerative diseases or early-stage cancer – will be an important contribution to retain the health of elderly workers. Another examples are health-associated databases: the data that we are now beginning to store in such databases are growing strongly, and making use of this "big data" is already part of new technologies. I am convinced that technological development, in particular in the manufacturing industries, will offer many opportunities to positively influence the safety of workplaces and worker's health.

Digital networking may offer further opportunities. For example, new technologies may better assess intermittent exposures which are caused by non-standardized and flexible working hours and conditions. New technologies may also unravel the complex interaction between work- and environmental-associated causes of disease.

2

What kind of challenges do you see with regard of these developments?

The many changes taking place at the same time will, in my opinion, develop an enormous momentum of their own. The countless technical innovations are inevitably accompanied by new types of risk and will ultimately lead to equally dynamic changes in the risk scenarios at the workplace with, most likely, adverse consequences that are neither intended, nor predictable at the present time. Transparency, overview and control are all at risk of being lost. Differences between countries in their regulatory provisions and assessment criteria will make things even worse. In addition, these changes are by no means taking place within structures that are well organized and stable. On the contrary: non-standardized and flexible working hours with intermittent exposures will increase. It will become increasingly difficult to ascertain the causes of work-related diseases in the years to come and to clearly distinguish work-related diseases from those which are associated to the environment and based on individual lifestyle factors. A particular challenge is that potential causes of diseases (such as exposure to hazardous substances, an unbalanced diet or irregular eating, lack of exercise) may equally occur at the workplace and in everyday life. Therefore, the risks of occupational, lifestyle and environmental factors are converging. This means that recognizing and assigning these risks and separating them from each other will become an almost impossible task.



3

What needs to be done?

We must adapt our research in occupational medicine to the upcoming changes in exposure conditions and risk scenarios at the workplace. We need new studies and measures to evaluate hazards and risk which are based on the best available scientific standards and by using the latest technologies in the field. If we are to have any hope of coping with the momentum, we need to implement, as I would say, a predictive research concept which is capable of quickly transferring the results which have been obtained from one risk scenario to another. Such a concept must have two essential cornerstones: the identification of key mechanisms which can lead to work-related diseases and the development of markers for the early detection of diseases. The former is most important for hazard assessment and to prevent workers from becoming ill, the latter for

health surveillance in case health hazards are not being recognized at all or recognized too late. Effective organizational measures are also required. This means more intensive cooperation between researchers, industry, and regulatory authorities in occupational medicine. The aim is to make most efficient use of national and international networks. This also includes the use of the unique knowledge of the highly specialized members of the statutory accident insurance institutions in Germany. Finally, we must establish an efficient early-warning system for emerging risks at the workplace.

Of course, it will not be possible to fully investigate hazards and risks in the future either. For example, there will be always workplaces where contact or handling of hazardous substances cannot be avoided. There, a greater emphasis is needed on secondary health preventive measures. Everyone needs to benefit from the progress in safety and health resulting from Industry 4.0.

The IPA

our Competences

The IPA is organized in the five competence centers of medicine, toxicology, allergology/immunology, molecular medicine, and epidemiology. The competence centers cooperate closely.

Medicine

The Competence Center of Medicine comprises the following sections:

- Occupational Medical Research and Consultancy
- Outpatient Clinic/Pneumology
- Occupational Dermatology
- Experimental Occupational Medicine

Traditionally, research by the Competence Center of Medicine has focused primarily on respiratory diseases caused by hazardous substances. The problems addressed range from prevention of and compensation for diseases caused by silica dust, asbestos and organic dusts, through occupational allergies, to acute and chronic irritative effects. The center uses a large number of cutting-edge medical diagnostic methods, in some cases in close cooperation with the Bergmannsheil University Hospital, in order to prevent and assess

occupational diseases. Among these, non-invasive diagnostic methods are of growing importance. 700 to 800 patients are examined in the outpatient clinic each year. To these several hundred test subjects taking part in the numerous IPA experiments and field studies are added.

In the area of clinical and experimental occupational dermatology, studies are performed into occupational skin diseases and their prevention. Clinical studies are also conducted with respect to skin cancer caused by UV radiation, and experimental *in vivo* and *in vitro* studies regarding 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 occupationally relevant substances for possible occupational contact allergies. For this purpose, the expertise in occupational dermatology and allergology is combined with the IPA's analytical and toxicological expertise.



Experimental occupational medicine focuses on clarifying the acute effects and their mechanisms following occupational exposure to hazardous substances. Examples of the issues to be addressed are inflammatory effects of (nano-)particles and the mutagenic action of carcinogens in cells, and also acute effects of irritants in the human respiratory tract. Methods employed range from experiments on cell cultures to controlled studies on human study participants in the exposure laboratory (ExpoLab). 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 Competence Center of Medicine extensively consults with the German Social Accident Insurance (DGUV) and the individual accident insurance institutions on issues of prevention and compensation. In addition, the competence center's researchers participate in state and research advisory committees. Besides conducting research studies, the occupational physicians conduct medical surveillance examinations of employees of various companies.

Toxicology

The Competence Center of Toxicology comprises three closely interconnected sections:

- Human biomonitoring of Exposure
- Effect Monitoring
- Hazard and Risk Assessment

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 exposure and effect biomarkers. The main focus is on the effects of carcinogenic, mutagenic and reprotoxic substances in humans. All routes of uptake (inhalative, dermal and oral) are taken into account and the resulting biologi-

cal effects are quantitatively measured. Studies on human subjects are performed concurrently with studies in cells (*in vitro*), in order to decode the mechanism of action of the damage caused by the hazardous substances. The results obtained from such studies are relevant to the development of preventive measures and for the compensation of work-related diseases.

In addition to research, members of the Competence Center of Toxicology participate on 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 Ger-



man Research Foundation (DFG), and on 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 in developing and implementing health preventive measures at the workplace. For example, the center supports the accident insurance institutions in issues of primary and secondary prevention, based upon the latest sound-scientific knowledge. Hazardous substances currently in the spotlight are carcinogenic and reprotoxic substances for which health-based occupational exposure limits are unavailable due to the lack of data.

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

Finally, the Competence Center of Toxicology offers a wide range of human biomonitoring analysis methods for detecting exposure to hazardous substances commonly found at the workplace. Quality-assured methods 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. These analyses can be used to distinguish between work-related and environmental exposures and to directly support preventive measures at the member companies of the statutory health insurance.

Allergology/Immunology

The Competence Center of Allergology/Immunology comprises the following sections:

- Allergology
- Immunology
- Consultancy and Diagnostics

The competence center focuses on the study of pathomechanisms which lead to the incidence and persistence of respiratory diseases caused by occupational allergens and irritative 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 and characterization of occupational sources of sensitization. Besides the irritative and sensitizing effects of occupational hazardous substances, substances with annoying effects and their influence upon immunological processes are increasingly being addressed. Research activities include studies of occupational allergies caused by flours, enzymes, mites, fungi, natural rubber latex, animal dander, wood dust, and low-molecular substances such as isocyanates and acid anhydrides. Immunological methods are also created for allergens and microbial components in order to monitor and quantify these agents with high sensitivity at workplaces. To detect inflammatory processes, non-invasive methods for collecting samples for various parts of the respiratory tract are increasingly being applied for analyzing cellular and soluble components, among other parameters.



The results obtained by the competence center are integrated into the standardized methods for the diagnosis of allergic diseases of the respiratory tract and into assessment of the clinical and diagnostic relevance of non-invasive methods. The competence center's researchers are involved in the conception of national guidelines and international consensus papers on 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 on national and international boards of scientific societies, and on the WHO/IUIS Allergen Standardization Committee and the IUIS Allergen Nomenclature Sub-Committee.

For the statutory accident insurance institutions and for the production of expert opinions related to workplace-related health disorders, the Competence Center of Allergology/Immunology offers specific serological antibody detection, primarily to occupational allergens, and also the quantification of selected occupational allergens in material, dust, and airborne dust samples.

Another 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 of Molecular Medicine is divided into the following sections:

- Molecular Cancer Research
- Molecular Genetics

The Competence Center of Molecular Medicine uses modern molecular biological methods and biobanking to address a wide range of issues affecting 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 major impact upon affected insured individuals, is a particular focus of the competence center's research activity. Effective and minimally invasive early detection of disease is an important addition to the traditional methods of follow-up examinations.

The competence center studies specific effects of hazardous substances upon genes and their regulation, and thus the mechanisms of cancer development. Cutting-edge analysis methods are employed in order to identify specific patterns in gene expression and new biomarkers for early detection of cancer, with a priority on biomarker validation in large-scale prospective studies which includes the establishment of a large biobank of prediagnostic samples. A further research focus lies upon the relationship between sequence variations in the genes of enzymes metabolizing foreign substances, and susceptibility to occupational hazardous 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 threshold values. As a result, expertise and the latest findings from research into molecular interrelationships can be channeled directly into regulatory committees, such as the MAK Commission of the German Research Foundation (DFG).

The acquisition of sufficient and suitable samples from exposed subjects and the interpretation of complex findings gained from these samples requires close cooperation with the other competence centers and international partners. Together with all other competence centers, interdisciplinary approaches are pursued regarding early detection of cancer by biomarkers in follow-up examinations for employees formerly exposed to hazardous occupational agents. In cooperation with partners in Australia, Mexico, Greece and other countries, a large network for improving diagnosis of mesotheliomas has been established. The successful development of a new blood test for mesotheliomas has resulted from these collaborative activities.



Epidemiology

The Competence Center of Epidemiology is divided into the following sections:

- [Epidemiology](#)
- [Statistics](#)
- [Epidemiological Consulting](#)

The Competence Center of Epidemiology supports the German Social Accident Insurance and its members, and various other bodies, in evaluating the epidemiological evidence of the effects of hazardous substances and working conditions on health. Examples of current research and consulting projects include health effects of shift and night work, occupational exposure to asbestos, welding fumes, metals (such as hexavalent chromium and nickel), dusts (particularly fine silica dust), polycyclic aromatic hydrocarbons, and aromatic amines. Furthermore, research into biomarkers for the early detection of cancer and into subclinical markers, for example in welders, have been major topics of the competence center's work. The competence center supports the IPA by contributing 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 the AGS Committee for Hazardous Substances of the Federal Ministry of Labour and Social Affairs (BMAS). Epidemiological evaluation is crucial in the context of the classification of hazardous substances and the determination of occupational exposure limits. The institute's interdisciplinary expertise ensures a perspective that also considers mechanisms and molecular aspects.

The competence center's key research approaches are exposure assessment based on measurement data and molecular epidemiology for evaluation of the carcinogenicity of hazardous substances, particularly when substances exert synergistic effects, and the early detection of disease. These activities are usually conducted in multi-center projects and in collaboration with experts from other research institutions.

In addition, the Competence Center of Epidemiology supports the IPA's other competence centers in the planning and performance of studies according to good epidemiological practice. For quality-assured results, a wide range of study instruments including operation manuals with detailed SOPs and quantitative exposure assessment are required. A central element of the evaluation strategies includes the application of appropriate statistical methods, which take into account possible influencing factors for the analysis of complex datasets.

The IPA

advises and supports

It is important to the IPA that its research findings be requested and well known by accident insurance institutions and state regulatory bodies. This results in the findings being taken into consideration in these bodies' preventive and legislative work and often translated into daily practice. The institute's expertise is frequently requested. The IPA reacts promptly to the research and consultancy needs of the statutory accident insurance institutions. This goal is also achieved by participation in and close cooperation with national and international regulatory bodies and specialist associations.

The IPA is therefore active at 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 Committees for Hazardous Substances (AGS), Biological Agents (ABAS) and Occupational Medicine (AfAMed) 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) and the Ordinance on bio-

logical agents (BioStoffV), and the introduction of the Ordinance on preventive occupational medical care (ArbMedVV) – have led to a considerable increase in the committee work required by the accident insurance institutions for occupational medical issues.

Some years ago, a risk acceptance concept (Technical Rule Hazardous Substances 910) was developed in Germany that outlines an acceptable and tolerable risk at the workplace. Through the derivation of health-based exposure-risk relationships for specific carcinogenic substances, this approach allows separate, risk-based limit values according to previously defined acceptable and tolerable risk levels.

Staff of the IPA participates in relevant working groups responsible for risk acceptance and risk assessment which develops guidelines on how to derive the new exposure-risk relationships – or, if the assumed mechanisms allow, threshold limit values for individual carcinogenic substances.

The IPA is also active in working groups concerning metals, fibres, dusts etc. Major achievements were





the adoptions of new general limit values for PCBs and diesel engine emissions by the AGS.

Conversely, for non-carcinogenic hazardous substances, the most sensitive reaction is the local irritative effect. In recent years, occupational exposure limit values (OELs) for various local irritants affecting the eyes and the upper respiratory tract have been adopted by the AGS and the MAK Commission based on a guidance concept prepared by a generic working group with several members from the IPA. The working group had concluded that, extrapolating from animal studies, an interspecies extrapolation factor of 3

should be applied for local sensory irritants without reliable human data, unless individual data argue for a substance-specific approach.

In addition, the AGS recently adopted a new OEL for naphthalene which was based on a comprehensive study led by the IPA on naphthalene-exposed workers at abrasives production plants in Germany and Austria.

Results of other research projects such as the IPA studies of workers exposed to bitumen or of welders are also likely to be relevant in current and future discussions of the regulation of related exposures.



The IPA is also represented on AfAMed (the committee responsible for occupational medicine) of the BMAS. This committee develops rules and provides suggestions for the application of the new Ordinance on preventive occupational medical care (ArbMedVV), drafts recommendations for optional check-ups and concepts for workplace preventive healthcare, and advises the BMAS in all issues of preventive occupational medical care and occupational medicine.

Criteria for mandatory examinations, in particular for carcinogenic substances, are also discussed in this

committee. The Ordinance on occupational preventive medical care lists various tasks involving hazardous substances for which mandatory examinations are specified. However, since 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 regarding conceptualizing of basic principles for the development of action values and setting of standards for the implementation of various occupational medical preventive measures.

Through the German gene diagnostics act (GenDG), adopted in 2009, the German lower house has for the first time defined statutory framework conditions for genetic studies on human beings. One section of this act governs genetic studies in working life and has the purpose of ensuring 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 sets 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 by committees at international level, such as the Joint FAO/WHO Expert Committee on Food Additives and the ACGIH/BEI Committee on Threshold Limits of Hazardous Substances in Biological Materials.



The IPA *teaches and trains*

The IPA is a full member of the medical faculty of the Ruhr University Bochum and gives lectures on occupational medicine and health protection within the scope of the German medical licensing act for physicians.

Next to studying the basic principles of the German social security system medical students in their second year attend a cycle of lectures focusing on educational targets in occupational medicine, work-related diseases, and skills in toxicology, epidemiology, preventive instruments and methods. The students are introduced to practical examination methods from their first study year, practising problem-oriented learning in small student teams. In-depth clinical knowledge is extended by case reports. Skills in day-to-day clinical routines are practised in repeated exercises and regularly evaluated. Organized site inspections in a number of industrial sectors afford first-hand knowledge on the tasks of occupational physicians. By inspecting different branches of industry, students acquire knowledge on strategies and measures for health protection directly

at workplaces and talk to safety experts and occupational physicians in companies.

In addition, IPA staff lecture students in the faculty of biology and biochemistry in the areas of immunology, experimental allergology and molecular medicine. Work placements are also offered for these subjects. A doctoral thesis can be completed at the IPA. Over ten internal and external doctoral candidates are currently being supervised by scientists at the various competence centers.

Together with the Universities of Duisburg-Essen and Dortmund, the IPA conducts the structured PhD programme "Epidemiology and Clinical Research". The aim of this programme is to equip young scientists in epidemiology and medicine for their own research activities through methodically oriented, structured training.

The IPA provides state-of-the-art graduate training in





occupational toxicology as part of the federal state of North Rhine-Westphalia master's degree program in toxicology at the University of Düsseldorf. The aim is to educate and train the next generation of young and talented scientists to conduct innovative research, particularly at higher education institutions, in order to improve overall human health.

In cooperation with the medical association of Westphalia-Lippe, the IPA offers a full course of training in occupational medicine leading to the qualification as a consultant in occupational medicine and supplementary qualification in occupational medicine. Furthermore, it conducts monthly training colloquia on up-to-date topics relevant to the work of occupational physicians.

IPA researches

Interdisciplinary and in close Cooperation

The IPA pursues an interdisciplinary strategy in developing and applying biomarkers for the early detection of cancers, among other things for use in the field of follow-up screening of insured persons with already recognized occupational diseases. The five competence centers conduct interdisciplinary work in close cooperation with each other. Together, they address issues arising in the field of prevention and occupational diseases.

The focus of IPA's research lies upon the impact of workplace hazards upon health such as:

- Inflammation research
- Epidemiology of Occupational Cancer
- Early Detection of Cancer
- Research into Hazardous Substances
- Occupational Allergies
- Occupational Dermatology
- Impact of Shift work
- IPA-Biobank

Inflammation Research

Inflammatory processes are involved in a large number of occupational diseases, and are particularly common in the early stages of diseases associated with exposure to hazardous substances. From a regulatory perspective, the avoidance of inflammatory processes is therefore often the decisive criterion for the setting of limit values. This applies not only to hazardous sub-



stances acting locally on the respiratory tract or the skin, but also to noxae with a systemic effect. Acute inflammatory processes are an early and beneficial defence mechanism of the organism, and usually fade away without effect. Depending upon the level, duration and repetition of exposure, an acute inflammation can however become a chronic inflammation, resulting in manifest damage to tissue and/or impairment of function.

It is therefore crucial to better understand the inflammatory processes and their significance in the development of diseases using a human-based approach in order to derive successful concepts for prevention, including the setting of limit values.

A particular challenge is to estimate the adversity of inflammatory processes caused by hazardous substances. While clinically evident changes can be assessed with respect to their adversity and considered during the setting of limit values, it is often unclear to what extent initial deviations, particularly changes in the concentration of individual inflammatory markers, should be regarded as physiological (immune) responses without further consequences, or as initial indicators of



processes that are harmful to health and thus relevant to the setting of preventive measures or limit values.

At the IPA, non-invasive methods are used to detect processes in the target organ: the upper and lower respiratory tract, lungs and skin. In addition to clinical and skin physiological findings, biochemical, molecular or cellular changes to the organism are used as biomarkers that reflect the scale of exposure to the hazardous substance or the biological reactions resulting from exposure. On the one hand, the questions are dealt with in field studies. On the other hand, standardized exposures to skin-irritative substances are carried out in the skin physiology laboratory of the IPA. Particles or gaseous irritants are studied on suitable test subjects in a special exposure laboratory (ExpoLab). Inflammation processes, including mechanisms of action of cellular signal transmission, can be studied down to the molecular level in *in vitro* studies on cell cultures (in the cell laboratory); test systems for rapid and low-cost assessment of the toxic effects of new and legacy substances (including nanoparticles and diesel-engine emissions) are also developed and employed.

Non-invasive Methods

Effect monitoring is a suitable strategy for detecting biochemical and immunological effects occurring in the chain of events between exposure and a resulting health disorder. At the IPA, non-invasive methods (NIM) such as the collection and analysis of nasal lavage fluid (NALF), exhaled breath condensate (EBC) or induced sputum are increasingly being applied for the monitoring of effects caused by occupational exposure

in the upper and lower respiratory tract and the lung. Inflammatory biomarkers including differential cell counts aid in the subtyping of respiratory diseases and help to define asthma and COPD phenotypes.

Assessment of NO in active exhalate (FeNO)

Assessment of NO in active exhalate (FeNO) is a standardized procedure reflecting the lower respiratory tract. For the upper respiratory tract, aspiration has proved to be a reliable technique for determining the levels of nasal nitric oxide (nNO). Levels of nNO can be used as a means of evaluating allergic rhinitis. Analysis of cells and mediators in induced sputum has been widely applied for studying bronchial inflammation. Besides the material properties of the condenser, dilution is still an issue in the comparison of effect biomarkers detected in EBC.

Due to differences in perception and functional reserves of the cardiopulmonary system, the presence and extent of disease may not be reflected accurately by clinical symptoms or lung function tests nor does the degree of airflow limitation assessed by spirometry always correlate to the severity of symptoms or health-related quality of life. In this case, the use of NIM in a variety of studies has for example produced information on inflammatory changes caused by specifically occupational or non-occupational (e.g. smoking) exposure in the respiratory tract in otherwise asymptomatic subjects. Moreover, analysis of EBC and NALF composition may also assist in determining the exposure to foreign substances within the target organs of the lung and the nose.

Biomarkers in specimens collected non-invasively may be used for both diagnostic and prognostic purpose, for example in order to identify subjects with different outcomes. They reflect exposure, effects and susceptibility and are therefore valuable in preventive strategies, since they assess lung injury in its early stages.

Exposure Laboratory

In the IPA exposure laboratory (ExpoLab), quality-assured human short-time inhalation studies can be performed in order to clarify the fundamental mechanisms involved in the cause and development of occupational diseases. The technology permits exposures to hazardous chemicals, particles or allergens. Two separate ventilation circuits also enable co-exposures to be simulated. A broad range of methods permit objective and quantitative investigation into local and systemic effects.

A decisive advantage of the ExpoLab compared to examinations at the workplace is the precisely adjustable level of exposure and its comprehensive monitoring. Furthermore, unwanted co-exposures to other hazardous substances can be excluded, which is seldom possible at the workplace. The safety of the volunteer study subjects is assured by continuous redundant exposure measurements, which are also documented in conjunction with the responsible ethics committee of the Ruhr University.

Studies performed under controlled exposure conditions yield valuable findings for the prevention of acute and chronic diseases caused by particles and hazardous substances, particularly for the setting of exposure limits.



Research into Particles

Occupational diseases resulting in death are most commonly caused by particles, including fibers. They can initially cause acute inflammation, becoming chronic under prolonged exposure, and ultimately severe diseases such as chronic obstructive pulmonary disease (COPD), fibrosis (e.g. silicosis and asbestosis) and cancer. Newly developed particles, in particular nanoparticles and fibrous materials, are discussed as being particularly pro-inflammatory. "Multi-walled carbon nanotubes" (MWCNT), for example, have proven even more carcinogenic in animal experiments than asbestos fibers. For this reason, systematic research into different particle effects is among the priorities of the IPA's preventive research. For this purpose, controlled human studies and cell culture-based methods are used.

To ensure standardized and reproducible conditions, validation experiments were conducted with regard to the homogeneous distribution of the particles and long-term stability of the target concentration. Particle



tests were first carried out with a soot-generating spark generator. A flame generator was later developed to produce nanoscale metal oxides from aqueous metal salt solutions by means of pyrolysis.

Cell experimental studies into the effects of particles

In order to model the mode of action of inflammatory particles, the Particle-Induced Cell Migration Assay (PICMA) was developed at the IPA. The test displays acute inflammatory particle effects with high differentiation, sensitivity and reproducibility, and permits classification of particles into those without effect, with medium and with strong effect.

Examination of further particles and comparison with animal and human data will be used to test the transferability of the PICMA results. Furthermore, parameters used as measures of inflammatory processes in animal or human studies can be confirmed experimentally by means of PICMA. Early non-toxic effects, indicating particle effects

which in the case of chronic exposure may result in serious diseases, can be identified by means of this new method.

Effect and Evaluation of Odors at Indoor Workplaces

The German Social Accident Insurance Institutions have been addressing the topic of indoor air quality and subjective health disorders at indoor workplaces for many years. One aim of these studies has been to use standardized methods to detect and evaluate chemical contaminants in indoor workplace atmospheres. Such standardized methods assist in the systematic assessment of health disorders associated with contaminants: for example, reliable reference values have been set for atmospheric hazardous substances in indoor work premises and in particular in offices.

However, measurements in indoor air and evaluation by reference values do not always lead to a satisfactory explanation of the problem. Complaints of subjective disorders and nuisance odors may arise even when the relevant guideline or reference values are observed. Evaluation of a complaint situation must take into account that a certain background prevalence of complaints can also be observed even in indoor areas without such problems.

The objective of current research into odors is therefore for surveys of the frequency of complaints concerning the room climate, health disorders, and statements concerning the perception and nuisance of odors in office areas free of contaminants in companies and institutions to be used to determine comparative values.

Epidemiology of Occupational Cancer



The derivation of scientifically robust occupational exposure limits and exposure-risk relationships for carcinogenic substances has been a focus of IPA's work for many years.

A particular challenge is distinguishing occupational causes from non-occupational (e.g. lifestyle-related) factors, which can be studied soundly only within sufficiently large epidemiological studies. This is necessary to come to valid conclusions for occupational safety and health, for example as dose-effect relationships. For many hazardous substances sound occupational exposure limits have not yet been adequately determined; these values however serve as a basis for the prevention of occupational diseases and work-related health hazards in the context of primary prevention.

Basis for an effective risk assessment is the quantification of occupational exposures. Actual measured exposure data are increasingly used for this purpose.



SYNERGY

Pooled Analysis of Case-Control Studies on the Joint Effects of Occupational Carcinogens in the Development of Lung Cancer

The international SYNERGY study examines the interaction of occupational carcinogens in lung cancer development, in order to derive scientifically sound data for prevention and for the German legislation governing compensation for occupational diseases. The project, in which a number of leading epidemiologists are involved, is coordinated 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 16 case-control studies were pooled in an epidemiological database. With 19,370 cases of lung cancer and 23,674 control subjects from 16 countries, this is the largest collection of data for risk assessment of occupational lung carcinogens to date.

Available measurements from international secondary databases for crystalline silica, asbestos, polycyclic aromatic hydrocarbons, chromium, and nickel were transferred into an exposure database. This database, Expo-SYN, currently contains approximately 375,000 personal and stationary measurements, of which approximately

100,000 are personal measurements. Using statistical modelling, a job-exposure matrix (SYN-JEM) was created to estimate each study subject's average exposure level by occupation, calendar year, and region.

By linking SYN-JEM to the occupational histories, cumulative exposure to the five selected pulmonary carcinogens can be assessed quantitatively. SYNERGY aims at calculating dose-effect relationships for each individual carcinogen (including smoking) and their mutual interaction. Each risk estimate is adjusted for smoking, as the main confounder for lung cancer, and employment in jobs with exposure to other occupational lung carcinogens. The large epidemiological database also allows for stratified analyses by smoking status and other important sub-groups.

Several results from SYNERGY have now been published in major peer-reviewed journals. These concern a large number of job-related lung cancer risks, such as for welders, bricklayers, miners, cooks, hairdressers, firefighters, and bakers, as well as risk estimates for workers exposed to organic dust and to diesel exhaust fumes. In addition, risks for smoking behaviour have been addressed according to histological subtypes of lung cancer and to social occupational prestige and status. Regarding the results for the five model carcinogens in SYNERGY, dose-effect relationships for occupational asbestos exposure were published in 2017, revealing increased lung cancer risks even at low exposure levels, and a positive interaction with smoking behaviour on an additive scale. Analyses for the other lung carcinogens and their mutual interactions are underway.

Early Detection of Cancer



Occupational cancers continue to present a major challenge for the prevention work of the German Social Accident Insurance Institutions. The figures published by the European Union speak for themselves: 53% of work-related deaths are attributable to cancer. Throughout the EU, around 120,000 workers develop an occupational cancer each year. The costs resulting from exposure to carcinogenic work materials are estimated at €2.4 billion per year. These figures, and the

fates of individuals behind them, show clearly that a major need for action exists.

Cancers of occupational origin continue to form a large proportion of the formally recognized cases of occupational disease, and are responsible for over half of the fatal cases. Exposure to asbestos in particular continues to be a major cause. As part of secondary prevention, the aim of follow-up screening is to detect possible cancers in formerly exposed insured persons at an earlier stage. The earlier a cancer is detected, the better are the chances for successful therapy. Early detection of cancer requires suitable and ideally minimally or non-invasive diagnostic methods that are not stressful for individuals. Molecular markers (biomarkers) that can be detected easily in blood, saliva, urine or other body fluids are suitable for this purpose. In some areas, such as early detection of lung cancer, combination of biomarkers with radiological methods could further improve diagnosis in the future.

The IPA has built up expertise over many years in the area of molecular epidemiology, a combination of molecular medicine and epidemiology. Further expertise is provided by PURE (Protein-Research Unit Ruhr within Europe). These endeavours create synergies, both through extension of the technology platforms already available, and through the procurement of additional third-party funding and the formation of networks. Several studies are being conducted on this basis at the IPA in order to identify, verify and validate biomarkers for the early detection of cancer.

The MoMar, UroFollow and PURE projects are concerned with various aspects of the development and validation of biomarkers for the early detection of cancer.

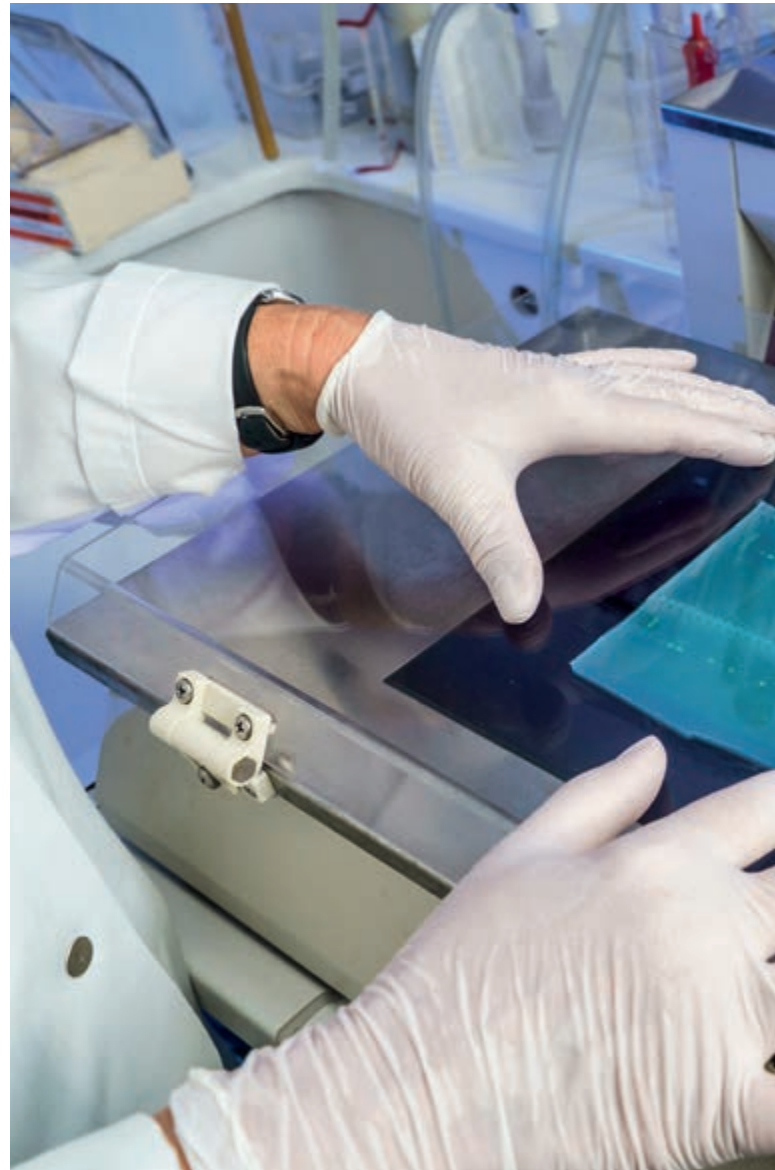


MoMar:
Molecular Markers for early Detection of Cancer

The “MoMar“ project (molecular markers for early detection of cancer) deals with the development of molecular markers for the early detection of asbestos-related cancer of the lung and pleura and their validation in medical practice. Mesothelioma, a pleural cancer caused by asbestos, constitutes a major occupational health issue owing to its long latency and rising number of cases. Substantial research efforts are therefore still needed. The objective of the prevention study is to validate new molecular markers for early detection in high-risk collectives using a 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 some imaging methods. The markers have the potential to complement radiological methods and may help to reduce radiation exposure. The high-risk collective comprises more than 2,700 workers formerly exposed to asbestos and exhibiting asbestosis, who were recruited from 2008 until 2017 and examined annually over a period of up to ten years.

In contrast to previous 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. So far, the proteins calretinin and mesothelin have been validated as tumor markers for the early detection of mesothelioma.

The combined markers are able to detect almost 50% of mesothelioma cases up to a year before classical di-





agnosis, with only 2% false-positive test results. In the future, the more than 180,000 aliquots of blood and plasma samples that have been stored in a biobank will serve as a valuable source for the validation of other new biomarkers.

UroFollow:

Marker-based secondary prevention of bladder tumors of low malignant potential

An important aspect in the prevention of occupational cancers is the development of secondary prevention measures for insured individuals who in the past were exposed at work to potentially bladder-carcinogenic substances. This objective is being addressed by the joint UroFollow project (marker-based follow-up of patients with non-muscle-invasive low/intermediate risk bladder cancer). The project is being conducted in collaboration with the urological clinics in Erlangen, Rostock, Herne and Tübingen.

In this randomized clinical study (RCT), the suitability of various non-invasive urine-based tumor tests is to be studied in comparison with cystoscopy (endoscopy of the urinary bladder, the standard procedure, which is considered painful by many patients) during the follow-up treatment of non-muscle-invasive low/intermediate-risk bladder cancer. Low/intermediate-risk bladder cancer have low malignant potential, but constitute a major challenge for patient care, because a large proportion of these patients suffer a relapse. A systematic longitudinal study into the follow-up care of bladder cancer patients is necessary if non-invasive diagnostics and follow-up care are to be integrated into urological guidelines. The approach of UroFollow is

unique worldwide in using a randomized clinical trial in order to validate biomarkers for the early detection of bladder cancer.

The objective of UroFollow is to demonstrate the equivalence of non-invasive follow-up care employing urine-based markers to the invasive method of cystoscopy. The study is based upon tests approved by the US Food and Drug Administration such as cytology, the UroVysion® test, the quantitative detection of the nuclear matrix protein 22 (NMP22), and other markers/assays, in some cases experimental.

In addition, a sample database is being established in UroFollow, which will allow identification, clinically testing and simultaneously validation of markers in a much shorter period of time in the future. Also for marker identification, a prospective study design is substantially superior to a cross-sectional study, since pre-diagnostic material is archived that can be analyzed promptly for conspicuous markers in the course of the follow-up following diagnosis of a cancer. Parallel to validation of the established biomarkers in the marker arm of UroFollow, experimental markers such as Survivin, FGFR3, UBC® Rapid and the Xpert Bladder Cancer Monitor Assay, which to date have hardly been used at all in routine clinical diagnostics, are to be evaluated in the usual care arm.

PURE

The IPA is a central pillar of PURE (Protein Research Unit Ruhr within Europe), founded in 2010. PURE's main goal is to develop biological markers to detect cancer and neurodegenerative diseases at an early stage, and

thereby to improve secondary preventive measures at the workplace and in clinical settings. PURE covers all steps from the development of a biomarker concept, through its identification and validation, to validation of assays in the field. For this purpose, researchers of the Ruhr University Bochum have joined forces with the IPA. This research project constitutes a major benefit for developing and implementing secondary health preventive measures at the workplace.

PURE is a consortium of several research institutes at the Ruhr University Bochum. Its aim is to identify biomarkers for the early detection of widespread chronic diseases, in particular cancer and neurodegenerative disease. PURE was funded by the Ministry of Cultural Affairs and Science of the federal state of North Rhine-Westphalia (NRW) and is currently financially supported through 2018.

PURE's underlying objective is to use a clinical network across Germany to identify biomarkers for the early detection of cancer and neurodegenerative diseases, to validate them in large-scale molecular epidemiological studies, and subsequently to integrate them into preventive healthcare. Within PURE, the IPA is responsible for epidemiology and for molecular tumor biology, thus representing a gateway for all participating research institutions and for occupational practice. IPA focuses on work-related cancers of the urogenital system and the respiratory tract, which are of particular relevance for the German Social Accident Insurance.

The validation of newly identified markers in prospective high-risk cohorts from follow-up examinations of the German Social Accident Insurance, e.g. workers

exposed to asbestos or to aromatic amines, will be of key importance in the near future. External grants totaling approximately €5.3 million have been secured for the “PURE Lung“ and “UroFollow“ projects. The PURE Lung collaboration has already resulted in a number of promising biomarker candidates for the detection of lung cancer. It has been successfully transferred to the second stage of biomarker development, i.e. verification in an independent hospital collective.

IPA is one of the three founding members of PURE, the other two being the Department of Biophysics and the “Medical Proteome Center” at the Ruhr University Bochum.

Early Detection of Bladder Cancer

Bladder cancer can be caused by occupational exposure to aromatic amines or polycyclic aromatic hydrocarbons (PAH). Occupational exposure is often unavoidable. Workers at risk such as those formerly exposed to aromatic amines or PAHs are a group in which it would be of particular advantage for bladder cancer to be diagnosed at an early stage by means of non-invasive methods. At present however, no quality-assured methods for such diagnoses are available, despite the prospects for successful treatment specifically of bladder cancer being particularly high when it is detected early.

The IPA is therefore currently developing new, non-invasive methods for the diagnosis of bladder cancer, including epigenetic and protein biochemistry methods for the detection of biomarkers in urine. The challenge here lies in not only identifying but also verifying and validating new marker candidates, particularly with regard to their specificity with respect to other cancers and non-tumorous or in-

flammatory diseases of the genito-urinary system. Accordingly, the IPA is working in the wider Ruhr region not only with hospitals, but also with resident urologists and gynaecologists in order to verify the biomarkers under real-case conditions. Overriding objectives are the development of a transregional network and of low-cost tests that in the long term will enable marker verification to be performed on site on hospital wards or in doctors’ surgeries.

The studies on humans are being supplemented by *in vitro* laboratory studies to investigate the role of the identified biomarkers for bladder cancer. These studies are being performed at the cellular and molecular levels with the use of different bladder cancer cell lines. An understanding of whether and if so which specific functions are assumed by these molecules in the cell during the development or progression of bladder cancer can yield crucial strategies for new treatments for bladder cancer.



Research into Hazardous Substances



Substances or mixtures that could be dangerous or harmful for human beings or the environment are by definition hazardous substances. Employees from various sectors come into contact with hazardous substances. Thanks to intensive occupational safety efforts, exposure levels to harmful substances have been reduced to a minimum. As a consequence, acute and sub-chronic effects of substances, i.e. effects arising within a few days to weeks (including classic symptoms of intoxication), now hardly ever occur at workplaces.

The focus is now shifting to chronic effects, i.e. effects that become apparent only after many years or even decades as a result of very low but continuous occupational exposure. Due to the long latency periods, these effects are however increasingly difficult to distinguish from non-occupational causes such as lifestyle or environmental factors.

Due to this changed situation, research into hazardous substances is reacting with increasingly sensitive and specific detection methods. An example of this are detection methods for monitoring workplace exposure by means of human biomonitoring, by which the internal stress and strain upon human beings under exposure to hazardous substances is measured. Conventionally, the concentration of a hazardous substance or one of its metabolites is determined in biological material, particularly in blood and urine.

Whereas in the past a single test may have been sufficient to determine a relationship between exposure and disease, several test methods must now be performed in parallel in order to assemble the individual pieces of the jigsaw to form a complete picture. Stud-

ies into the mechanisms of action of hazardous substances, including by *in vitro* cell experiments, are in particular becoming an important supplement to exposure measurements. These studies link exposure to disease, thus revealing a measure for the probability of a relationship. Cell experiments also permit selective studies under controlled conditions to investigate the effects of different hazardous substances in combination, since the complex exposure situation at the workplace normally prevents such effects from being evaluated by conventional occupational medical and epidemiological studies.

Correspondingly diverse study methods have been established in recent years at the IPA in order to study the effects of hazardous substances upon human beings and to consider them from the most diverse perspectives possible. From the outset, attention was paid not only to researching and understanding the effects of known hazardous substances in even greater detail, but also to the proactive study of new substances arising at workplaces, of which not enough, if indeed anything, is known as yet about their harmful effects.

Human biomonitoring

Human biomonitoring (HBM) detects hazardous substances or their metabolic products in body fluids. It enables the quantities of hazardous substances actually absorbed by an individual to be determined, and in the case of substances ubiquitous in the environment, the occupational and non-occupational exposures to the substance to be differentiated.

HBM is growing in importance as a means of charac-

terizing hazardous substance exposures at the workplace, and also environmental exposures. Its major advantage is that in contrast to ambient monitoring, it characterizes the actual personal exposure through all possible routes of uptake (inhalative, dermal, oral). HBM has developed into an important component of preventive occupational medical care and now forms part of the German ordinances on hazardous substances (GefStoffV) and on Occupational Health Care (ArbMedVV).

Depending upon the elimination kinetics of individual metabolic products, HBM often permits conclusions not only regarding exposure to hazardous substances occurring in the very recent past, i.e. in the order of hours or during the last working shift (short-time markers), but also regarding the average exposure over the preceding days and months (long-time markers). Against this background, HBM methods that measure several metabolic products of a hazardous substance simultaneously are frequently used in studies at the IPA, thereby enabling the most comprehensive picture possible of the exposure situation and the potential hazard resulting from it to be obtained. In the studies of the metabolism, new, specific metabolites for hazardous substances currently being discussed are continually being identified, studied with regard to their metabolization and excretion kinetics, and established as new biomarkers.

The spectrum of HBM methods has consequently been extended progressively in recent years with regard to issues of importance to the accident insurance institutions. This applies to the areas of organic trace analysis and metal trace analysis. The sensitivity of the

methods enables not only workplace exposure to be determined reliably, but also the environmental background exposure of the general population, and the two to be differentiated from each other.

In all methods, the strictest standards are placed upon the reliability and integrity of the analysis results, in addition to the requirement for scientific relevance.

The integrity of the results is guaranteed by thorough quality assurance within the laboratory and by participation in external quality assurance programs, such as round-robin tests. At the same time, the IPA's HBM laboratory serves as a reference laboratory for several providers of round-robin tests and for providers of certified control material. The IPA actively contributes its experience in the areas of method development, establishment of biomarkers and quality assurance to national and international research projects.

New and substitute Substances

The toxicity of a large number of new and substitute substances is not known, or is disputed scientifically owing to the paucity of available data. At the same time, exposure to one and the same substitute product may vary considerably between different workplaces or different tasks. Assessment methods are therefore required as a basis for the hazard and risk assessment by which both the exposure and the effect of new and substitute substances can be assessed reliably.

The IPA develops quality-assured methods for monitoring the exposure and for studying the biological effects of substitute products. This particularly means identi-





ifying the routes of uptake prevailing at the workplace in order to perform a suitable hazard and risk assessment and avoid danger to the employees' health.

The focus of the studies lies upon studying substances serving as substitutes for carcinogenic, mutagenic and reprotoxic hazardous substances. The substitutes (which often possess a similar structure) are suitable owing to their application and product characteristics. Examples are substitutes for solvents, and phthalate plasticizers, presenting a threat to health. Research is also focused upon the ingredients of sunscreen creams, including substances that are used as UV fil-

ters or as skin anti-ageing agents. Finally, newly developed fragrances for cosmetic products and air-conditioning units are also studied. Owing to their ubiquity, these substances are particularly relevant for persons sensitive to them.

The results enable companies and workers alike to integrate prevention measures swiftly and effectively into industrial practice, and also to monitor these measures effectively. This particularly includes monitoring hygiene measures and the efficacy of personal protective equipment in order to reduce exposure to a minimum.

HBM4EU: Human Biomonitoring for Europe

For many chemicals to which human beings are exposed on almost a daily basis, the effects upon their health are either largely unexplored, or indicators of adverse effects have already been obtained from animal experiments and epidemiological studies. The joint HBM4EU: Human Biomonitoring for Europe project, launched in January 2017 with EU funding and initially scheduled to run for a five-year term, therefore has the aim of monitoring human internal exposure to chemicals and protecting against it.

A total of 109 project partners from 27 European countries and Israel are involved in this project. Its key objective is to create a sound and comparable body of data on the exposure of the general population to industrial and environ-

mental chemicals in Europe. HBM serves here as a key tool for the recording of all forms of exposure and as a basis for the determining of possible health risks to human beings. It is to be used at both scientific and policy level to counter potentially adverse effects of hazardous substance exposure at an early stage, and also as an instrument for describing the success of regulatory/exposure-reducing measures. Political representatives, interest groups and researchers are working together to protect the European population against exposure to both known and new chemicals and against possible health hazards.

The development of new methods is being supported by the IPA's activities in the area of human biomonitoring. The team of experts at the IPA also provides scientific support in the evaluation and selection of existing established analysis methods and in the formation of a network of participating laboratories.



HBM data in the focus of political, public and scientific interest and beneficial and suitable for HBM in the general population are to be recorded and evaluated throughout Europe for a predefined list of prioritized substances. These include phthalate plasticizers and new types of substitute for them, bisphenols (BPA and substitutes), brominated flame retardants, polycyclic aromatic hydrocarbons, and heavy metals such as chromium and cadmium.

Biomonitoring in Practise: Biomonitoring of Fire Services Personnel

Fire services personnel are frequently exposed to hazardous situations when fighting fires. These personnel should be protected and able to behave in such a way that harmful – not to say carcinogenic – effects upon them are prevented. This is attained by personal protective equipment (PPE) and by organizational measures. Personal hygiene, by which hazardous substances are prevented from being transferred from contaminated clothing to the body, is also relevant in this context. The use of suitable PPE cannot always protect fire services personnel against contact with the hazardous substances, however. Smoke from fires and carcinogenic substances contained within it, such as polycyclic aromatic hydrocarbons, may be deposited on the skin even where protective clothing is worn. The health risk presented by the possible uptake of hazardous substances through the skin during a firefighting operation has not yet been adequately clarified.

In order to obtain reliable data on this aspect, the IPA is using biomonitoring to study the exposure of fire services personnel to carcinogenic substances in

typical real-case fire situations. The project is being conducted in conjunction with the DGUV, the Institute for Occupational Safety and Health of the DGUV (IFA), several of the German Social Accident Insurance Institutions, full-time fire services, and the DFV, the German fire service association. The overriding objective of the project is to develop strategies for primary prevention of the exposure of fire services personnel to carcinogenic substances. Since the hazardous substances may be taken up not only via the lung but also through the skin, hygiene is one of the foci of the project. The results are to deliver specific indications of how fire services personnel can protect themselves or can be protected. In the course of the study, biomonitoring is being used to measure the uptake of polycyclic aromatic hydrocarbons in up to 250 fire services personnel from two fire services during firefighting operations. The exposure of the skin is recorded on a subset of the study participants by special cotton underwear worn below the protective clothing. This is to determine where ingress points for the smoke from the fire exist in the protective clothing, what parts of the body are particularly exposed, and where soot is most typically deposited.

Cell Toxicology: Methods for Studying the Mechanisms of Action

Studies at cellular and molecular levels complement epidemiological and animal experimental studies for evaluating the risks presented by hazardous substances at the workplace. Defined cell systems, such as cell cultures, can be used to study the mechanisms of action of hazardous substances in a standardized, reproducible and quality-assured manner.

Cell culture systems suitable for addressing the problems, which are often study-specific, are identified and characterized at the IPA with regard to their growth behaviour and whether they possess xenobiotic-metabolizing enzymes. At present, suitable cell lines are being used to study the cellular processes of hazardous substances that cause lung cancer or bladder cancer.

The dose-dependent and time-dependent effects of lung and bladder carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and aromatic amines are typically tested at a molecular level. Early and possibly reversible changes (such as the induction of xenobiotic-metabolizing enzymes) and irreversible effects (e.g. apoptosis, necrosis) are recorded in order to obtain the most comprehensive picture possible of the effect of these hazardous substances.

Extremely sensitive protein chemistry methods (such as western blot and luminescence assays) and cytogenetic methods (comet assay, micronucleus test) are also used. Specifically for PAHs, a chemical analytical method for the detection of DNA adducts of benzo[*a*]pyrene is available that provides insights into the initial stages of carcinogenic action of PAHs. By contrast, effects upon the cell cycle and cell proliferation are studied by biological analytical methods, including flow cytometry, which in turn provides insights into the progression and growth of the cells treated with a hazardous substance. Cytotoxic effects, i.e. hazardous substance concentrations that lead to cell death, are also studied. The full picture of observed effects and mechanisms permits an estimation of the concentration above which adverse effects may be anticipated, and an indication of what strategies may be

needed at the cellular level to prevent these effects.

Combination Effects of Hazardous Substances *in vitro*

Human beings are frequently exposed to mixtures of substances, both at the workplace and in the environment. Many risk assessments are based upon knowledge of discrete substances, however. It is frequently unclear whether and if so how different substances act in combination in the event of simultaneous exposure, i.e. whether they reinforce the toxic effect already known for a discrete substance, or may in fact mitigate it. *In vitro* studies of cell cultures following their treatment with hazardous substances or defined hazardous substance mixtures constitute a particularly useful tool for the investigation of problems such as these, since in contrast to workplace studies, they are free of further influencing factors and can therefore be performed under precisely defined conditions.

The IPA specifically studies combined effects and processes of hazardous substances that are responsible for the incidence of lung and bladder cancer. Of particular interest here is the mutual influence of compounds known to be carcinogenic and compounds not classified as carcinogenic. With regard to lung cancer, the tumor-promoting and tumor-initiating properties of different high-molecular and low-molecular PAHs in particular are being studied in cooperation with the University of Colorado, since these substances always occur in combination at workplaces. Similar joint studies are being conducted with the University of Minnesota into the carcinogenic action of PAHs and aromatic amines.



The results of these studies are used to estimate the relative contributions made by different hazardous substances or hazard substance classes to the incidence of cancer under mixed exposure conditions, and in particular in determining whether – where reinforcing effects are established – these effects are additive or over-additive in nature.



Occupational Allergies: From Exposure to Disease

The number of persons in Germany suffering from allergic diseases has risen significantly in recent years. Occupational allergic diseases are the fifth most common type of occupational disease. The primary routes of uptake for the occupational allergens are the respiratory tract and the skin. Occupational allergy research in Germany has been sporadic up to now. Tools for the diagnosis of these diseases are only insufficiently available. The same applies to research into early recognition. Since virtually no data are available on dose-effect relationships, and development of sensitization is also dependent upon individual predisposition, it is not possible for health-based limit values to be set for occupational sensitizers.

Quantification/Monitoring of Allergens

At many workplaces, the environment is very complex and a wide variety of workplace agents can cause occupational airway diseases by inhalation. More than 400 occupational agents are identified and documented as being “respiratory sensitizers” capable of triggering the development of occupational asthma (OA) and/or occupational rhinitis (OR), usually by means of a specific immune response.

A primary goal of occupational safety and health are optimal preventive measures to avoid sensitization by occupational substances. This requires knowledge of allergy triggers and whether and in what concentration the allergens are present at the workplace. Standard

measurement protocols for the determination of allergens at workplaces are being developed and applied in the course of the project. For this purpose, methods are being improved and developed for sample collection at workplaces determination of allergen load and the assessment of the measured values. The allergen quantification methods for dust collectes from workplaces have been continually developed and validated in recent years with regard to their sensitivity. This enables the IPA to offer the metrological services of the German Social Accident Insurance Institutions a standardized measurement method for numerous allergens relevant to workplaces, including various mite allergens, wheat and rye flour, various enzymes, animal allergens and allergens from obeche wood. The repertoire of validated methods is being extended according to the requirements in the field.

Animal Allergens

Occupational contact with furry animals, particularly cats, dogs, cattle, horses, mice and rats, but also guinea pigs, hamsters and rabbits, can give rise to allergic reactions.

Although the exposure to allergens at workplaces can be reduced by prevention measures, it is unavoidable at many workplaces, for example when handling animals in veterinary medicine. Occupational exposure to microbial constituents and chemical substances must also be taken into account. Sufficient data are however not available on the level of allergen exposure arising during specific tasks and its significance for the development of sensitization and allergic complaints. Data are also lacking on transfer of the allergens from the workplace to the domestic environment.



Incidence of Allergies and Allergen Exposure among skilled Veterinary Staff

The occupational groups affected include employees who work with laboratory animals, primarily mice and rats, as well as employees in veterinary medicine. The knowledge on the prevalence of allergies in veterinary practices is at present inadequate.

A research project conducted jointly with the German Social Accident Insurance Institution for the health and welfare services and the Hamburg-Eppendorf University clinic is to answer questions regarding the prevalence of sensitization and allergic diseases among veterinary assistants working in veterinary practices; the level of allergen exposure arising in these practices, during certain working procedures and the transfer of allergens into the domestic environment.

Exposure to Animal Allergens in Veterinary Medicine

Studies clearly show that increasing numbers of children and young people are affected by asthma and hay fever. This also means, that at the beginning of their careers, growing numbers of young people already have an allergic predisposition, i.e. a susceptibility to allergies, and will begin their training or studies in areas that involve an elevated risk of sensitization.

In order to measure and evaluate the influence of allergen exposure upon the development of sensitization and disorders of the respiratory tract and skin, the IPA is conducting a longitudinal study in collaboration with

the German Social Accident Insurance Institution for the public sector in Hesse. The study is examining exposure to animal allergens and accompanying components in the complex area of veterinary medicine.

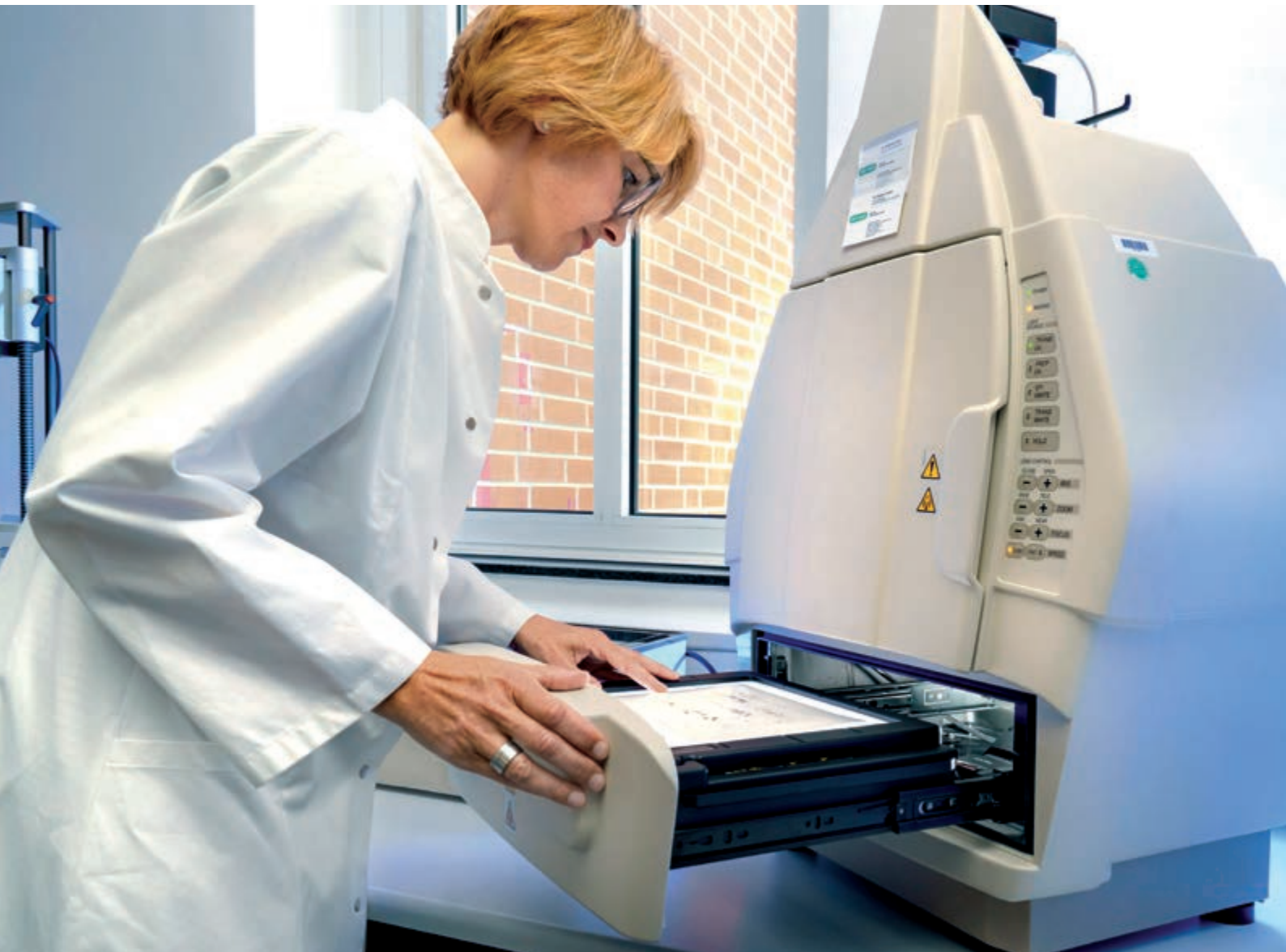
In particular, longitudinal studies of young professionals, apprentices and students in their first semester enable substantial conclusions regarding the risk of occupational diseases of the respiratory tract, since the frequency of work-related complaints peaks in the two to three years after the first allergen exposure. Besides a questionnaire particularly covering the respondent's medical history with regard to an allergic predisposition, examinations of pulmonary function and documentation of the skin conditions of the hands, and detection of specific IgE antibodies against relevant allergens, exposure measurements were performed on campus and also in the students' domestic environments.

Occupational allergies must be avoided, and concepts developed by which persons suffering from allergies or workers with an allergic predisposition can remain in their professions in the long term without complaints.

Moulds Sensitizing, irritative and inflammatory Effects

Moisture damages associated with increased mould and bacterial exposure may present a health risk to exposed persons. Exposure to mould may be a problem not only in residential buildings, but also in several workplaces and in public institutions such as children's day-care facilities and schools. The relationships between the occurrence of mould and possible health





effects are very complex. Various disorders such as infections, irritations and annoyances as well as allergies can be caused by moulds, but only rarely is there a clear connection between the symptoms and the exposure. There is therefore a major need to improve the diagnosis of mould IgE-mediated allergies. In addition, the exposure assessment must be optimized, if appropriate by means of new biomarkers and test systems. An IPA project is studying firstly how mould allergy diagnostics can be improved and secondly the cellular mechanisms of action of mould.

The commercially available skin-prick test solutions of mould allergens were tested by means of established

protein biochemical and immunological test methods and subsequently verified with prick testing in a multi-center study. Based upon the study results, the use of skin tests involving mould extracts with a high antigen content, supplemented by determining of specific IgE against mould mixture, can be recommended for diagnosis of mould allergies. Since the mechanisms of action of disorders associated with mould are not yet known in detail, they are characterized both with regard to an environmental exposure analysis, for example in dust samples, and by analysis of the personal load (immunological response of the affected person).

The mechanistic studies enhance understanding of the action of mould exposure and enable parameters to be validated that are currently being discussed in the context of extended diagnostics and early detection of the relevant effects of mould exposure.

Bioaerosols

Bioaerosols (also termed organic dust) are a subcategory of particles released from terrestrial and marine ecosystems into the atmosphere. They consist of both living and non-living components including organisms, such as fungi, bacteria, viruses, and pollen, which can occur in inhalable sizes from 10 nm for virus particles to 100 µm for pollen grains. Bioaerosols can transmit microbial pathogens, endotoxins, and allergens and can excrete components inducing a response, primarily inflammatory, in the respiratory tract. Bioaerosols thus pose a health risk in the form of infections and toxic and allergic reactions. Studies suggest inflammatory adverse health effects following exposure to bioaerosols, in particular at workplaces. However, health-re-



lated protection measures based on experimental or epidemiological studies from the working environment are still lacking.

Workplace bioaerosol concentrations are greatest in agriculture, farming, waste handling and similar facilities. However, biological agents occur at almost every workplace, including schools and daycare centers. Specific risks of infections exist at hospitals and other healthcare centers.

The IPA conducted several studies at waste handling facilities and discovered elevated risks for inflammatory toxic disorders and allergies at composting and recycling facilities. Waste collectors also exhibited an increased risk of inflammatory reactions such as chronic bronchitis. In addition to assessment of workplace-related allergen exposure, aspects of exposure to components of bioaerosols are also being examined, including in studies involving veterinary assistants and biolaboratory technicians, and in particular in cohorts such as students undergoing veterinary training. The results of these studies are being used by regulatory committees to implement new or optimized protective measures in an occupational safety and health context.

In addition, the IPA develops and validates techniques to detect and quantify components of bioaerosols using the whole blood assay, by stimulation of peripheral blood cells of the innate immune system and quantification of released mediators by means of specific immunoassays. The validation and standardization of methods to quantify specific antibodies against workplace and environment-related moulds and bacteria are also part of this project.



Occupational Dermatology



Due to their particularly high incidence – currently accounting for 42% of all reported cases of suspected occupational diseases in Germany, equating to over 30,000 cases per year – work-related skin diseases, particularly formally recognized occupational diseases (BK) 5101 (abbreviated below as hand eczema) and (BK) 5103 (abbreviated below as skin cancer caused by UV radiation), are a particular focus of the German Social Accident Insurance. The IPA's occupational dermatology research focuses on the prevention and verification of factors that can lead to the development of skin diseases.

Skin Protection inside Gloves

The air-tight sealing-off of the skin by gloves („occlusion“) does not lead to measurable changes in the skin barrier. However, after subsequent contact with detergents, there is a stronger inflammatory reaction than in the case of non-preoccluded skin (increased sensitivity). The use of skin protection preparations should – according to the manufacturers' information – help to reduce barrier disorders caused by occlusion and thus lead to better stabilization of the *stratum corneum*. In addition, suitable ingredients are intended to induce a reduction

in sweat secretion. As yet, no standardized scientific analyses are available by which this information can be reviewed. The reaction of the skin barrier following occlusion stress with and without skin protection gels and creams was studied in experiments on test subjects. A stabilizing effect of the skin barrier could neither be proven clinically nor by bioengineering methods. At present, no experimental evidence exists that an objectifiable improvement in the barrier function following occlusion (protective effect) can be achieved by the use of designated skin products.

Virucides

Due to the spread of viral infections (caused for example by noroviruses) in communal facilities, hand disinfectants specifically declared as „virucidal“ are now increasingly being used. Clinical observations have shown that the use of special virucidal products is accompanied by elevated skin irritability, despite the supplementary use of moisturizing ingredients. To date, no comparative experimental and user-oriented *in vivo* studies have been published of the skin tolerance of virucidal hand disinfectants. Hand disinfectants with



a range of compositions were tested in a number of exposure scenarios and in different forms of application. Open applications did not lead to any detectable changes *in vivo* within two to five days. Closed forms of application were then used in a randomized blinded study in volunteers.

Stronger irritative reactions were caused by products containing some combination of phosphoric acids and low concentrated alcohols than in products containing highly concentrated alcohols. The results further indicate that the ingredients discussed so far, such as dilute phosphoric acid, may not be responsible for the increased irritative reactions, so that the low concentrated alcohols may probably be responsible for the irritative potency.

UV Radiation and Skin Cancer

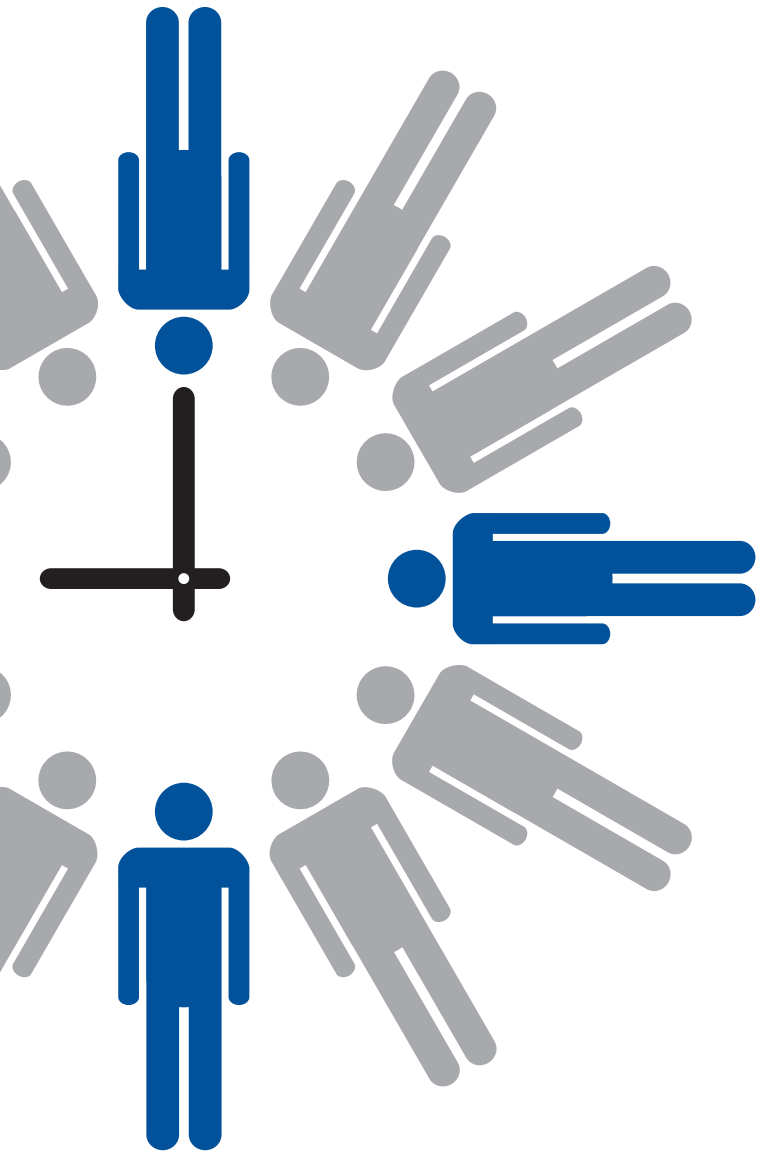
Natural UV radiation is considered a significant risk factor for the incidence of cutaneous squamous-cell carcinomas and basal-cell carcinomas.

Squamous-cell carcinoma or multiple actinic keratoses of the skin caused by natural UV radiation, which has been formally recognized in Germany since 2015 as occupational disease (BK) 5103, requires a sufficient set of instruments to assess the risk of UV exposure to spontaneous squamous cell carcinomas and basal cell carcinomas of the skin, taking particular account of occupational and non-occupational factors. For this purpose, methods were developed within a multi-center project with the help of which occupational UV exposure can be determined as precisely as possible.

The follow-on project then addressed estimation of the risk of UV exposure causing spontaneous squamous-cell carcinomas and basal-cell carcinomas of the skin. It was shown that persons with high overall exposure to UV radiation have a significantly higher risk of developing a squamous-cell carcinoma of the skin than persons with average overall exposure. For persons with a basal-cell carcinoma, this relationship could not be verified with statistical significance; a clear trend was however demonstrated. For both tumour entities, occupational groups with a particularly high risk of developing the disease were found in the sectors of agriculture, animal and plant breeding, outdoor construction work, and metalworkers/fitters/pipe layers (with outdoor employment).

These two research projects have already contributed substantially to clarifying the issue; further questions have yet to be answered, however. For successful primary prevention, it is necessary to know in which chronological order squamous cell carcinomas and basal cell carcinomas occur, as well as the course and the quantity of UV radiation that causes them.

Impact of Shift Work upon Health



Shift work is a suspected cause of a large number of health disorders. The natural alternation between day-light and darkness synchronizes the body's internal clock to the day/night rhythm. This is largely governed by the neurohormone melatonin. Its synthesis begins with the onset of darkness but can be suppressed by light-at-night, e.g. by artificial light at the workplace during night shifts.

Important physiological processes such as sleep-wake 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 influences such as night-shift work is considered to be an important component responsible for the occurrence of several health disorders.

Employees, particularly those working night shifts, often suffer sleep disorders which may lead to fatigue or gastrointestinal disturbances. Beyond these complaints, epidemiological studies also indicate that shift work may be a contributory factor in the causation of diabetes mellitus, cardiovascular diseases and mental disorders. In 2007, the IARC classified shift work that involves circadian disruption as „probably carcinogenic to humans“ (Category 2A), mainly based on epidemiological evidence for female breast cancer. Scientific debate continues regarding an association between circadian disruption, breast cancer and other tumours such as prostate and colon cancer.

In order to study health effects and mechanisms of circadian disruption in humans, the IPA is involved in a number of research projects for the purpose of recom-

mending concepts for shift work with lower circadian disruption and reducing health risks. In cooperation with the Bergmannsheil University Hospital in Bochum and the Helmholtz Centre in Munich, a study was conducted to examine the influence of shift work on sleep patterns, hormonal balance, and metabolic factors.

The IPA cooperates with the Federal Institute for Occupational Safety and Health (BAuA) to study effects of permanent night-shift work on activity patterns and selected biomarkers of circadian disruption. Furthermore, it is involved in an international pooled study on shift work and breast cancer including studies with complete occupational histories.

IPA-Biobank – Significance for Occupational Practice

Biobanks, i.e. collections of human biomaterials and associated subject data, which are stored over an extended period, constitute the basis of investigating changes in the human organism before and during the development of a disease. They allow for the identification of molecular variations in healthy persons that potentially may promote the development of a disease as well as the identification of biomarkers that may indicate the beginning of a pathological process (e.g., cancer). In combination with biomonitoring techniques, biological samples permit a more precise measurement of occupational exposures which may serve primary prevention purposes in the surveillance of health risks associated with hazardous substance exposure.

Frequently, such research questions require prospective and repeated collection of biological samples over an extended period of time, which may only develop their full potential aided by biobanks. Those biobanks, requiring sample acquisition over many years, are an

important prerequisite for quality-assured research in marker-based secondary prevention and permit not only current, but also analyses with future methods that are not yet available.

The IPA currently realizes the concept of an institutional biobank which will be a lasting and important investment into the institute's future. Similar collections with occupational medical focus are rare in Germany.

The IPA-biobank will feature the following components:

- Central and decentralized storage of biomaterials
- Robot-controlled sample storage in cryo tanks with liquid nitrogen (down to -196°C)
- Introduction of standardized storage and processing protocols
- Introduction of standards in documentation and processes

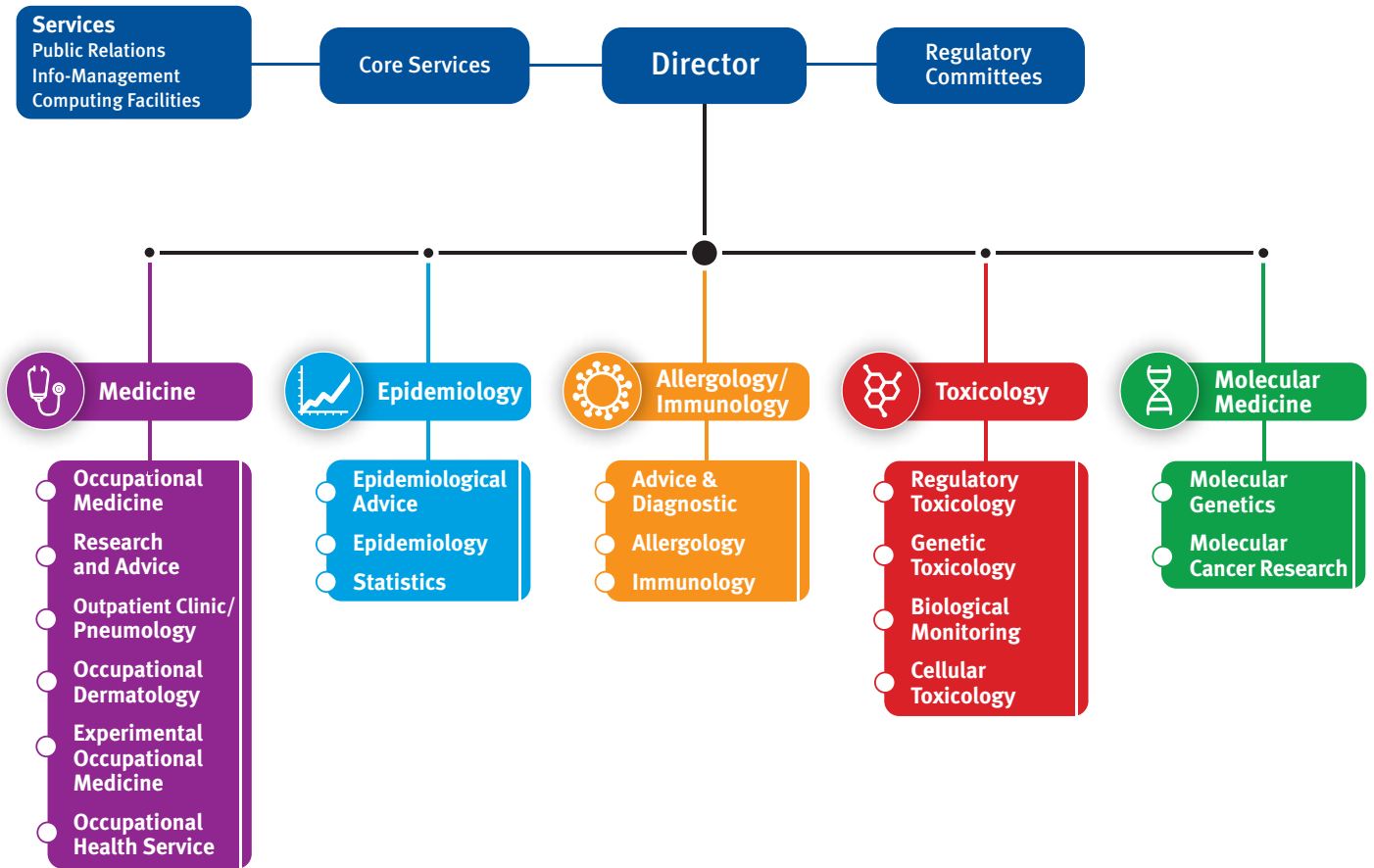
- A uniform emergency concept
- A central biobank IT structure
- Central guidelines for sample use and transfer

The IPA-biobank concept and the associated data safety requirements were recently discussed and acknowledged by the „AG Datenschutz“ of the “Technologie- und Methodenplattform für die vernetzte medizinische Forschung (TMF)“, which is an important step for national and international recognition of the IPA-biobank.

Therefore, the IPA-biobank may serve as a high-quality research platform in which biosamples may not only be used in IPA-associated projects, but may also be networked with other national and international occupational medical and biomedical biobanks. When the biobank concept has been fully realized, IPA will have a seminal and unique feature that will strengthen the institute’s position internationally in the field of prevention and occupational medicine.



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